Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Risk Management Plan
CONCERTA® (methylphenidate hydrochloride)

Issue Date:	23 NOVEMBER 2009
Version No:	2.0
Supersedes Version:	1.0* - 16 October 2008 (EDMS-PSDB-9077740:2.0)
Document Number:	EDMS-PSDB-10643608:2.0

* The title page for the previous RMP dated 16 October 2008 noted Version 2 (referring to the internal document number) rather than Version 1 (the official version of the RMP noted in the body of the report).

Confidentiality Statement

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is *privileged* or *confidential* and may not be further disclosed by them. These restrictions on disclosure will apply equally to *all* future information supplied to you, which is indicated as *privileged* or *confidential*.

TABLE OF CONTENTS

LIST OF TABLES 5

LIST OF ABBREVIATIONS 7

PRODUCT DETAILS 8

PART I 10

1. SAFETY SPECIFICATION 10

1.1. Nonclinical 10

1.1.1. Safety Concerns That Have Not Been Adequately Addressed by Clinical Data or Which Are of Unknown Significance 10

1.1.1.1. Potential for Carcinogenicity 10

1.1.1.1.1. Genetic Toxicology and Carcinogenicity Studies 10

1.1.1.1.2. Evaluation of Cytogenetic Endpoints in Human Ex Vivo Studies 12

1.1.1.2. Effects on Growth 15

1.1.1.3. Potential Cardiovascular Effects 16

1.1.2. Additional Nonclinical Data 17

1.2. Clinical: Limitations of the Human Safety Database 17

1.2.1. Exposure in Clinical Trials 19

1.2.1.1. Exposure in Randomised Blinded Trials 19

1.2.1.2. Exposure in All Clinical Trials Including Open Extensions 19

1.2.1.3. Exposure in Phase 1 Studies 20

1.2.1.4. Exposure in Special Populations 21

1.2.2. Epidemiologic Study Exposure 21

1.2.3. Postmarketing (Nonstudy) Exposure 21

1.3. Populations Not Studied in the Preauthorisation Phase 24

1.3.1. Paediatric Patients: Less Than 6 Years of Age 27

1.3.2. Adult and Geriatric Patients 27

1.3.3. Hepatic Insufficiency 28

1.3.4. Renal Insufficiency 28

1.3.5. Pregnancy 28

1.3.6. Nursing Mothers 28

1.3.7. Populations With Genetic Polymorphism 29

1.3.8. Patients With Cardiovascular Risk Factors 29

1.3.9. Effect of Gender 29

1.3.10. Effect of Ethnicity 29

1.4. Post-Authorisation Experience 29

1.4.1. Actual Post-Authorisation Usage Data 30

1.4.2. Regulatory Action Taken 30

1.4.2.1. Cytogenicity 30

1.4.2.2. Product Information - SmPC 31

TABLE OF CONTENTS (Continued)

1.4.2.3. Product Information - Package Leaflet 31
1.4.2.4. Suicidality 31
1.4.2.5. Long-Term Safety 31
1.4.2.6. Drug Utilisation 31
1.4.2.7. Educational Tools 31
1.4.2.8. PSUR Work-Sharing 31
1.5. Adverse Events/Adverse Reactions 32
1.5.1. Newly Identified Safety Concerns 32
1.5.2. Details of Important Identified and Potential Risks 32
1.6. Identified and Potential Interactions With Other Medicinal Products, Food, and Other Substances 144
1.7. Epidemiology of the Indication (Attention Deficit Hyperactivity Disorder) and Important Adverse Events 150
1.7.1. Incidence, Prevalence, Mortality and Demographic Profile of the Target Population (Attention Deficit Hyperactivity Disorder) 150
1.7.1.1. Incidence of ADHD 151
1.7.1.2. Prevalence of ADHD 151
1.7.1.3. Mortality Associated With ADHD 152
1.7.1.4. Potential Health Risk of ADHD 152
1.7.1.5. Demographic Profile of Target Population With ADHD 153
1.7.2. Comorbidity in the Target Population 154
1.7.3. Epidemiology of the Identified/Potential Risk in the Target Population (ADHD) When Unexposed to the Product 157
1.8. Pharmacological Class Effects 172
1.9. Additional EU Requirements 172
1.9.1. Potential for Overdose 172
1.9.2. Potential for Misuse for Illegal Purpose 173
1.9.3. Potential for Off-Label Use 173
1.9.4. Potential for Off-Label Paediatric Use 174
1.10. Summary - Ongoing Safety Concerns 174

2. PHARMACOVIGILANCE PLAN 175
2.1. Routine Pharmacovigilance Practices 175
2.1.1. Objectives 175
2.1.2. Data Sources 175
2.1.2.1. SCEPTRE 175
2.1.2.2. FDA AERS/SRS Database 176
2.1.2.3. WHO Vigibase 176
2.1.3. Surveillance Methods 176
2.1.4. Operational Plan 176
2.2. Summary of Safety Concerns and Planned Pharmacovigilance Actions 177

TABLE OF CONTENTS (Continued)

2.3. Detailed Action Plan for Specific Safety Concerns 179
2.4. Overview of Study Protocols for the Pharmacovigilance Plan 184
2.5. Details of Updates to the EU-RMP 184
2.6. Summary of Outstanding Actions, Including Milestones 186

PART II 187

3. EVALUATION OF THE NEED FOR RISK MINIMISATION ACTIVITIES 187
3.1. Planned Actions for Each Safety Concern 187
3.2. Potential for Medication Errors 192

4. RISK MINIMISATION PLAN 192

5. SUMMARY OF THE EU RISK MANAGEMENT PLAN 194

6. CONTACT PERSON FOR THIS EU-RMP 198

7. REFERENCES 199

ANNEX 1 MEDICINAL PRODUCT CODE (FROM EUDRAVIGILANCE) 213

ANNEX 2 SUMMARY OF PRODUCT CHARACTERISTICS 264

ANNEX 3 TABLE OF STUDIES 285

ANNEX 4 EUROPEAN COMMISSION DECISION ANNEX III AND ANNEX IV 289

ANNEX 4.1 EUROPEAN COMMISSION DECISION ANNEX III 290

ANNEX 4.2 EUROPEAN COMMISSION DECISION ANNEX IV 315

LIST OF IN-TEXT TABLES

Table 1:	Safety Concerns Not Adequately Addressed by Clinical Data or of Unknown Significance	10
Table 2:	Safety and Efficacy Clinical Trials of CONCERTA in the Treatment of Children and Adolescents With Attention Deficit Hyperactivity Disorder	18
Table 3:	Clinical Trial Exposure for Randomised, Blinded Trials by Duration	19
Table 4:	Clinical Trial Exposure for Randomised, Blinded Trials by Dose	19
Table 5:	Clinical Trial Exposure for Randomised, Blinded Trials by Age Group and Gender	19
Table 6:	Clinical Trial Exposure for Randomised, Blinded Trials by Ethnic Origin and Gender	19
Table 7:	Clinical Trial Exposure for All Clinical Trial Populations by Duration	19
Table 8:	Clinical Trial Exposure for All Clinical Trial Populations by Dose	20
Table 9:	Clinical Trial Exposure for All Clinical Trial Populations by Age Group and Gender	20
Table 10:	Clinical Trial Exposure for All Clinical Trial Populations by Ethnic Origin and Gender	20
Table 11:	Cumulative Exposure From Launch Through 30 September 2009 by Region	22
Table 12:	Cumulative Exposure to CONCERTA From Launch Through 30 September 2009 by Major Country	22
Table 13:	Cumulative Exposure to CONCERTA From Launch Through 30 September 2009 by Dose and Country	23
Table 14:	Postmarketing (Nonstudy) Exposure by Age Group (IMS MIDAS, January 2003 Through June 2009)	23
Table 15:	Postmarketing (Nonstudy) Exposure by Gender (IMS MIDAS, January 2003 Through June 2009)	24
Table 16.1:	Important Exclusion Criteria Across Studies	25
Table 16.2:	Important Exclusion Criteria in Individual Studies	27
Table 17.1:	Important Identified Risk: Hypertension	34
Table 17.2:	Important Identified Risk: Tachycardia	38
Table 17.3:	Important Identified Risk: Raynaud's Phenomenon	41
Table 17.4:	Important Identified Risk: Hallucinations (Auditory, Skin Sensation, Visual Disturbance)	44
Table 17.5:	Important Identified Risk: Psychosis/Mania	48
Table 17.6:	Important Identified Risk: Anorexia	53
Table 17.7:	Important Identified Risk: Decreased Rate of Growth	55
Table 18.1:	Important Potential Risk: Migraine	60
Table 18.2:	Important Potential Risk: Repetitive Behaviours	63
Table 18.3:	Important Potential Risk: QT Prolongation	66
Table 18.4:	Important Potential Risk: Cyanosis	70
Table 18.5:	Important Potential Risk: Arrhythmias	73
Table 18.6:	Important Potential Risk: Sudden Death	78
Table 18.7:	Important Potential Risk: Cerebrovascular Disorders	83
Table 18.8:	Important Potential Risk: Aggression	87
Table 18.9:	Important Potential Risk: Hostility	91

LIST OF IN-TEXT TABLES (Continued)

Table 18.10:	Important Potential Risk: Depression	94
Table 18.11:	Important Potential Risk: Suicidality	97
Table 18.12:	Important Potential Risk: Tics, Tourette's Syndrome, Dystonias	101
Table 18.13:	Important Potential Risk: Effect on Final Height	106
Table 18.14:	Important Potential Risk: Sexual Maturation (Delayed)	109
Table 18.15:	Important Potential Risk: Carcinogenicity	113
Table 18.16:	Important Potential Risk: Off-Label Use	117
Table 18.17:	Important Potential Risk: Diversion	123
Table 18.18:	Important Potential Risk: Withdrawal Syndrome	125
Table 18.19:	Important Potential Risk: Drug Abuse and Drug Dependence	127
Table 18.20:	Important Potential Risk: Lymphocytic Leukaemia	132
Table 18.21:	Important Potential Risk: Neonatal Cardio-Respiratory Toxicity (Neonatal/Foetal Tachycardia, Respiratory Distress/Apnoea)	137
Table 18.22:	Important Potential Risk: Neonatal Effects on Growth (Via Lactation)	141
Table 19:	Identified Interactions With Other Medicinal Products	145
Table 20:	Selected Country-Specific Prevalence of ADHD	152
Table 21:	Important Comorbidities of Attention Deficit Hyperactivity Disorder	154
Table 22.1:	Epidemiology of Each Identified Risk in Patients With ADHD When Unexposed to CONCERTA	158
Table 22.2:	Epidemiology of Each Potential Risk in Patients With ADHD When Unexposed to CONCERTA	162
Table 23:	Summary of On-Going Safety Concerns	174
Table 24:	Summary of Safety Concerns and Planned Pharmacovigilance Actions	178
Table 25:	Detailed Action Plan for Specific Safety Concerns	180
Table 26:	Present List of Actions to be Completed (Ongoing and Planned) With Milestones and Timelines	186
Table 27:	Planned Actions for Each Safety Concern	188
Table 28:	Additional Risk Minimisation Measures Planned (Educational Tools)	193
Table 29:	Overall Summary of the Risk Management Plan	195

LIST OF ABBREVIATIONS

ADHD	attention-deficit/hyperactivity disorder
ADR	adverse drug reaction
AERS/SRS	Adverse Event Reporting System/Spontaneous Reporting System
AHRQ	US Agency for Healthcare Research and Quality
APD	Action potential duration
ASR	age-specific rates
AUC	area under the concentration-time curve
BRM	Benefit Risk Management
CA	chromosome aberration
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EC	European Commission
ED	emergency departments
EU	European Union
FDA	US Food and Drug Administration
IBD	international birth date
IMS	International Medical Statistics
KPMCP	Kaiser Permanente Medical Care Program
MAHs	Marketing Authorisation Holders
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MN	micronuclei
MTA	Multimodal Treatment Study of ADHD
MTF	Monitoring the Future
NIMH	National Institute of Mental Health
NOAEL	no-observed-adverse-effect level
NSR	Nonclinical Study Report
NTP	National Toxicology Program
PhVWP	European Pharmacovigilance Working Party
PPAA	[α-phenyl-α(2-piperidyl)] acetic acid
PSURs	Periodic Safety Update Reports
RMP	Risk Management Plan
SAG	Scientific Advisory Group
SCE	sister chromatid exchange
SmPC	Summary of Product Characteristics
SMR	standardised morbidity ratio
SPECT	single photon emission computed tomography
SUD	substance use disorder
UK	United Kingdom
US	United States
WHO	World Health Organization

PRODUCT DETAILS

Invented name of the medicinal product (product short name):	CONCERTA XL, CONCERTA LP, CONCERTA
Active substance(s) (INN or common name):	Methylphenidate hydrochloride
Pharmaco-therapeutic group (ATC Code):	Psychoanaleptics, psychostimulants and nootropics, centrally acting sympathomimetics: (ATC code: N06BA04)
Medicinal Product Code (From EudraVigilance)	See Annex 1
Authorisation procedure(s) (central, mutual recognition, decentralised, national)	Mutual recognition procedure
Name of Marketing Authorisation Holder or Applicant:	Austria: Janssen-Cilag Pharma GmbH Belgium: Janssen-Cilag N.V. Bulgaria: Johnson & Johnson d.o.o. Slovenia Cyprus: Janssen-Cilag International N.V. Czech Republic: Janssen-Cilag s.r.o. Denmark: Janssen-Cilag A/S Estonia: Johnson & Johnson UAB Finland: Janssen-Cilag Oy France: Janssen-Cilag SA Germany: Janssen-Cilag GmbH Greece: Janssen-Cilag Pharmaceutical S.A.C.I Iceland: Janssen-Cilag AB Ireland: Janssen-Cilag Ltd Latvia: UAB Johnson & Johnson Lithuania: UAB Johnson & Johnson Luxembourg: Janssen-Cilag N.V. Malta: Janssen-Cilag International N.V. Netherlands: Janssen-Cilag B.V. Norway: Janssen-Cilag AS Poland: Janssen-Cilag International N.V. Portugal: Janssen-Cilag Farmaceutica, Lda Romania: Janssen-Pharmaceutica N.V. Slovakia: Johnson & Johnson, s. r. o. Slovenia: Johnson & Johnson d.o.o. Spain: Janssen-Cilag S.A. Sweden: Janssen-Cilag AB United Kingdom: Janssen-Cilag Ltd
Date and country of first authorisation worldwide	01 Aug 2000; United States
Date and country of first launch worldwide	01 Aug 2000; United States
Date and country of first authorisation in the EEA	19 Feb 2002; United Kingdom
Date and country of first launch in the EEA	04 Mar 2002; United Kingdom
Brief description of product (chemical class, mode of action etc)	Methylphenidate is a central nervous system stimulant thought to block the reuptake of norephinephrine and dopamine into presynaptic neurons and increase the release of these monoamines into the extraneuronal space. Methylphenidate is a racemic mixture comprised of the d- and l-isomers. The d-isomer is more pharmacologically active than the l-isomer. Methylphenidate is a recommended first-line pharmacotherapy for the management of attention-deficit/hyperactivity disorder (ADHD) and has been used to manage symptoms of this disorder for over 50 years. The efficacy of methylphenidate in the management of the core symptoms of ADHD has been well established. However, immediate-release methylphenidate has duration of effect of only 3-4 hours, which has led to the development of extended-release formulations. Pharmacodynamic studies demonstrated that in order to achieve duration of effect with

PRODUCT DETAILS (CONTINUED)

Brief description of product (chemical class, mode of action etc) (Continued)	methylphenidate of up to 12 hours, a controlled release generating an ascending plasma concentration profile for methylphenidate would be required. This has been achieved using OROS technology, and allowed the development of CONCERTA (OROS methylphenidate), a prolonged-release formulation with duration of effect of 12 hours. Based on the OROS technology, following oral administration, the drug overcoat dissolves providing an initial maximum drug concentration at about 1-2 hours. Delivery of the drug substance begins from the drug core when the volumetric expansion of the osmotic push layer begins to "push" the drug suspension through the orifice. Peak plasma concentrations are achieved at about 6 to 8 hours after which plasma levels of methylphenidate hydrochloride gradually decrease. The place of methylphenidate in the treatment of ADHD is well established and CONCERTA has been approved in the European Union (EU) for the management of ADHD in children and adolescents since 2002.	
Indication(s)	CONCERTA is indicated as part of a comprehensive treatment program for ADHD in children (over 6 years of age) and adolescents when remedial measures alone prove insufficient.	
Dosage	Dosage may be adjusted in 18 mg increments to a maximum of 54 mg/day taken once daily in the morning. In general, dosage adjustment may proceed at approximately weekly intervals. Treatment must be initiated under the supervision of a specialist conversant with childhood and/or adolescent behavioural disorders. Dosage should be individualised according to the needs and responses of the patient.	
Pharmaceutical form(s) and strength(s)	Prolonged-release tablet Capsule-shaped yellow tablet with "alza 18" printed on one side in black ink Capsule-shaped grey tablet with "alza 27" printed on one side in black ink Capsule-shaped white tablet with "alza 36" printed on one side in black ink Capsule-shaped brownish-red tablet with "alza 54" printed on one side in black ink **Strengths** Available in 18-mg, 36-mg, and 54-mg tablet strengths. A 27-mg tablet strength is available in the United Kingdom and authorised via mutual recognition in 12 other member states (Austria, Belgium, Finland, France, Germany, Iceland, Ireland, Luxembourg, Netherlands, Norway, Spain, Sweden). National approvals are still pending for the 27-mg tablet strength in Greece and Portugal.	
Data lock point for EU Risk Management Plan (RMP)	Preclinical/clinical trial data from completed studies. Postmarketing cut-off dates vary due to the different sources (Period Safety Update Reports [PSURs] and ad hoc reports): 10 Aug 2007, 30 Sep 2007, 10 Aug 2009, and 31 Aug 2009.	Version 2

PART I

1. SAFETY SPECIFICATION

The reference safety information for CONCERTA is provided in the Summary of Product Characteristics (SmPC) that is included as Annex 2.

1.1. Nonclinical

1.1.1. Safety Concerns That Have Not Been Adequately Addressed by Clinical Data or Which Are of Unknown Significance

The European Pharmacovigilance Working Party (PhVWP) specified the following areas of concern for which the sources of evidence that may impact benefit-risk arise from preclinical data: potential for carcinogenicity and effects on growth (Table 1). An additional area of concern addressed in this section is cardiovascular toxicity.

Table 1: Safety Concerns Not Adequately Addressed by Clinical Data or of Unknown Significance

SAFETY CONCERN (from nonclinical studies)	RELEVANCE TO HUMAN USAGE
Carcinogenicity	There is weak and insufficient evidence to conclude that methylphenidate is likely to be a human carcinogen. Initial data from ex vivo cytogenicity testing that suggested chromosomal abnormalities in children exposed to methylphenidate could not be replicated in 4 independent studies. The risk that CONCERTA is a causative agent for cancer in man is minimal.
Developmental toxicity	There is insufficient evidence to suggest a developmental risk to child or adolescent patient populations administered CONCERTA.
Cardiovascular toxicity	Other than the increase in blood pressure, there were no unexpected or statistically significant cardiovascular effects. No new pharmacologic effects were documented.

1.1.1.1. Potential for Carcinogenicity

1.1.1.1.1. Genetic Toxicology and Carcinogenicity Studies

The carcinogenic potential of methylphenidate has been assessed in a battery of nonclinical genetic toxicology and carcinogenicity studies.

Methylphenidate was assessed for mutagenicity in several genetic toxicology studies. Methylphenidate was non-mutagenic in the in vitro Ames test with or without microsomal activation (Mortelmans 1986). In addition, methylphenidate did not induce mutations in mammalian cells in culture (mouse lymphoma assay) in the presence or absence of metabolic activation (Rudd 1983). Finally, methylphenidate did not cause primary DNA damage in an in vivo unscheduled DNA synthesis assay (Mirsalis 1983).

The potential clastogenicity of methylphenidate was evaluated in several genetic toxicology assays. Methylphenidate was non-clastogenic in an in vivo mouse

micronucleus assay (Nonclinical Study Report [NSR] TR-98-5607-054, 1999). However, in vitro assays that evaluated the clastogenic effects of methylphenidate yielded variable effects.

In Chinese Hamster Ovary (CHO) cells, methylphenidate slightly increased sister chromatid exchange (SCE) rates in the presence of S-9 microsomal activation, but not in its absence, in 1 of 2 laboratories (Galloway 1987). In the second laboratory (National Toxicology Program [NTP] 1995), methylphenidate was considered negative for induction of SCEs in both the absence and presence of microsomal activation.

There were conflicting results of chromosomal aberration assays in CHO cells, like the SCE results, between the same 2 laboratories. The chromosomal aberration assay in the absence of S-9 microsomal activation was negative at 1 laboratory (Galloway 1987) and positive at a second laboratory (NTP 1995). At 1 laboratory, the aberration test in CHO cells with microsomes was considered positive, but no dose response relationship was evident, and the aberration level in controls was unusually low (Galloway 1987). At the second laboratory, the aberration assay in CHO cells with microsomal activation was considered equivocal (NTP 1995). Overall, methylphenidate was positive for chromosomal aberrations in CHO cells in the absence of microsomal activation in 1 of 2 laboratories, and equivocally positive for the induction of chromosomal aberrations in the presence of microsomal activation.

Most importantly, the carcinogenic potential of methylphenidate was assessed by the National Toxicology Program (NTP) in 4 rodent carcinogenicity studies. A lifetime carcinogenicity study in B6C3F1 mice (NTP 1995; Dunnick 1995) documented that methylphenidate caused an increase in hepatocellular adenomas and hepatoblastomas (males only), at a dose of 60 mg/kg/day, when compared to controls. This dose is approximately 30 times and 4 times the 54 mg/day human dose of CONCERTA on a mg/kg and mg/m² basis, respectively. The significance of these findings to humans is unknown as hepatoblastoma is a relatively rare malignant tumour in rodents, and there was no increase in total malignant hepatic tumours. Moreover, this strain of mouse is sensitive to the development of hepatic tumours.

Consequently, 2 mouse carcinogenicity studies were conducted in transgenic mice. One was conducted for 24 weeks in p53+/- transgenic mice, a strain of mouse known to be sensitive to genotoxic carcinogens (Freeman 1998; NTP 1997). In this study, there was no evidence of carcinogenicity up to and including the high doses of 60 to 75 mg/kg/day. The second was also 24 weeks in duration, and employed the TgAC transgenic strain of mouse known to be sensitive to nongenotoxic carcinogens (Freeman 1998; NTP 1997).

There was no evidence of carcinogenicity in this study up to and including the high doses of 70 to 74 mg/kg/day.

Finally, a fourth carcinogenicity study was conducted in F344 rats (NTP 1995; Dunnick 1995). In this lifetime study, methylphenidate did not cause any increases in tumour types at doses up to and including 45 mg/kg/day, the highest dose tested. These doses were approximately 22 times and 5 times the 54 mg/day human dose of CONCERTA on a mg/kg and mg/m² basis, respectively.

In summary, the NTP B6C3F1 mouse lifetime carcinogenicity study showed some evidence of carcinogenicity, but at doses 4 to 30 times greater than the maximum recommended human dose of CONCERTA in children (54 mg), on a mg/m² and mg/kg basis, respectively. However, this strain of mouse is known to be very sensitive to the development of hepatic tumours. Hence, the relevance of this finding to man is unclear. More importantly, a second NTP lifetime study in rats documented that methylphenidate is not a carcinogen. Finally, methylphenidate was not carcinogenic in 2 NTP carcinogenicity studies that employed transgenic mouse strains known to be highly sensitive to genotoxic and nongenotoxic carcinogens.

In addition, the weight of the evidence from the genetic toxicology studies supports the conclusion that methylphenidate is neither mutagenic nor clastogenic, and therefore, not carcinogenic. In the most important of these tests, methylphenidate was non-mutagenic in the Ames test, and non-clastogenic in the mouse micronucleus assay. Several other genetic toxicology studies were also negative, although weak clastogenic effects and some increase in SCEs were seen in CHO cells in vitro.

Consideration of the results obtained from these studies support the conclusion that there is weak and insufficient evidence to conclude that methylphenidate is likely to be a human carcinogen. Consequently, the risk that CONCERTA is a causative agent for cancer in man is considered to be minimal.

1.1.1.1.2. Evaluation of Cytogenetic Endpoints in Human Ex Vivo Studies

A manuscript by El-Zein (2005) describes an evaluation of 3 cytogenetic endpoints in 12 children who were treated with therapeutic doses of methylphenidate (20-54 mg/day). Analysis was performed on peripheral blood lymphocytes obtained pre-exposure, and after 3 months of methylphenidate treatment. All 12 children were found to exhibit a significant increase in chromosome aberration (CA), SCE, and micronuclei (MN); the mean frequency increase in each of the above cytogenetic biomarkers was 3-, 4.3-, and 2.4-fold, respectively. These authors concluded that the findings warrant further investigations of the possible health effects of methylphenidate in humans.

Numerous difficulties exist in the El-Zein study including design and methodology as well as the conclusions that were reached. Particular limitations include the small sample size and the very small number of cells analysed per individual, as well as the lack of specific detail provided for the lymphocyte culture methods used, and lack of discussion relating to the development of treatment confounders. Although each child served as its own control, the normal baseline values for each of the assays were not given.

There is general consensus amongst the scientific community that the data are considered preliminary and too limited to allow the conclusion that therapeutic doses of methylphenidate result in an increase in chromosomal abnormalities or carcinogenic risk. The clinical relevance of the finding of this study is unknown. Although this study has many shortcomings and numerous difficulties exist in interpreting this study, the changes seen in cytogenetic biomarkers require explanation and further evaluation. (Spinner and Biegel, written communication, 21 April 2005, Thomas R Insel, written communication, 18 April 2005, Jose Cordero written communication, 18 April 2005).

Another study (Walitza 2007) assessed genomic damage, as characterised by the formation of micronuclei, before and after 1, 3, and 6 months of methylphenidate treatment in groups of 30, 21, and 8 children with ADHD, respectively. Furthermore, a group of 9 children who had been treated with methylphenidate for 6 to 24 months was also evaluated. The children were recruited within a study of the Clinical Research Group on ADHD in the Department of Child and Adolescent Psychiatry and Psychotherapy of the University of Wuerzburg. Assessment and treatment of patients were performed during inpatient or outpatient health care. Exclusion criteria included current smoking, current or recent infection, extreme food patterns (vegan), certain psychiatric diagnoses, certain neurological disorders, a history of brain damage or foetal alcohol syndrome, premature delivery, or any maternal reports of prenatal, perinatal, or postnatal complications. This study documented that methylphenidate treatment resulted in no significant alteration in micronucleus frequency, and that the findings published in 2005 by El-Zein et al. could not be replicated. Therefore, the authors concluded “the concern regarding a potential increase in the risk of developing cancer later in life following long-term methylphenidate treatment is not supported”.

The study by Walitza et al (Walitza 2007) was repeated with a larger sample size (Walitza 2009). A healthy control group and a chronically treated group (greater than 12 months) were added in addition to the drug naïve group. Also, this study included positive control slides and the analysis for genomic damage of buccal mucosa cells in addition to lymphocytes. Samples were analysed at the 3- and 6-month time periods. The authors concluded that “no indication for genomic damage induced by methylphenidate was obtained” in this study. Combined with the previous study, the total number of

children treated with methylphenidate was 68 (30 chronically treated and 38 prospectively followed) in addition to 23 healthy controls.

A study at Duke University Medical Center assessed cytogenetic damage in children with ADHD treated with methylphenidate and Adderall®. Sixty-three children, aged 6 to 12 years inclusive, of either sex and of any ethnicity and race, diagnosed with ADHD (any subtype) for whom pharmacological treatment with stimulants was indicated were enrolled in this study (Witt 2008). Children were eligible for enrolment if they had no comorbid psychological conditions, had no physical conditions that contraindicated stimulant treatment, were ADHD-drug naïve, and had not received diagnostic x-rays in the past 3 months. Forty-seven children were randomly assigned to treatment and completed the 3-month study: 25 children in the methylphenidate group and 22 children in the amphetamine group. The same 3 measures of cytogenetic damage (increase in CA, SCE, and MN) that were analysed by El-Zein et al were assessed in lymphocyte samples. No significant treatment related increases were observed in any of these 3 measures of cytogenetic damage in any study participant, including the 16 children who did not complete the study.

Another study designed to repeat the methodology followed by El-Zein et al but with a larger sample size (109 children with any type of ADHD) was conducted in the United States (US) (Tucker 2009). Children (6-12 years of age) were randomly assigned to the methylphenidate treatment group (includes behaviour therapy) or the control group (behaviour therapy only). Subjects were excluded for previous exposure to methylphenidate or any amphetamine-based medication. Based on the analysis of lymphocytes using the same 3 measures of cytogentic damage (ie, CA, MN, SCE) in samples obtained prior to therapy and after 3 months, there was no evidence of cytogenetic anomalies in the samples from these children.

A recent study conducted in Spain (Ponsa 2009) assessed cytogenetic damage in paediatric and adult patients with ADHD treated with methylphenidate. Nineteen Caucasian subjects of either sex with a new diagnosis of ADHD for whom pharmacological treatment with stimulants was indicated were enrolled: 7 children (7-11 years of age), 5 adolescents (13-14 years of age), and 7 adults (21-58 years of age). Subjects were eligible for enrolment if they had no comorbid psychological conditions, had no physical conditions that contraindicated stimulant treatment, and had not previously received methylphenidate. The same 3 measures of cytogenetic damage (ie, CA, MN, and SCE) that were analysed by El-Zein et al were assessed in lymphocyte samples after 3 months of treatment with methylphenidate. No significant treatment-related increases were observed in any of these 3 measures of cytogenetic damage.

1.1.1.2. Effects on Growth

A preclinical study (NSR TR-02-5607-001, 2004) was conducted to assess the toxicity of methylphenidate when administered to juvenile rats orally. The objective of this study was to evaluate the potential effects of long-term administration of methylphenidate on growth, development, behaviour and reproductive performance of juvenile rats when treatment was initiated at weaning. An additional objective was to determine the pharmacokinetic profile of methylphenidate and its metabolite [α-phenyl-α(2-piperidyl)] acetic acid (PPA) following approximately 4.5 months of daily exposure in these rats.

In this study, methylphenidate was administered orally via gavage, twice daily, to 4 groups of Crl:CD® (SD) IGS BR rats, each group consisting of 25 males and 25 females. Eight Fo pups per litter obtained from breeder dams were assigned to the study when they were 11 to 15 days old. The Fo males and females were dosed for 66 to 70 days prior to mating, throughout the mating period, and continuing for 139 to 143 days of dosing. Total dosage levels were 0, 5, 12.5 and 30 mg/kg/day, administered as 2 equally divided doses of 0, 2.5, 6.25 and 15 mg/kg, respectively. The Fo rats were observed for in-life parameters such as clinical observations, body weights, clinical pathology, behavioural effects, and attainment of developmental milestones. They were also bred and the F_1 pups examined. Post-mortem pathology examinations were performed as well on the Fo rats. Other groups of Fo rats were assigned to the pharmacokinetic phase of the study. They were administered the same doses, and blood was collected for methylphenidate and PPA determinations.

Extended pharmacologic clinical signs were observed throughout the treatment period in both males and females in the 12.5 and 30 mg/kg/day groups. Methylphenidate-related adverse effects on body weight and motor activity were observed only in males of the 30-mg/kg/day group. No methylphenidate-related adverse effects were observed in females from the 30-mg/kg/day groups or in rats of either sex from the 5 and 12.5 mg/kg/day groups. F_1 developmental toxicity was indicated in the 30-mg/kg/day group by reduced pup weights during the pre-weaning period. In summation, there were no adverse effects on growth or developmental milestones at the 5 and 12.5 mg/kg/day doses.

Exposures to methylphenidate and PPA tended to increase in a slightly more than dose proportional manner over the range of doses tested in both sexes. There was no significant accumulation of methylphenidate over the approximately 4.5 month treatment period. This treatment period spans the usual development course of the rat through adolescence to adulthood. The area under the concentration-time curve (AUC) values for

methylphenidate were 1.4 to 3.5 fold higher in females than in males, and the ratio of the AUC for methylphenidate to that of PPA typically increased with increasing dosage.

Based on the results of this study, the "no-observed-adverse-effect level" (NOAEL) for toxicity in juvenile rats following the oral administration of methylphenidate for approximately 4.5 months was 12.5 mg/kg/day for males and 30 mg/kg/day for females. A dose level of 12.5 mg/kg/day was considered to be the NOAEL for developmental toxicity of their F_1 offspring. The NOAELs for juvenile toxicity were 12.5 mg/kg/day for males and 30 mg/kg/day for females, which were approximately 12 to 28 times greater on a mg/kg basis, and approximately 2 to 5 times greater on a mg/m^2 basis than the maximum human adolescent dosage of 54 mg/day. These safety factor calculations are based on an assumption of a body weight of 50 kg, and a body surface area (m^2) conversion factor of 37. Consequently, these data support the conclusion that the evidence is insufficient to suggest a developmental risk to child or adolescent patient populations administered CONCERTA.

1.1.1.3. Potential Cardiovascular Effects

Three cardiovascular safety pharmacology studies using racemic methylphenidate have been conducted by the Sponsor according to International Conference on Harmonisation (ICH) and good laboratory practice (GLP) guidelines (NSRs FBM05-9740, 2006; FBM05-9739, 2006; FBM05-4548, 2006). These studies documented that the administration of methylphenidate had no effect upon either the rapidly activating delayed rectifier potassium current in the hERG assay or the action potential duration in isolated guinea pig papillary muscle at concentrations up to and including 1 µg/mL (=3.7 µM), the highest dose tested. This dose was chosen because it is approximately 30 times the estimated maximum plasma concentration measured in a Japanese clinical study with doses up to 54 mg/day in 6 to 12 year old children.

In conscious dogs orally administered methylphenidate at a dose of 30 mg/kg, a statistically significant increase in blood pressure was demonstrated. Lower doses of methylphenidate had no significant effect upon blood pressure. This increase in blood pressure seen with 30 mg/kg was transient, occurring immediately after dosing and persisted for 4 hours postdosing and is consistent with the known pharmacologic properties of methylphenidate. Most importantly, other than the increase in blood pressure, no unexpected or statistically significant cardiovascular effects were observed at any of the doses tested in this dog study, including no significant changes in QTcF, the QT-interval corrected for heart rate using the Fridericia correction. Also in this study no drug-related arrhythmias were observed at any dose. The 30-mg/kg dose is at least 10 times the maximum expected clinical dose on a body weight (mg/kg) basis.

As there were no effects of the racemic mixture of methylphenidate, it can be concluded that there would be no effects of either of its isomeric components (each up to 50% of the concentrations given) on hERG, APD prolongation, or QTcF prolongation. As the mixture was tested in vivo, and observations continued up 24 hours after administration, with no effects on QT prolongation, it can also be concluded that any isomeric metabolites of methylphenidate formed in the dog are also without QT prolonging effects. In summation, the cardiovascular safety studies documented no new pharmacologic effects.

During the Article 31 referral, and in response to a request in Committee for Medicinal Products for Human Use (CHMP's) 30 May 2008 List of Outstanding Issues to evaluate the risk of QT prolongation in children and adolescents using methylphenidate-containing products, a number of studies on the effects of d- and d/l-methylphenidate on QT interval were evaluated (16 October 2008 Response to the Second List of Outstanding Issues). These studies included preclinical data from a series of GLP safety studies conducted in Japan (hERG channel study, action potential duration [APD] of guinea pig papillary muscle study, and conscious dog study) that found no effect of methylphenidate on hERG or APD in studies in vitro, or QTcF in a study in vivo (Wakamatsu 2009).

It was concluded by Marketing Authorisation Holders (MAHs) of methylphenidate-containing products that there is a lack of clear experimental or epidemiological evidence that methylphenidate causes QT prolongation at therapeutic doses. It was also concluded from in vitro studies that methylphenidate does not have an effect on potassium channels that would suggest that there is a plausible mechanism for QT prolongation to occur. In addition, there is sufficient evidence to suggest that d-methylphenidate does not prolong the QTcF interval in healthy adult volunteers, and although the effects of d/l-methylphenidate on the QT interval of children are not known, any concern is minimal.

1.1.2. Additional Nonclinical Data

There are no additional nonclinical data.

1.2. Clinical: Limitations of the Human Safety Database

For the purposes of this RMP, the clinical trials included in the database are summarised in Table 2; a table of studies is provided in Annex 3.

Table 2: Safety and Efficacy Clinical Trials of CONCERTA in the Treatment of Children and Adolescents With Attention Deficit Hyperactivity Disorder

Sponsor	Study Number (references)	Study Type	Number Enrolled/ Received CONCERTA	Age Range (years)
ALZA	C-97-025 (CSR C-97-025, 1999)	Double-Blind	70/68	6-12
ALZA	C-98-003 (CSR C-98-003, 1999)	Double-Blind	64/62	6-12
ALZA	C-98-005 (CSR C-98-005, 1999)	Double-Blind	312/104	5-13
ALZA	C-98-007-002 (CSR C-98-007-02, 1999)	Open-Label	111/110	6-12
ALZA	C-98-012 (CSR C-98-012, 2003)	Open Label	436/432 (Part I) 278/278 (Part II)	6-13
ALZA	C-99-018 (CSR C-99-018, 2003)	Open Label	1082/1082	5-66
McNeil	01-146 (CSR 01-146, 2003)	Open-label Run-in/Double-Blind/ Open Label	220/220 177/87 171/171	13-18
McNeil	12-101 (CSR 12-101, 2004)	Open Label	1322/850	3-19
Janssen-Ortho Canada	CON-CAN-1 (CSR CON-CAN-1, 2005)	Open Label	145/72	6-12
Janssen-Ortho Canada	CON-CAN-2 (CSR CON-CAN-2, 2005)	Open Label	119/116	6-12
Janssen-Cilag Europe	C-2000-045 (CSR C-2000-045, 2005)	Open Label	105/105	6-16

A limitation inherent to a clinical database is its limited number of patients studied. In total, 2,854 patients with ADHD (children and adolescents) (Section 1.2.1.2) have been studied, versus an estimated postmarketing exposure of 8.5 million patient years (Section 1.2.3).

The duration of exposure in controlled studies is up to 4 weeks only, although the duration of open-label study exposure is as long as 27 months, which is greater than the average treatment duration in clinical practice (Section 1.2.1.2). Certain postmarketing studies studied CONCERTA in a "real life" setting in which patients were selected according to the SmPC (C-2000-045) or the Canadian product monograph (CON-CAN-1 and 2) and followed up with simple Clinical Global Impression Scale evaluations (C–2000-045, CON-CAN-1 and 2 included other scales). Such postmarketing study exposure comes close to the naturalistic postmarketing exposure to the drug as covered by pharmacovigilance, while safety documentation in the studies is much more precise.

Study C-99-018 included paediatric and adult subjects and Study 01–146 allowed doses up to 72 mg/day in adolescents; ie, exposure documenting potential off-label use.

1.2.1. Exposure in Clinical Trials

1.2.1.1. Exposure in Randomised Blinded Trials

The randomised blinded-trials were comprised of C97-025, C-98-003, C-98–005, and 01-146 representing a total of 639 subjects (321 received CONCERTA and 318 received placebo). Exposure to CONCERTA in these trials is presented by duration, dose, age and gender, and ethnic origin in Table 3, Table 4, Table 5, and Table 6, respectively.

Table 3: Clinical Trial Exposure for Randomised, Blinded Trials by Duration

Duration of Exposure	Persons	Person time (years)
Cumulative exposure <2 weeks	214	5.1
Cumulative exposure <4 weeks	321	12.6

Table 4: Clinical Trial Exposure for Randomised, Blinded Trials by Dose

Dose of Exposure	Persons	Person time (years)
18 mg	68	3.2
36 mg	138	5.2
54 mg	82	3.2
72 mg	33	1.0

Table 5: Clinical Trial Exposure for Randomised, Blinded Trials by Age Group and Gender

Age Group	Male	Person time – Male (years)	Female	Person Time – Female (years)
≤17	252	9.7	62	2.7
≥18	4	0.1	3	0.1

Table 6: Clinical Trial Exposure for Randomised, Blinded Trials by Ethnic Origin and Gender

Ethnic Origin	Male	Person time – Male (years)	Female	Person Time – Female (years)
Black	17	0.8	4	0.1
Caucasian	213	8.0	54	2.4
Other	26	1.0	7	0.3

1.2.1.2. Exposure in All Clinical Trials Including Open Extensions

Exposure to CONCERTA in all clinical trials (2,854 subjects) is presented by duration, dose, age and gender, and ethnic origin in Table 7, Table 8, Table 9, and Table 10, respectively. In addition to the double-blind studies in the previous section, the exposure tables include open-label studies C–98–007-02, C-98-012, C-99-018, 01-146, 12-101, CON-CAN-1, CON–CAN–2, and C-2000-045.

Table 7: Clinical Trial Exposure for All Clinical Trial Populations by Duration

Duration of Exposure	Persons	Person time (years)
Cumulative exposure <1 month	954	49.5
Cumulative exposure <3 months	1358	112.7
Cumulative exposure <6 months	1565	182.1
Cumulative exposure <12 months	2551	901.4
Cumulative exposure <24 months	2774	1279.1
Cumulative exposure <30 months	2844	1426.1

Note: Exposure duration was unknown for 10 subjects

Table 8: Clinical Trial Exposure for All Clinical Trial Populations by Dose

Dose of Exposure	Persons	Person Time (years)
18 mg	1618	227.8
27 mg	277	15.2
36 mg	1987	630.3
54 mg	1242	538.1
72 mg	164	13.6
90 mg	2	0.008
108 mg	1	0.003

Note: 10 occurrences of invalid mg dose amounts are not included in this table (eg, 5, 10 and 15 mg)

Table 9: Clinical Trial Exposure for All Clinical Trial Populations by Age Group and Gender

Age Group	Male	Person time – Male (years)	Female	Person Time – Female (years)
≤17	2131	1099.5	573	249.1
≥18	95	51.7	52	25.6

Note: Age data was missing for 2 subjects and gender data was missing for 1 subject

Table 10: Clinical Trial Exposure for All Clinical Trial Populations by Ethnic Origin and Gender

Ethnic Origin	Male	Person time – Male (years)	Female	Person Time – Female (years)
Black	200	64.1	49	16.4
Caucasian	1762	955.6	521	238.0
Other	173	80.8	41	13.9

Note: Race data missing for 108 subjects

1.2.1.3. Exposure in Phase 1 Studies

The Company conducted all but 2 pharmacokinetic studies of CONCERTA in healthy adults. Two pharmacokinetic studies were conducted in children and adolescents with ADHD (CSR C-97-033-03, 1999 and CSR 12-001, 2003).

Study C-97-033 was a bioavailability study of CONCERTA under various breakfast conditions compared with Ritalin. This single-centre, double-blind, double-dummy study compared the pharmacokinetics and characterised the pharmacodynamics of 5 methylphenidate treatments: CONCERTA administered once a day after a high-fat breakfast, after a normal breakfast, and after an overnight fast; and immediate-release Ritalin administered 3 times a day after a normal breakfast and after an overnight fast. Patients were divided into 2 groups. Each group received 3 of the 5 treatments for 1 day each in a 3 period, 6-sequence, randomised crossover design. Patients were assigned to 1 of 3 dosage levels, depending upon their usual prestudy dose: 18 mg, 36 mg, and 54 mg given once a day for CONCERTA and 5 mg, 10 mg, and 15 mg given 3 times a day for Ritalin. Thirty-two patients entered the study; the majority of these patients were male (26 patients, 81.3%), 10 to 12 years of age (22 patients, 68.8%; 10 patients, 31.3%, aged 6 to 9 years), and Caucasian (22 patients, 68.8%; black 1 patient, 3.1%; Hispanic 3 patients, 9.4%, Other 6 patients, 18.8%).

Study 12-001 was a multi-centre, multiple-dose, open-label, 5-dose parallel design study assessing the steady-state pharmacokinetics of d- and l-methylphenidate from multiple doses of CONCERTA tablets in healthy adolescents (13-17 years of age) with ADHD taking CONCERTA at their prescribed dose. The daily dose of CONCERTA for any subject could have been 18, 27, 36, and 54 mg, or higher if prescribed. Subjects were instructed to take their medication at the same time each day for 5 days. Twenty-six patients between the ages of 13 to 16 entered the study; the majority of these patients were male (19 patients, 73.0%) and Caucasian (20 patients, 76.9%; black 4 patients, 15.4%; Other 2 patients, 7.7%).

1.2.1.4. Exposure in Special Populations

No studies of CONCERTA in special populations in children or adolescents with ADHD have been conducted in support of its authorisation in the EU.

1.2.2. Epidemiologic Study Exposure

No epidemiologic studies of CONCERTA have been conducted.

1.2.3. Postmarketing (Nonstudy) Exposure

When providing an estimate of patient exposure in a safety update containing postmarketing surveillance data, it is important to stress the limitations of reporting rates for evaluation of adverse drug reactions. Reporting rates do not reflect occurrence rates. Numerous factors influence the reporting of spontaneous experiences and therefore, caution must be exercised in the analysis and evaluation of spontaneous reports. In addition, the product exposure is estimated at the time of distribution, not the time of consumption.

Postmarketing patient exposure to CONCERTA is estimated from company sales and distribution data. Estimates of exposure are based upon finished product. CONCERTA should be taken once per day. The average month is 30.4 days. Therefore, 30.4 tablets equal 1 person-month of exposure.

The cumulative exposure estimate from launch through 30 September 2009 by region can be found in Table 11. Based on the 3,093,068,022 tablets sold or distributed, the estimated exposure to CONCERTA is 101,745,656 person-months or 8,478,803 person-years from launch (01 August 2000) through 30 September 2009 (Table 12).

Table 11: Cumulative Exposure From Launch[a] Through 30 September 2009 by Region

Region	Tablets	Person-months
European Union	332,737,548	10,945,314
North America	2,577,507,663	84,786,436
Rest of World	182,822,811	6,013,908
Total[b]	**3,093,068,022**	**101,745,658**

[a] Launch occurred in 2000 in the US and 2002 in the EU and other parts of the world.
[b] Note that the totals for tablets and person-months may not exactly match these figures in other exposure tables due to rounding.

Worldwide Exposure by Country and Dose

Cumulative exposure from launch through 30 September 2009 is presented by major country in Table 12.

Table 12: Cumulative Exposure to CONCERTA From Launch Through 30 September 2009 by Major Country

Region	Country	Tablets	Person-Months	Person-Years
European Union	Austria	3,289,530	108,208	9,017
	Belgium	8,372,700	275,418	22,951
	Bulgaria	39,000	1,283	107
	Cyprus	273,480	8,996	750
	Czechia	83,700	2,753	229
	Denmark	4,908,900	161,477	13,456
	Estonia	20,460	673	56
	Finland	6,365,730	209,399	17,450
	France	12,415,368	408,400	34,033
	Germany	83,730,390	2,754,289	229,524
	Greece	495,960	16,314	1,360
	Ireland	3,508,140	115,399	9,617
	Lativia	1,500	49	4
	Lithuania	10,320	339	28
	Malta	18,360	604	50
	Netherlands	38,240,430	1,257,909	104,826
	Poland	1,299,270	42,739	3,562
	Portugal	5,164,080	169,871	14,156
	Roumenia	318,120	10,464	872
	Slovakia	21,570	710	59
	Slovenia	148,110	4,872	406
	Spain	47,230,800	1,553,645	129,470
	Sweden	20,412,810	671,474	55,956
	U.K.	96,368,820	3,170,027	264,169
Subtotal		332,737,548	10,945,312	912,108
North America		2,577,507,663	84,786,436	7,065,536
Rest of World		182,822,811	6,013,908	501,159
Total[a]		**3,093,068,022**	**101,745,656**	**8,478,803**

[a] Note that the totals for tablets and person-months may not exactly match these figures in other exposure tables due to rounding.

Cumulative exposure from launch through 30 September 2009 is presented by dose and country in Table 13.

Table 13: Cumulative Exposure to CONCERTA From Launch Through 30 September 2009 by Dose and Country

Country	18 mg (Tablets)	27 mg (Tablets)	36 mg (Tablets)	54 mg (Tablets)	Combi (Tablets)	Person-Months
France	5,740,924	-	5,737,984	936,460		408,400
Germany	22,862,850	474,210	44,600,310	15,793,020		2,754,289
Spain	15,943,560	95,520	23,298,780	7,892,940		1,553,645
UK	40,079,220	4,294,350	51,995,250	-		3,170,027
US	538,827,316	270,669,200	987,646,432	633,066,100		79,941,087
All Other Countries	142,995,532	43,693,180	157,477,456	78,650,488	296,640	13,918,201
Total[a]	**766,449,402**	**319,226,460**	**1,270,756,212**	**736,339,008**	**296,640**	**101,745,649**

Combi = Combination pack with 18mg and 36mg tablets

[a] Note that the totals for tablets and person-months may not exactly match these figures in other exposure tables due to rounding.

Age and gender distribution is available from International Medical Statistics (IMS) for retail prescriptions of CONCERTA. IMS data provide the best available picture on age and gender distribution of patients who got a CONCERTA prescription. IMS prescription data have been collected for France, Germany, Spain and the United Kingdom (UK), as well as the US. The 4 named EU countries represent about two-thirds of CONCERTA use in the EU (based on 2009 figures), and together with the US account for the majority of worldwide CONCERTA use. These IMS figures cover the years 2003 up to and including June 2009. IMS only provides age groups in 5-year blocks. Therefore, it is not possible to present data for patients less than or equal to 17 years and those more than 17 years in the 16 to 20 year age group. Postmarketing exposure by age group and gender can be found in Table 14 and Table 15, respectively.

Table 14: Postmarketing (Nonstudy) Exposure by Age Group (IMS MIDAS, January 2003 Through June 2009)

Age groups (years)	EU (G4) (5,080 Rx)[a]	Total (29,406 Rx)[a]
<6	0.4%	2%
6-20	94.0%	85%
21-65	5.4%	10%
>65	0.1%	0%
Age not specified	0.1%	3%

[a] (000)

EU (G4) = France (launch = May 2004), Germany (launch = January 2003), Spain (launch = April 2004), and UK (launch = March 2002)

Rx = prescription

Table 15: Postmarketing (Nonstudy) Exposure by Gender
(IMS MIDAS, January 2003 Through June 2009)

	Females	Males	No Data
Total US and EU (29,406 Rx)[a]	24.8%	73.0%	2.2%
EU (5,080 Rx)	16.9%	82.7%	0.4%
France (108)	12.6%	82.1%	5.3%
Germany (2,195)	17.7%	82.2%	0.1%
Spain (1,636)	19.5%	79.7%	0.8%
United Kingdom (1,140)	12.0%	88.0%	0.0%

[a] (000)
Rx = prescription

1.3. Populations Not Studied in the Preauthorisation Phase

The following summarises the populations not studied in the preauthorisation phase (Tables 16.1 and 16.2).

Table 16.1: Important Exclusion Criteria Across Studies[a,b]

Indication: ADHD (paediatric subjects): C-97-025, C-98-003, C-98-005, C-98-007, C-98-012, C-99-018, 01-146, 12-101, CON-CAN-1, CON-CAN-2, C-2000-045 (See footnotes for number of subjects exposed and age ranges for each study)[c]
Adult subjects (The upper limit for most studies was 12 to 18 years; C-98-018 included adults up to 66 years) [SmPC (Annex 2)]
Adolescent women of either childbearing potential (after they reached menarche – early studies) or adolescent or adult women who were pregnant or nursing (later studies) [SmPC Section 4.6 (Annex 2)]
Clinically significant gastrointestinal problems, including narrowing (pathologic or iatrogenic) of the gastrointestinal tract. Some protocols provide these specific examples: small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudoabsorption, or Meckel's diverticulum. [SmPC (Annex 2)]
Subjects who had (not listed 98-012) [SmPC (Annex 2)]
Seizures disorder
Diagnosis of Tourette's (307.23, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV] 1994)/some protocols added a family history of Tourette's (not listed 99-018)
Glaucoma
The protocols listed a number of psychiatric conditions; listed in various terms across protocols: [SmPC (Annex 2)]
Marked anxiety, tension, or agitation (97-025, 99-018, 01-146, CON-CAN-1, CON-CAN-2, C-2000-045), Aggression (CON-CAN-1 and CON-CAN-2)
Psychotic disorders (97-025, 98-003, 98-005, 98-007, 01-146, CON-CAN-1, CON-CAN-2, C-2000-045)
Subjects whose primary focus of treatment was for other psychiatric conditions such as depressive disorders, bipolar disorders, or other mood disorders, oppositional-defiant disorder, conduct disorder, or tics (C-97-025 and C-98-003), tics (12-101)
Clinical depression and were suicidal or required immediate treatment for depression (98-005, 98-007, 98-012, 98-018, C-2000-045), depressed (C-97-025)
Bipolar disorder. Subjects who required drug therapy or hospitalization for treatment of a mood or anxiety disorder (01-146, CON-CAN-1, CON-CAN-2)
Co-morbid psychiatric condition other than oppositional defiant disorder (12-101)
Substance disorder (12-101), positive result for drug of abuse or who had a history of drug or alcohol abuse or dependence (C-98-018), drug or alcohol abuse or dependence within 6 months (01-146 CON-CAN-1, CON-CAN-2), current known or suspected substance abuse, or a history of substance abuse (C-2000-045)
Eating disorder (01-146, CON-CAN-1, CON-CAN-2)
Coexisting medical condition that was likely to interfere with safe administration of methylphenidate in the investigator's opinion (Not specifically listed in C-97-025 and 12-101) [SmPC (Annex 2)]
Known hypersensitivity to methylphenidate [some protocols added - other components of the product] [SmPC (Annex 2)]
Subjects were currently having significant adverse experiences from methylphenidate/stimulant therapy as verified by parent and/or physician. (Specifically listed: C-97-025, 98-003, 98-005, 98-007, C-2000-045) [SmPC (Annex 2)]

Footnotes appear on last page of table (Continued)

Table 16.1: Important Exclusion Criteria Across Studies[a,b] (Continued)

Indication: ADHD (paediatric subjects): C-97-025, C-98-003, C-98-005, C-98-007, C-98-012, C-99-018, 01-146, 12-101, CON-CAN-1, CON-CAN-2, C-2000-045 (See footnotes for number of subjects exposed and age ranges for each study)[c] (Continued)
Medications in addition to methylphenidate for ADHD during the study (implied, if not specifically listed, in most studies) Study C-97-025 specifically stated: Medications in addition to methylphenidate for ADHD in the past 4 weeks (eg, indicated – pemoline, amphetamine, d–amphetamine, or not indicated – clonidine, antidepressants). [SmPC (Annex 2)]
Concomitant medication that could likely interfere with the safe administration of methylphenidate (protocols listed prohibited medications in a variety of ways) [SmPC (Annex 2)]
Concomitant medication that could likely interfere with the safe administration of methylphenidate (Not specifically listed in C-97-025) Medications excluded by the package inserts of CONCERTA or Straterra (12-101)
Sedatives/hypnotics for methylphenidate-associated insomnia or treatment of ADHD symptoms (eg, clonidine), anticonvulsant (C-97-025)
Clonidine, pressor agents, MAO (monoamine oxidase) inhibitors, alpha-2 adrenergic receptor agonists, tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs), theophylline, Coumadin, or anticonvulsants. (Study 98-018)
Monoamine oxidase inhibitor or who had taken a monoamine oxidase inhibitor in the 14 days before initiation of study medication (01-146, CON-CAN-1 and CON-CAN-2, C-2000-045)
Clonidine or other alpha-2 adrenergic receptor agonists, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), theophylline, coumarin, or anticonvulsants. SSRI or who had taken an SSRI in the 35 days before initiation of the study medication, prescription or over-the-counter medications to induce sleep, natural or herbal products for any comorbid disorder (01-146)
Clonidine or other alpha-2 adrenergic receptor agonists, tricyclic antidepressants, theophylline, coumarin, or anticonvulsants (C-2000-045)
Theophylline, coumadin, anticonvulsants (CON-CAN-1 and CON-CAN-2)
Unable to swallow the medication whole (01-146, CON-CAN-1 and CON-CAN-2, C-2000-045) [SmPC (Annex 2)]
Blood pressure measurements (systolic or diastolic) equal to or greater than the 95th percentile for age, sex, and height (history of hypertension added C-98-012) (Not listed 12-101, CON-CAN-1, CON-CAN-2, C-2000-045) [SmPC (Annex 2)]

[a] Exclusion criteria apply to all studies listed, unless otherwise specified.

[b] Exclusion criteria related to study conduct to allow unconfounded assessment of efficacy and safety were not included in this table. For completeness the exclusion criteria not listed include: mental retardation, significant learning disorder, severe developmental disorder (ie, severe cerebral palsy, autism) (C-97-025, C-98-003, 12-101, 01-146, CON-CAN-1, CON-CAN-2, 12-101); clinically significant urinalysis, haematological and blood chemistry values (C-98-005, C-98-007, C-98-012); subjects, who in the opinion of the investigator, could not understand or follow the instructions given in the study; and subjects who were known to be non-responders to methylphenidate.

[c] Studies (N = Number of exposed subjects, age range): C-97-025 (N=68, 6-12 yrs), C-98-003 (N=62, 6-12 yrs), C-98-005 (N=104, 5-13 years), C-98-007 (N=110, 6-12 years), C-98-012 (N=432 [Part 1] and 278 [Part 2], 6-13 yrs), C-99-018 (N=1082, 5-66 yrs), 01-146 (N=220, 13-18 yrs), 12.-101 (N=850, 3-19 yrs), CON-CAN-1 (N=72, 6-12 yrs), CON-CAN-2 (N=116, 6- 12 years), C-2000-045 (N=105, 6-16 yrs).

Table 16.2: Important Exclusion Criteria in Individual Studies[a]

Indication: ADHD (paediatric subjects): C-97-025, C-98-003, C-98-005, C-98-007, C-98-012, C-99-018, 01-146, 12-101, CON-CAN-1, CON-CAN-2, C-2000-045 (See footnotes for number of subjects exposed and age ranges for each study)[b]	
C-97-025 C-98-003	Medications in the past 7 days that had central nervous system or performance effects (eg, sedating antihistamines) or medications that affect blood pressure and pulse including some medications for the treatment of asthma and some cough/cold preparations Subjects with a concurrent illness or condition with symptoms that might affect performance on any of the tests administered
01-146	ECG abnormalities that were deemed clinically significant
C-2000-045 12-101	Cardiovascular disease including moderate to severe hypertension, hyperexcitability or agitated states or hyperthyroidism (C-2000-045), hyperthyroidism (12-101)
01-146 CON-CAN-1 CON-CAN-2 C-2000-045	Were to commence or modify a behavioural program for ADHD [during the first 21 days of the study period – C-2000-045)

[a] The following minor exclusion criteria not included above: criteria regarding participation in previous studies (C-98-005); exclusion due to family members in study (C-98-005, 01-146); previous study participation (01-146, CON-CAN-1); related to those persons involved in study conduct (01-146, CON-CAN-1, CON-CAN-2); subject's parent/caregiver with drug/substance abuse problem (CON-CAN-1, CON-CAN-2); criteria regarding possibly allergic reaction due to use of EMLA as optional local anaesthetic for blood draws: lidocaine, prilocaine, or any other local anaesthetic, or a history of methaemoglobinaemia, or G6PD deficiency (C–98–003).

[b] Studies (N = Number of exposed subjects, age range): C-97-025 (N=68, 6-12 yrs), C-98-003 (N=62, 6-12 yrs), C-98-005 (N=104, 5-13 years), C-98-007 (N=110, 6-12 years), C-98-012 (N=432 [Part 1] and 278 [Part 2], 6-13 yrs), C-99-018 (N=1082, 5-66 yrs), 01-146 (N=220, 13-18 yrs), 12.-101 (N=850, 3-19 yrs), CON-CAN-1 (N=72, 6-12 yrs), CON-CAN-2 (N=116, 6- 12 years), C-2000-045 (N=105, 6-16 yrs).

1.3.1. Paediatric Patients: Less Than 6 Years of Age

The safety of CONCERTA has not been studied in children less than 6 years of age. This is addressed in Section 4.4 of the currently approved SmPC that states that CONCERTA should not be used in children under 6 years old, as the safety and efficacy in this age group have not been established.

1.3.2. Adult and Geriatric Patients

There is no approval in the EU for use of CONCERTA in the adult population and therefore, there is no reference to adult populations within the SmPC. However, 3 placebo-controlled studies (1 study included an open-label extension) and 3 open-label studies (1 study included a randomised withdrawal phase) in adults with ADHD have been completed. One additional study (C-99-018) in the paediatric submission included adult subjects through the age of 65 years (682 paediatric, 264 adolescent, and 136 adult subjects, total of 1,082 subjects).

The safety of CONCERTA has not been studied in elderly greater than 65 years of age.

1.3.3. Hepatic Insufficiency

There has been no experience with the use of CONCERTA in patients with hepatic insufficiency. Use of CONCERTA in this population is addressed in Section 4.4 of the currently approved SmPC.

1.3.4. Renal Insufficiency

There has been no experience with the use of CONCERTA in patients with renal insufficiency. Use of CONCERTA in this population is addressed in Section 4.4 of the currently approved SmPC.

1.3.5. Pregnancy

There is a limited amount of data from the use of methylphenidate in pregnant women.

As part of the Article 31(2) referral, the CHMP requested MAHs for methylphenidate to provide relevant data relating to safety in pregnancy and lactation from all sources from the earliest possible date to May 2008.

The aim of this assessment was to evaluate the available safety data (pre-clinical and clinical) in pregnancy and lactation with a view to achieving harmonisation of the information provided to healthcare professionals in the proposed core SmPC for Sections 4.3, 4.6, and 5.3.

The Medicines and Healthcare products Regulatory Agency (MHRA) as Rapporteur, in the 3 December 2008 Assessment Report for the Article 31 Referral, sought advice from the CHMP Safety Working Party with regards to the need for a contraindication in pregnancy as was in the SmPC of some methylphenidate-containing products in EU. On 15 December 2008, a finalised core methylphenidate SmPC was forwarded to MAHs informing that pregnancy was not contraindicated, but that a warning would appear in Section 4.6 stating that methylphenidate is not recommended for use during pregnancy unless a clinical decision is made that postponing treatment may pose a greater risk to the pregnancy. Section 4.6 of the SmPC also states that “cases of neonatal cardio-respiratory toxicity, specifically foetal tachycardia and respiratory distress have been reported in spontaneous case reports.” A statement regarding studies in animals that have shown evidence of reproductive toxicity at maternally toxic doses is provided in Sections 4.6 and 5.3.

1.3.6. Nursing Mothers

Methylphenidate has been found in the breast-milk of a woman treated with methylphenidate.

The MHRA as Rapporteur, in the 3 December 2008 Assessment Report for the Article 31 Referral, sought advice from the CHMP Safety Working Party with regards to the use of methylphenidate during breast-feeding. On 15 December 2008, a finalised core methylphenidate SmPC was forwarded to MAHs informing that a warning would appear in Section 4.6 that methylphenidate has been found in the breast-milk of a woman treated with methylphenidate. Section 4.6 also warns that a risk to the suckling child cannot be excluded and informs that there was a case report of an infant who experienced an unspecified decrease in weight during the period of exposure but recovered and gained weight after the mother discontinued treatment with methylphenidate. Section 4.6 states that a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from methylphenidate therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

1.3.7. Populations With Genetic Polymorphism

There has been no experience with the use of CONCERTA in subpopulations with genetic polymorphism.

1.3.8. Patients With Cardiovascular Risk Factors

There has been no experience with the use of CONCERTA in subpopulations with structural cardiovascular abnormalities.

1.3.9. Effect of Gender

Of the 2,854 patients in clinical studies of CONCERTA where gender was collected, 78.1% were male and 21.9% were female (Table 9). No important differences in the safety profile of CONCERTA between male and female patients were observed.

1.3.10. Effect of Ethnicity

Of the 2,854 patients in clinical studies of CONCERTA where ethnicity was collected, 83.1% were white, 9.1% were black or African-American, and 7.8% were of other racial background (Table 10).

1.4. Post-Authorisation Experience

The international birth date (IBD) for CONCERTA is 01 August 2000, based on first approval in the US. CONCERTA was first authorised in the European Union (EU) on 19 February 2002 in the UK. CONCERTA is licensed for the treatment of ADHD in children (over 6 years of age) and adolescents at a recommended daily dose of 18, 36, or 54 mg. A 27-mg dose strength is available in the United Kingdom and authorised via mutual recognition in 12 other member states in which local approvals have recently been granted in Iceland, Netherlands, Spain, Ireland, Austria, and Germany. CONCERTA is also approved for use in adults (up to 65 years of age) with ADHD in a number of

countries including Canada (15 April 2008), the US (27 June 2008), Australia (21 January 2009), and Switzerland (15 July 2009).

1.4.1. Actual Post-Authorisation Usage Data

Post-authorisation usage data is presented in Section 1.2.1.2, Post Marketing (Nonstudy) Exposure. Safety concerns arising since product authorisation are summarised in Section 1.4.2, Regulatory Action Taken.

1.4.2. Regulatory Action Taken

On 23 July 2007, the CHMP initiated an Article 31 referral procedure for all MAHs of methylphenidate containing products. This was due to concerns about cardiovascular adverse events including sudden death, cerebrovascular disorders, and psychiatric disorders. Following discussions between the CHMP and MAHs, a final opinion was issued on 22 January 2009; the Rapporteur's (MHRA) final Assessment Report was issued on 3 December 2008. The CHMP concluded that there was no need for a restriction on the use of methylphenidate-containing products, but that new recommendations on pre-treatment screening and ongoing monitoring of patients were required in the prescribing information. A number of post-referral commitments for the marketing authorisations of methylphenidate-containing products were also adopted by the CHMP (provided in this section). The CHMP opinion was ratified by the European Commission (EC) on 27 May 2009 (Annex 4). The following actions have been taken or are in progress by the Company since the October 2008, Version 1 of the RMP to fulfil the conditions of its Marketing Authorisations as adopted by the CHMP (Annex IV of the EC decision; Annex 4).

1.4.2.1. Cytogenicity

The reports of Studies CRIT124D2201 (An open-label, behavioural treatment controlled evaluation of the effects of extended-release methylphenidate [Ritalin LA] on the frequency of cytogenetic abnormalities in children 6-12 years old with attention deficit hyperactivity disorder) (published by Tucker 2009) and NCT 00341029 (Measurement of Cytogenetic Endpoints in Lymphocytes of Children Diagnosed With Attention Deficit/Hyperactivity Disorder (ADHD) and Treated With Methylphenidate or Adderall) (published by Witt 2008) submitted by one of the MAHs were evaluated by the MAHs of methylphenidate-containing products and the findings were submitted to the MHRA and CHMP members for assessment on 30 March 2009. These findings, in addition to those of Walitza (2007 and 2009) and Ponsa (2009), concluded that methylphenidate does not pose a mutagenic and/or carcinogenic risk associated with cytogenetic damages to exposed humans. The studies mentioned in this paragraph are described in Section 1.1.1.1.2 in greater detail. As of the preparation of this RMP update, the MHRA/CHMP assessment is ongoing.

1.4.2.2. Product Information - SmPC

As of the preparation of this RMP update, the Company is in the process of submitting updated product information in EU Member States to align with the core SmPC text ratified by the CHMP (refer to Annex III of the EC decision, Annex 4).

1.4.2.3. Product Information - Package Leaflet

The Company (with the other MAHs) has revised the core Patient Information Leaflet (PIL) text provided in Annex III of the EC decision (Annex 4) to improve patient readability and will user test the proposed text prior to filing with EU Health Authorities.

1.4.2.4. Suicidality

The Company (with the other MAHs) has completed its investigation of the feasibility of carrying out a meta-analysis of the risk of suicidality associated with the use of methylphenidate in children and adolescents with ADHD on the basis of data from placebo-controlled studies available to the MAHs. This was submitted to MHRA on 31 July 2009.

1.4.2.5. Long-Term Safety

The Company (with the other MAHs) will provide a detailed feasibility assessment for a scientifically valid, well designed and suitably powered long-term safety study to examine specific endpoints for adverse cognitive and psychiatric outcomes.

1.4.2.6. Drug Utilisation

The Company (with the other MAHs) will provide all available retrospective drug utilisation data using health-related electronic databases in all Member States where methylphenidate is used, to allow an evaluation of changes in usage over time. An evaluation of methylphenidate usage in 2008 will be submitted for assessment.

1.4.2.7. Educational Tools

The Company (with the other MAHs) will produce fully harmonised risk minimisation tools (physician's guide to prescribing and prescriber's checklist) which will contain all of the important information from the Clinical Particulars section of the core SmPC for assessment.

1.4.2.8. PSUR Work-Sharing

At the request of the EU Member States, the Company (with the other MAHs) will harmonise the PSUR reporting schedule for methylphenidate containing products. As a result, the new data lock point for CONCERTA will be moved to October. The transition will occur this year (2009) and an addendum will be prepared covering the period from 11 August 2009 to 10 October 2009 to support the transition to the new data lock point. Thereafter in the EU, once yearly PSURs will be submitted for the next 3 years.

A copy of the current SmPC is provided in Annex 2.

1.5. Adverse Events/Adverse Reactions

1.5.1. Newly Identified Safety Concerns

The identified and potential risks presented in Version 1 of the RMP were determined by the CHMP as stated in the Second List of Outstanding Issues dated 30 May 2008. The identified and potential risks presented in this document (Version 2) were defined in the Rapporteur's (MHRA) Assessment Report dated 3 December 2008. Three new potential risks were identified by the Assessment Report: lymphocytic leukaemia, neonatal cardio-respiratory toxicity (neonatal/foetal tachycardia, respiratory distress/apnoea), and neonatal effects on growth (via lactation). The Company also conducted a review of the risks for CONCERTA and has identified no new safety concerns beyond those mentioned in the recent Assessment Report presented in Section 1.5.2.

1.5.2. Details of Important Identified and Potential Risks

The list of identified and potential risks ratified by the European Commission in the Final Assessment Report dated 22 January 2009 differs from the list of identified and potential risks provided in the Rapporteur's (MHRA) Assessment Report dated 3 December 2008. In response to an inquiry from the Company, the MHRA advised that the RMP follow those of the Assessment Report dated 3 December 2008.

The following identified risks for methylphenidate containing products for ADHD were identified in the Rapporteur's (MHRA) Assessment Report dated 3 December 2008:

- Hypertension
- Tachycardia
- Raynaud's phenomenon
- Hallucinations (auditory, skin sensation, visual disturbance)
- Psychosis/Mania
- Anorexia
- Decreased rate of growth

Of these risks, psychosis (of the combined Psychosis/Mania identified risk) and decreased rate of growth were not identified as adverse drug reactions (ADRs) for CONCERTA based on paediatric clinical studies and postmarketing surveillance. These identified risks are characterised in Tables 17.1 to 17.7. Postmarketing data is only provided for those terms not identified as ADRs from the CONCERTA clinical trials database.

The following potential risks for methylphenidate containing products for ADHD were identified in the Rapporteur's (MHRA) Assessment Report dated 3 December 2008:

- Migraine
- Repetitive behaviours
- QT prolongation
- Cyanosis
- Arrhythmias
- Sudden death
- Cerebrovascular disorders
- Aggression
- Hostility
- Depression
- Suicidality
- Tics/Tourette's syndrome/Dystonias
- Effect on final height
- Sexual maturation (delayed)
- Carcinogenicity
- Off-label use
- Diversion
- Withdrawal syndrome
- Drug abuse and drug dependence
- Lymphocytic leukaemia
- Neonatal cardio-respiratory toxicity (neonatal/foetal tachycardia, respiratory distress/apnoea)
- Neonatal effects on growth (via lactation)

Of these potential risks, a causal relationship with CONCERTA was established for Aggression, Tics, and Depression. The potential risks are characterised in Tables 18.1 to 18.22. Postmarketing data is provided for those terms not identified as ADRs from the CONCERTA clinical trials database.

The Rapporteur's (MHRA) Assessment Report dated 3 December 2008 identified long-term safety as an area of important missing information. Long-term safety is listed in Table 23: Summary of Ongoing Safety Concerns. Also, routine and additional pharmacovigilance activities are listed for this concern in Part 2 of this RMP.

Table 17.1: Important Identified Risk: Hypertension

	Population From Double-Blind Trials		Population From All Trials
Identified Risk: ***Hypertension****	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	1 (0.3)	0	26 (0.9)
Rate per 1000 person-year†	*	*	18.2
95% confidence interval‡	*	*	11.9, 26.7
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	1
Discontinued Treatment	0	0	5
Resolved/Recovered	0	0	20
Resolved with Continuing Effects	1	0	1
Not Resolved/Not Yet Recovered/Continuing	0	0	5
Severity§			
Mild	0	0	20
Moderate	1	0	5
Severe	0	0	1

* Reported Medical Dictionary for Regulatory Activities (MedDRA) preferred terms include: blood pressure increased; blood pressure diastolic increased; blood pressure systolic increased; and hypertension.

** A subject is counted only once regardless of the number of events.

† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.

‡ Confidence Intervals (CI) are two-sided 95% exact Poisson

§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

On the basis of the review of aggregate safety data from clinical trials of CONCERTA, a causal relationship was established for Hypertension and Blood pressure increased. A causal relationship was not established for any other adverse event that may be relevant for this important identified risk.

Nature of the Risk	Methylphenidate is a sympathomimetic agent that has the propensity to stimulate the sympathetic nervous system, resulting in changes in vital signs, including blood pressure elevation. Drug-induced blood pressure elevation should be distinguished from hypertension. Drug-induced elevation in blood pressure is reversible when the drug is discontinued. Hypertension is a chronic state that persists when medications are withdrawn. Methylphenidate is associated with blood pressure elevations that do not persist when therapy is discontinued. The average increase from baseline in systolic and diastolic blood pressure seen in CONCERTA clinical trials in the paediatric population was 3 to 4 mm Hg.

(Continued)

Table 17.1: Important Identified Risk: Hypertension (Continued)

Background Incidence / Prevalence	There have been no known published reports showing an increased prevalence of hypertension in children or adolescents diagnosed with ADHD. As a mechanism to provide background rates, screening surveys of junior and high school-aged children have found the prevalence of hypertension to be between 1% and 2% (Flynn 2001a). A review of studies performed in referral centres suggests that the frequency of primary hypertension among children is increasing over time (Feld and Springate 1988, Arar 1994, Flynn 2001b). The proportion of all hypertension in children that was classified as primary has increased from 16% in 1988 to 23% in 1994, and most recently was reported as 48.6%.
Risk Groups or Risk Factors	In assessing the background risk (independent of drug) for cardiovascular events, including hypertension, it is important to identify whether children between 5 and 17 years of age, diagnosed with ADHD, have a different background rate or higher prevalence of cardiovascular risk factors than the general population of the same age. The medical literature was reviewed for reports of an incidence/prevalence rate in ADHD children or an association between ADHD and hypertension. To the best of our knowledge, there have been no published reports indicating an increased risk in children with ADHD for hypertension. Two population-based studies have looked at the relationship of overweight/obesity (ie, as cardiovascular risk factor) and ADHD in children (Holtkamp 2004, Curtin 2005). One study found ADHD children were more likely to be obese, while the second did not.
Potential Mechanisms	Methylphenidate is a catecholaminergic agent (noradrenergic and dopaminergic) and has sympathomimetic properties. Sympathomimetics can induce heart rate and blood pressure increases.
Preventability	Early detection, monitoring and therapy including pharmacotherapy, nutritional and life style changes Patient's blood pressure should be monitored at appropriate intervals if CONCERTA is prescribed, especially if the patient has hypertension. Blood pressure and pulse should be recorded at each adjustment of dose and subsequently as clinically needed. Use appropriate caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate. CONCERTA should not be prescribed for children or adolescents with severe hypertension according to EU SmPC.

(Continued)

Table 17.1: Important Identified Risk: Hypertension (Continued)

Potential Public Impact of Safety Concern	The clinical trial database and the postmarketing database demonstrate CONCERTA treatment confers a risk of small increases in blood pressure and heart rate. Given that CONCERTA is a sympathomimetic compound, these are pharmacologically-expected effects. Clinically significant increases in blood pressure are not expected. If a clinically significant blood pressure increase occurs and is believed to be drug related, CONCERTA therapy should be discontinued and the effect will dissipate. The overall number of individuals affected is small. Therefore, drug-induced increases in blood pressure are not expected to have an impact with respect to overall public health. CONCERTA is currently contraindicated in patients with severe hypertension. Additionally, the following precautionary language is included in section 4.4 Special warnings and precautions for use of current EU SmPC for CONCERTA (Annex 4 refer to Annex III of the EC decision): Use cautiously in patients with hypertension. Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and then at least every 6 months. Patients using methylphenidate may commonly experience changes in diastolic and systolic blood pressure of over 10 mmHg relative to controls. Therefore, caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate.
Regulatory Action Taken	Annex IV of the May 2009 EC decision (Conditions of the Marketing Authorisation) states the report of a study that is currently being conducted by the US Food and Drug Administration (FDA)/US Agency for Healthcare Research and Quality (AHRQ) AHRQ/Vanderbilt University should be evaluated, when available, as it is intended to evaluate the following: 1) Assess the relationship between use of medications for ADHD and the risk of serious cardiovascular disease in children and youth, aged 2-24 years 2) Assess the relationship between use of medications for ADHD and the risk of serious cardiovascular disease in adults, aged 25-64 years 3) Perform additional analyses that are relevant to decision makers such as clinicians, state Medicaid programs, and parents/patients The MAHs will evaluate the final report of the study, when published, and will update the Core RMP, and where appropriate the Core SmPC/PIL, to reflect the findings. Methylphenidate is contraindicated in patients with severe hypertension.

(Continued)

Table 17.1: Important Identified Risk: Hypertension (Continued)

Regulatory Action Taken (Continued)	Because of possible increases in blood pressure, interaction text states CONCERTA should be used cautiously with vasopressor agents (SmPC, section 4.5). Interaction with antihypertensive drugs in Section 4.5 cautions use with methylphenidate, as it may decrease the effectiveness of drugs used to treat hypertension. Because of possible hypertensive crisis, methylphenidate is contraindicated in patients being treated (currently or within the preceding 2 weeks) with non-selective, irreversible MAO-inhibitors (see Section 4.3). There is additional text regarding blood pressure under pre-treatment screening and ongoing monitoring in Section 4.2. Posology and method of administration. Additionally, in Section 4.4 precautionary language is included under cardiovascular status: "Cardiovascular status should be carefully monitored. Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and then at least every 6 months." Hypertension is listed as an ADR in Section 4.8 of the EU SmPC with a frequency of common.
Evidence Source	Arar MY (1994), Hogg RJ, Arant BS Jr, Seikaly MG. Etiology of sustained hypertension in children in the southwestern United States. Pediatr Nephrol 1994;8:186-189. Curtin C (2005), Bandini LG, Perrin EC, Tybor DJ, Must A. Prevalence of overweight in children and adolescents with attention deficit hyperactivity disorder and autism spectrum disorders: a chart review. BMC Pediatr 2005;5:48. Flynn JT (2001a). Characteristics of children with primary hypertension referred to a tertiary center. Am J Hypertens 2001;14:239. Flynn JT (2001b). What's new in pediatric hypertension? Curr Hypertens Rep 2001;3:503-510. Feld LG (1988), Springate JE. Hypertension in children. Curr Probl Pediatr 1988, 18:317-373. Holtkamp K (2004), Konrad K, Muller B, et al. Overweight and obesity in children with Attention-Deficit/Hyperactivity Disorder. Int J Obes Relat Metab Disord 2004;28(5):685-689.

Table 17.2: Important Identified Risk: Tachycardia

	Population From Double-Blind Trials		**Population From All Trials**
Identified Risk: ***Tachycardia****	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	0	0	17 (0.6)
Rate per 1000 person-year†	*	*	11.9
95% confidence interval‡	*	*	6.9, 19.1
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	0
Discontinued Treatment	0	0	3
Resolved/Recovered	0	0	15
Resolved with Continuing Effects	0	0	0
Not Resolved/Not Yet Recovered/Continuing	0	0	2
Severity§			
Mild	0	0	9
Moderate	0	0	6
Severe	0	0	2

* Reported MedDRA preferred terms include: heart rate increased, tachycardia.

** A subject is counted only once regardless of the number of events.

† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.

‡ CI are two-sided 95% exact Poisson

§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

On the basis of the review of aggregate safety data from clinical trials of CONCERTA, a causal relationship was established for Tachycardia. A causal relationship was not established for any other adverse event that may be relevant for this important identified risk.

Nature of Risk	Methylphenidate is a sympathomimetic agent that has the propensity to stimulate the cardiovascular system resulting in changes in vital signs, including increase in heart rate. Drug-induced elevations in the heart rate should be distinguished from co-morbid conditions or genetic structural abnormalities that might cause arrhythmia. Drug-induced increase in heart rate is reversible when the drug is discontinued. Methylphenidate is associated with increases in heart rate that do not persist when therapy is discontinued.

(Continued)

Table 17.2: Important Identified Risk: Tachycardia (Continued)

Background Incidence / Prevalence	There have been no published reports of an association between arrhythmias and ADHD among children and adolescents. A study out of Japan looked at the prevalence of cardiac rhythm disturbances in the general population of children (Niwa 2004). Any kind of cardiac rhythm disturbance was found in 1.25% of elementary students and 2.32% of junior high students, with the prevalence higher in males than females (2.0% vs 1.38%). A study that included 26 US community emergency departments (ED) and 2.3 million ED visits found that primary cardiac arrhythmias in those under 18 years of age was an infrequent presentation to the ED (Sacchetti 2001). The incidence of clinically significant arrhythmias in these patients was reported as 5.7 per 100,000 emergency department visits. Atrial tachyarrhythmias were the most common presentation in this study population.
Risk Group or Risk Factors	In assessing the background risk (independent of drug) for cardiovascular events, it is important to identify whether children between 5 and 17 years of age, diagnosed with ADHD, have a different background rate or higher prevalence of cardiovascular risk factors than the general population of the same age. The medical literature was reviewed for reports of an incidence/prevalence rate in ADHD children or an association between ADHD and arrhythmias. To our knowledge, there have been no published reports indicating an increased risk in children with ADHD for arrhythmias, including tachycardia.
Potential Mechanisms	Methylphenidate is a catecholaminergic agent (noradrenergic and dopaminergic) and has sympathomimetic properties. Sympathomimetics can induce heart rate and blood pressure increases.
Preventability	Education of patients, caregivers and prescribes. Early detection, monitoring and therapy, including life style changes (avoid stimulants such as caffeine, nicotine, some decongestants and illegal drugs). Use appropriate caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate. CONCERTA should not be prescribed for children or adolescents with severe angina pectoris or cardiac arrhythmias according to EU SmPC.

(Continued)

Table 17.2: Important Identified Risk: Tachycardia (Continued)

Potential Public Impact of Safety Concern	The clinical trial database and the postmarketing database demonstrate CONCERTA treatment confers a risk of small increases in heart rate. Given that CONCERTA is a sympathomimetic compound, these are pharmacologically-expected effects. The overall number of individuals affected is small and the pharmacologic effect dissipates when the drug is withdrawn. Therefore, increased heart rate is not expected to have an impact with respect to overall public health.
Regulatory Action Taken	The EU SmPC for CONCERTA (Annex 2) contraindicates use in patients with pre-existing cardiovascular disorders such as angina and potentially life-threatening cardiac arrhythmias. Precautionary language is included in Section 4.4 Special warnings and precautions for use in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate. Pre-treatment screening advice requires a baseline evaluation of a patient's cardiovascular status including heart rate as well as continuous monitoring of blood pressure and heart rate at each adjustment of dose and then at least every 6 months (Section 4.2). Section 4.4 of the CONCERTA EU SmPC also advises that heart rate, as well as blood pressure, should be monitored (centile chart) at each adjustment of dose and then at least every 6 months. Tachycardia is listed as an ADR in Section 4.8 of the EU SmPC with a frequency of common.
Evidence Source	Niwa K (2004), Warita N, Sunami Y, Shimura A, Tateno S, Sugita K. Prevalence of arrhythmias and conduction disturbances in large population-based samples of children. Cardiol Young 2004;14(1):68-74. Sacchetti A (1999), Moyer V, Baricella R, Cameron J, Moakes ME. Primary cardiacarrhythmias in children. Pediatr Emerg Care 1999;15(2):95-98.

Table 17.3: Important Identified Risk: Raynaud's Phenomenon

	Population From Double-Blind Trials		**Population From All Trials**
Identified Risk: ***Raynaud's Phenomenon****	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	0	0	0
Rate per 1000 person-year†	--	--	0.0
95% confidence interval‡	--	--	0.0, 2.6
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	0
Discontinued Treatment	0	0	0
Resolved/Recovered	0	0	0
Resolved with Continuing Effects	0	0	0
Not Resolved/Not Yet Recovered/Continuing	0	0	0
Severity§			
Mild	0	0	0
Moderate	0	0	0
Severe	0	0	0

* Reported MedDRA preferred terms include: none.

** A subject is counted only once regardless of the number of events.

† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.

‡ CI are two-sided 95% exact Poisson

§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

No adverse events for this important identified risk were reported in clinical trials of CONCERTA. As a result, the causal relationship of relevant adverse events for this identified risk could not be evaluated on the basis of aggregate safety data from clinical trials of CONCERTA.

(Continued)

Table 17.3: Important Identified Risk: Raynaud's Phenomenon (Continued)

Postmarketing

A summary of Raynaud's phenomenon events from the postmarketing database is presented below:

Cumulative Count of Selected Preferred Terms (MedDRA) Reported at Least Once Between 11 August 2008 and 10 August 2009 by Seriousness: Raynaud's Phenomenon

	Number of Events 01 August 2000 to 10 August 2009	
Preferred Term	**Nonserious[a]**	**Serious[a]**
Pallor	16	3
Peripheral Coldness	17	4
Raynaud's Phenomenon	7	28
Cyanosis	5	11

[a] At event level.

Source: Benefit Risk Management (BRM) Period Safety Update Report 2009: This search of the worldwide postmarketing safety database for Raynaud's phenomenon was conducted using the following MedDRA preferred terms: Raynaud's phenomenon, Pallor, Peripheral Coldness, and Cyanosis.

Raynaud's phenomenon has been identified as an ADR during postmarketing experience with CONCERTA.

Nature of the Risk	Raynaud's phenomenon is characterised by episodic digital ischaemia, manifested clinically by the sequential development of digital blanching, cyanosis, and rubor (reddening) of the fingers or toes generally following cold exposure and subsequent rewarming. Emotional stress may also precipitate Raynaud's phenomenon. In Raynaud's phenomenon, as distinguished from Raynaud's disease, the condition reverses once the precipitating agent is withdrawn. A few reports of Raynaud's phenomenon have occurred in children taking methylphenidate; however, it is a drug induced vascular effect on the digits and is reversible when the drug is discontinued.
Background Incidence / Prevalence	A published literature search was conducted for relevant publications regarding a potential association between CONCERTA or methylphenidate use and Raynaud's phenomenon. No published reports were identified. No literature was identified indicating an increased prevalence of Raynaud's phenomenon in children or adolescents diagnosed with ADHD. A population-based study of 720 children, ages 12 to 15 years, in England found that 14.9% reported symptoms consistent with Raynaud's disease. The prevalence was higher in girls (17.6%) than in boys (12.2%), and increased with age. The Framingham Offspring Study cohort consisted of 1,358 adults (mean age=53.5) that were followed for a mean of 7.1 years (Jones 2003). At baseline, 10.9% of females and 7.8% of males were found to have Raynaud's disease. During follow-up, new, incident Raynaud's disease was observed in 2.2% of females and 1.5% of males (Suter 2005).

(Continued)

Table 17.3: Important Identified Risk: Raynaud's Phenomenon (Continued)

Risk Groups or Risk Factors	To our knowledge, there have been no published literature reports indicating an increased risk of Raynaud's disease in children and adolescents with ADHD.
Potential Mechanisms	Methylphenidate is catecholaminergic agent (noradrenergic and dopaminergic) and has sympathomimetic properties. Catecholamine can produce constriction or vasospasm of the smaller blood vessels such as those in the digits. Patients with underlying vascular sensitivity may have worsening of their symptoms when they are started on methylphenidate (Syed and Moore 2008).
Preventability	Protection from cold.
Potential Public Impact of Safety Concern	There were no reports of Raynaud's phenomenon in the clinical trials database. Although very rarely reported in the spontaneous postmarketing database, the pharmacologic mechanism and the evidence analysis of cases are consistent with a possible causal association between CONCERTA and Raynaud's phenomenon. However, this effect is reversible in nature and is not expected to have an impact with respect to overall public health.
Regulatory Action Taken	Raynaud's phenomenon is listed as an ADR in section 4.8 of the CONCERTA EU SmPC (Annex 2) with a frequency of very rare.
Evidence Source	Benefit Risk Management Report (PSUR 2009). Periodic Safety Update Report. OROS® methylphenidate HCl (From 11Aug2008-10Aug2009). Document ID No. EDMS-USRA-EDMS-USRA-11227189. J&JPRD (25 September 2009). Jones GT (2003), Herrick AL, Woodham SE, Baildam EM, Macfarlane GJ, Silman AJ. Occurrence of Raynaud's phenomenon in children ages 12-15 years: prevalence and association with other common symptoms. Arthritis Rheum 2003;48:3518-3521. Suter LG (2005), Murabito JM, Felson DT, Fraenkel L. The incidence and natural history of Raynaud's phenomenon in the community. Arthritis Rheum 2005;52:1259-1263. Syed RH (2008), Moore TL. Methylphenidate and dextroamphetamine-induced peripheral vasculopathy. J Clin Rheumatol 2008;14:30-33.

Table 17.4: Important Identified Risk: Hallucinations (Auditory, Skin Sensation, Visual Disturbance)

	Population From Double-Blind Trials		**Population From All Trials**
Identified Risk: *Hallucinations (Auditory, Skin Sensation, Visual Disturbance)* *	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	0	0	5 (0.2)
Rate per 1000 person-year†	*	*	3.5
95% confidence interval‡	*	*	1.1, 8.2
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	1
Discontinued Treatment	0	0	2
Resolved/Recovered	0	0	4
Resolved with Continuing Effects	0	0	0
Not Resolved/Not Yet Recovered/Continuing	0	0	1
Severity§			
Mild	0	0	1
Moderate	0	0	2
Severe	0	0	2

* Reported MedDRA preferred terms include: hallucination, auditory; hallucination, visual; hypnagogic hallucination.

** A subject is counted only once regardless of the number of events.

† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.

‡ CI are two-sided 95% exact Poisson

§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

On the basis of the review of aggregate safety data from clinical trials of CONCERTA, a causal relationship was not established for any of the adverse events that may be relevant for this important identified risk.

(Continued)

Table 17.4: Important Identified Risk: Hallucinations (Auditory, Skin Sensation, Visual Disturbance) (Continued)

Postmarketing

A summary of hallucination events from the postmarketing database is presented below:

Cumulative Count of Selected Preferred Terms Reported at Least Once Between 11 August 2008 and 10 August 2009 by Seriousness: Hallucination, Hallucination Auditory, Hallucination Visual, and Hallucination Mixed

	Number of events 01 August 2000 to 10 August 2009	
Preferred Term	**Nonserious[a]**	**Serious[a]**
Hallucination, auditory	9	27
Hallucination, visual	16	29
Hallucinations, mixed	3	7
Hallucination	25	69

[a] At event level.

Source: BRM Period Safety Update Report 2009: This search of the worldwide postmarketing safety database for Hallucinations was conducted using the following MedDRA preferred terms: Hallucination, Hallucination, auditory; Hallucination, visual; and Hallucination, mixed.

Hallucination, hallucination auditory, and hallucination visual are ADRs identified during postmarketing experience with CONCERTA.

Nature of the Risk	Hallucinations can be mediated by dopamine, a neurotransmitter that is increased in concentration with methylphenidate therapy; therefore, they should be immediately reversible upon drug discontinuation. In the CONCERTA clinical trial database, visual, auditory, and tactile hallucinations have been reported as acute reactions in children with ADHD with no previous history of psychosis. Hallucinations seemed to occur early in treatment as sporadic events. In some cases, the hallucinations were transient and did not recur despite continued exposure.
Background Incidence / Prevalence	There is very little published research on the frequency of psychosis, including hallucinations, in young persons with ADHD. The incidence of psychiatric events in the relevant general population (children and adolescents ages 5 to 17) is the first measure of the underlying background rate for a specific population of interest (users of CONCERTA). Poulton and co-authors (2000) reported 14% of 11 years old adolescents in the general paediatric population had either delusional beliefs or hallucinatory experiences.

(Continued)

Table 17.4: Important Identified Risk: Hallucinations (Auditory, Skin Sensation, Visual Disturbance) (Continued)

Risk Groups or Risk Factors	The medical literature was reviewed for reports of an incidence/prevalence rate in ADHD children for suicidal behaviour, major depression, anger or aggression, and psychosis/hallucinations, or for reports of an elevated relative risk associated with ADHD and the psychiatric events of interest. Children and adolescents with ADHD were found to have a high prevalence of co-morbid psychiatric disorders (oppositional-defiant disorder, major depression, anxiety, mania, psychosis).
Potential Mechanisms	CONCERTA is known to increase dopamine and norepinephrine in the interneuronal space. Both of these neurotransmitters have important roles in the aetiology of psychiatric symptoms. While the specific pathways that are responsible for stimulant-induced psychosis, for example, are not mapped out in detail, the pharmacological basis of this ADR is well accepted.
Preventability	Education of prescribers. Early detection and management of symptoms. Methylphenidate should not be prescribed to patients with psychotic disorder. Caution should be exercised in patients with co-morbid psychiatric disorders. Careful monitoring of patients for adverse events, especially early on in treatment, is prudent. Psychotic or manic symptoms have been reported in patients without a prior history of psychotic illness or mania. If symptoms occur, per the proposed SmPC (section 4.4) consideration should be given to given to a possible causal role for methylphenidate, and discontinuation of treatment may be appropriate.
Potential Public Impact of Safety Concern	In the CONCERTA clinical trial database, visual, auditory, and tactile hallucinations have been reported rarely in children with ADHD without a previous history of psychosis; the event is transient, resolves fully upon discontinuation of the medication, and is sometimes related to concomitant abuse of an intoxicating substance. The overall number is small and due to its reversible nature it is not expected to have an impact with respect to overall public health.

(Continued)

Table 17.4: Important Identified Risk: Hallucinations (Auditory, Skin Sensation, Visual Disturbance) (Continued)

Regulatory Action Taken	The CONCERTA EU SmPC (Annex 2) contraindicates use in patients with diagnosis or history of psychotic symptoms. Precautionary text in Section 4.4 recommends discontinuation of treatment with methylphenidate if a causal role can be established for emergent psychotic symptoms (visual/tactile/auditory hallucinations) at usual dosages of methylphenidate. The development or worsening of psychiatric disorders should be monitored at every adjustment of dose, then at least every 6 months, and at every visit; discontinuation of treatment may be appropriate (Section 4.4). There is additional text regarding pre-treatment screening for psychiatric disorder in Section 4.2. Posology and method of administration. There is also text in Section 4.2 regarding ongoing monitoring for development of de novo or worsening of pre-existing psychiatric disorders and that these should be monitored at every adjustment of dose and then at least every 6 months and at every visit. Hallucinations are listed as an ADR in Section 4.8 of the CONCERTA EU SmPC with a frequency of uncommon.
Evidence Source	Benefit Risk Management Report (PSUR 2009). Periodic Safety Update Report. OROS® methylphenidate HCl (From 11Aug2008-10Aug2009). Document ID No. EDMS-USRA-EDMS-USRA-11227189. J&JPRD (25 September 2009). Poulton R (2000), Caspi A, Moffitt TE, Cannon M, Murray R, Harrington H. Children's self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. Arch Gen Psychiatry 2000;57(11):1053-1058.

Table 17.5: Important Identified Risk: Psychosis/Mania

	Population From Double-Blind Trials		**Population From All Trials**
Identified Risk: *Psychosis / Mania**	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	0	0	8 (0.3)
Rate per 1000 person-year†	*	*	5.6
95% confidence interval‡	*	*	2.4, 11.1
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	4
Discontinued Treatment	0	0	6
Resolved/Recovered	0	0	7
Resolved with Continuing Effects	0	0	0
Not Resolved/Not Yet Recovered/Continuing	0	0	1
Severity§			
Mild	0	0	0
Moderate	0	0	3
Severe	0	0	5

* Reported MedDRA preferred terms include: delusion: hallucination, auditory; hallucination, visual; mania: paranoia.

** A subject is counted only once regardless of the number of events.

† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.

‡ CI are two-sided 95% exact Poisson

§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

On the basis of the review of aggregate safety data from clinical trials of CONCERTA, a causal relationship was not established for any of the adverse events that may be relevant for this important identified risk.

(Continued)

Table 17.5: Important Identified Risk: Psychosis/Mania (Continued)

Postmarketing

A summary of mania and psychotic disorders events from the postmarketing database is presented below:

Cumulative Count of Selected Preferred Terms Reported at Least Once Between 11 August 2008 and 10 August 2009 by Seriousness: Psychotic Disorders/Mania

	Number of Events 01 August 2000 to 10 August 2009	
Preferred Term[a]	**Nonserious**[b]	**Serious**[b]
Mania	4	13
Psychotic disorder	3	61

[a] Preferred terms from the search terms that are not listed here were not received in the current reporting period.

[b] At event level

Source: BRM Report, PSUR 2009. This search of the worldwide postmarketing safety database was conducted using the following MedDRA preferred terms: Abnormal behaviour, Formication, Obsessive rumination, Affect liability, Hallucination, Paranoia, Affective disorder, Hallucination auditory, Psychotic behaviour, Apathy, Hallucination visual, Psychotic disorder, Asocial behaviour, Hallucinations mixed, Schizoaffective disorder, Delirium, Hypomania, Social avoidant behaviour, Delusion, Logorrhoea, Speech disorder, Delusional disorder, persecutory type, Mania.

Mania is an ADR identified during postmarketing experience with CONCERTA. This review of spontaneous postmarketing reports of psychotic disorder found no evidence of a drug-event link with CONCERTA.

Nature of the Risk	Manic symptoms have been reported in children with ADHD treated with methylphenidate at usual doses. Central nervous system stimulants are thought to mediate mania via an increase in central catecholamine levels (ie, dopamine). Therefore, the symptoms are immediately reversible when the medication is withdrawn and central catecholamine levels return to baseline. In the CONCERTA clinical trial database, psychotic and manic symptoms have been reported as acute reactions in children with ADHD with no previous history of psychosis/mania as a mental illness. These acute reactions seemed to occur early in treatment as sporadic events at usual doses of methylphenidate.
Background Incidence / Prevalence	There is very little published research on the frequency of psychosis in young persons with ADHD. The incidence of psychiatric events in the relevant general population (children and adolescents ages 5 to 17) is the first measure of the underlying background rate for a specific population of interest (users of CONCERTA). Poulton and co-authors (2000) reported 14% of 11 years old adolescents in the general paediatric population had either delusional beliefs or hallucinatory experiences.

(Continued)

Table 17.5: Important Identified Risk: Psychosis/Mania (Continued)

Risk Groups or Risk Factors	The medical literature was reviewed for reports of an incidence/prevalence rate in ADHD children for suicidal behaviour, major depression, anger or aggression, and psychosis/hallucinations, or for reports of an elevated relative risk associated with ADHD and the psychiatric events of interest. Children and adolescents with ADHD were found to have a high prevalence of co-morbid psychiatric disorders (oppositional-defiant disorder, major depression, anxiety, mania, psychosis).
Potential Mechanisms	CONCERTA is known to increase dopamine and norepinephrine in the interneuronal space. Both of these neurotransmitters have important roles in the aetiology of certain psychiatric symptoms including mood disorders, impulse-control disorders, psychosis, attention disorders, and anxiety disorders. While the specific pathways that are responsible for stimulant-induced psychosis, for example, are not mapped out in detail, the pharmacological basis of this ADR is well accepted.
Preventability	Education of prescribers. Early detection and management of psychiatric symptoms. Methylphenidate should not be prescribed to patients with psychotic disorder. Caution should be exercised in patients with co-morbid psychiatric disorders. Careful monitoring of patients for adverse events, especially early on in treatment, is prudent. Psychotic or manic symptoms have been reported in patients without a prior history of psychotic illness or mania. If such symptoms occur, discontinuation of treatment may be appropriate. If symptoms occur, per the proposed SmPC (section 4.4) consideration should be given to given to a possible causal role for methylphenidate, and discontinuation of treatment may be appropriate.
Potential Public Impact of Safety Concern	In the CONCERTA clinical trial database, psychotic and manic symptoms have been reported rarely in children with ADHD without a previous history of psychosis; the event is transient, resolves fully upon discontinuation of the medication, and is sometimes related to concomitant abuse of an intoxicating substance. The overall number is small and due to its reversible nature it is not expected to have an impact with respect to overall public health.

(Continued)

Table 17.5: Important Identified Risk: Psychosis/Mania (Continued)

Regulatory Action Taken	The CONCERTA EU SmPC (Annex 2) contraindicates use in patients who have a diagnosis or history of psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder, and severe and episodic (Type I) Bipolar (affective) Disorder (that is not well controlled). There is precautionary language on the exacerbation of existing psychotic or manic symptoms included in Section 4.4, Special warnings and precautions, for use "In psychotic patients, administration of methylphenidate may exacerbate symptoms of behavioural disturbance and thought disorder." There is additional precautionary language (Section 4.4) in the case of emergence of psychotic or manic symptoms: "Treatment-emergent psychotic symptoms (visual/tactile/ auditory hallucinations and delusions) or mania in children and adolescents without prior history of psychotic illness or mania can be caused by methylphenidate at usual doses. If manic or psychotic symptoms occur, consideration should be given to a possible causal role for methylphenidate, and discontinuation of treatment may be appropriate." The following ongoing monitoring statement is applied in Section 4.4: "Development or worsening of psychiatric disorders should be monitored at every adjustment of dose, then at least every 6 months, and at every visit; discontinuation of treatment may be appropriate." There is additional precautionary language in Section 4.4 concerning long-term use (more than 12 months): "Patients on long-term therapy... must have careful ongoing monitoring for ... development of de novo or worsening of pre-existing psychiatric disorders. Psychiatric disorders to monitor for are described below, and include (but are not limited to) motor or vocal tics, aggressive or hostile behaviour, agitation, anxiety, depression, psychosis, mania, delusions, irritability, lack of spontaneity, withdrawal, and excessive perseveration." Additional text regarding pre-treatment screening and ongoing monitoring of psychiatric disorder is included in Section 4.2. Posology and method of administration. Psychotic disorders are listed as an ADR in Section 4.8 of the EU SmPC with a frequency of uncommon. (Psychotic disorders was not identified as an ADR based on review of the clinical trial or postmarketing database for CONCERTA; this term was included as an ADR based on the Article 31 referral of methylphenidate-containing products.) Mania is also listed as an ADR with a frequency of rare.

(Continued)

Table 17.5: Important Identified Risk: Psychosis/Mania (Continued)

Evidence Source	Benefit Risk Management Report (PSUR 2009). Periodic Safety Update Report. OROS® methylphenidate HCl (From 11Aug2008-10Aug2009). Document ID No. EDMS-USRA-EDMS-USRA-11227189. J&JPRD (25 September 2009). Poulton R (2000), Caspi A, Moffitt TE, Cannon M, Murray R, Harrington H. Children's self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. Arch Gen Psychiatry 2000;57 (11):1053-1058.

Table 17.6: Important Identified Risk: Anorexia

	Population From Double-Blind Trials		**Population From All Trials**
Identified Risk: *Anorexia**	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	6 (1.9)	0	306 (10.7)
Rate per 1000 person-year†	*	*	214.6
95% confidence interval‡	*	*	184.2, 240.7
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	0
Discontinued Treatment	0	0	24
Resolved/Recovered	2	0	167
Resolved with Continuing Effects	0	0	8
Not Resolved/Not Yet Recovered/Continuing	4	0	128
Missing Resolution	0	0	3
Severity§			
Mild	5	0	185
Moderate	1	0	110
Severe	0	0	6
Missing	0	0	5

* Reported MedDRA preferred terms include: Anorexia, decreased appetite, oral intake reduced.
** A subject is counted only once regardless of the number of events.
† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.
‡ CI are two-sided 95% exact Poisson
§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

On the basis of the review of aggregate safety data from clinical trials of CONCERTA, a causal relationship was established for Anorexia and Decreased appetite. A causal relationship was not established for any other adverse event that may be relevant for this important identified risk.

Nature of the Risk	Methylphenidate has pharmacologic properties that can cause appetite suppression. This is a drug-induced pharmacologic effect that resolves when the drug is discontinued. This is usually reported as "decreased appetite" or "anorexia" in clinical trials. While decreased appetite refers to a reduction in usual appetite, anorexia technically means absence of appetite, but is often used to convey a decrease in appetite. Anorexia (reduced appetite) needs to be distinguished from anorexia nervosa, a serious eating disorder that can have associated morbidities and even mortality. Drug-induced anorexia is not a chronic eating disorder, but a reversible side effect associated with stimulant medications.

(Continued)

Table 17.6: Important Identified Risk: Anorexia (Continued)

Background Incidence / Prevalence	In 2000 the age- and gender-adjusted incidence of anorexia nervosa diagnosed in primary care was 4.7 per 100,000 population. The incidence rate varied dramatically according to the age-gender group. The incidence rate for females was 8.6 per 100,000 compared with 0.7 per 100,000 for males. This translated to a relative risk for females to males of 12:1. The highest incidence, 34.6 per 100,000 population, was found in females aged 10 to 19 years (Currin 2005). However, no incidence rates could be identified for anorexic symptoms as opposed to anorexia nervosa.
Risk Groups or Risk Factors	Data available from CONCERTA clinical trials do not indicate any group is at particular risk for anorexic symptoms, whereas the disease, anorexia nervosa, primarily affects females.
Potential Mechanisms	Central acting stimulants, such as methylphenidate have previously been found to produce weight loss in early studies of patients with narcolepsy, and have subsequently been used in the treatment of obesity. The drug promotes weight loss by suppressing appetite, rather than by increasing energy expenditure. Therefore, based on its pharmacologic effect, CONCERTA may cause appetite suppression that is fully reversible when the medication is discontinued. This appetite suppression is distinct from the disease of anorexia nervosa.
Preventability	Education of prescribers, patients and caregivers. Early detection and management of symptoms (counselling, encouraging a healthy attitude to eating and weight). Also, the proposed EU SmPC advises that appetite should be monitored during methylphenidate treatment and that patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted (Section 4.4).
Potential Public Impact of Safety Concern	Since appetite suppression is an acute and limited effect, it may in fact be of no consequence in most individuals. If appetite suppression becomes a concern due to low body weight, discontinuing the methylphenidate will fully reverse the effect; therefore, this is expected to have minimal public impact or safety concern.
Regulatory Action Taken	The CONCERTA EU SmPC (Annex 2) contraindicates use in patients who are diagnosed with or have a history of anorexia nervosa/anorexic disorders. Monitoring of weight/appetite is recommended in Sections 4.2 (under ongoing monitoring) and 4.4 (under Long-term use and Growth) of the CONCERTA EU SmPC. Patients who are not growing or gaining height or weight as expected are advised to have their treatment interrupted. Anorexia is listed as an ADR in Section 4.8 of the EU SmPC with a frequency of common.
Evidence Source	Currin L (2005), Schmidt U, Treasure J, Jick H. Time trends in eating disorder incidence. Br J Psychiatry 2005;186:132-135.

Table 17.7: Important Identified Risk: Decreased Rate of Growth

	Population From Double-Blind Trials		Population From All Trials
Identified Risk: *Decreased Rate of Growth**	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	0	0	3 (0.1)
Rate per 1000 person-year†	--	--	2.1
95% confidence interval‡	--	--	0.4, 6.1
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	0
Discontinued Treatment	0	0	2
Resolved/Recovered	0	0	1
Resolved with Continuing Effects	0	0	0
Not Resolved/Not Yet Recovered/Continuing	0	0	2
Severity§			
Mild	0	0	1
Moderate	0	0	1
Severe	0	0	0
Missing	0	0	1

* Reported MedDRA preferred terms pertain only to weight gain, poor.
** A subject is counted only once regardless of the number of events.
† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.
‡ CI are two-sided 95% exact Poisson
§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

On the basis of the review of aggregate safety data from clinical trials of CONCERTA, a causal relationship was not established for any of the adverse events that may be relevant for this important identified risk.

Postmarketing

A summary of growth retardation events from the postmarketing database is presented below:

Cumulative Count of Selected Preferred Terms Reported at Least Once Between 11 August 2008 and 10 August 2009 by Seriousness: Growth Retardation

	Number of Events 01 August 2000 to 10 August 2009	
Preferred Term[a]	**Nonserious[b]**	**Serious[b]**
Growth retardation	7	34

[a] Preferred terms from the search terms that are not listed here were not received in the current reporting period.
[b] At event level

Source: BRM Report, PSUR 2009. This search of the worldwide postmarketing safety database was conducted using the following MedDRA preferred terms: Blood cortisol increased, Blood growth hormone decreased, Blood prolactin increased, Blood thyroid stimulating hormone abnormal, Body height abnormal, Delayed puberty, Growth retardation, Hyperthyroidism, Precocious puberty.

This review of spontaneous postmarketing reports of growth retardation found no evidence of a drug event link with CONCERTA.

(Continued)

Table 17.7: Important Identified Risk: Decreased Rate of Growth (Continued)

Nature of the Risk	Preclinical and clinical data do not identify decreased rate of growth as a risk with CONCERTA therapy. This topic has, and continues to be aggressively studied. At present, there are no definitive conclusions. Data has emerged to implicate ADHD itself as having a role (Spencer 1996, 1998). The most recent set of data coming from the 3 year follow up on the Multimodal Treatment Study of ADHD (MTA) study indicates that there is some risk for children taking methylphenidate; although it is not yet known if that represent a reversible issue at a particular age or if it affects final height (Swanson 2007).
Background Incidence / Prevalence	Population norms of height-for-age in US children have been established and monitored by the Centers for Disease Control (CDC) and its publication of growth charts that depict stature as a function of age (Ogden 2002). These charts have been widely used by paediatricians to assess individual growth. By definition, a child could be identified as being at a certain percentile for height, given their age. There is no agreed-upon threshold that represents a growth deficit among healthy children. However, the CDC data is used to compare specific groups to the population and to determine the value of growth deficits by converting group means to Z-scores (Ogden 2002). Stunting, or marked growth failure, is defined by the World Health Organization (WHO) as being greater than 2 standard deviations below the population mean of height-for-age. In a 2000 report from the WHO (WHO 2000), the prevalence of stunting among children was estimated to be 2.1% in the US, 5.6% in Japan, and 33% in developing countries.
Risk Groups or Risk Factors	Many factors affect rate of growth, with genetics playing a prominent role. Population norms of height-for-age in European and US children have been established. These charts have been widely used by paediatricians to assess individual growth (Cole 1994). There is no agreed-upon threshold that represents a growth deficit among healthy children. However, the data are used to compare specific groups to the population and to determine the value of growth deficits by converting group means to Z-scores. Stunting, or marked growth failure, is defined by the WHO as being greater than 2 standard deviations below the population mean of height-for-age (WHO 2000). In that report (WHO 2000), the prevalence of stunting among children was estimated to be 2.1% in the US, 5.6% in Japan, and 33% in developing countries. Note that, by definition, if height-for-age follows a normal distribution, 2.5% of children will be classified as "stunted," simply based on statistical principles, because that is the expected percentage of children beyond 2 standard deviations from the mean. Short stature is most commonly of genetic determination and correlates well with parental stature.
Potential Mechanisms	In August of 2007, the 3 year follow up from the MTA study, conducted via the National Institutes on Mental Health in the US, was published, and provides additional information on the effects of stimulant medication in the long-term treatment of paediatric ADHD patients (Jensen 2007).

(Continued)

Table 17.7: Important Identified Risk: Decreased Rate of Growth (Continued)

Potential Mechanisms (Continued)	The MTA study was a prospective study in children (7 to 9 years of age at enrolment) with ADHD. They were treated with methylphenidate or a non-medication regimen. Patients were randomised for the first 14 months of the study after which they were followed up under naturalistic circumstances (Jensen 2007, Swanson 2007). The 3-year data on growth were published in August 2007 and 4 naturalistic subgroups were analysed. Results were presented in z-scores for both height and bodyweight comparing the study population with growth norms. At the 36-month assessment, the average relative size (z-height and z-weight) of the naturalistic subgroups was negatively related to the average cumulative exposure to stimulant medication. The results from this study indicate that: Stimulant use is associated with a reduced growth of about 2 cm over a 24 months period with subsequent growth rate normalization during the third year. Stimulant use is associated with a reduction in bodyweight gain of about 2 kg during the first 14 months of treatment after which bodyweight gain follows a pattern similar to the non-medicated control group. There is no indication for a rebound effect within the 36 months study period. ADHD may be related to an accelerated growth and maturation. All bodyweight z-scores and all height z-scores except in the Cons Med subgroup were above the norms both at baseline and during the study. Results on stimulants and growth in the literature can be expected to vary according to pre-baseline exposure to stimulants. The effect (if any) on final adult height and weight remains to be determined. Preclinical data do not indicate an effect of CONCERTA on growth and sexual maturation. No hormonal effects were observed that would indicate such an effect in animals or in humans. Decreased appetite and weight decrease are known adverse reactions of CONCERTA. It is possible, therefore, that the effect on height is caused by the reduced caloric intake as a result of appetite suppression. The effect on weight seems limited, however, to the first few months after starting treatment.

(Continued)

Table 17.7: Important Identified Risk: Decreased Rate of Growth (Continued)

Potential Mechanisms (Continued)	It has been hypothesised that a persistent, stimulant-induced, increase in hypothalamic dopamine may affect pituitary function, thus slowing growth. Acute administration of methylphenidate increases growth hormone and decreases prolactin, but no consistent changes in plasma levels of these hormones have been documented during chronic treatment. A transient decrease in insulin-dependent growth factor was reported in a small number of children with ADHD after 4 months of treatment but not after 8 and 14 months (Vitiello 2008).
Preventability	Patients, caregivers and prescribers should be aware of the possible impact of long-term use of CONCERTA on linear growth.
Potential Public Impact of Safety Concern	Patients requiring long-term therapy should be carefully monitored. Patients who are not growing or gaining weight as expected should have their treatment interrupted temporarily. Temporary slowing of linear growth does not appear to have a major public health impact however it may be an individual concern.
Regulatory Action Taken	Annex IV of May 2009 EC decision (Conditions of the Marketing Authorisation) states the following study report should be evaluated when available: MTA Study (Effects of stimulant medication on growth in the MTA) follow-up, carried out by the MTA Cooperative Group. The MAHs will evaluate the final report of the study, when published, and will update the RMP, and where appropriate the SmPC/PIL, to reflect the findings. Section 4.4 of the CONCERTA EU SmPC (Annex 2) includes the following warning: "Moderately reduced weight gain and growth retardation have been reported with the long-term use of methylphenidate in children. The effects of methylphenidate on final height and final weight are currently unknown and being studied. Growth should be monitored during methylphenidate treatment: height, weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart. Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted." There is additional precautionary language in Section 4.4 concerning long-term use (more than 12 months): "Patients on long-term therapy...must have careful ongoing monitoring for... growth, appetite..." At pre-treatment screening (Section 4.2), prescribers are advised to accurately record pre-treatment height and weight on a growth chart. For ongoing monitoring (Section 4.2) there is a statement to emphasise that height, weight, and appetite should be monitored at least 6 monthly intervals with maintenance of a growth chart. "Growth retardation during prolonged use in children" is listed as an ADR in Section 4.8 of the CONCERTA EU SmPC with a frequency of common.

(Continued)

Table 17.7: Important Identified Risk: Decreased Rate of Growth (Continued)

Evidence Source	Benefit Risk Management Report (PSUR 2009). Periodic Safety Update Report. OROS® methylphenidate HCl (From 11Aug2008-10Aug2009). Document ID No. EDMS-USRA-EDMS-USRA-11227189. J&JPRD (25 September 2009). Cole TJ (1994). Do growth chart centiles need a face lift? BMJ 1994;308(6929): 641-642. Jensen PS (2007), Arnold LE, Swanson JM, et al. 3-Year follow-up of the NIMH MTA Study. J Am Acad Child Adolesc Psychiatry 2007;46(8);989-1002. Ogden CL (2002), Kuczmarski RJ, Flegal KM, et al. Centers for Disease Control and Prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. Pediatrics 2002;109(1):45-60. Spencer TJ (1996), Biederman J, Harding M, O'Donnell D, Faraone SV, Wilens TE. Growth deficits in ADHD children revisited: evidence for disorder-associated growth delays? J Am Acad Child Adolesc Psychiatry 1996;35(11):1460-1469. Spencer T (1998), Biederman J, Wilens T. Growth deficits in children with attention deficit hyperactivity disorder. Pediatrics 1998;102:501-506. Swanson JM (2007), Elliott GR, Greenhill LL, et al. Effects of stimulant medication on growth rates across 3 years in the MTA follow-up. J Am Acad Child Adolesc Psychiatry 2007;46(8):1015-1027. Vitiello B (2008). Understanding the risk of using medications for attention deficit hyperactivity disorder with respect to physical growth and cardiovascular function. Child Adolesc Psychiatric Clin N Am 2008;17:459-474. World Health Organization (WHO) (2000) Global Database on Child Growth and Malnutrition. Geneva: WHO 2000.

Table 18.1: Important Potential Risk: Migraine

	Population From Double-Blind Trials		**Population From All Trials**
Potential Risk: *Migraine**	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	0	0	11 (0.4)
Rate per 1000 person-year†	--	--	7.7
95% confidence interval‡	--	--	3.9, 13.8
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	0
Discontinued Treatment	0	0	0
Resolved/Recovered	0	0	9
Resolved with Continuing Effects	0	0	0
Not Resolved/Not Yet Recovered/Continuing	0	0	2
Severity§			
Mild	0	0	2
Moderate	0	0	7
Severe	0	0	2

* Reported MedDRA preferred terms include: migraine.
** A subject is counted only once regardless of the number of events.
† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.
‡ CI are two-sided 95% exact Poisson
§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

On the basis of the review of aggregate safety data from clinical trials of CONCERTA, a causal relationship was not established for any of the adverse events that may be relevant for this important potential risk.

(Continued)

Table 18.1: Important Potential Risk: Migraine (Continued)

Postmarketing

A summary of migraine events from the postmarketing database is presented below:

Cumulative Count of Selected Preferred Terms Reported at Least Once Between 11 August 2008 and 10 August 2009 by Seriousness: Migraine

Preferred Term	Number of Cases 01 August 2000 to 10 August 2009	
	Nonserious[a]	Serious[a]
Headache	268	29
Migraine	10	3
Migraine with aura	0	1

[a] At event level

Source: BRM Report, PSUR 2009. This search of the worldwide postmarketing safety database was conducted using the following MedDRA preferred terms: Headache, Migraine, and Migraine with aura.

This review of spontaneous postmarketing reports of migraine found no evidence of a drug-event link with CONCERTA.

Nature of the Risk

Migraine is the second most common cause of headache, afflicting approximately 15% of women and 6% of men. It is usually an episodic headache that is associated with certain features such as sensitivity to light, sound, or movement; nausea and vomiting often accompany the headache. A useful description of migraine is a benign and recurring syndrome of headache associated with other symptoms of neurologic dysfunction in varying combinations. Migraine is often recognised by its activators, which are referred to as triggers. Drug-induced migraine episodes may occur in patients with migraine as a primary headache disorder. The episodes are usually self-limiting and may not require permanent discontinuation of medication.

Background Incidence / Prevalence

According to data from the UK-based General Practice Research Database (GPRD), the age-specific incidence rates (per 1000 person-years) of medically diagnosed migraine in the general population was reported as follows (with incidence rates for men versus women in parentheses): 1 to 9 years, 1.29 (1.23 vs. 1.35); 10 to 19 years, 6.43 (5.04 vs. 7.89); 20 to 29 years, 4.52 (2.15 vs. 6.77); 30 to 39 years, 4.50 (2.09 vs. 6.83); 40 to 49 years, 4.61 (2.06 vs. 7.11); 50 to 59 years, 3.34 (1.64 vs. 5.01); 60 to 69 years, 2.06 (1.25 vs. 2.82); 70 to 79 years, 1.32 (0.81 vs. 1.70) (Becker 2008). ADHD was not identified as a co-occurring condition among migraine patients.

(Continued)

Table 18.1: Important Potential Risk: Migraine (Continued)

Risk Groups or Risk Factors	Risk factors for migraine include female gender post adolescence and increasing age with a peak observed in the fourth decade of life. The risk of migraine decreases after the fourth decade of life. Migraine has been linked to several disorders including stroke, hypertension, diabetes, asthma, and obesity (Jensen 2008)
Potential Mechanisms	The mechanism by which CONCERTA may cause migraine has not been determined. Conversely, stimulants such as dexamphetamine have also been shown efficacious in the prevention of headache in patients with migraine (Haas 2004). The mechanism of action for the putative therapeutic effect of stimulants in the prevention of migraine headaches is not known.
Preventability	Early introduction of abortive therapy and/or preventive therapy; it is important to note however that the frequency of headaches usually declines in many children after starting methylphenidate.
Potential Public Impact of Safety Concern	There is no clear epidemiological, clinical trial, or pharmacovigilance evidence that methylphenidate is a primary cause of migraine; however, it may indirectly increase the frequency of headaches in patients with existing migraine by suppressing appetite. Migraine headaches are unpleasant and painful; they temporarily reduce functioning but very rarely result in permanent sequelae. Any increased incidence of migraine episodes would therefore be predominantly an individual concern and is expected to have a minor impact on public health.
Regulatory Action Taken	Migraine is listed as an ADR in Section 4.8 of the CONCERTA EU SmPC (Annex 2) with a frequency of not known. (Migraine was not identified as an ADR based on review of the clinical trial or postmarketing database for CONCERTA; this term was included as an ADR based on the Article 31 referral of methylphenidate-containing products.)
Evidence Source	Becker C (2008), Brobert GP, Almqvist PM, et al. Migraine incidence, comorbidity and health resource utilization in the UK. Cephalalgia 2008;28:57. Benefit Risk Management Report (PSUR 2009). Periodic Safety Update Report. OROS® methylphenidate HCl (From 11Aug2008-10Aug2009). Document ID No. EDMS-USRA-EDMS-USRA-11227189. J&JPRD (25 September 2009). Haas DC (2004), Sheehe PR. Dextroamphetamine pilot crossover trials and n of 1 trial in patients with chronic tension-type and migraine headache. Headache 2004;44:1029-1037. Jensen R (2008). Stovner LJ. Epidemiology and comorbidity of headache. Lancet Neurol 2008;7:354-361.

Table 18.2: Important Potential Risk: Repetitive Behaviours

	Population From Double-Blind Trials		**Population From All Trials**
Potential Risk: *Repetitive Behaviours**	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	0	0	2 (0.1)
Rate per 1000 person-year†	--	--	1.4
95% confidence interval‡	--	--	0.2, 5.1
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	0
Discontinued Treatment	0	0	0
Resolved/Recovered	0	0	0
Resolved with Continuing Effects	0	0	1
Not Resolved/Not Yet Recovered/Continuing	0	0	1
Severity§			
Mild	0	0	2
Moderate	0	0	0
Severe	0	0	0

* Reported MedDRA preferred terms include: bruxism.

** Includes all subjects who had one or more occurrences of a relevant adverse event that coded to the MedDRA preferred term of bruxism; a subject is counted only once regardless of the number of events.

† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.

‡ CI are two-sided 95% exact Poisson

§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

On the basis of the review of aggregate safety data from clinical trials of CONCERTA, a causal relationship was not established for any of the adverse events that may be relevant for this important potential risk.

(Continued)

Table 18.2: Important Potential Risk: Repetitive Behaviours (Continued)

Postmarketing

A summary of repetitive behaviours and obsessive-compulsive disorders events from the postmarketing database is presented below:

Cumulative Count of Selected Preferred Terms Reported at Least Once Between 11 August 2008 and 10 August 2009 by Seriousness: Repetitive Behaviours and Obsessive-Compulsive Disorders

Preferred Term	Number of Events 01 August 2000 to 10 August 2009	
	Nonserious[a]	Serious[a]
Obsessive-compulsive disorder	4	4
Stereotypy	10	2
Compulsive lip biting	2	0
Compulsions	5	4

[a] At event level

Source: BRM Report, PSUR 2009. This search of the worldwide postmarketing safety database was conducted using the following MedDRA preferred terms: Obsessive-compulsive disorder, Stereotypy, Compulsive lip biting and Compulsions.

This cumulative review of spontaneous postmarketing reports of repetitive behaviours and obsessive-compulsive disorders found no evidence of a drug-event link with CONCERTA.

Nature of the Risk	Repetitive behaviour or "stereotypy" is characterised by the frequent almost mechanical repetition of the same posture, movement, or form of speech occurring in disorders such as autistic disorder and schizophrenia. Drug-induced stereotypy has also been observed in conjunction with the therapeutic or recreational use of stimulants (dopamine agonists). Drug-induced stereotypy is nearly always reversible when the drug is discontinued.
Background Incidence / Prevalence	The rates of repetitive behaviours among populations with ADHD have not been described in the published literature
Risk Groups or Risk Factors	To our knowledge, there have been no published literature reports indicating an increased risk of repetitive behaviours in children and adolescents with ADHD.
Potential Mechanisms	Historically, stimulant medications were reported to exacerbate stereotypy in autism. High doses of stimulants can also induce stereotypy in laboratory animals and healthy human subjects. Preclinical data suggests that both dexamphetamine- and methylphenidate-induced stereotypy depend on serotonin (5-HT) that is centrally available. Pre-treatment of laboratory animals with a 5-HT synthesis inhibitor differentially affects stereotypy induced by dexamphetamine and methylphenidate, suggesting that the role of 5-HT in the induction of stereotypy differs between stimulants (Roffman 1997).

(Continued)

Table 18.2: Important Potential Risk: Repetitive Behaviours (Continued)

Preventability	It can be assumed that repetitive behaviours also occur in children and adolescents with ADHD while they are not taking any stimulant medication. Clinical trial and postmarketing data suggest that the risk of repetitive behaviours associated with the use of methylphenidate in subjects with ADHD is very small. Patients should be monitored for the appearance, or worsening, of repetitive behaviours during initiation of treatment with methylphenidate.
Potential Public Impact of Safety Concern	Repetitive behaviours are rare and do not appear to have a major impact on public health; however, they may be an individual concern.
Regulatory Action Taken	Repetitive behaviours is listed as an ADR in Section 4.8 of the CONCERTA EU SmPC (Annex 2) with a frequency of very rare. (Repetitive behaviours was not identified as an ADR based on review of the clinical trial or postmarketing database for CONCERTA; this term was included as an ADR based on the Article 31 referral of methylphenidate-containing products.)
Evidence Source	Benefit Risk Management Report (PSUR 2009). Periodic Safety Update Report. OROS® methylphenidate HCl (From 11Aug2008-10Aug2009). Document ID No. EDMS-USRA-EDMS-USRA-11227189. J&JPRD (25 September 2009). Roffman JL (1997), Raskin LA. Stereotyped behavior: Effects of d-amphetamine and methylphenidate in the young rat. Pharmacol Biochem Behav 1997;58:1095–1102.

Table 18.3: Important Potential Risk: QT Prolongation

	Population From Double-Blind Trials		**Population From All Trials**
Potential Risk: *QT Prolongation**	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	0	0	0
Rate per 1000 person-year†	--	--	0.0
95% confidence interval‡	--	--	0.0, 2.6
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	0
Discontinued Treatment	0	0	0
Resolved/Recovered	0	0	0
Resolved with Continuing Effects	0	0	0
Not Resolved/Not Yet Recovered/Continuing	0	0	0
Severity§			
Mild	0	0	0
Moderate	0	0	0
Severe	0	0	0

* Reported MedDRA preferred terms include: none.

** A subject is counted only once regardless of the number of events.

† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.

‡ CI are two-sided 95% exact Poisson

§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

No adverse events for this important potential risk were reported in clinical trials of CONCERTA. As a result, the causal relationship of relevant adverse events for this potential risk could not be evaluated on the basis of aggregate safety data from clinical trials of CONCERTA.

(Continued)

Table 18.3: Important Potential Risk: QT Prolongation (Continued)

Postmarketing

A summary of QT prolonged events from the postmarketing database is presented.

Cumulative Count of Selected Preferred Terms Reported at Least Once Between 11 August 2008 and 10 August 2009 by Seriousness: Cardiac Disorders: QT Prolonged

	Number of Events 01 August 2000 to 10 August 2009	
Preferred Term[a]	**Nonserious**[b]	**Serious**[b]
Electrocardiogram QT prolonged	1	18

[a] Preferred terms from the search terms that are not listed here were not received in the current reporting period.

[b] At event level.

Source: BRM Report, PSUR 2009. This search of the worldwide postmarketing safety database was conducted using the MedDRA preferred term Electrocardiogram QT prolonged. Electrocardiogram QT prolonged was part of the search for Cardiac Disorders that included the following MedDRA preferred terms: Angina pectoris, Arrhythmia, Atrial fibrillation, Atrioventricular block first degree, Blood pressure diastolic, Increased, Blood pressure fluctuation, Blood pressure increased, Blood pressure systolic increased, Bradycardia, Cardiac arrest, Cardiac disorder, Cardiac failure, Cardiac fibrillation, Cardiomegaly, Cardiomyopathy, Circulatory collapse, Congestive cardiomyopathy, Coronary artery disease, Cyanosis, Electrocardiogram PQ interval, Prolonged, Electrocardiogram QT prolonged, Electromechanical dissociation, Extrasystoles, Heart rate decreased, Heart rate increased, Heart rate irregular, Heart valve incompetence, Hypertension, Hypotension, Left ventricular, Hypertrophy, Myocardial infarction, Myocardial ischaemia, Pericarditis, Sinoatrial block, Sinus arrest, Sinus arrhythmia, Sinus tachycardia, Supraventricular extrasystoles, Supraventricular tachycardia, Tachycardia, Ventricular arrhythmia, Ventricular extrasystoles, Ventricular fibrillation , Wolff-Parkinson-White syndrome.

This review of spontaneous postmarketing reports of QT prolongation found no evidence of a drug-event link with CONCERTA.

Nature of the Risk	Patients with a genetic predisposition related to what appear to be sporadic mutations and/or single nucleotide polymorphisms can develop marked QT prolongation in response to drugs that alter repolarisation currents. The QT prolongation and associated polymorphic ventricular tachycardia (Torsade de Pointes) are more frequently seen in women and may be a manifestation of subclinical Long QT Syndrome. Drug-induced long QT and Torsade de Pointes may be potentiated by the development of hypokaliemia and bradycardia. The offending drugs typically block the potassium I_{Kr} channel. Since most drug effects are dose-dependent, important drug-drug interactions that alter metabolism and/or alterations in elimination kinetics because of hepatic or renal dysfunction may contribute to the arrhythmias.
Background Incidence / Prevalence	The rates of QT prolongation among populations with ADHD have not been described in the published literature.
Risk Groups or Risk Factors	There are no available reports identifying risk groups or risk factors among children with ADHD.

(Continued)

Table 18.3: Important Potential Risk: QT Prolongation (Continued)

Potential Mechanisms	Clinical data suggests that methylphenidate used for the treatment of ADHD in children causes an increase in QT dispersion rather than an increase in QT interval. Methylphenidate can be expected to increase QT dispersion via its known sympathomimetic effect. After administration of methylphenidate, heart rate increases to various extents in a substantial number of subjects. When Bazett's formula is applied to the calculation of QTc, the QTc value is derived by dividing QT dispersion by the square root of the RR interval in seconds. Under this formula, QTc values increase as heart rate increases. Various clinical studies have suggested that increased QT dispersion may increase the risk for ventricular arrhythmia and sudden death (Ilgenli 2007).
Preventability	Patients who are considered for treatment with methylphenidate should have a careful history taken (including assessment for a family history of sudden death or ventricular arrhythmia).
Potential Public Impact of Safety Concern	Prolongation of the QTc interval is a rare but potentially serious complication of therapy with several widely prescribed drugs. Preclinical data from a series of GLP safety studies in Japan (hERG channel study, action potential duration [APD] of guinea-pig papillary muscle study, and conscious dog study) found no effect of methylphenidate on hERG or APD in studies in vitro, or QTcF in a study in vivo (Wakamatsu 2009) . Clinical data from a recent QT/QTc study demonstrated the lack of an effect of d-methylphenidate on the QT interval in adults. A double-blind, randomised, placebo-controlled, single-dose QT/QTc study (CRIT124E2401) demonstrated that d-methylphenidate does not lengthen QT or corrected QT intervals. (These unpublished studies were submitted to the CHMP as part of the 16 October 2008 Response to the Second List of Outstanding Issues, except for the first clinical study which was submitted to the CHMP in March 2008.) There is no clear experimental or epidemiological evidence that d- or d/l-methylphenidate in therapeutic dosages causes clinically important prolongation of the QTc interval.

(Continued)

Table 18.3: Important Potential Risk: QT Prolongation (Continued)

Regulatory Action Taken	During the Article 31 referral, and in response to a request in CHMP's 30 May 2008 List of Outstanding Issues to evaluate the risk of QT prolongation in children and adolescents using methylphenidate-containing products, a number of clinical studies on the effects of d- and d/l-methylphenidate on QT interval were evaluated (16 October 2008 Response to the Second List of Outstanding Issues). These studies reported no significant effect of methylphenidate, a decreased QT interval or a decreased or unchanged corrected QT interval. It was concluded by MAHs that there is a lack of clear experimental or epidemiological evidence that methylphenidate causes QT prolongation at therapeutic doses. It was also concluded from in vitro studies that methylphenidate does not have an effect on potassium channels that would suggest that there is a plausible mechanism for QT prolongation to occur. In addition, there is sufficient evidence to suggest that d-methylphenidate does not prolong QTcF interval in adult healthy volunteers, and, although the effects of d/l-methylphenidate on the QT interval of children are not known, the concern in this population is minimal. The MHRA as Rapporteur, in its 17 December 2008 Assessment Report for the Article 31 Referral, concluded that due to the lack of clinical trial data and concerns raised from a review of spontaneous data, the issue of QT interval prolongation in children would continue to be followed up in the context of the RMP. No other regulatory action taken.
Evidence Source	Benefit Risk Management Report (PSUR 2009). Periodic Safety Update Report. OROS® methylphenidate HCl (From 11Aug2008-10Aug2009). Document ID No. EDMS-USRA-EDMS-USRA-11227189. J&JPRD (25 September 2009). Ilgenli TF (2007), Congologlu A, Ozturk C, et al. Acute effect of methylphenidate on QT dispersion in children with attention deficit disorder. Adv Ther 2007;24:182-188. Wakamatsu A (2009), Nomura S, Tate Y, Shimizu S, Harada Y. Effects of methylphenidate hydrochloride on the cardiovascular system in vivo and in vitro: A safety pharmacology study. J Pharmacol Toxicol Methods 2009;59(3):128-134.

Table 18.4: Important Potential Risk: Cyanosis

	Population From Double-Blind Trials		Population From All Trials
Potential Risk: *Cyanosis**	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	0	0	0
Rate per 1000 person-year†	--	--	0.0
95% confidence interval‡	--	--	0.0, 2.6
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	0
Discontinued Treatment	0	0	0
Resolved/Recovered	0	0	0
Resolved with Continuing Effects	0	0	0
Not Resolved/Not Yet Recovered/Continuing	0	0	0
Severity§			
Mild	0	0	0
Moderate	0	0	0
Severe	0	0	0

* Reported MedDRA preferred terms include: none.
** A subject is counted only once regardless of the number of events.
† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.
‡ CI are two-sided 95% exact Poisson
§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

No adverse events for this important potential risk were reported in clinical trials of CONCERTA. As a result, the causal relationship of relevant adverse events for this potential risk could not be evaluated on the basis of aggregate safety data from clinical trials of CONCERTA.

(Continued)

Table 18.4: Important Potential Risk: Cyanosis (Continued)

Postmarketing

A summary of cyanosis events from the postmarketing database is presented below:

Cumulative Count of Selected Preferred Terms Reported at Least Once Between 11 August 2008 and 10 August 2009 by Seriousness: Cyanosis

	Number of Events[b] 01 August 2000 to 10 August 2009	
Preferred Term[a]	**Nonserious[c]**	**Serious[c]**
Cyanosis	5	11

[a] Preferred terms from the search terms that are not listed here were not received in the current reporting period.
[b] Cases may have had more than 1 event of interest.
[c] At event level.

Source: BRM Report, PSUR 2009. This search of the worldwide postmarketing safety database was conducted using the preferred term Cyanosis. Cyanosis was part of the Cardiac Disorders search that included the following MedDRA preferred terms: Angina pectoris, Arrhythmia, Atrial fibrillation, Atrioventricular block first degree, Blood pressure diastolic, Increased, Blood pressure fluctuation, Blood pressure increased, Blood pressure systolic increased, Bradycardia, Cardiac arrest, Cardiac disorder, Cardiac failure, Cardiac fibrillation, Cardiomegaly, Cardiomyopathy, Circulatory collapse, Congestive cardiomyopathy, Coronary artery disease, Cyanosis, Electrocardiogram PQ interval, Prolonged, Electrocardiogram QT prolonged, Electromechanical dissociation, Extrasystoles, Heart rate decreased, Heart rate increased, Heart rate irregular, Heart valve incompetence, Hypertension, Hypotension, Left ventricular, Hypertrophy, Myocardial infarction, Myocardial ischaemia, Pericarditis, Sinoatrial block, Sinus arrest, Sinus arrhythmia, Sinus tachycardia, Supraventricular extrasystoles, Supraventricular tachycardia, Tachycardia, Ventricular arrhythmia, Ventricular extrasystoles, Ventricular fibrillation , Wolff-Parkinson-White syndrome.

This review of spontaneous postmarketing reports of cyanosis found no evidence of a drug-event link with CONCERTA.

Nature of the Risk	Cyanosis refers to a bluish colour of the skin and mucous membranes resulting from an increased quantity of reduced haemoglobin, or of haemoglobin derivatives, in the small blood vessels of those areas. It is usually most marked in the lips, nail beds, ears, and malar eminences. Drug-induced cyanosis is most often the result of methaemoglobinaemia.
Background Incidence / Prevalence	There are no published reports on the incidence or prevalence of cyanosis among children with ADHD.
Risk Groups or Risk Factors	There are no published reports on risk groups or risk factors for cyanosis among children with ADHD.
Potential Mechanisms	Drug-induced cyanosis is most often the result of methaemoglobinaemia. Drugs producing methaemoglobinaemia may either directly oxidise haemoglobin or they may require metabolic activation to an oxidising species. The most clinically relevant direct methaemoglobin formers include local anaesthetics as well as amyl nitrite and isobutyl nitrite. Indirect, or metabolically activated, methaemoglobin formation by dapsone and primaquine may also cause cyanosis.
Preventability	Closely observe for clinical signs and symptoms of acral cyanosis, livedo reticularis, or Raynaud's phenomenon.

(Continued)

Table 18.4: Important Potential Risk: Cyanosis (Continued)

Potential Public Impact of Safety Concern	There is no clear epidemiological, clinical trial, or pharmacovigilance evidence that methylphenidate is a primary cause of peripheral cyanosis; however, it may indirectly increase the frequency and/or severity of episodes in patients with an existing tendency to experience cold-induced vasospasm of the extremities. Peripheral cyanosis may have an aesthetic impact and may sometimes be alarming. Any increased incidence of episodes would therefore be predominantly an individual concern and is expected to have a minor impact on public health.
Regulatory Action Taken	No regulatory action taken.
Evidence Source	Benefit Risk Management Report (PSUR 2009). Periodic Safety Update Report. OROS® methylphenidate HCl (From 11Aug2008-10Aug2009). Document ID No. EDMS-USRA-EDMS-USRA-11227189. J&JPRD (25 September 2009).

Table 18.5: Important Potential Risk: Arrhythmias

	Population From Double-Blind Trials		Population From All Trials
Potential Risk: *Arrhythmias**	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	0	0	1 (0.1)
Rate per 1000 person-year†	--	--	0.7
95% confidence interval‡	--	--	0.0, 3.9
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	0
Discontinued Treatment	0	0	0
Resolved/Recovered	0	0	0
Resolved with Continuing Effects	0	0	0
Not Resolved/Not Yet Recovered/Continuing	0	0	1
Severity§			
Mild	0	0	1
Moderate	0	0	0
Severe	0	0	0

* Reported MedDRA preferred terms include: sinus arrhythmia.
** A subject is counted only once regardless of the number of events.
† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.
‡ CI are two-sided 95% exact Poisson
§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

On the basis of the review of aggregate safety data from clinical trials of CONCERTA, a causal relationship was not established for any of the adverse events that may be relevant for this important potential risk.

(Continued)

Table 18.5: Important Potential Risk: Arrhythmias (Continued)

Postmarketing

A summary of arrhythmia events from the postmarketing database is presented below.

Cumulative Count of Selected Preferred Terms Reported at Least Once Between 11 August 2008 and 10 August 2009 by Seriousness: Arrhythmia

	Number of Events 01 August 2000 to 10 August 2009	
Preferred Term[a,b]	Nonserious[c]	Serious[c]
Arrhythmia	4	21
Cardiac fibrillation	0	1
Atrioventricular block first degree	2	1
Bradycardia	2	7
Extrasystoles	2	3
Heart rate irregular	6	2
Sinus arrhythmia	0	8
Supraventricular extrasystoles	1	2
Ventricular arrhythmia	0	2
Ventricular fibrillation	0	3
Wolff-Parkinson-White syndrome	0	2

[a] Preferred terms from the search terms that are not listed here were not received in the current reporting period.

[b] Preferred terms related to Tachycardia were not presented in this table.

[c] At event level.

Source: BRM Report, PSUR 2009; This search of the worldwide postmarketing safety database was conducted using preferred term related to arrhythmias that were part of the Cardiac Disorders search that included the following MedDRA preferred terms: Angina pectoris, Arrhythmia, Atrial fibrillation, Atrioventricular block first degree, Blood pressure diastolic, Increased, Blood pressure fluctuation, Blood pressure increased, Blood pressure systolic increased, Bradycardia, Cardiac arrest, Cardiac disorder, Cardiac failure, Cardiac fibrillation, Cardiomegaly, Cardiomyopathy, Circulatory collapse, Congestive cardiomyopathy, Coronary artery disease, Cyanosis, Electrocardiogram PQ interval, Prolonged, Electrocardiogram QT prolonged, Electromechanical dissociation, Extrasystoles, Heart rate decreased, Heart rate increased, Heart rate irregular, Heart valve incompetence, Hypertension, Hypotension, Left ventricular, Hypertrophy, Myocardial infarction, Myocardial ischaemia, Pericarditis, Sinoatrial block, Sinus arrest, Sinus arrhythmia, Sinus tachycardia, Supraventricular extrasystoles, Supraventricular tachycardia, Tachycardia, Ventricular arrhythmia, Ventricular extrasystoles, Ventricular fibrillation, Wolff-Parkinson-White syndrome.

This review of spontaneous postmarketing reports of arrhythmia found no drug-event link with CONCERTA.

(Continued)

Table 18.5: Important Potential Risk: Arrhythmias (Continued)

Nature of the Risk	Patients with cardiac arrhythmias exhibit a wide spectrum of clinical presentations from asymptomatic ECG abnormalities to survival from cardiac arrest. Cardiac arrhythmias result from abnormalities of impulse generation, conduction, or both. It is difficult to establish with certainty an underlying mechanism for many clinical arrhythmias. It is clear that molecular changes in the heart predispose to the development of abnormalities of cardiac rhythm. Patients may have a genetic predisposition for drug-induced cardiac arrhythmias (see also Table 18.3).
Background Incidence / Prevalence	The prevalence of cardiac rhythm disturbances in the general population of children has been estimated from large population-based samples from Japan (Niwa 2004). A sample of 152,322 school children, including 71,855 elementary students (ages 5 to 6 years) and 80,467 junior high students (ages 12 to 13 years), was screened for several types of arrhythmias. Any cardiac rhythm disturbance was found in 1.25% of elementary students and 2.32% of junior high students, with the prevalence higher in males than females (2.0% vs 1.38%). A study that included 26 US community emergency departments (ED) and 2.3 million ED visits found that primary cardiac arrhythmias in those under 18 years of age was a infrequent presentation to the ED (Sacchetti 1999). The incidence of clinically significant arrhythmias in these patients was reported as 5.7 per 100,000 emergency department visits. Atrial tachyarrhythmias were the most common presentation in this study population. There have been no published reports of an association between arrhythmias and ADHD among children and adolescents.
Risk Groups or Risk Factors	Risk factors for cardiac arrhythmias among children and adolescents with ADHD have not been described in the literature.
Potential Mechanisms	Ventricular arrhythmias have been more commonly associated with amphetamines than methylphenidate. Both stimulants are potent blockers of dopamine uptake and may exert their therapeutic effect via this mechanism. The electrophysiological effects of amphetamines may be the result of the release of norepinephrine stores from presynaptic vesicles and blockade of norepinephrine reuptake, which are specific for this stimulant (Vetter 2008).

(Continued)

Table 18.5: Important Potential Risk: Arrhythmias (Continued)

Preventability	CONCERTA is contraindicated in patients with cardiac arrhythmia. Contraindications also apply to the use of methylphenidate in patients with underlying medical conditions that may be compromised by changes in heart rate and rhythm, such as severe hypertension, heart failure, or recent myocardial infarction.
Potential Public Impact of Safety Concern	Small dose-related increases in resting heart rate are a predictable and relatively frequent result of treatment with methylphenidate and these increases appear to have little clinical significance. Clinically significant arrhythmia may occur as a very rare side effect of treatment in otherwise healthy patients who are prescribed therapeutic doses of methylphenidate.
Regulatory Action Taken	Annex IV of the May 2009 EC decision (Conditions of the Marketing Authorisation) states the report of a study that is currently being conducted by the FDA/AHRQ/Vanderbilt University should be evaluated, when available, as it is intended to evaluate the following: 1) Assess the relationship between use of medications for ADHD and the risk of serious cardiovascular disease in children and youth, aged 2 to 24 years 2) Assess the relationship between use of medications for ADHD and the risk of serious cardiovascular disease in adults, aged 25 to 64 years 3) Perform additional analyses that are relevant to decision makers such as clinicians, state Medicaid programs, and parents/patients The MAHs will evaluate the final report of the study, when published, and will update the Core RMP, and where appropriate the Core SmPC/PIL, to reflect the findings. CONCERTA is currently contraindicated in patients with potentially life threatening arrhythmias in the EU SmPC (Annex 2). Wording in Section 4.4, under Cardiovascular status, contains precautionary text regarding malignant arrhythmias and palpitations: "Patients who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden cardiac or unexplained death or malignant arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further specialist cardiac evaluation if initial findings suggest such history or disease. Patients who develop symptoms such as palpitations...should undergo a prompt specialist cardiac evaluation." Arrhythmia is listed as an ADR in Section 4.8 of the EU SmPC with a frequency of common. (Arrhythmia was not identified as an ADR based on review of the clinical trial or postmarketing database for CONCERTA; this term was included as an ADR based on the Article 31 referral of methylphenidate-containing products.)

(Continued)

Table 18.5: Important Potential Risk: Arrhythmias (Continued)

Evidence Source	Benefit Risk Management Report (PSUR 2009). Periodic Safety Update Report. OROS® methylphenidate HCl (From 11Aug2008-10Aug2009). Document ID No. EDMS-USRA-EDMS-USRA-11227189. J&JPRD (25 September 2009). Niwa K (2004), Warita N, Sunami Y, Shimura A, Tateno S, Sugita K. Prevalence of arrhythmias and conduction disturbances in large population-based samples of children. Cardiol Young 2004;14(1):68-74. Sacchetti A (1999), Moyer V, Baricella R, Cameron J, Moakes ME. Primary cardiacarrhythmias in children. Pediatr Emerg Care 1999;15(2):95-98. Vetter VL (2008), Elia J, Erickson C, et al. Cardiovascular monitoring of children and adolescents with heart disease receiving stimulant drugs. Circulation 2008;117:2407-2423.

Table 18.6: Important Potential Risk: Sudden Death

	Population From Double-Blind Trials		Population From All Trials
Potential Risk: *Sudden Death**	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	0	0	0
Rate per 1000 person-year†	*	*	0.0
95% confidence interval‡	*	*	0.0, 2.6
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	0
Discontinued Treatment	0	0	0
Resolved/Recovered	0	0	0
Resolved with Continuing Effects	0	0	0
Not Resolved/Not Yet Recovered/Continuing	0	0	0
Severity§			
Mild	0	0	0
Moderate	0	0	0
Severe	0	0	0

* Reported MedDRA preferred terms include: none.
** A subject is counted only once regardless of the number of events.
† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.
‡ CI are two-sided 95% exact Poisson
§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

No adverse events for this important potential risk were reported in clinical trials of CONCERTA. As a result, the causal relationship of relevant adverse events for this potential risk could not be evaluated on the basis of aggregate safety data from clinical trials of CONCERTA.

Postmarketing Database	The postmarketing database was searched for paediatric cases involving sudden death as the Preferred MedDRA terminology. From 01 August 2000 (IBD) through 30 September 2007 there were 3 spontaneous cases that involved death worldwide (BRM Report on Fatal Outcomes, Jan 2008; search term for sudden death was fatal outcome). Review of spontaneous postmarketing reports found no evidence of a link between sudden death and the use of CONCERTA. A recent assessment of events of sudden death reported worldwide is consistent with the previous evaluation. No new cases of sudden death were reported in PSURs 2008 and 2009 (BRM Report, PSUR 2009).

(Continued)

Table 18.6: Important Potential Risk: Sudden Death (Continued)

Nature of the Risk

Sudden cardiac death is defined as an unexpected natural death from cardiac causes within a short time (≤1 hour) from the onset of symptoms and in a person with no previous history of serious cardiac disease (Atwood 2005). This definition is difficult to apply in clinical and epidemiological studies; therefore, out-of-hospital cardiac death is a widely used surrogate for sudden cardiac death. This approach has been validated in population data from the US and found to be reasonably good (Goraya 2000). Sudden death in the paediatric population is usually due to trauma, sudden infant death syndrome, respiratory aetiology, or submersion (Young 2004). It is estimated that as many as 14,000 paediatric sudden deaths (from all of the above causes) occur in the U.S. each year (Myerburg 1993).

Background Incidence / Prevalence

Sparse data on the incidence of sudden death in children exists.

Event	Rate (per person years)	Population	Ref
Cardiac arrest	2.6 – 19.7 per 100,000	< 18 years	Donoghue 2005
Stroke	Approx 1.0 per 100,000	5 – 19 years	Fullerton 2003
Cardiac arrhythmias	5.7 per 100,000 ETD visits	<18 years	Sacchetti 1999
Sudden cardiac death	1.3 – 8.5 per 100,000	1 – 19 years	Liberthson 1996
Risk factor			
Hypertension	1% - 2%	10 – 15 years	Flynn 2001b
Congenital heart disease	0.3% - 0.4%	<18 years	Moller 1998 Rosenthal 1998
Obesity	16.0%	6 – 19 years	Hedley 2004
Lack of physical activity	26.2% 45%	14 year olds 18 year olds	Donoghue 2005

The data contained in the table provides examples of incidence / prevalence data in paediatric populations for various events and risk factors.

Risk Groups or Risk Factors

The incidence rates for sudden cardiac death and sudden unexpected death (SUD) increase with age and they were found to be higher in males than females in all age groups and populations. Known risk factors for CV disease include cigarette smoking, hypertension, physical inactivity, obesity, dyslipidaemia, hyperinsulinaemia, homocysteinaemia and poor nutrition. ADHD has not been identified as a risk factor in sudden death. However, it is believed that children with structural cardiac abnormalities may be at a greater risk of sudden death when treated with methylphenidate.

Potential Mechanisms

The precise mechanism of sudden death in children with ADHD being treated with stimulants is poorly understood. There is speculation that children with structural cardiac abnormalities may be at higher risk of developing a malignant arrhythmia or asystole when being treated with methylphenidate (Vetter 2008, Vitiello 2008).

(Continued)

Table 18.6: Important Potential Risk: Sudden Death (Continued)

Preventability	Early detection and management of cardiovascular risk factors by health care professionals.
Potential Public Impact of Safety Concern	Sudden death has been reported in association with the use of stimulants of the central nervous system at usual doses in children with structural cardiac abnormalities. Although some structural cardiac abnormalities alone may carry an increased risk of sudden death, stimulant products are not recommended in children or adolescents with known structural cardiac abnormalities. Although the rates are low when viewed in the context of general population data and causality cannot be established, the serious nature of the events means that the public should be warned due to impacts on families (economic, emotional and social effects). Due to the seriousness of this issue language is included in the SmPC to advise that sudden death has been reported in association with the use of stimulants of the central nervous system at usual doses in children with structural cardiac abnormalities.
Regulatory Action Taken	Annex IV of the May 2009 EC decision (Conditions of the Marketing Authorisation) states the report of a study that is currently being conducted by the FDA/AHRQ/Vanderbilt University should be evaluated, when available, as it is intended to evaluate the following: 1) Assess the relationship between use of medications for ADHD and the risk of serious cardiovascular disease in children and youth, aged 2 to24 years 2) Assess the relationship between use of medications for ADHD and the risk of serious cardiovascular disease in adults, aged 25 to 64 years 3) Perform additional analyses that are relevant to decision makers such as clinicians, state Medicaid programs, and parents/patients The MAHs will evaluate the final report of the study, when published, and will update the Core RMP, and where appropriate the Core SmPC/PIL, to reflect the findings. The EU SmPC for CONCERTA (Annex 2) of the CHMP opinion contraindicates use in patients with pre-existing cardiovascular disorders such as angina and potentially life-threatening cardiac arrhythmias. Additionally precautionary language is included in Section 4.4, Special warnings and precautions, under “Sudden death and pre-existing cardiac abnormalities or other serious cardiac disorders”, sub-heading regarding sudden death and patients with pre-existing structural cardiac abnormalities or other serious cardiac disorders including cardiomyopathy and serious heart rhythm abnormalities. There is also additional wording in Section 4.4 in the “Cardiovascular status” sub-heading: “Patients who are being considered for treatment with stimulant medication should have a careful history (including assessment for a family history of sudden cardiac or unexplained death...”

(Continued)

Table 18.6: Important Potential Risk: Sudden Death (Continued)

Regulatory Action Taken (Continued)	Precautionary language regarding the risk of sudden death with misuse of methylphenidate (Sec 4.4, SmPC) and concomitant use with clonidine (Sec 4.5, SmPC) "Sudden cardiac death" is listed as an ADR in Section 4.8 of the EU SmPC (Annex 2) with a frequency of very rare. (Sudden cardiac death was not identified as an ADR based on review of the clinical trial or postmarketing database for CONCERTA; this term was included as an ADR based on the Article 31 referral of methylphenidate-containing products.)
Evidence Source	Atwood C (2005), Eisenberg MS, Herlitz J, Rea TD. Incidence of EMS-treated out-of-hospital cardiac arrest in Europe. Resuscitation 2005;67(1):75-80. Benefit Risk Management Report (PSUR 2009). Periodic Safety Update Report. OROS® methylphenidate HCl (From 11Aug2008-10Aug2009). Document ID No. EDMS-USRA-EDMS-USRA-11227189. J&JPRD (25 September 2009). Benefit Risk Management Report (2008). Cumulative Review of postmarketing reports of fatal outcomes in patients treated with CONCERTA® (OROS® methylphenidate hydrochloride). Document ID: EDMS-USRA-10665441; J&JPRD (Jan 08). Donoghue AJ (2005), Nadkarni V, Berg RA, et al. CanAm Pediatric Cardiac Arrest Investigators. Out-of-hospital pediatric cardiac arrest: an epidemiologic review and assessment of current knowledge. Ann Emerg Med 2005;46(6):512-522. Flynn JT (2001b). What's new in pediatric hypertension? Curr Hypertens Rep 2001b;3:503-510. Fullerton HJ (2003), Wu YW, Zhao S, Johnston SC. Risk of stroke in children: Ethnic and gender disparities. Neurology 2003;61(2):189-194. Goraya TY (2000), Jacobsen SJ, Belau PG, et al. Validation of death certificate diagnosis of out-of-hospital coronary heart disease deaths in Olmsted County, Minnesota. Mayo Clinic Proc 2000;75:681-687. Hedley AA (2004), Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999-2002. JAMA 2004;291(23):2847 2850. Liberthson R (1996). Sudden death from cardiac causes in children and young adults. NEJM 1996:334(16);1039 1044.

(Continued)

Table 18.6: Important Potential Risk: Sudden Death (Continued)

Moller JH (1998), ed. Surgery of Congenital Heart Disease Pediatric Cardiac Care Consortium 1984-1995. Prevalence and incidence of cardiac malformations. Armonk, NY: Futura Publishing Company, 1998:20. Vol.6.

Myerburg RJ (1993), Kessler KM, Castellanos A. Sudden cardiac death: epidemiology, transient risk, and intervention assessment. Ann Intern Med 1993;119(12):1187-1197.

Rosenthal GR (1998). Prevalence of congenital heart disease. In: Chapter 48 of the Science & Practice of Pediatric Cardiology. 2nd ed. Baltimore, MD: Williams and Wilkins; 1998:1083-1105.

Sacchetti A (1999), Moyer V, Baricella R, Cameron J, Moakes ME. Primary cardiacarrhythmias in children. Pediatr Emerg Care 1999;15(2):95-98.

Vetter VL (2008), Elia J, Erickson C, et al. Cardiovascular monitoring of children and adolescents with heart disease receiving stimulant drugs. Circulation 2008;117:2407-2423.

Vitiello B (2008). Understanding the risk of using medications for attention deficit hyperactivity disorder with respect to physical growth and cardiovascular function. Child Adolesc Psychiatric Clin N Am 2008;17:459-474.

Young KD (2004), Gausche-Hill M, McClung CD, Lewis RJ. A prospective, population-based study of the epidemiology and outcome of out-of-hospital pediatric cardiopulmonary arrest. Pediatrics 2004;114(1):157 164.

Table 18.7: Important Potential Risk: Cerebrovascular Disorders

	Population From Double-Blind Trials		Population From All Trials
Potential Risk: *Cerebrovascular Disorders**	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	0	0	0
Rate per 1000 person-year†	--	--	0.0
95% confidence interval‡	--	--	0.0, 2.6
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	0
Discontinued Treatment	0	0	0
Resolved/Recovered	0	0	0
Resolved with Continuing Effects	0	0	0
Not Resolved/Not Yet Recovered/Continuing	0	0	0
Severity§			
Mild	0	0	0
Moderate	0	0	0
Severe	0	0	0

* Reported MedDRA preferred terms include: none.
** A subject is counted only once regardless of the number of events.
† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.
‡ CI are two-sided 95% exact Poisson
§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

No adverse events for this important potential risk were reported in clinical trials of CONCERTA. As a result, the causal relationship of relevant adverse events for this potential risk could not be evaluated on the basis of aggregate safety data from clinical trials of CONCERTA.

Postmarketing Database

A summary of cerebrovascular disorders events from the postmarketing database is presented below.

Cumulative Count of Selected Preferred Terms Reported at Least Once Between 11 August 2008 and 10 August 2009 by Seriousness: Cerebrovascular Disorders

	Number of Events 01 August 2000 to 10 August 2009	
Preferred Term	**Nonserious[a]**	**Serious[a]**
Basal ganglia infarction	0	2
Trans cerebral ischaemia	0	1
Haemorrhage intracranial	0	3
Transient ischaemic attack	0	5

[a] At event level.
Source: BRM Report, PSUR 2009. The following MedDRA preferred terms were included in the search: Basal ganglia infarction, Trans cerebral ischaemia, Haemorrhage intracranial, and Transient ischaemic attack.

The review of spontaneous postmarketing reports of cerebrovascular disorders found no drug-event link with CONCERTA.

(Continued)

Table 18.7: Important Potential Risk: Cerebrovascular Disorders (Continued)

Nature of the Risk	There have only been a few cases of cerebrovascular events recorded in children with ADHD being treated with methylphenidate. Several of these cases are poorly documented. To date, the nature of a cerebrovascular disorder that may occur when being treated with methylphenidate appears to be similar to such events that can occur in healthy children. These events range from transient symptoms of central neuronal deficits such as aphasia or haemiparesis, to large vascular accidents that may lead to death. Unique characteristics of the events that have been reported in children taking methylphenidate have not been identified.
Background Incidence / Prevalence	In relation to readily available national information, data from the Canadian Paediatric Ischemic Stroke Registry reveals the incidence of ischemic stroke was 1.08 per 100,000 children (Williams 2000). This data source also cited French data on stroke incidence rates, from the city of Dijon where childhood rates were higher than most published data at 13 per 100,000 children. Data reviewed from the US National Institute of Neurological Disorders and Stroke (Lynch 2002) revealed the incidence rate of childhood stroke (defined as occurring between 30 days and 18 years of age) was between 2 and 3 per 100,000 children in the US, with a 2:1 male to female predominance. The US mortality rate attributable to stroke in children age 1 to 15 is 0.6 per 100,000 children (Lynch 2002).
Risk Groups or Risk Factors	General data on stroke rates (from 1990) from various parts of the world (Murray 1996) revealed the incidence of a first ever stroke for men ranged from 8.1 per 100,000 males to 28.4 per 100,000 males in the 15 to 44 year-old age group. The range was from 119.6 to 226.8 per 100,000 males for the 45 to 59 year-old age group. The range was even higher above age 60 years. For women, the incidence of a first ever stroke ranged from 13.8 per 100,000 females to 29.5 per 100,000 females in the 15 to 44 year-old age group. The range was from 101.9 to 272.4 per 100,000 females for the 45 to 59 year-old age groups, and it also increased above age 60 years. Known risk factors for cerebrovascular disorders include smoking, hypertension, obesity, dyslipidaemia, diabetes mellitus, and vascular disorders. ADHD is not a known risk factor.
Potential Mechanisms	Potential mechanisms for stimulant-induced stroke include hypertension, vasculitis and thrombocytopenia. There is little evidence to support any of these mechanisms in the cases that have been identified to date.
Preventability	Early detection and management of risk factors by health care professionals Blood pressure should be monitored at appropriate intervals in patients taking CONCERTA, especially patients with hypertension. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate.

(Continued)

Table 18.7: Important Potential Risk: Cerebrovascular Disorders (Continued)

Preventability(Continued)	CONCERTA should not be prescribed for children or adolescents with severe hypertension or pre-existing cerebrovascular disorders, cerebral aneurysm, and vascular abnormalities (including vasculitis or stroke) according to the EU SmPC. In addition, the EU SmPC provides precautionary text regarding cerebral vasculitis, a very rare idiosyncratic reaction to methylphenidate exposure (Sec 4.4).
Potential Public Impact of Safety Concern	The risk of stroke increases with age but it may occur in children as well. Stroke in the young may potentially create a long-term burden for the victims, their families, and the community. The rare occurrence of these events is not expected to have an impact on public health in general.
Regulatory Action Taken	Annex IV of the May 2009 EC decision (Conditions of the Marketing Authorisation) states the report of a study that is currently being conducted by the FDA/AHRQ/Vanderbilt University should be evaluated, when available, as it is intended to evaluate the following: 1) Assess the relationship between use of medications for ADHD and the risk of serious cardiovascular disease in children and youth, aged 2 to24 years 2) Assess the relationship between use of medications for ADHD and the risk of serious cardiovascular disease in adults, aged 25 to 64 years 3) Perform additional analyses that are relevant to decision makers such as clinicians, state Medicaid programs, and parents/patients The MAHs will evaluate the final report of the study, when published, and will update the Core RMP, and where appropriate the Core SmPC/PIL, to reflect the findings. The EU SmPC for CONCERTA (Annex 2 of the CHMP opinion) contraindicates use in patients with pre-existing cerebrovascular disorders, cerebral aneurysm, and vascular abnormalities including vasculitis or stroke. Precautionary language for cerebrovascular disorders identifies that patients with additional risk factors (such as a history of cardiovascular disease, concomitant medications that elevate blood pressure) should be assessed at every visit for neurological signs and symptoms after initiating treatment with methylphenidate (Section 4.4). There is also additional precautionary text regarding cerebral vasculitis, a very rare idiosyncratic reaction to methylphenidate exposure (Section 4.4). "Cerebrovascular disorders (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion)" is listed as an ADR in Section 4.8 of the EU SmPC (Annex 2) with a frequency of not known. (Cerebrovascular disorders was not identified as an ADR based on review of the clinical trial or postmarketing database for CONCERTA; this term was included as an ADR based on the Article 31 referral of methylphenidate-containing products.)

(Continued)

Table 18.7: Important Potential Risk: Cerebrovascular Disorders (Continued)

Evidence Source	Benefit Risk Management Report (PSUR 2009). Periodic Safety Update Report. OROS® methylphenidate HCl (From 11Aug2008-10Aug2009). Document ID No. EDMS-USRA-EDMS-USRA-11227189. J&JPRD (25 September 2009). Lynch JK (2000), Hirtz D, DeVeber G, et al. Report of the National Institute of Neurological Disorders and Stroke Workshop on Perinatal and Childhood Stroke. Pediatrics 2002;109(1):116-123. Murray CJL (1996), Lopez AD. Global health statistics: a compendium of incidence, prevalence, and mortality estimates for over 200 conditions, World Health Organization, Harvard University Press, 1996. Williams AN (2000). Childhood stroke-beyond re-inventing the wheel. Europ J Paediatr Neurol 2000;4:103-107.

Table 18.8: Important Potential Risk: Aggression

	Population From Double-Blind Trials		Population From All Trials
Potential Risk: *Aggression**	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	0	0	59 (2.1)
Rate per 1000 person-year†	*	*	41.4
95% confidence interval‡	*	*	31.5, 53.4
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	6
Discontinued Treatment	0	0	19
Resolved/Recovered	0	0	47
Resolved with Continuing Effects	0	0	1
Not Resolved/Not Yet Recovered/Continuing	0	0	11
Severity§			
Mild	0	0	13
Moderate	0	0	34
Severe	0	0	10
Missing	0	0	2

* Reported MedDRA preferred terms include: aggression, anger, and belligerence.
** A subject is counted only once regardless of the number of events.
† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.
‡ CI are two-sided 95% exact Poisson
§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

On the basis of the review of aggregate safety data from clinical trials of CONCERTA, a causal relationship was established for Anger. A causal relationship was not established for any other adverse event that may be relevant for this important potential risk.

Postmarketing

A summary of anger and aggression events from the postmarketing database is presented below.

Cumulative Count of Selected Preferred Terms Reported at Least Once Between 11 August 2008 and 10 August 2009 by Seriousness: Anger and Aggression

	Number of Events 01 August 2000 to 10 August 2009	
Preferred Term[a]	**Nonserious[b]**	**Serious[b]**
Anger	47	5
Aggression	120	77

[a] Preferred terms from the search terms that are not listed here were not received in the current reporting period.
[b] At event level

Source: BRM Report, PSUR 2009. This search of the worldwide postmarketing safety database was conducted using the following MedDRA preferred terms: Abnormal behaviour, Disturbance in social behaviour, Paranoia, Affect lability, Hypomania, Hostility, Personality disorder, Aggression, Impulsive behaviour, Psychomotor hyperactivity, Agitation, Injury, Psychotic behaviour, Anger, Intentional self-injury, Psychotic disorder, Conduct disorder, Irritability, Screaming, Delusional disorder, persecutory type, Mania, skin laceration.

The review of spontaneous postmarketing reports found a relationship between aggression and the use of CONCERTA.

(Continued)

Table 18.8: Important Potential Risk: Aggression (Continued)

Nature of the Risk	Aggression is a common co-morbid symptom in children with ADHD. Nevertheless, underlying aggression can be exacerbated by methylphenidate treatment. Aggressive behaviour has also been reported in children with ADHD with stimulant treatment, when previous aggressive behaviour did not exist.
Background Incidence / Prevalence	The incidence of psychiatric events in the relevant general population (children and adolescents ages 5 to 17) is the first measure of the underlying background rate for a specific population of interest (users of CONCERTA). Several incidence rates have been established for the occurrence of anger/aggression in the general (non-ADHD) population, depending on the age of the child. In high-school age children, the Center for Disease Control and Prevention (CDC 2004) estimates the prevalence to be approximately 33% (with 4.2% requiring medical attention), whereas it is estimated higher at 61% for middle-school age children (Clubb 2001) and approximately 51% for children 8 to 11 years of age (Boulton 1993).
Risk Groups or Risk Factors	The medical literature was reviewed for reports of an incidence/prevalence rate in ADHD children for suicidal behaviour, major depression, anger or aggression, and psychosis/hallucinations, or for reports of an elevated relative risk associated with ADHD and the psychiatric events of interest. Children and adolescents with ADHD were found to have a high prevalence of co-morbid psychiatric disorders (oppositional-defiant disorder, major depression, anxiety, mania, psychosis). An estimated 20 to 40% of children with ADHD will also develop conduct disorder, which can be characterised by aggressive behaviour towards people, animals, or property (National Institute of Mental Health [NIMH] 2004). Rates of certain co-morbid psychiatric conditions associated with aggressive behaviour are higher in ADHD patients. For example, one study found the odds ratios for the comorbid conditions of oppositional defiant disorder and conduct disorder to be 17.7 and 5.5 respectively (Guervara 2002).
Potential Mechanisms	ADHD is a collection of symptoms, ie, inattention, impulsivity and hyperactivity that can occur in conjunction with other mental health conditions. Aggression is a common symptom in paediatric psychiatric disorders. As such, aggressive behaviour probably reflects a common developmental trajectory frequently expressed in children and adolescents who are diagnosed with any psychiatric disorder, rather than being a specific symptom of ADHD (Tauscher-Wisniewksi 2006). The mechanism by which CONCERTA may have a role in the occurrence or worsening of aggression has not been determined.

(Continued)

Table 18.8: Important Potential Risk: Aggression (Continued)

Preventability	Education of caregivers, prescribers, early detection and management of risk factors and symptoms. Careful monitoring of patients for adverse events, especially early on in treatment, is prudent. Patients beginning treatment with CONCERTA should be monitored for the appearance or worsening of aggressive behaviour, which has been reported during treatment with CONCERTA. If the aggression is thought to be a symptom from the use of methylphenidate versus being attributed to the individuals' underlying pathology, discontinue the methylphenidate and the symptoms should dissipate.
Potential Public Impact of Safety Concern	As indicated in the table above, aggression has been reported in the clinical database. Since drug-induced aggression is reversible upon discontinuation of methylphenidate, should it occur, it is not anticipated to have a significant public health impact.
Regulatory Action Taken	The CONCERTA EU SmPC (Annex 2) includes the following precautionary language in Section 4.4 Special warnings and precautions for use: "The emergence or worsening of aggression or hostility can be caused by treatment with stimulants. Patients treated with methylphenidate should be closely monitored for the emergence or worsening of aggressive behaviour or hostility at treatment initiation, at every dose adjustment and then at least every 6 months and every visit. Physicians should evaluate the need for adjustment of the treatment regimen in patients experiencing behaviour changes." There is additional precautionary language in Section 4.4 regarding ongoing monitoring for aggressive or hostile behaviour when patients are on long-term therapy (more than 12-months). Aggression is listed as an ADR in Section 4.8 of the EU SmPC with a frequency of common.

(Continued)

Table 18.8: Important Potential Risk: Aggression (Continued)

Evidence Source	Benefit Risk Management Report (PSUR 2009). Periodic Safety Update Report. OROS® methylphenidate HCl (From 11Aug2008-10Aug2009). Document ID No. EDMS-USRA-EDMS-USRA-11227189. J&JPRD (25 September 2009). Boulton MJ (1993). Proximate causes of aggressive fighting in middle school children. Br J Educ Psychol 1993;63(2):231-244. Centers for Disease Control and Prevention (CDC) (2004). Miniño AM, Arias E, Kochanek KD, Murphy SL, Smith BL. Deaths: final data for 2000. National Vital Statistics Reports, 50(15). Hyattsville, MD: National Center for Health Statistics, 2002. Surveillance Summaries, 21 May 2004. MMWR 2004:53 (No.SS-2). Clubb PA (2001), Browne DC, Humphrey AD, Schoenbach V, Meyer B, Jackson M; RSVPP Steering Committee. Violent behaviours in early adolescent minority youth: results from a "middle school youth risk behaviour survey". Matern Child Health J 2001;5(4):225-235. Guevara J (2002), Lozano P, Wickizer T, Mell L, Gephart H. Psychotropic medication use in a population of children who have attention-deficit/hyperactivity disorder. Pediatrics 2002;109(5): 733-739. National Institute of Mental Health (NIMH) (2004). Bethesda (MD): US Department of Health and Human Services; 2004 Attention Deficit Hyperactivity Disorder. http://www.nimh.nih.gov/ publicat/NIMHadhdpub.pdf. Tauscher-Wisniewski S (2006). Aggression in attention-deficit/ hyperactivity disorder children: diagnostic or comorbid symptom? Expert Rev Neurotherapeutics 2006;6:197-199.

Table 18.9: Important Potential Risk: Hostility

	Population From Double-Blind Trials		Population From All Trials
Potential Risk: *Hostility**	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	0	0	1 (0.1)
Rate per 1000 person-year†	--	--	0.7
95% confidence interval‡	--	--	0.0, 3.9
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	0
Discontinued Treatment	0	0	1
Resolved/Recovered	0	0	1
Resolved with Continuing Effects	0	0	0
Not Resolved/Not Yet Recovered/Continuing	0	0	0
Severity§			
Mild	0	0	1
Moderate	0	0	0
Severe	0	0	0

* Reported MedDRA preferred terms include: hostility.
** A subject is counted only once regardless of the number of events.
† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.
‡ CI are two-sided 95% exact Poisson
§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

On the basis of the review of aggregate safety data from clinical trials of CONCERTA, a causal relationship was not established for any of the adverse events that may be relevant for this important potential risk.

Postmarketing	The postmarketing database was searched for cases involving Hostility as the Preferred MedDRA terminology. From 01 August 2000 (IBD) through 10 August 2008, there were a total of 9 spontaneous cases that reported hostility worldwide. This review found no evidence of a drug-event association with CONCERTA (BRM Report, PSUR 2008). Hostility has been identified as an event of potential significance with CONCERTA (BRM Report, PSUR 2008). A recent assessment of events of Hostility reported worldwide is consistent with the previous evaluation; no cases of Hostility were identified in this search from 11 Aug 2008 to 10 Aug 2009 (BRM Report, PSUR 2009). This search of the postmarketing safety database was conducted using the following MedDRA preferred terms: Abnormal behaviour, Disturbance in social behaviour, Paranoia, Affect lability, Hypomania, Hostility, Personality disorder, Aggression, Impulsive behaviour, Psychomotor hyperactivity, Agitation, Injury, Psychotic behaviour, Anger, Intentional self-injury, Psychotic disorder, Conduct disorder, Irritability, Screaming, Delusional disorder, persecutory type, Mania, skin laceration.

(Continued)

Table 18.9: Important Potential Risk: Hostility (Continued)

Nature of the Risk	Hostility is a common comorbid symptom in children with ADHD.
Background Incidence / Prevalence	Rates of hostility independent of aggression have not been described in the literature to date.
Risk Groups or Risk Factors	Risk groups and risk factors of hostility independent of aggression have not been described in the literature to date.
Potential Mechanisms	Multiple factors influence the expression of hostile behaviour, including genetics, neurotransmitters, hormones, and psychosocial factors. While hostile behaviour is primarily associated with abnormalities in serotoninergic neurotransmission, catecholamines are also involved. Perceived threats cause plasma norepinephrine and epinephrine levels to rise. Stimulant medications exert their therapeutic effect in ADHD by increasing synaptic norepinephrine. As such, stimulants may also facilitate the expression of hostile behaviour. The precise mechanism by which CONCERTA may have a role in the occurrence of hostility has not been determined.
Preventability	Education of caregivers, prescribers, early detection and management of risk factors and symptoms. Careful monitoring of patients for adverse events, especially early on in treatment, is prudent. Patients beginning treatment with CONCERTA should be monitored for the appearance or worsening of hostility. If the hostility is thought to be a symptom from the use of methylphenidate versus being attributed to the individuals' underlying pathology, discontinue the methylphenidate and the symptoms should dissipate.
Potential Public Impact of Safety Concern	Since drug-induced hostility is reversible upon discontinuation of methylphenidate, should it occur, it is not anticipated to have a significant public health impact.
Regulatory Action Taken	The CONCERTA EU SmPC (Annex 2) includes the following precautionary language in Section 4.4 Special warnings and precautions for use: "The emergence or worsening of aggression or hostility can be caused by treatment with stimulants. Patients treated with methylphenidate should be closely monitored for the emergence or worsening of aggressive behaviour or hostility at treatment initiation, at every dose adjustment and then at least every 6 months and every visit. Physicians should evaluate the need for adjustment of the treatment regimen in patients experiencing behaviour changes." There is additional precautionary language in Section 4.4 regarding ongoing monitoring for aggressive or hostile behaviour when patients are on long-term therapy (more than 12-months).

Table 18.9: Important Potential Risk: Hostility (Continued)

Evidence Source	Benefit Risk Management Report (2008). Periodic Safety Update Report. OROS® methylphenidate HCl (From 11Aug2007-10Aug2008). Document ID No. EDMS-USRA-10859695:2.0. J&JPRD (25 September 2008). Benefit Risk Management Report (PSUR 2009). Periodic Safety Update Report. OROS® methylphenidate HCl (From 11Aug2008-10Aug2009). Document ID No. EDMS-USRA-EDMS-USRA-11227189. J&JPRD (25 September 2009).

Table 18.10: Important Potential Risk: Depression

	Population From Double-Blind Trials		Population From All Trials
Potential Risk: *Depression**	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	1 (0.3)	0	52 (1.8)
Rate per 1000 person-year†	--	--	36.5
95% confidence interval‡	--	--	27.2, 47.8
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	3
Discontinued Treatment	1	0	18
Resolved/Recovered	1	1	26
Resolved with Continuing Effects	0	0	4
Not Resolved/Not Yet Recovered/Continuing	0	0	22
Severity§			
Mild	0	1	23
Moderate	1	0	25
Severe	0	0	4

* Reported MedDRA preferred terms include: depressed mood, depression, depressive symptom, and dysphoria.

** A subject is counted only once regardless of the number of events.

† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.

‡ CI are two-sided 95% exact Poisson

§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

On the basis of the review of aggregate safety data from clinical trials of CONCERTA, a causal relationship was established for Depression. A causal relationship was not established for any other adverse event that may be relevant for this important potential risk.

Nature of Risk	Children with ADHD are known to have an increased prevalence of affective disorders, including major depression, compared to children without ADHD. The depressive symptoms observed in children with ADHD being treated with methylphenidate are similar in nature and severity to the depressive symptoms observed in children without ADHD. Reported symptoms range from a transient low mood with a duration of a few hours to a few days, to classic depressive symptoms, which sometimes progress to suicidal thoughts or suicidal behaviour. Children with ADHD who were treated with methylphenidate or placebo in clinical trials reported a range of adverse events that may be more appropriately categorised as situational reactions to life events, rather than a cluster of symptoms that would meet Diagnostic and Statistical Manual of Mental Disorders (DSM) IV diagnostic criteria for major depression.

(Continued)

Table 18.10: Important Potential Risk: Depression (Continued)

Background Incidence / Prevalence	In one series of studies, the lifetime prevalence of severe depression among children with ADHD (280 subjects) was 15% in females and 29% in males compared with 1% to 2% of males and females without ADHD (Fishman 2007). An increased risk for major depression in children and adolescents with ADHD has been consistently reported in the medical literature (Biederman 1998). Epidemiologic studies have reported that comorbid depression may be found in roughly 20 to 30% of ADHD cases (Anderson 1987). The MTA was a National Institute of Mental Health (NIMH) US-sponsored clinical study of 579 children (ages 7-10 years) with ADHD. At baseline assessment, 3.8% of the ADHD subjects were found to have major depression, as measured by parent and teacher responses. This represents an elevated prevalence in comparison to the general population estimate of 2.5% for that age group (Jensen 2001). In a 4-year follow-up of 76 children with a diagnosis of ADHD and depression, the two conditions were found to have independent disease courses (Milberger 1995). This suggested that depression in ADHD children was actual depression and not demoralization associated with their ADHD. Additionally, clinical research has concluded that the comorbidity of ADHD with affective disorders, such as depression, is not due to their overlapping symptoms (Milberger 1995).
Risk Groups or Risk Factors	When assessing the background risk (independent of drug), depression in ADHD children is complex and not well understood. Both a family (ie, genetics) as well as a disease component may be possible.
Potential Mechanisms	CONCERTA is known to increase dopamine and norepinephrine in the interneuronal space. Both of these neurotransmitters have important roles in the aetiology of certain psychiatric disorders including mood disorders.
Preventability	Early detection, appropriate diagnosis and management including timely pharmacotherapy and psycho-therapy to prevent relapses; education of prescribers, patients and caregivers. Careful monitoring of patients for adverse events, especially early on in treatment, is prudent. CONCERTA should not be prescribed for children or adolescents who have a diagnosis or history of severe depression and severe and episodic (Type I) Bipolar (affective) Disorder (that is not well controlled) according to the EU SmPC.
Potential Public Impact of Safety Concern	Depression itself does impact public health. However, the frequency of depressive symptoms that occur in methylphenidate clinical trials in children with ADHD is not above what is expected in an ADHD population. Based on the available evidence, no impact on public health of methylphenidate-induced depression is expected.

(Continued)

Table 18.10: Important Potential Risk: Depression (Continued)

Regulatory Action Taken	The EU SmPC (Annex 2) for CONCERTA contraindicates use in patients with diagnosis or history of severe depression and severe and episodic (Type I) Bipolar (affective) Disorder (that is not well controlled) according to the EU SmPC. Prescribers are advised to adequately screen for comorbid depressive symptoms and family history of suicide prior to initiating treatment in patients with comorbid bipolar disorder (Section 4.4, Forms of bipolar disorder sub-heading). When monitoring for emergent or pre-existing psychiatric disorder, prescribers are advised to monitor for depression in Section 4.4 (Long-term use sub-heading). Further warning under the Withdrawal sub-heading calls for careful supervision during withdrawal from abusive use as severe depression may occur (Section 4.4). Depression is listed as an ADR in Section 4.8 of the EU SmPC with a frequency of common.
Evidence Source	Anderson JC (1987), Williams S, McGee R, Silva PA. DSM-III disorders in preadolescent children. Prevalence in large sample from the general population. Arch Gen Psych 1987;44(1) 69-76. Biederman J (1998), Mick E, Faraone SV. Depression in attention deficit hyperactivity disorder (ADHD) children: “True” depression or demoralization? J Affective Disorder 1998;47:113-122. Fishman PA (2007), Stang PE, Hogue SL. Impact of comorbid attention deficit disorder on the direct medical costs of treating adults with depression in managed care. J Clin Psychiatry 2007;68(2):248-253. Jensen PS (2001), Hinshaw SP, Kraemer HC, et. al. ADHD comorbidity findings from the MTA study: comparing comorbid subgroups. J Am Acad Child Adolesc Psychiatry 2001;40(2):147-158. Milberger S (1995), Biederman J, Faraone SV, Murphy J, Tsuang MT. Attention deficit hyperactivity disorder and comorbid disorders: Issues of overlapping symptoms. Am J of Psychiatry 1995; 152(12):1793-1799.

Table 18.11: Important Potential Risk: Suicidality

	Population From Double-Blind Trials		Population From All Trials
Potential Risk: *Suicidality**	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	0	0	7 (0.2)
Rate per 1000 person-year†	--	--	4.9
95% confidence interval‡	--	--	2.0, 10.1
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	5
Discontinued Treatment	0	0	2
Resolved/Recovered	0	0	3
Resolved with Continuing Effects	0	0	3
Not Resolved/Not Yet Recovered/Continuing	0	0	1
Severity§			
Mild	0	0	1
Moderate	0	0	2
Severe	0	0	4

* Reported MedDRA preferred terms include: depression suicidal, intentional self-injury, and suicidal ideation.

** A subject is counted only once regardless of the number of events.

† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.

‡ CI are two-sided 95% exact Poisson

§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

On the basis of the review of aggregate safety data from clinical trials of CONCERTA, a causal relationship was not established for any of the adverse events that may be relevant for this important potential risk.

Postmarketing

A summary of suicidality reports from the postmarketing database is presented below.

Cumulative Count of Selected Preferred Terms Reported at Least Once Between 11 August 2008 and 10 August 2009 by Seriousness: Suicidality

	Number of Events 01 August 2000 to 10 August 2009	
Preferred Term	**Nonserious[a]**	**Serious[a]**
Completed suicide	0	14
Intentional self-injury	1	6
Suicide attempt	0	52
Suicidal ideation	1	56
Self-injurious ideation	0	1

[a] At event level

Source: BRM Report, PSUR 2009. This search of the worldwide postmarketing safety database was conducted using the following Standard MedDRA Query (SMQ): Depression and Suicide/Self-Injury

This review of spontaneous postmarketing reports of suicidality found no evidence of a drug-event link with CONCERTA.

(Continued)

Table 18.11: Important Potential Risk: Suicidality (Continued)

Nature of the Risk	Suicide is a complex act that represents the end result of a combination of factors in an individual. These factors include biological vulnerabilities, life history, present social circumstances, and the availability of means for committing suicide. While these factors do not "cause" suicide, some people are at greater risk of self-harm than others. Children with ADHD have a higher risk than other children of developing psychiatric problems such as depressive disorders, antisocial behaviour, substance misuse, and dependence. These comorbid conditions, as well as impulsivity and aggression, are recognised predisposing factors for suicide.
Background Incidence / Prevalence	In the United States, the annual rate of completed suicide for those ages 10 to 19 years was 4.6 per 100,000 persons (CDC 2004). Within this age group, the occurrence of suicide is related to age. For males, the suicide rate in the prepubertal age group (ages 6-12 years) is approximately 0.45 per 100,000, while the rate for male adolescents (ages 13-19 years) is 9.85 per 100,000. From the CDC Youth Risk Behavior Surveillance System in the US, it was found that 8.8% of 9th to 12th graders reported making a suicide attempt in the past year (CDC 2004), and that 16.9% reported experiencing suicidal ideation in the past year (CDC 2004). However, the predictive relationship between suicidal ideation and attempts to completed suicide may be weak and is controversial (Klein 2006).
Risk Groups or Risk Factors	The available literature contains reports that young people with an ADHD diagnosis are at increased risk for suicidal behaviour, as compared to their population age group. A review of the literature by James et al (James 2004) determined that the rate of completed suicide in males (aged 5 to 24 years) with ADHD was between 32 and 39 per 100,000 patients per year, which is roughly 3 times greater than in the general population. A separate study using a US managed care database (Swensen 2002) determined that patients with an ADHD diagnosis (adults and children) were nearly 3 times more likely to make a suicide attempt (OR=2.9 95% CI: 2.4, 3.5) than age and gender-matched controls.
Potential Mechanisms	Patients with ADHD appear to be at higher risk for suicide-related behaviour than the general population. The link between psychotropic medication use and suicide-related behaviour is poorly understood. Certain antidepressants increase the risk for suicidal ideation in paediatric patients when compared to placebo treatment. Stimulant medications exert their therapeutic effect in ADHD by increasing dopamine and norepinephrine in the interneuronal space. Both of these neurotransmitters may have a role in the aetiology of psychiatric symptoms such as suicidal ideation.

(Continued)

Table 18.11: Important Potential Risk: Suicidality (Continued)

Preventability	Early detection by parents and prescribers by noticing signs of suicidal ideation. Prior to initiating treatment with a stimulant, patients with ADHD and comorbid depressive symptoms should be adequately screened to determine if they are at risk of suicidal behaviour. Methylphenidate is not to be prescribed for patients with a diagnosis or history of suicidal tendencies.
Potential Public Impact of Safety Concern	Suicide rate seems to be higher in patients with ADHD. This increased risk impacts families, hospitals (economic, emotional and social effects) due to hospitalizations and / or fatalities. Although a serious impact on the patient, the number of cases so far suggests a more limited public health impact for the population using the drug.
Regulatory Action Taken	Annex IV of May 2009 EC decision (Conditions of the Marketing Authorisation) states the following: "The MAHs will investigate the feasibility of carrying out a meta-analysis of the risk of suicidality associated with the use of methylphenidate in children and adolescents with ADHD on the basis of the clinical trial data of methylphenidate that is currently available to the MAHs. If the analysis on the basis of the currently available data is deemed feasible, the MAHs will make the resources available to support the analysis and update the RMP to reflect its findings." The EU SmPC (Annex 2) for CONCERTA contraindicates use in patients with diagnosis or history of suicidal tendencies. Additionally, the CONCERTA EU SmPC introduces precautionary text in Section 4.4 (Suicidal tendency subheading): "Patients with emergent suicidal ideation or behaviour during treatment for ADHD should be evaluated immediately by their physician. Consideration should be given to the exacerbation of an underlying psychiatric condition and to a possible causal role of methylphenidate treatment. Treatment of an underlying psychiatric condition may be necessary and consideration should be given to a possible discontinuation of methylphenidate." Additionally, prescribers are advised to adequately screen for comorbid depressive symptoms and family history of suicide prior to initiating treatment in patients with comorbid bipolar disorder (Section 4.4, Forms of bipolar disorder sub-heading). Suicidal ideation is listed as an ADR in Section 4.8 of the EU SmPC with a frequency of uncommon. Additionally, the ADR "Suicidal attempt (including completed suicide)" is listed as very rare. (Suicidal ideation and suicidal attempt were not identified as ADRs based on review of the clinical trial or postmarketing database for CONCERTA; these terms were included as ADRs based on the Article 31 referral of methylphenidate-containing products.)

(Continued)

Table 18.11: Important Potential Risk: Suicidality (Continued)

Evidence Source	Benefit Risk Management Report (PSUR 2009). Periodic Safety Update Report. OROS® methylphenidate HCl (From 11Aug2008-10Aug2009). Document ID No. EDMS-USRA-EDMS-USRA-11227189. J&JPRD (25 September 2009). Centers for Disease Control and Prevention (CDC) (2004). Miniño AM, Arias E, Kochanek KD, Murphy SL, Smith BL. Deaths: final data for 2000. National Vital Statistics Reports, 50(15). Hyattsville, MD: National Center for Health Statistics, 2002. Surveillance Summaries, 21 May 2004. MMWR 2004:53 (No.SS-2). James A (2004), Lai FH, Dahl C. Attention deficit hyperactivity disorder and suicide: a review of possible associations. Acta Psychiatr Scand 2004;110:408-415. Klein D (2006). The flawed basis for FDA post-marketing safety decisions: The example of anti-depressants and children. Neuropsychopharmacol 2006;31:689-699. Swensen AR (2002), Allen AJ, Kreusi M, et al. Increased risk of self-injury and suicide risk for patients with attention deficit/hyperactivity disorder. Eur Neuropsychopharmacol 2002;12:S421.

Table 18.12: Important Potential Risk: Tics, Tourette's Syndrome, Dystonias

	Population From Double-Blind Trials		Population From All Trials
Potential Risk: *Tics, Tourette's Syndrome, Dystonias ****	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	0	4 (1.3)	78 (2.7)
Rate per 1000 person-year†	*	*	54.7
95% confidence interval‡	*	*	43.2, 68.3
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	0
Discontinued Treatment	0	1	22
Resolved/Recovered	0	3	35
Resolved with Continuing Effects	0	0	2
Not Resolved/Not Yet Recovered/Continuing	0	1	40
Worsened			1
Severity§			
Mild	0	3	45
Moderate	0	1	28
Severe	0	0	5

* Reported MedDRA preferred terms include: tic.

** A subject is counted only once regardless of the number of events.

† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.

‡ CI are two-sided 95% exact Poisson

§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

On the basis of the review of aggregate safety data from clinical trials of CONCERTA, a causal relationship was established for Tic.

Postmarketing

A summary of Tourette's syndrome, tic, and dystonia is presented below.

Cumulative Count of Selected Preferred Terms Reported at Least Once Between 11 August 2008 and 10 August 2009 by Seriousness: Tourette's syndrome, Tic and Dystonia

	Number of Events 01 August 2000 to 10 August 2009	
Preferred Term	**Nonserious[a]**	**Serious[a]**
Tic	4	11
Tourette's disorder	135	56
Dystonia	3	7

[a] At event level

Source: BRM Report, PSUR 2009. This search of the worldwide postmarketing safety database was conducted using the following MedDRA preferred terms: Tourette's disorder, Tic, Dystonia

This review of spontaneous postmarketing reports of Tourette's syndrome and dystonia found no evidence of a drug-event link with CONCERTA. (Tic was identified as an ADR based on data from clinical trials.)

(Continued)

Table 18.12: Important Potential Risk: Tics, Tourette's Syndrome, Dystonias (Continued)

Nature of the Risk	Tics are a fairly common co-morbidity in the paediatric ADHD population. Tics occur as new onset movements as well as exacerbations of previously existing tics in methylphenidate-treated patients. Tics usually have cosmetic implications and do not commonly have a functional component. Depending on the setting, tics can be somewhat disruptive. Both vocal and motor tics have been reported in children with ADHD. No symptom unambiguously allows for a distinction to be made between psychogenic and organic dystonias (Van Harten 1999) Consequently, dystonia may have an inaccurate diagnosis in the subset of patients in whom psychiatric disorders manifesting movement disorders, or in patients with anxiety or somatoform disorders (APA 1994).
Background Incidence / Prevalence	Incidence: Not relevant for tics. A study was conducted to find the epidemiological distribution of Tourette's syndrome in Swedish school children aged 7 to 15 years (Khalifa 2003). A total population of 4,479 children and their parents were asked to fill in a questionnaire covering vocal tics. Tourette's syndrome, according to DSM-IV criteria, was found in 0.6% of the total population. Prevalence of different tic disorders was higher among younger children and in males, and was highly associated with school dysfunction. The prevalence of Tourette's syndrome was higher than was previously thought but other tic disorders were more common in this childhood population. Another study (Hornsey 2001) on the prevalence of Tourette's syndrome found the condition to be extremely rare, although recent survey indicates motor components of Tourette's syndrome (without speech disorder) may have prevalence of 2-5% in the general population of adolescents. Prevalence of different tic disorders was higher among younger children and in males, and was highly associated with school dysfunction. There have been few epidemiological studies of dystonia. Most previous studies have provided estimates based on few cases. A European prevalence study was undertaken to provide more precise rates of dystonia by pooling data from 8 European countries. Diagnosed cases of dystonia were ascertained by adult neurologists with specialist movement disorders (and botulinum toxin) clinics. The crude annual period prevalence rate (1996-1997) for primary dystonia was 152 per million (95% confidence interval 142-162), with focal dystonia having the highest rate of 117 per million (ESDE 2000).

(Continued)

Table 18.12: Important Potential Risk: Tics, Tourette's Syndrome, Dystonias (Continued)

Risk Groups or Risk Factors	ADHD and tics disorders, including Tourette's Syndrome are common disorders of childhood, with ADHD affecting 4 to 10% of school age children in the US and Tourette's syndrome affecting 1 to 3% (AAP 2000). The occurrence of tics in special education classes in the US has been reported as high as 25% (Comings 1990, Kurlan 1994, Mason 1998). Stimulants, the recognised first-choice of pharmacotherapy for ADHD, carry a warning in the US label that they should not be used in children with a prior history of tics or a family history of Tourette's syndrome. New studies have been conducted and existing data analysed to better understand the appropriateness of the use of methylphenidate in 2 co-existing, co-morbid disorders. Palumbo and colleagues (2004) analysed data from 5 trials (2 placebo-controlled, active controlled and 3 open label), which lasted from 1 to 4 weeks to 2 years. Pooled data demonstrated that the incidence of tics was not significantly different across treatment groups (OROS methylphenidate (CONCERTA) 4%; methylphenidate 2.4%; placebo 3.7%; p value = 0.5249). The observational data that is responsible for this labelled warning may be explained in part by the complexity of these co-morbid conditions. The onset of ADHD often precedes the onset of tics and Tourette's syndrome by 2.4 to 3 years. Thus children were often receiving ADHD therapy when the motor issues were first recognised. Gadow and colleagues (2007) conducted a placebo-controlled trial to determine the safety and efficacy of immediate-release methylphenidate in children with ADHD and Tourette's syndrome as rated by the investigators, teachers, and parents. Methylphenidate was found to be both safe and effective for the treatment of ADHD and without significant exacerbation of Tourette's syndrome. In fact, overall teachers rated patients receiving methylphenidate as having improvement in symptoms. The researchers conclude that overall, methylphenidate is effective in the treatment of ADHD, and in this study, did not exacerbate existing Tourette's syndrome or cause the onset of new tics or Tourette's syndrome. In addition, they acknowledge that this topic requires more research, but also that the existing contraindication in the US label for methylphenidate products in children with a family history of Tourette's syndrome was based on observational data and should be revisited.
Potential Mechanisms	Movement disorders such as tics are believed to have a dopaminergic component. CONCERTA is known to increase dopamine in the interneuronal space. The specific pathways that are responsible for stimulant-induced tics have not been elucidated. The data from open label trials indicates that the incidence of tics in the treated population does not exceed the background incidence. Although the issues are difficult to separate, the development of tics is believed to primarily be from the disease state, and not the treatment.

(Continued)

Table 18.12: Important Potential Risk: Tics, Tourette's Syndrome, Dystonias (Continued)

Preventability	Tourette's syndrome - timely and accurate diagnosis, education, and behaviour or pharmacologic interventions (neuroleptics and dopamine receptor antagonists). Tics and dystonias - timely and accurate diagnosis, pharmacotherapy (dopamine receptor blocking agents). Family history should be assessed.
Potential Public Impact of Safety Concern	A comprehensive evaluation for tics should be performed prior to starting any therapy. The long-term outcome is generally favourable. Nevertheless, movement disorders may result in a moderate to severe level of functional impairment in school-age children. The data from open label trials indicates that the incidence of tics in the treated population does not exceed the background incidence; however, it is higher in the ADHD diagnosed population. This is not expected to rise to the level of a public safety concern.
Regulatory Action Taken	The EU SmPC (Annex 2) for CONCERTA contains the following precautionary language in Section 4.4 Special warnings and precautions for use: "Methylphenidate is associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported. Family history should be assessed and clinical evaluation for tics or Tourette's syndrome in children should precede use of methylphenidate. Patients should be regularly monitored for the emergence or worsening of tics during treatment with methylphenidate. Monitoring should be at every adjustment of dose and then at least every 6 months or every visit." There is additional precautionary language in Section 4.4 concerning long-term use (more than 12 months): "Patients on long-term therapy (ie, over 12 months) must have careful ongoing monitoring for... development of de novo or worsening of pre-existing psychiatric disorders...and include (but are not limited to) motor or vocal tics..." Dystonia: No regulatory action taken. "Tics" and "Worsening of pre-existing tics of Tourette's syndrome" are both listed as ADR in Section 4.8 of the EU SmPC with a frequency of uncommon. (Tourette's syndrome was not identified as an ADR based on review of the clinical trial or postmarketing database for CONCERTA; this term was included as an ADR based on the Article 31 referral of methylphenidate-containing products.)

(Continued)

Table 18.12: Important Potential Risk: Tics, Tourette's Syndrome, Dystonias (Continued)

Evidence Source	American Academy of Pediatrics (AAP) (2000). Clinical Practice Guideline: Diagnosis and Evaluation of the Child With Attention-Deficit/Hyperactivity Disorder Pediatrics 2000;105:1158-1170. American Psychiatric Association (APA) (1994). Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition. Washington, DC: American Psychiatric Association; 1994. Benefit Risk Management Report (PSUR 2009). Periodic Safety Update Report. OROS® methylphenidate HCl (From 11Aug2008-10Aug2009). Document ID No. EDMS-USRA-EDMS-USRA-11227189. J&JPRD (25 September 2009). Comings DE (1990), Himes JA, Comings BG. An epidemiologic study of Tourette's Syndrome in a single school district. J Clin Psychiatry 1990;5111:463-469. Epidemiological Study of Dystonia in Europe (ESDE) Collaborative Group (2000). A prevalence study of primary dystonia in eight European countries. J Neurol 2000;247(10):787-792. Gadow KD (2007), Sverd J, Nolan EE, Sprafkin J, Schneider J. Immediate-release methylphenidate for ADHD in children with comorbid chronic multiple tic disorder. J Am Acad Child Adolesc Psychiatry 2007;46(7):840-848. Hornsey H (2001), Banerjee S, Zeitlin H, Robertson M. Prevalence of Tourette's syndrome in 13-14 year olds in mainstream schools. J Child Psychol Psychiatry 2001;42(8):1035-1039. Khalifa N (2003), Von Knorring AL. Prevalence of tic disorders and Tourette's syndrome in a Swedish school population. Dev Med Child Neurol 2003;45(5):315-319. Kurlan R (1994), Whitmore D, Irvine C, McDermott MP, COMO PG. Tourette's syndrome in a special education population: A pilot study involving a single school district. Neurology 1994;44(4)699-702. Mason A (1998), Barnerjee S, Eapen V, Zeitlin H, Robertson MM. The prevalence of Tourette's syndrome in a mainstream school population. Dev Med Child Neurol 1998;4:292-296. Palumbo D (2004), Spencer T, Lynch J, Co-Chien H, Faraone SV. Emergence of tics in children with ADHD: impact of once-daily OROS methylphenidate therapy. J Child Adolesc Psychopharmacol 2004;14(2):185-194. Van Harten PN (1999), Hoek HW, Kahn RS. Acute dystonia induced by drug treatment. BMJ 1999;319(7210):623-626.

Table 18.13: Important Potential Risk: Effect on Final Height

	Population From Double-Blind Trials		**Population From All Trials**
Potential Risk: *Effect on Final Height**	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	0	0	0
Rate per 1000 person-year†	*	*	0.0
95% confidence interval‡	*	*	0.0, 2.6
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	0
Discontinued Treatment	0	0	0
Resolved/Recovered	0	0	0
Resolved with Continuing Effects	0	0	0
Not Resolved/Not Yet Recovered/Continuing	0	0	0
Severity§			
Mild	0	0	0
Moderate	0	0	0
Severe	0	0	0

* Reported MedDRA preferred terms include: none.
** A subject is counted only once regardless of the number of events.
† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.
‡ CI are two-sided 95% exact Poisson
§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

No adverse events for this important potential risk were reported in clinical trials of CONCERTA. As a result, the causal relationship of relevant adverse events for this potential risk could not be evaluated on the basis of aggregate safety data from clinical trials of CONCERTA.

Postmarketing Database	None (The postmarketing database does not allow to reach conclusions of long-term exposure safety specifically, as can be done in long-term controlled clinical studies.)
Nature of the Risk	Temporary slowing in the rate of growth does not indicate there will be a final and permanent effect on height. Data from the 3 year follow up in the MTA study indicates that patients on methylphenidate achieved a height above the norm (Swanson 2007). Preclinical and clinical data did not identify decreased rate of growth as a risk with CONCERTA therapy. This topic has, and continues to be aggressively studied. At present, there are no definitive conclusions. Data has emerged to implicate ADHD itself as having a role (Spencer 1996, 1998).

(Continued)

Table 18.13: Important Potential Risk: Effect on Final Height (Continued)

Background Incidence / Prevalence	Population norms of height-for-age in US children have been established and monitored by the Center for Disease Control (CDC) and its publication of growth charts that depict stature as a function of age (Ogden 2002). These charts have been widely used by paediatricians to assess individual growth. By definition, a child could be identified as being at a certain percentile for height, given their age. There is no agreed-upon threshold that represents a growth deficit among healthy children. However, the CDC data is used to compare specific groups to the population and to determine the value of growth deficits by converting group means to Z-scores (Ogden 2002). Stunting, or marked growth failure, is defined by the WHO as being greater than 2 standard deviations below the population mean of height-for-age. In a 2000 report from the WHO (WHO 2000), the prevalence of stunting among children was estimated to be 2.1% in the US, 5.6% in Japan, and 33% in developing countries. Long-term research is still being conducted in this area and the effect of methylphenidate on final height is not yet known with certainty.
Risk Groups or Risk Factors	Many factors affect rate of growth, with genetics playing a prominent role. Short stature is commonly encountered in clinical practice. It is recommended that short stature be comprehensively evaluated if a patient's height is greater than 3 standard deviations below the mean for age or if growth rate has decelerated. Short stature is most commonly of genetic determination and correlates well with parental stature.
Potential Mechanisms	Preclinical data do not indicate an effect of CONCERTA on growth and sexual maturation. No hormonal effects were observed that would indicate such an effect in animals or in humans. Decreased appetite and weight decrease are known adverse reactions of CONCERTA. It is possible, therefore, that the effect on height is caused by the reduced caloric intake as a result of appetite suppression. The effect on weight seems limited, however, to the first few months after starting treatment.
Preventability	Patients requiring long-term therapy should be carefully monitored. Patients who are not growing or gaining weight as expected should have their treatment interrupted temporarily.
Potential Public Impact of Safety Concern	No cases of effect on final height were reported in the clinical or postmarketing database. The data from the 3-year follow up in the MTA study (Swanson 2007) indicates that there is unlikely to be any affect on final height, but long-term research is still being conducted. Three cases of "weight gain poor" were reported in the clinical database. A review of the cumulative cases of reported growth retardation in the postmarketing database did not provide evidence of causality applying the Council for International Organizations of Medical Sciences (CIOMS) III/V threshold criteria for causal assessment. The literature, although not conclusive tends to support a temporary slow down of growth. Any effects on final height are yet uncertain, but even children treated for 3 years with methylphenidate measured above normal.

(Continued)

Table 18.13: Important Potential Risk: Effect on Final Height (Continued)

Regulatory Action Taken	Pre-treatment, the SmPC calls for prescribers to accurately record pre-treatment height and weight on a growth chart, and for ongoing monitoring to be conducted at least 6-monthly intervals (Sec 4.2, SmPC). Section 4.4 of the CONCERTA EU SmPC (Annex 2) includes the following warning: The effects of methylphenidate on final height and final weight are currently unknown and being studied. Growth should be monitored during methylphenidate treatment: height, weight and appetite should be recorded at least every 6 months with maintenance of a growth chart. Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.
Evidence Source	Ogden CL (2002), Kuczmarski RJ, Flegal KM, et al. Centers for Disease Control and Prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. Pediatrics 2002;109(1):45-60. Spencer TJ (1996), Biederman J, Harding M, O'Donnell D, Faraone SV, Wilens TE. Growth deficits in ADHD children revisited: evidence for disorder-associated growth delays? J Am Acad Child Adolesc Psychiatry 1996;35(11):1460-1469. Spencer T (1998), Biederman J, Wilens T. Growth deficits in children with attention deficit hyperactivity disorder. Pediatrics 1998;102:501-506. Swanson JM (2007), Elliott GE, Greenhill LL, et al. Effects of stimulant medication on growth rates across 3 years in the MTA follow-up. J Am Acad Child Adolesc Psychiatry 2007;46(8):1015-1027. World Health Organization (WHO) (2000). Global Database on Child Growth and Malnutrition. Geneva: WHO 2000.

Table 18.14: Important Potential Risk: Sexual Maturation (Delayed)

	Population From Double-Blind Trials		**Population From All Trials**
Potential Risk: *Sexual Maturation (Delayed)**	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	0	0	0
Rate per 1000 person-year†	--	--	0.0
95% confidence interval‡	--	--	0.0, 2.6
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	0
Discontinued Treatment	0	0	0
Resolved/Recovered	0	0	0
Resolved with Continuing Effects	0	0	0
Not Resolved/Not Yet Recovered/Continuing	0	0	0
Severity§			
Mild	0	0	0
Moderate	0	0	0
Severe	0	0	0

* Reported MedDRA preferred terms include: None

** A subject is counted only once regardless of the number of events.

† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.

‡ CI are two-sided 95% exact Poisson

§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

No adverse events for this important potential risk were reported in clinical trials of CONCERTA. As a result, the causal relationship of relevant adverse events for this potential risk could not be evaluated on the basis of aggregate safety data from clinical trials of CONCERTA.

(Continued)

Table 18. 14: Important Potential Risk: Sexual Maturation (Delayed) (Continued)

Postmarketing

A summary of events related to sexual maturation (delayed) from the postmarketing database is presented below.

Count of Selected Preferred Terms Reported at Least Once Between 11 August 2007 to 10 August 2008 or 11 August 2008 and 10 August 2009 by Seriousness: Sexual Maturation (Delayed)

	Number of Events	
Preferred Terms[a]	**Nonserious**[b]	**Serious**[b]
Body height decreased[c]	0	1
Delayed puberty[c]	1	3
Growth retardation[d]	7	34
Precocious puberty[c]	3	0
Blood growth hormone decreased[d]	0	3
Body height abnormal[d]	0	1

[a] Preferred terms from the search terms that are not listed here were not received in the specified reporting period of either 11 August 2007 to 10 August 2008 (PSUR 2008) or 11 August 2008 to 10 August 2009 (PSUR 2009).

[b] At event level

[c] Data from 01August 2000 to 10 August 2008. **Source:** BRM Report, PSUR 2008. This search of the worldwide postmarketing safety database was conducted using the following MedDRA preferred terms: Blood growth hormone decreased, Body height decreased, Delayed puberty, Growth retardation, Precocious puberty

[d] Data from 01August 2000 to 10 August 2009. **Source:** BRM Report, PSUR 2009. This search of the worldwide postmarketing safety database was conducted using the following MedDRA preferred terms: Blood cortisol increased, Blood growth hormone decreased, Blood prolactin increased, Blood thyroid stimulating hormone abnormal, Body height abnormal, Delayed puberty, Growth retardation, Hyperthyroidism, Precocious puberty.

This review of spontaneous postmarketing reports of sexual maturation (delayed) found no evidence of a drug-event link with CONCERTA.

Nature of the Risk	Puberty is delayed in boys if it has not ensued by age 14, an age that is 2 to 2.5 standard deviations above the mean for healthy children. In girls, delayed puberty is defined as the absence of secondary sexual characteristics by age 13. Delayed puberty is more common in boys than in girls. There are 4 main categories of delayed puberty: (1) constitutional delay of growth and puberty (~60% of cases); (2) functional hypogonadotropic hypogonadism caused by systemic illness or malnutrition (~20% of cases); (3) hypogonadotropic hypogonadism caused by genetic or acquired defects in the hypothalamic-pituitary region (~10% of cases); and (4) hypergonadotropic hypogonadism secondary to primary gonadal failure (~15% of cases). Functional hypogonadotropic hypogonadism is more common in girls than in boys. Girls appear to be particularly susceptible to the adverse effects of abnormalities in energy balance that result from exercise, dieting, and/or eating disorders.
Background Incidence / Prevalence	The timing of sexual maturity has been collected on a population level in the US to establish reference data for age at entry into well-established stages. The NHANES III assessed Tanner stage in 4,263 children and adolescents ages 8 to 19 years (Sun 2002). This data provides median age of menarche and median age at entry into Tanner stages 2 through 5. The Spencer et al (1996) study assessed pubertal development to see if height deficits in ADHD were potentially related to delays in puberty. The age of onset for Tanner stages was collected and no difference was found between boys with ADHD and control subjects. In a cross-sectional study comparing ADHD girls (6-17 years) with non-ADHD controls, no meaningful associations were identified between ADHD or its treatment and pubertal development (Biederman 2003).

(Continued)

Table 18 .14: Important Potential Risk: Sexual Maturation (Delayed) (Continued)

Risk Groups or Risk Factors	Risk factors and causes among males and females for delayed sexual maturation include gonadotropin deficiency, tumours, sarcoidosis, panhypopituitarism, Turner's syndrome, Prader-Willi syndrome, Laurence-Moon-Biedl syndrome, Kallmann's syndrome, Klinefelter's syndrome, chronic inflammatory bowel disease, asthma, cardiac disease, rheumatoid arthritis, glucocorticoid excess, anorexia nervosa, marijuana use, GPR53 mutations, Xq deletion, alkylating chemotherapy, craniopharyngioma, hypothalamic hamartoma, central nervous system infection, GPR54 mutations causing autosomal recessive idiopathic hypogonadoptropic hypogonadism, and environmental exposure to lead. Additional risk factors for females include premature ovarian failure, inadequate follicle-stimulating hormone/luteinizing hormone, prolactinoma, inadequate body fat, exercise-induced hypothalamic dysfunction, and genital tract abnormalities - imperforate hymen, vaginal and uterine agenesis (Mullerian agenesis, Rokitansky-Kuster-Hauser syndrome).
Potential Mechanisms	It has been hypothesised that a persistent, stimulant-induced, increase in hypothalamic dopamine may affect pituitary function, thus delaying sexual maturation. Acute administration of methylphenidate increases growth hormone and decreases prolactin, but no consistent changes in plasma levels of these hormones have been documented during chronic treatment (Vitiello 2008). A single preclinical study evaluated the effects of chronic methylphenidate administration on the reproductive axis of adolescent female rats. The study suggested that chronic methylphenidate administration during adolescence might perturb pubertal onset, adversely affect maturation of the female reproductive axis by retarding pituitary luteinizing hormone release, and adversely affect ovarian folliculogenesis (Chatterjee-Chakrabarty 2005).
Preventability	Early detection and management of risk factors by health care professionals.
Potential Public Impact of Safety Concern	Delayed puberty does not appear to have a major public health impact; however, it may be an individual concern. When detected Expert opinion should be sought and appropriate management should be initiated.
Regulatory Action Taken	Annex IV of the May 2009 EC decision (Conditions of the Marketing Authorisation) states that the data from an investigator-initiated study (IIS) should be evaluated, when available, to inform the potential risk of delayed sexual maturation: "This is a 2-year, long-term, open-label, prospective investigator initiated study in the US on 150 adolescents (12-17 years) with ADHD, to determine whether treatment with CONCERTA will prevent smoking in this population. Although the study focuses on smoking prevention, Tanner staging examinations will occur every 6 months during the 2-year follow-up and will monitor each subject's pubertal development to demonstrate whether CONCERTA has any effect on adolescent growth and development compared to population norms." No further regulatory action taken.

(Continued)

Table 18.14: Important Potential Risk: Sexual Maturation (Delayed) (Continued)

Evidence Source	Benefit Risk Management Report (2008). Periodic Safety Update Report. OROS® methylphenidate HCl From 11Aug2007-10Aug2008. Document ID No. EDMS-USRA-10859695:2.0. J&JPRD (25 September 2008). Benefit Risk Management Report (PSUR 2009). Periodic Safety Update Report. OROS® methylphenidate HCl (From 11Aug2008-10Aug2009). Document ID No. EDMS-USRA-EDMS-USRA-11227189. J&JPRD (25 September 2009). Biederman J (2003), Faraone SV, Monuteaux MC, Plunkett EA, Gifford J, Spencer T. Growth deficits and Attention-Deficit/Hyperactivity Disorder revisited: Impact of gender, development and treatment. Pediatrics 2003;111(5):1010-1016. Chatterjee-Chakrabarty S (2005), Miller BT, Collins TJ, Nagamani M. Adverse effects of methylphenidate on the reproductive axis of adolescent female rats. Fertil Steril 2005;84(Suppl 2):1131-1138. Spencer TJ (1996), Biederman J, Harding M, O'Donnell D, Faraone SV, Wilens TE. Growth deficits in ADHD children revisited: evidence for disorder-associated growth delays? J Am Acad Child Adolesc Psychiatry 1996;35(11):1460-1469. Sun SS (2002), Schubert CM, Chumlea WC, et al. National estimates of the timing of sexual maturation and racial differences among US children. Pediatrics 2002;110(5):911-919. Vitiello B (2008). Understanding the risk of using medications for attention deficit hyperactivity disorder with respect to physical growth and cardiovascular function. Child Adolesc Psychiatric Clin N Am 2008; 17:459-474.

Table 18.15: Important Potential Risk: Carcinogenicity

	Population From Double-Blind Trials		**Population From All Trials**
Potential Risk: *Carcinogenicity**	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	0	0	8 (0.3)
Rate per 1000 person-year†	*	*	5.6
95% confidence interval‡	*	*	2.4; 11.1
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	0
Discontinued Treatment	0	0	0
Resolved/Recovered	0	0	4
Resolved with Continuing Effects	0	0	0
Not Resolved/Not Yet Recovered/Continuing	0	0	4
Severity§			
Mild	0	0	7
Moderate	0	0	1
Severe	0	0	0

* Reported MedDRA preferred terms include: benign neoplasm of testis; skin papilloma.
** A subject is counted only once regardless of the number of events.
† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.
‡ CI are two-sided 95% exact Poisson
§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

On the basis of the review of aggregate safety data from clinical trials of CONCERTA, a causal relationship was not established for any of the adverse events that may be relevant for this important potential risk.

Postmarketing Database	A review of the worldwide safety database from first authorisation (01 August 2000) through late April 2005 identified 11 cases within the MedDRA Neoplasm SOC (BRM Response to Swissmedic May 2005). These cases exhibited no observable pattern with regard to type of cancer, organ system affected, patient age, gender, CONCERTA dose or duration of use. Five of the cases reported nonmalignant neoplasm (antral lipoma, pseudolymphoma, benign breast cyst, benign lymphadenopathy, and dysplastic nevi). Safety data revealed no signal for neoplasm overall, or malignant neoplasm in particular, associated with the use of CONCERTA. A recent assessment of carcinogenicity is consistent with the previous evaluation (see table).

(Continued)

Table 18.15: Important Potential Risk: Carcinogenicity (Continued)

Postmarketing (Continued)

Cumulative Count of Selected Preferred Terms Reported at Least Once Between 11 August 2008 and 10 August 2009 by Seriousness: Carcinogenicity

	Number of Events 01 August 2000 to 10 August 2009	
Preferred Term	**Nonserious[a]**	**Serious[a]**
Lipoma	2	0
Neoplasm malignant	0	1
T-cell lymphoma	0	1

[a] At event level

Source: BRM Report, PSUR 2009. The following MedDRA preferred terms were selected to identify events for review: Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps).

There were no cases presenting evidence of a drug-event association between CONCERTA and cytogenic abnormality from this updated review. This conclusion is unchanged from the original review.

Nature of Risk	A manuscript by El-Zein (2005) describes an evaluation of 3 cytogenetic endpoints in 12 children who were treated with therapeutic doses of methylphenidate (20 to 54 mg/day) for 3 months. Analysis was performed on peripheral blood lymphocytes obtained pre-exposure, and after three months of methylphenidate treatment. All 12 children were found to exhibit a significant increase in chromosome aberration (CA), sister chromatid exchange (SCE), and micronuclei (MN); the mean frequency increase in each of the above cytogenetic biomarkers was 3-, 4.3-, and 2.4-fold, respectively. These authors concluded that the findings warrant further investigations of the possible health effects of methylphenidate in humans. In 4 recent, similar studies, the findings originally published by El-Zein et al could not be replicated (Walitza 2007, Walitza 2009, Witt 2008, Tucker 2009, Ponsa 2009). Section 1.1.1.1.2 (Evaluation of Cytogenetic Endpoints in Human Ex Vivo Studies) provides additional information regarding these studies. Therefore, the presently available data do not support the conclusion that therapeutic doses of methylphenidate result in an increase in chromosomal abnormalities or carcinogenic risk. As with adults, childhood cancer is not one disease entity, but rather is a spectrum of different malignancies. Over 50% of childhood cancers are either leukaemia, the most common type being acute lymphocytic leukaemia, brain, or other central nervous system tumours. The overall average annual age-specific rates (ASR) for cancer in children in Europe in the 1990s were 140 per million, based on 48847 cases. The ASR for the age-range 0–19 years was 157 per million, and for adolescents was 193 per million (n=7109). In all age groups, incidence was significantly higher in boys than in girls. In adolescents, the highest incidence rates were for lymphomas (European age-specific rate 47.4 per million), followed by carcinomas (38.1), central nervous system tumours (24.6), germ-cell tumours (24.5), and leukaemia (23.4) (Steliarova-Foucher 2004).

(Continued)

Table 18.15: Important Potential Risk: Carcinogenicity (Continued)

Background Incidence / Prevalence	The overall incidence rates of cancer have been increasing over time in all ages. The difference in age-specific rates between the first and the last decade was significant at all ages, and it was largest at the beginning and end of the age-range. Based on 100596 children with cancer, the average ASR per million was 118 in the 1970s, 124 in the 1980s, and approximately 140 in the 1990s. The average annual change was 1·0% ($p<0·0001$): 0·8% ($p<0·0001$) between the 1970s and 1980s and 1·3% ($p<0·0001$) between the 1980s and 1990s (Steliarova-Foucher 2004).
Risk Groups or Risk Factors	Pre-clinical studies conducted by the Company as well as in the published literature have revealed no carcinogenicity effects. The findings of recent studies were not suggestive of a cytogenic potential of methylphenidate (Walitza 2007, Walitza 2009, Witt 2008, Tucker 2009, Ponsa 2009).
Potential Mechanisms	Methylphenidate alters dopamine levels and dopamine was found genotoxic in vitro at high doses as early as 1983 (Stopper 2008). Dopamine induced strand breaks, mutations in mammalian cells but not in bacterial assays, and bound to calf thymus DNA. This was considered due to the oxidation of dopamine and the generation of reactive oxygen radicals, semiquinones and quinones. Dopamine was considered unlikely to be genotoxic in vivo (Stopper 2008). Recent studies did not replicate the findings suggestive of a cytogenic potential of methylphenidate reported in a previous publication by El-Zein et al. (Walitza 2007, Walitza 2009, Witt 2008, Tucker 2009, Ponsa 2009).
Preventability	Not applicable. The need for continuing drug treatment should be evaluated periodically.
Potential Public Impact of Safety Concern	Carcinogenicity, particularly in paediatric patients, is always of concern. At present, no cases have been reported in double-blind trials and 7 benign neoplasm cases have been reported in open-label paediatric studies. A review of the postmarketing database revealed no signal for neoplasm overall, or malignant neoplasm in particular, associated with the use of CONCERTA. Based on the overall use of the product and the limited reports to date, it is not expected to have an impact with respect to overall public health.
Regulatory Action Taken	The reports of Studies CRIT124D2201 (An open label, behavioural treatment controlled evaluation of the effects of extended release methylphenidate [Ritalin LA] on the frequency of cytogenetic abnormalities in children 6-12 years old with attention deficit hyperactivity disorder) (published by Tucker 2009) and NCT 00341029 (Measurement of Cytogenetic Endpoints in Lymphocytes of Children Diagnosed With Attention Deficit/Hyperactivity Disorder (ADHD) and Treated With Methylphenidate or Adderall) (published by Witt 2008) should be evaluated by the MAHs of methylphenidate-containing products as part of the conditions of the Marketing authorisation (Annex IV, EC decision, Annex 4)

(Continued)

Table 18.15: Important Potential Risk: Carcinogenicity (Continued)

Regulatory Action Taken (Continued)	The following text is provided in Section 5.3 of the CONCERTA EU SmPC (Annex 2): "In life-time rat and mouse carcinogenicity studies, increased numbers of malignant liver tumours were noted in male mice only. The significance of this finding to humans is unknown.
Evidence Source	Benefit Risk Management Report (2005). Response to Swissmedic Request for information regarding CONCERTA® (OROS® methylphenidate hydrochloride) and cytogenetic abnormalities. J&JPRD. Document ID: EDMS-USRA-9503507 (05 May 2005). Benefit Risk Management Report (PSUR 2009). Periodic Safety Update Report. OROS® methylphenidate HCl (From 11Aug2008-10Aug2009). Document ID No. EDMS-USRA-EDMS-USRA-11227189. J&JPRD (25 September 2009). El-Zein RA (2005), Abdel-Rahman SZ, Hay MJ, et al. Cytogenetic effects in children treated with methylphenidate. Cancer Lett 2005;1-8. Ponsa I (2009), Ramos-Quiroga JA, Ribases M et al. Absence of cytogenetic effects in children and adults with attention-deficit/hyperactivity disorder treated with methylphenidate. Mutation Research 2009; 666:44-49. Steliarova-Foucher E (2004), Stiller C, Kaatsch P, et al. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCIS project): an epidemiological study. Lancet 2004;364(9451): 2097-2105. Stopper H (2008), Walitza S, Warnke A, Gerlach M. Brief review of available evidence concerning the potential induction of genomic damage by methylphenidate. J Neural Transm 2008;115:331-334. Tucker JD (2009), Suter W, Petibone DM et al. Cytogenetic assessment of methylphenidate treatment in pediatric patients treated for attention deficit hyperactivity disorder. Mutation Research 2009; 677:53-58. Walitza S (2009), Kampf K, Artamonov N, et al. No elevated genomic damage in children and adolescents with attention deficit/hyperactivity disorder after methylphenidate therapy. Toxicol Lett 2009;184(1):38-43. Walitza S (2007), Werner B, Romanos M, et al. Does methylphenidate cause a cytogenetic effect in children with attention deficit hyperactivity disorder? Environ Health Perspect 2007;115:936-940. Witt KL (2008), Shelby MD, Itchon-Ramos N, et al. Methylphenidate and amphetamine do not induce cytogenetic damage in lymphocytes of children with ADHD. J Am Acad Child Adolesc Psychiatry 2008:47:1375-1383.

Table 18.16: Important Potential Risk: Off-Label Use

	Population From Double-Blind Trials		**Population From All Trials**
Potential Risk: *Off-Label Use**	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	0	0	0
Rate per 1000 person-year†	--	--	0.0
95% confidence interval‡	--	--	0.0, 2.6
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	0
Discontinued Treatment	0	0	0
Resolved/Recovered	0	0	0
Resolved with Continuing Effects	0	0	0
Not Resolved/Not Yet Recovered/Continuing	0	0	0
Severity§			
Mild	0	0	0
Moderate	0	0	0
Severe	0	0	0

* Reported MedDRA preferred terms include: none.
** A subject is counted only once regardless of the number of events.
† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.
‡ CI are two-sided 95% exact Poisson
§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

Clinical trials are not an appropriate basis for the evaluation of this important potential risk. As a result, there was no assessment of the causal relationship of relevant adverse events for this potential risk on the basis of clinical trials of CONCERTA.

(Continued)

Table 18.16: Important Potential Risk: Off-Label Use (Continued)

Postmarketing

The published estimated proportion of off-label use of methylphenidate was 2.0% (Novak 2007). Based on a review of the medical literature, the most significant indications for off-label use are presented below.

Significant Off-Label Indications for OROS methylphenidate HCl Based on Published Literature

Specific Indication	**Published Literature**
Vascular depression	Mantani 2008
Resistant depression	Patkar 2006
Chronic fatigue syndrome	Valdizan 2008 Hanna 2006
ADHD in adults[a]	Wilens 2008 Kurscheidt 2008
Pathologic aggression in children	Barzman 2008 Singh 1985
Developmental coordination disorder	Flapper 2008
Conduct disorder	Masi 2008
Disruptive behaviour disorders	Waschbusch 2007
Autism spectrum disorders	McCarthy 2007
Augmentation major depressive disorder	Nelson 2007, Buhagiar 2007
Geriatric depression	Ben-Itzhak 2008, Lavretsky 2006, Ng 2008
Asthenia in patients with advanced cancer	Laval 2008, Breitbart 2007
Depression in advanced cancer	Homsi 2001
Cancer patients receiving strong narcotics	Wilwerding 1995
Delirium	Morita 2000
Brain tumour patients	Meyers 1998
Acute drug poisoning	Bastecky 1996
Nicotine withdrawal	Robinson 1995
Traumatic brain injury	Pavlovskaya 2007
Parkinson disease	Mendonca 2007 Pollak 2007

[a] CONCERTA is currently authorised for the treatment of ADHD in adults in regions outside of the EU; trials have been conducted to support the authorisation of CONCERTA for use in adults in the EU.

Postmarketing (Commercial Data)

According to IMS covering CONCERTA retail prescriptions in the 4 major European countries where CONCERTA is available (Germany, France, Spain, and United Kingdom), from January 2003 to June 2009, the vast majority (94.0%) of retail prescriptions of CONCERTA were prescribed to children and adolescents between the ages of 6 and 20 years (no split <17 and ≥17 years is feasible). Approximately 78.9% of European CONCERTA prescriptions were prescribed for the treatment of ADHD or ADHD-related symptoms, based on IMS data for the time period from January 2005 to June 2009 (diagnosis data earlier than 2005 are not available). The most common indications for off-label use of CONCERTA in this age category, based upon cumulative IMS data for the time period from January 2005 through June 2009 were conduct disorder, childhood autism, and Asperger's syndrome; conditions known to have a high comorbidity with ADHD. Only 0.4% of all prescriptions were for children below the age of 6 years.

(Continued)

Table 18.16: Important Potential Risk: Off-Label Use (Continued)

Nature of the Risk	Off-label use refers to the use of a prescription medication for a disease or condition outside the indication for which it is approved.
Background Incidence / Prevalence	Unknown
Risk Groups or Risk Factors	Unknown
Potential Mechanisms	Methylphenidate may be used off-label for the following potential indications: • Major depressive disorder (monotherapy or adjunctive therapy to antidepressants) • Excessive daytime sleepiness associated with narcolepsy, shift work sleep disorder, and obstructive sleep apnoea syndrome • Obesity (appetite suppression) • Female sexual dysfunction • Cognitive impairment in Alzheimer's disease, Down's syndrome, Parkinson's disease. • Cocaine dependence; cigarette smoking (cessation and maintenance of abstinence) • Cancer-related fatigue The efficacy of methylphenidate, which was shown for some of these conditions in placebo-controlled trials, is either due to the increase in dopamine and norepinephrine in the interneuronal space or the known sympathomimetic effects of the compound.
Preventability	Prescribers have access to the regulatory approved product label, which should be used to make well-informed prescribing decisions based on the best available estimate of the benefit/risk ratio.
Potential Public Impact of Safety Concern	There is no published prevalence data for off-label use in Europe. The prevalence of off-label use of CONCERTA in children less than 6 years of age is estimated at 0.4% of all the prescriptions of CONCERTA in France, Germany, Spain, and the UK (Table 14, Section 1.2.3)
Regulatory Action Taken	The Company (with the other MAHs) as part of the conditions of the Marketing authorisation (Annex IV, EC decision), must provide all available retrospective drug utilisation data using health-related electronic databases in all Member States where methylphenidate is used, to allow an evaluation of changes in usage over time including off-label use on an annual review basis for the next five years. An evaluation of methylphenidate usage in 2008 will be submitted for assessment. The CONCERTA EU SmPC (Annex 2) includes the following information in Section 4.2 (the same information is repeated in Section 4.4): "Adults: Methylphenidate is not licensed for use in adults in ADHD. Safety and efficacy have not been established in this age group Elderly: Methylphenidate should not be used in the elderly. Safety and efficacy has not been established in this age group. Children (under 6 years): Methylphenidate should not be used in children under the age of 6 years. Safety and efficacy in this age group has not been established." The CONCERTA EU SmPC states in Section 4.4 under "Fatigue" that CONCERTA is not indicated for use in treating this condition.

(Continued)

Table 18.16: Important Potential Risk: Off-Label Use (Continued)

Evidence Source	Bastecky J (1996). Methylphenidate (Ritalin) in the treatment of acute drug poisoning. Ceska a Slovenska Psychiatrie 1996:92(Suppl 1):68-69. Barzman DH (2008). Findling RL. Pharmacological treatment of pathologic aggression in children. Int Rev Psychiatry 2008; 20:151-157. Ben-Itzhak R (2008). Giladi N. Gruendlinger L. Hausdorff JM. Can methylphenidate reduce fall risk in community-living older adults? A double-blind, single-dose cross-over study. J Am Geriatr Soc 2008;56(4):695-700. Breitbart W (2007). Alici-Evcimen Y. Update on psychotropic medications for cancer-related fatigue. J. Natl. Compr. Cancer Netw 2007;5:1081-1091. Buhagiar K (2007). Cassar J. Methylphenidate augmentation of fluvoxamine for treatment-resistant depression: a case report and review literature. Turk Psikiyatri Dergisi 2007;18:179-183. Flapper BC (2008). Schoemaker MM. Effects of methylphenidate on quality of life in children with both developmental coordination disorder and ADHD. Dev Med Child Neurol 2008;50:294-299. Hanna A (2006), Sledge G, Mayer ML. Hanna N. Einhorn L. Monahan P. Daggy J. Bhatia S. A phase II study of methylphenidate for the treatment of fatigue. Support Care Cancer 2006;14:210-215. Homsi J (2001), Nelson KA, Sarhill N et al., A phase II study of methylphenidate for depression in advanced cancer. Am J Hosp Palliat Care 2001;18:403–407. Kurscheidt JC (2008), Peiler P, Behnken A, Abel S, Pedersen A, Suslow T, Deckert J. Acute effects of methylphenidate on neuropsychological parameters in adults with ADHD: possible relevance for therapy. J Neural Transm 2008;115:357-362. Laval G (2008), Paris A. Methylphenidate in palliative care in cancer patient: a double-blind randomised trial versus placebo. Bull Cancer 2008;95:241-246. Lavretsky H (2006), Park S, Siddarth P, et al. Methylphenidate enhanced antidepressant response to citalopram in the elderly: a double-blind, placebo-controlled pilot trial. Am J Geriatr Psychiatry 2006;14:181-185. Mantani A (2008), Fujikawa T, Ohmori N, Yamawaki S. Methylphenidate in the treatment of geriatric patients with vascular depression: a retrospective chart review. Am J Geriatr Psychiatry 2008;16(4):336-337.

(Continued)

Table 18.16: Important Potential Risk: Off-Label Use (Continued)

Evidence Source (Continued)	Masi G (2008), Milone A, Manfredi A, Pari C, Paziente A, Millepiedi S. Conduct disorder in referred children and adolescents: clinical and therapeutic issues. Compr Psychiatry 2008;49:146-153. McCarthy J (2007). Children with autism spectrum disorders and intellectual disability. Curr Opin Psychiatry 2007;20:472-476. Mendonca DA (2007), Menezes K, Jog MS. Methylphenidate improves fatigue scores in Parkinson disease: a randomized controlled trial. Movement Disorders 2007;22:2070-2076. Meyers CA (1998), Weitzner MA, Valentine AD, et al., Methylphenidate therapy improves cognition, mood, and function of brain tumor patients. J Clin Oncol 1998;16:2522–2527. Morita T (2000), Otani H, Tsunoda J, et al. Successful palliation of hypoactive delirium due to multi-organ failure by oral methylphenidate. Support Care Cancer 2000:8:134–137. Nelson JC (2007). Augmentation strategies in the treatment of major depressive disorder. Recent findings and current status of augmentation strategies. CNS Spectr 2007;12(Suppl 22):6-9. Ng B (2008). Methylphenidate and depression. J Clin Psychopharmacol 2008;28:116-117; author reply 117-118. Novak SP (2007), Kroutil LA, Williams RL, Van Brunt DL. The nonmedical use of prescription ADHD medications: results from a national Internet panel. Substance Abuse Treatment, Prevention, & Policy 2007;2:32. Patkar AA (2006), Masand PS, Pae CU, et al. A randomized, double-blind, placebo-controlled trial of augmentation with an extended release formulation of methylphenidate in outpatients with treatment-resistant depression. J Clin Psychopharmacol 2006;26:653-656. Pavlovskaya M (2007), Hochstein S, Keren O, Mordvinov E, Groswasser Z. Methylphenidate effect on hemispheric attentional imbalance in patients with traumatic brain injury: a psychophysical study. Brain Injury 2007;21:489-497. Pollak L (2007), Dobronevsky Y, Prohorov T, Bahunker S, Rabey JM. Low dose methylphenidate improves freezing in advanced Parkinson's disease during off-state. J Neural Transm 2007;72 (Suppl):145-148. Robinson MD (1995), Anastasio GD, Little JM, et al. Ritalin for nicotine withdrawal: Nesbitt's paradox revisited. Addictive Behaviors 1995;20(4):481-490.

(Continued)

Table 18.16: Important Potential Risk: Off-Label Use (Continued)

Evidence Source (Continued)	Singh NN (1985). Millichamp CJ. Pharmacological treatment of self-injurious behavior in mentally retarded persons. J Autism Dev Disord 1985;15:257-267. Valdizan Uson JR (2008). Idiazabal Alecha MA. Diagnostic and treatment challenges of chronic fatigue syndrome: role of immediate-release methylphenidate. Neurotherapeutics 2008;8(6):917-927. Waschbusch DA (2007), Carrey NJ, Willoughby MT, King S, Andrade BF. Effects of methylphenidate and behavior modification on the social and academic behavior of children with disruptive behavior disorders: the moderating role of callous/unemotional traits. J Clin Child Adolesc Psychol 2007;36:629-644. Wilens TE (2008). Pharmacotherapy of ADHD in adults. CNS Spectr 2008;13:11-13. Wilwerding MB (1995), Loprinzi CL, Mailliard JA, et al. A randomized, crossover evaluation of methylphenidate in cancer patients receiving strong narcotics. Support Care Cancer 1995;3:135–138.

Table 18.17: Important Potential Risk: Diversion

Clinical Database	Clinical trials are not an appropriate basis for the evaluation of this important potential risk. As a result, there was no assessment of the causal relationship of relevant adverse events for this potential risk on the basis of clinical trials of CONCERTA.
Postmarketing Database	A total of 3 adverse events with preferred terms of Drug diversion have been received in the postmarketing database cumulative 01 August 2000 to 10 August 2009 (BRM Report, PSUR 2009). The limited information does not allow conclusions to be made regarding this important potential risk.
Nature of the Risk	Diversion is understood as the entry of illicit pharmaceutical products onto the unregulated market through a number of channels, eg, thefts of product from the legitimate supply chain, or product obtained legitimately and subsequently diverted through various means such as Internet sales.
Background Incidence / Prevalence	Incidence: Unknown Prevalence: Data from the Monitoring the Future Study (MTF) (McCabe 2004), an annual, nationally representative survey that is based on a multistage probability sample of 8th, 10th, and 12th grade students in the US were used to examine the prevalence and factors associated with illicit methylphenidate use in a nationally representative sample of 8th, 10th, and 12th grade students.
Risk Groups or Risk Factors	In 2001, the unadjusted prevalence of illicit methylphenidate use in the past year for the entire sample was 4.0% with 5.1% of 12th grade students, 4.8% of 10th grade students, and 2.9% of 8th grade students reported non-medical use of methylphenidate in the previous year. After adjusting for other factors, white students were over 6 times more likely than African-American students to report illicit methylphenidate use. Students in higher-grade levels (10th and 12th grade) and those earning lower grade point averages had an increased likelihood of illicit methylphenidate use. In 2007 (Johnston 2007), 3.8% of 12th grade students, 2.8% of 10th grade students and 2.1% of 8th grade students reported nonmedical use of methylphenidate in the previous year. Individuals obtaining prescription medication through illegal, diverted means are at risk of receiving a medication that was not prescribed for them or potentially the improper medication as there is no health care involvement. Drugs are diverted illegally through a number of various illicit drug activities.
Potential Mechanisms	Mechanisms and processes that are used to prevent drug diversion and assist in ensuring appropriate distribution and sales include established controls that may vary from country to country, selling and distributing through legitimate sources, and following a chain of custody in countries that employ one for controlled substances.

(Continued)

Table 18.17: Important Potential Risks: Diversion (Continued)

Preventability	As methylphenidate is a controlled substance, distribution, prescription, and dispensing is restricted by national laws. From a review of public information sources, it appears that there are currently no databases in place at the EU or national Member State level to directly monitor pharmaceutical product diversion in the EU.
Potential Public Impact of Safety Concern	With regards to CONCERTA and other methylphenidate-containing medicinal products, some measure of the integrity of the pharmaceutical supply chain in the EU is afforded at a national level through the maintenance of records of import, export, distribution and in some Member States of supply to the patient. Such records may provide an opportunity for measuring the possibility of product diversion. However, taking the UK as an example, record keeping is not necessarily electronic and there is no one integrated system containing these records and hence that is capable of tracking product from import entry to the individual patient level. The situation for record keeping varies amongst member states. Illegal diversion of pharmaceutical products is always of concern. Safeguards are put in place in an attempt to preclude or limit illegal distribution. The SmPC Sections 4.2 and 4.4 advise that patients should be monitored for the risk of diversion and misuse of methylphenidate.
Regulatory Action Taken	The SmPC Sections 4.2 and 4.4 advise that patients should be monitored for the risk of diversion and misuse of methylphenidate.
Evidence Source	Benefit Risk Management Report (PSUR 2009). Periodic Safety Update Report. OROS® methylphenidate HCl (From 11Aug2008-10Aug2009). Document ID No. EDMS-USRA-EDMS-USRA-11227189. J&JPRD (25 September 2009). Johnston LD (2007), O'Malley PM, Bachman JG, Schulenberg JE (December 11, 2007). Overall, illicit drug use by American teens continues gradual decline in 2007. University of Michigan News Service: Ann Arbor, MI. [Online]. Available: www.monitoringthefuture.org; accessed 16 Jan 2008. McCabe SE (2004), Teter CJ, Boyd CJ, Guthrie SK. Prevalence and correlates of illicit methylphenidate use among 8th, 10th, and 12th grade students in the United States, 2001. J Adolesc Health 2004;35 (6):501-504.

Table 18.18: Important Potential Risk: Withdrawal Syndrome

	Population From Double-Blind Trials		**Population From All Trials**
Potential Risk: *Withdrawal Syndrome**	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	0	0	0
Rate per 1000 person-year†	--	--	0.0
95% confidence interval‡	--	--	0.0, 2.6
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	0
Discontinued Treatment	0	0	0
Resolved/Recovered	0	0	0
Resolved with Continuing Effects	0	0	0
Not Resolved/Not Yet Recovered/Continuing	0	0	0
Severity§			
Mild	0	0	0
Moderate	0	0	0
Severe	0	0	0

* Reported MedDRA preferred terms include: none.
** A subject is counted only once regardless of the number of events.
† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.
‡ CI are two-sided 95% exact Poisson
§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

No adverse events for this important potential risk were reported in clinical trials of CONCERTA. As a result, the causal relationship of relevant adverse events for this potential risk could not be evaluated on the basis of aggregate safety data from clinical trials of CONCERTA.

Postmarketing	The postmarketing database does not allow conclusions to be made regarding this important potential risk.
Nature of the Risk	Withdrawal syndrome refers to the development of a substance-specific syndrome that follows the cessation of, or reduction in, intake of a psychoactive substance that the person previously used regularly. The syndrome that develops varies according to the psychoactive substance used. Common symptoms include anxiety, restlessness, irritability, insomnia, and impaired attention. Generally, the effects observed are in an opposite direction from those produced by the drug. The intensity of the syndrome varies with the drug or chemical. Onset time and severity of the syndrome depend on the rate at which the drug disappears from the body.
Background Incidence / Prevalence	Unknown
Risk Groups or Risk Factors	Unknown

(Continued)

Table 18.18: Important Potential Risk: Withdrawal Syndrome (Continued)

Potential Mechanisms	In a small, open-label study in 5 children with ADHD, single photon emission computed tomography (SPECT) was used to investigate possible long-term alterations in the cerebral dopamine system after cessation of treatment with methylphenidate. Three months after initiation of treatment with methylphenidate, a reduction of the dopamine transporter in the striatal system was observed. Methylphenidate was administered over a period of 9 to 20 months in total. Follow-up with SPECT after cessation of methylphenidate treatment disclosed an increase in dopamine transporter activity relative to baseline. Whether this represented a simple rebound phenomenon or an active up regulation of dopamine transporters after cessation of treatment with methylphenidate was unclear (Feron 2005).
Preventability	Patients and their parents should be warned that they might experience some worsening of ADHD symptoms after the discontinuation of treatment, as the effect of methylphenidate wears off.
Potential Public Impact of Safety Concern	There is no evidence that this has a significant public health impact but it may be an individual concern.
Regulatory Action Taken	Current CONCERTA EU SmPC (Annex 2) contains precautionary text under withdrawal subheading (Section 4.4): Careful supervision is required during drug withdrawal, since this may unmask depression as well as chronic over-activity. Some patients may require long-term follow up. Careful supervision is required during withdrawal from abusive use since severe depression may occur.
Evidence Source	Feron FJM (2005), Hendrikson JGH, Van Kroonenburgh MJPG, et al. Dopamine transporter in attention-deficit hyperactivity disorder normalizes after cessation of methylphenidate. Pediatr Neurol 2005; 33:179-183.

Table 18.19: Important Potential Risk: Drug Abuse and Drug Dependence

	Population From Double-Blind Trials		Population From All Trials
Potential Risk: *Drug Abuse/Drug Dependence**	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	0	0	0
Rate per 1000 person-year†	*	*	0.0
95% confidence interval‡	*	*	0.0, 2.6
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	0
Discontinued Treatment	0	0	0
Resolved/Recovered	0	0	0
Resolved with Continuing Effects	0	0	0
Not Resolved/Not Yet Recovered/Continuing	0	0	0
Severity§			
Mild	0	0	0
Moderate	0	0	0
Severe	0	0	0

* Reported MedDRA preferred terms include: none.
** A subject is counted only once regardless of the number of events.
† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.
‡ CI are two-sided 95% exact Poisson
§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

No adverse events for this important potential risk were reported in clinical trials of CONCERTA. As a result, the causal relationship of relevant adverse events for this potential risk could not be evaluated on the basis of aggregate safety data from clinical trials of CONCERTA.

Postmarketing

A summary of the drug abuse and drug dependence events from the postmarketing database is presented below.

Cumulative Count of Selected Preferred Terms Reported at Least Once Between 11 August 2008 and 10 August 2009 by Seriousness: Drug Abuse and Drug Dependence

	Number of Events 01 August 2000 to 10 August 2009	
Preferred Term	**Nonserious[a]**	**Serious[a]**
Drug abuse	2	14
Dependence	0	1
Drug tolerance	5	1
Substance abuse	0	3

[a] At event level

Source: BRM Report, PSUR 2009. This search of the worldwide postmarketing safety database was conducted using the following MedDRA SMQ: Drug abuse, dependence and withdrawal.

The limited information does not allow conclusions to be made regarding this important potential risk.

(Continued)

Table 18.19: Important Potential Risk: Drug Abuse and Drug Dependence (Continued)

Nature of the Risk	CONCERTA has a unique pharmaceutical design that prohibits the dosage form from being crushed, opened, or emptied making it virtually impossible to abuse it through injection, snorting, or inhalation means. In addition, it is a long-acting prolonged-release product and high, spiking blood levels that individuals may perceive as euphoric effects cannot be achieved with an intact dosage form. Due to these characteristics the CONCERTA formulation would probably not be the preferred choice for methylphenidate abuse.
Background Incidence / Prevalence	Incidence: Not applicable Prevalence: Studies of ADHD and substance use disorder (SUD) include epidemiologic data of prevalence in patients with ADHD or SUD as the primary diagnosis. In studies of adolescents with SUD, the rates of comorbid ADHD have been noted to range from 23% to 31% (Hovens 1994, DeMilo 1989, Milin 1991). Adults with alcohol use disorder or SUD have high rates of childhood (35%-71%) and current (15%-25%) ADHD (Wilens 1995, Goodwin 1975, Levin 1998, Schubiner 2000). Another set of studies has prospectively followed children and adolescents with ADHD to determine what factors contributed the highest risk for developing SUD, including other disruptive behavioural disorders, and what reduced the risk of SUD in children and teens with ADHD. Investigators at the Massachusetts General Hospital conducted 2 large prospective studies that followed boys and girls with ADHD into adolescence and adulthood (Biederman 2006a; Biederman 2006b). They found an earlier onset and higher rates of substance abuse in children with ADHD than in their same-sex peers who did not have ADHD. In all, 13% of girls with ADHD had used illicit substances, and 4% had used alcohol in adolescence (control peers, 3% and 0%, respectively); 26% of boys had used alcohol and 21% reported drug abuse (control peers, 16% and 11%).
Background Incidence / Prevalence (Continued)	A recent study on age at initiation of methylphenidate treatment and the risk of substance abuse in later life reported that the later the age of initiation of methylphenidate treatment, the greater the chances of developing substance use disorders (Mannuzza 2008). However, subjects were entered in this observational study between the ages of 6 to 12 years, while the follow up of subjects occurred in adolescence or adulthood. A meta-analysis comparing stimulant-treated versus untreated youths with ADHD reported that for those patients receiving treatment in childhood a reduction (pooled estimate of the odds ratio indicated a 1.9-fold reduction) in the risk for substance abuse disorder was observed (Wilens 2003).
Risk Groups or Risk Factors	Patients with a history of drug dependence or alcoholism are potentially at risk as these patients may be more likely to abuse this product.

(Continued)

Table 18.19: Important Potential Risk: Drug Abuse and Drug Dependence (Continued)

Potential Mechanisms	CONCERTA is a central nervous system stimulant that regulates various neurotransmitter, most specifically dopamine. Numerous animal studies have examined the acute effects of methylphenidate on behaviour and neurochemistry. In the rat, both methylphenidate and amphetamine increase dopamine levels in all major terminal areas, including the nucleus accumbens and other areas of the brain reward circuitry, characteristic of drugs with abuse liability (Fone 2005). The long-term effects of psychostimulants on behaviour are controversial and are dependent on age, dose, and route of administration. Pre-exposure of young rats to low doses of methylphenidate (2-4 mg/kg) for 4 to 7 days starting at postnatal day 28-35 was shown associated with an increase in self-administration of cocaine, attenuation of stimulated striatal dopamine release, and reduced ventral segmental dopaminergic neuronal firing after 1-2 weeks of withdrawal. These effects are consistent with increased addiction liability following longer-term treatment of young rats (Fone 2005).
Preventability	In general, the abuse of methylphenidate may be reduced by accurate education of physicians, pharmacists, and patients about ADHD, including diagnosis and management, as this will increase understanding of the appropriate use, and abuse potential, of methylphenidate. CONCERTA should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence. Careful supervision is required during withdrawal from abusive use since severe depression may occur.
Potential Public Impact of Safety Concern	The limited number of paediatric reports in the postmarketing database supports that CONCERTA treatment confers a low risk of drug dependence. The formulation makes it difficult, if not impossible to effectively abuse; therefore, is not expected to have an impact with respect to overall public health.

(Continued)

Table 18.19: Important Potential Risk: Drug Abuse and Drug Dependence (Continued)

Regulatory Action Taken	The EU CONCERTA (Annex 2) SmPC states the following precautionary text in Section 4.4: "Patients should be carefully monitored for the risk of diversion, misuse and abuse of methylphenidate. Methylphenidate should be used with caution in patients with known drug or alcohol dependency because of a potential for abuse, misuse or diversion. Chronic abuse of methylphenidate can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes can occur, especially in response to parenteral abuse. Patient age, the presence of risk factors for substance use disorder (such as co-morbid oppositional-defiant or conduct disorder and bipolar disorder), previous or current substance abuse should all be taken into account when deciding on a course of treatment for ADHD. Caution is called for in emotionally unstable patients, such as those with a history of drug or alcohol dependence, because such patients may increase the dosage on their own initiative." Additionally, the EU CONCERTA SmPC states in Section 4.2 (ongoing monitoring) that patients should be monitored for the risk of diversion, misuse and abuse of methylphenidate. "Cases of abuse and dependence have been described, more often with immediate release formulations" is listed as an ADR in Section 4.8 of the EU SmPC with a frequency of not known.
Evidence Source	Biederman J (2006a), Monuteaux MC, Mick E, et al. Psychopathology in females with attention-deficit/hyperactivity disorder: a controlled, five-year prospective study. Biol Psychiatry 2006;60:1098-1105. Biederman J (2006b), Monuteaux MC, Mick E, et al. Young adult outcome of attention deficit hyperactivity disorder: a controlled 10-year follow-up study. Psychol Med 2006b;36:167-179. Benefit Risk Management Report (PSUR 2007). Periodic Safety Update Report. OROS methylphenidate HCl (From 01 Aug 2006 to 10 August 2007). Document ID No. EDMS-USRA-10519290:2.0. J&JPRD (26 Sep 2007). Benefit Risk Management Report (PSUR 2009). Periodic Safety Update Report. OROS® methylphenidate HCl (From 11Aug2008-10Aug2009). Document ID No. EDMS-USRA-EDMS-USRA-11227189. J&JPRD (25 September 2009). DeMilo L (1989). Psychiatric syndromes in adolescent substance abusers. Am J Psychiatry 1989;146:1212-1214. Fone KCF (2005), Nutt DJ. Stimulants: use and abuse in the treatment of attention deficit hyperactivity disorder. Curr Opin Pharmacol 2005;5:87–93. Goodwin DW (1975), Schulsinger F, Hermansen L, Guze SB, Winokur G. Alcoholism and the hyperactive child syndrome. J Nerv Ment Dis 1975;160:349-353.

(Continued)

Table 18.19: Important Potential Risk: Drug Abuse and Drug Dependence (Continued)

Evidence Source (Continued)	Hovens JG (1994), Cantwell DP, Kiriakos R. Psychiatric comorbidity in hospitalized adolescent substance abusers. J Am Acad Child Adolesc Psychiatry 1994;33:476-483. Levin FR (1998), Evans S, Kleber HD. Prevalence of adult attention-deficit/hyperactivity disorder among cocaine abusers seeking treatment. Drug Alcohol Depend 1998;52:15-25. Mannuzza S (2008), Klein RG, Truong NL. Age of methylphenidate treatment initiation in children with ADHD and later substance abuse: prospective follow-up into adulthood. Am J Psychiatry 2008;165:604-609. Milin R (1991), Halikas JA, Meller JE, Morse C. Psychopathology among substance abusing juvenile offenders. J Am Acad Child Adolesc Psychiatry 1991;30:569-574. Schubiner H (2000), Tzelepis A, Milberger S, et al. Prevalence of attention-deficit/hyperactivity disorder and conduct disorder among substance abusers. J Clin Psychiatry 2000;61:244-251. Wilens T (1995), Spencer T, Biederman J. Are attention-deficit/hyperactivity disorder and the psychoactive substance use disorders really related? Harv Rev Psychiatry 1995;3:260-262. Wilens TE (2003), Faraone SV, Biederman J, Gunawardene S. Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. Pediatrics 2003;111:179-185.

Table 18.20: Important Potential Risk: Lymphocytic Leukaemia

	Population From Double-Blind Trials		Population From All Trials
Potential Risk: *Lymphocytic leukaemia* *	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	0	0	0
Rate per 1000 person-year†	--	--	0.0
95% confidence interval‡	--	--	0.0, 2.6
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	0
Discontinued Treatment	0	0	0
Resolved/Recovered	0	0	0
Resolved with Continuing Effects	0	0	0
Not Resolved/Not Yet Recovered/Continuing	0	0	0
Severity§			
Mild	0	0	0
Moderate	0	0	0
Severe	0	0	0

* Reported MedDRA preferred terms include: none.

** A subject is counted only once regardless of the number of events.

† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.

‡ CI are two-sided 95% exact Poisson

§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

No adverse events for this important potential risk were reported in clinical trials of CONCERTA. As a result, the causal relationship of relevant adverse events for this potential risk could not be evaluated on the basis of aggregate safety data from clinical trials of CONCERTA.

(Continued)

Table 18.20: Important Potential Risk: Lymphocytic Leukaemia (Continued)

Postmarketing	To review postmarketing reports of lymphocytic leukaemia associated with the use of CONCERTA, a search was conducted of the BRM worldwide safety database (SCEPTRE) of reports received cumulatively through 31 August 2009 (BRM Ticket number HD0362214). It included all spontaneous, postmarketing study, literature, registry, and health-authority reports. The search included CONCERTA as a suspect or concomitant medication, without regard to formulation and dosage forms of the product, and retrieved adverse event reports with the MedDRA (Version 12.0) preferred terms: Acute lymphocytic leukaemia, Acute lymphocytic leukaemia (in remission), Acute lymphocytic leukaemia recurrent, Chronic lymphocytic leukaemia, Chronic lymphocytic leukaemia (in remission), Chronic lymphocytic leukaemia recurrent, Chronic lymphocytic leukaemia stage 0, Chronic lymphocytic leukaemia stage 1, Chronic lymphocytic leukaemia stage 2, Chronic lymphocytic leukaemia stage 3, Chronic lymphocytic leukaemia stage 4, Chronic lymphocytic leukaemia transformation, Lymphocytic leukaemia, T-cell chronic lymphocytic leukaemia. One case (1) of acute lymphatic leukaemia was retrieved (20061106448). Based on this limited information, applying CIOMS III/IV threshold criteria (CIOMS 1999), this review of spontaneous postmarketing reports of lymphocytic leukaemia (from first approval through 31 August 2009) found no evidence of a link with the use of CONCERTA.
Nature of the Risk	A study of automated pharmacy databases from the SEER affiliated cancer registry of Kaiser Permanente Medical Care Program (KPMCP) compared cancer rates at 18 sites among 35,400 subjects who received methylphenidate before the age of 20 years old. The study observed 23 cases of cancer among methylphenidate-exposed subjects versus an expected 20.4 cases as estimated from all KPMCP members (standardised morbidity ratio [SMR]=1.13; 95% CI=0.72-1.70). Methylphenidate use was associated with increased risk of lymphatic leukaemia (SMR=2.64; 95% CI=1.14 - 5.20) (Oestreicher 2007). Although overall incidence is rare, leukaemia is the most common type of childhood cancer, accounting for 30% of all cancers diagnosed in children younger than 15 years. Within this population, acute lymphocytic leukaemia (ALL) accounts for approximately three-quarters of all childhood leukaemia diagnoses. Childhood cases account for about 12% of all leukaemias but make up > 60% of ALL cases (Belson 2007).

(Continued)

Table 18.20: Important Potential Risk: Lymphocytic Leukaemia (Continued)

Background Incidence / Prevalence	The rates of lymphocytic leukaemia in populations with ADHD have not been described in the published literature. The annual incidence of ALL, the most common childhood malignancy, is 3 to 4 cases per 100,000 children (Bhatia 2002). The age specific incidence of ALL per 100,000 in the US has been estimated as follows: under 1 year, 1.8; ages 1-4 years, 7.0; ages 5-9 years, 3.2; ages 10-14 years, 1.8; ages 15-19 years, 1.1 (Redaelli 2005).
Risk Groups or Risk Factors	The pathogenetic events leading to the development of acute lymphoid leukaemia are unknown. Less than 5% of cases are associated with inherited, predisposing genetic syndromes, or with ionising radiation or exposure to specific chemotherapeutic drugs. There is increasing evidence of high birth weight as a potential risk factor, as well as conflicting or isolated reports of additional factors contributing to an increased risk, such as parental occupation, maternal reproductive history, parental tobacco or alcohol use, maternal diet, prenatal vitamin use, exposure to pesticides or solvents, and exposure to high levels of residential, power-frequency magnetic fields (Pui 2008).
Potential Mechanisms	Methylphenidate alters dopamine levels and dopamine was found genotoxic in vitro at high doses as early as 1983 (Stopper 2008): dopamine induced strand breaks, mutations in mammalian cells but not in bacterial assays, and bound to calf thymus DNA. This was considered due to the oxidation of dopamine and the generation of reactive oxygen radicals, semiquinones and quinones. Dopamine was considered unlikely to be genotoxic in vivo (Stopper 2008).
Preventability	Not applicable. The need for continuing drug treatment should be evaluated periodically.
Potential Public Impact of Safety Concern	At present, no cases of ALL have been reported in double-blind trials or open label paediatric studies. A review of the postmarketing database revealed no signal for ALL associated with the use of CONCERTA. Based on the overall use of methylphenidate and the limited reports of ALL to date, it is not expected that this risk will have an impact with respect to overall public health.
Regulatory Action Taken	As part of CHMP's 30 May 2008 second list of outstanding issues, an adequately designed and powered large case-control study was requested, to adequately evaluate the risk of lymphocytic leukaemia with methylphenidate. In the October 2008 response the MAHs of methylphenidate-containing products concluded that such a case-control study did not seem feasible. In November 2008, a Scientific Advisory Group (SAG) meeting concluded that they could not definitively answer the question regarding a signal for a potential increased risk of lymphocytic leukaemia from the study by Oestreicher and colleagues (2007) in the absence of suitably qualified experts. The SAG decided that it was a matter for CHMP to take up once all of the relevant (new) data had been obtained and assessed. MAHs submitted a response on 27 November 2008 to disprove the signal for lymphocytic leukaemia. In the December 2008 Assessment Report, the MHRA added lymphocytic leukaemia as a potential risk to the final core table of identified and potential risks of methylphenidate.

(Continued)

Table 18.20: Important Potential Risk: Lymphocytic Leukaemia (Continued)

Regulatory Action Taken (Continued)	The final study reports CRIT124D2201 (published by Tucker et al 2009) and NCT 00341029 (published by Witt et al 2008) were evaluated by MAHs of methylphenidate-containing products and the findings were submitted to the MHRA and CHMP members for assessment on 30 March 2009. The findings, in addition to similar studies by Walitza et al (2007, 2009) and Ponsa (2009), concluded that methylphenidate does not pose a mutagenic and/or carcinogenic risk associated with cytogenetic damages to exposed humans. The MHRA/CHMP assessment is ongoing.
Evidence Source	Belson M (2007), Kingsley B, Holmes A. Risk factors for acute leukemia in children: a review. Environ Health Perspect 2007;115:138-45. Bhatia S (2002), Sather HN, Heerema NA, et al. Racial and ethnic differences in survival of children with acute lymphoblastic leukemia. Blood 2002;100(6):1957-1964. Council for International Organizations of Medical Sciences (CIOMS) (1999) (Gordon AJ ed). Report of CIOMS Working Groups III and V. Guidelines for preparing core clinical-safety information on drugs 2nd ed. Geneva; 1999. Oestreicher N (2007), Friedman GD, Jiang SF, Chan J, Quesenberry C Jr, Habel LA. Methylphenidate use in children and risk of cancer at 18 sites: results of surveillance analyses. Pharmacoepidemiol Drug Saf 2007;16(12):1268-1272. Ponsa I (2009), Ramos-Quiroga JA, Ribases M et al. Absence of cytogenetic effects in children and adults with attention-deficit/hyperactivity disorder treated with methylphenidate. Mutation Research 2009; 666:44–49. Pui CH (2008), Robison LL, Look AT. Acute lymphoblastic leukaemia. Lancet 2008;371:1030-1043. Redaelli A (2005), Laskin BL, Stephens JM, Botteman MF, Pashos CL. A systematic literature review of the clinical and epidemiological burden of acute lymphoblastic leukaemia (ALL). Eur J Cancer Care 2005;14(1):53-62. Stopper H (2008), Walitza S, Warnke A, Gerlach M. Brief review of available evidence concerning the potential induction of genomic damage by methylphenidate. J Neural Transm 2008;115:331-334. Tucker JD (2009), Suter W, Petibone DM et al. Cytogenetic assessment of methylphenidate treatment in pediatric patients treated for attention deficit hyperactivity disorder. Mutation Research 2009; 677:53-58. Walitza S (2009), Kampf K, Artamonov N, et al. No elevated genomic damage in children and adolescents with attention deficit/hyperactivity disorder after methylphenidate therapy. Toxicol Lett 2009;184(1):38-43.

(Continued)

Table 18.20: Important Potential Risk: Lymphocytic Leukaemia (Continued)

Evidence Source (Continued)	Walitza S (2007), Werner B, Romanos M, et al. Does methylphenidate cause a cytogenetic effect in children with attention deficit hyperactivity disorder? Environ Health Perspect 2007;115:936-940. Witt KL (2008), Shelby MD, Itchon-Ramos N, et al. Methylphenidate and amphetamine do not induce cytogenetic damage in lymphocytes of children with ADHD. J Am Acad Child Adolesc Psychiatry 2008:47:1375-1383.

Table 18.21: Important Potential Risk: Neonatal Cardio-Respiratory Toxicity (Neonatal/Foetal Tachycardia, Respiratory Distress/Apnoea)

	Population From Double-Blind Trials		Population From All Trials
Potential Risk: ***Neonatal cardio-respiratory toxicity (neonatal/foetal tachycardia, respiratory distress/apnoea)****	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	0	0	0
Rate per 1000 person-year†	--	--	0.0
95% confidence interval‡	--	--	0.0, 2.6
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	0
Discontinued Treatment	0	0	0
Resolved/Recovered	0	0	0
Resolved with Continuing Effects	0	0	0
Not Resolved/Not Yet Recovered/Continuing	0	0	0
Severity§			
Mild	0	0	0
Moderate	0	0	0
Severe	0	0	0

* Reported MedDRA preferred terms include: none.

** A subject is counted only once regardless of the number of events.

† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.

‡ CI are two-sided 95% exact Poisson

§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

No adverse events for this important potential risk were reported in clinical trials of CONCERTA. As a result, the causal relationship of relevant adverse events for this potential risk could not be evaluated on the basis of aggregate safety data from clinical trials of CONCERTA.

(Continued)

Table 18.21: Important Potential Risk: Neonatal Cardio-Respiratory Toxicity (Neonatal/Foetal Tachycardia, Respiratory Distress/Apnoea) (Continued)

Postmarketing	To review neonatal cardio-respiratory toxicity in postmarketing safety data, a search was conducted of the BRM worldwide database (SCEPTRE) of reports received cumulatively through 31 August 2009 (BRM Ticket number HD0362214). It included all spontaneous, postmarketing study, literature, registry, and health-authority reports. All cases were retrieved independent of the reporter's relationship attribution. The search included CONCERTA as a suspect or concomitant medication, without regard to formulation and dosage forms of the product, and retrieved adverse event reports with the MedDRA (Version 12.0) preferred terms: Anaesthetic complication neonatal, Arrhythmia neonatal, Bradycardia foetal, Bradycardia neonatal, Cardiac arrest neonatal, Cardio-respiratory arrest neonatal, Cardiomyopathy neonatal, Circulatory failure neonatal, Death neonatal, Drug withdrawal syndrome neonatal, Foetal arrhythmia, Foetal distress syndrome, Foetal heart rate abnormal, Foetal heart rate deceleration, Foetal heart rate decreased, Foetal heart rate disorder, Foetal heart rate increased, Hypertension neonatal, Hypoventilation neonatal, Intrauterine death, Neonatal anoxia, Neonatal asphyxia, Neonatal aspiration, Neonatal cardiac failure, Neonatal hypotension, Neonatal hypoxia, Neonatal multi-organ failure, Neonatal respiratory acidosis, Neonatal respiratory alkalosis, Neonatal respiratory arrest, Neonatal respiratory depression, Neonatal respiratory distress syndrome, Neonatal respiratory failure, Neonatal tachycardia, Neonatal tachypnoea, Pulmonary oedema neonatal, Respiratory disorder neonatal, Tachycardia foetal. One case (1) with the MedDRA preferred term Intra-Uterine Death was identified (20050905614). The maternal case was also reviewed. This report involved a foetus in a 16-year-old female that died "after the 20th gestational week "due to insufficient supply via the placenta." Placental insufficiency has been associated with foetal and perinatal death (Whittle 2006). Applying CIOMS III/IV threshold criteria (CIOMS 1999), no drug-related link between CONCERTA and neonatal cardio-respiratory toxicity was found in the review of this case.

(Continued)

Table 18.21: Important Potential Risk: Neonatal Cardio-Respiratory Toxicity (Neonatal/Foetal Tachycardia, Respiratory Distress/Apnoea) (Continued)

Nature of the Risk	Methylphenidate is a sympathomimetic agent that has the propensity to stimulate the cardiovascular system resulting in changes in vital signs, including increase in heart rate. Drug-induced increase in heart rate is reversible when exposure to the drug ceases. Exposure of the foetus in utero to methylphenidate may potentially lead to an increase in heart rate after delivery. The 2005 report on methylphenidate from the US Center for the Evaluation of Risks to Human Reproduction (CERHR 2005) did not include any reference to cardiac or respiratory toxicity in neonates after exposure during pregnancy in humans or animals. In the EU, cases of neonatal cardio-respiratory toxicity, specifically foetal tachycardia and respiratory distress, have been reported in spontaneous case reports (Sec 4.6, EU SmPC).
Background Incidence / Prevalence	The rates of neonatal cardio-respiratory toxicity in populations with ADHD have not been described in the published literature. The rate of respiratory distress syndrome/hyaline membrane disease among all neonates in the US is 6.6 per 1000 live births (Ventura 1998). In a case series conducted in England, the incidence of respiratory distress syndrome at term was 2.2 per 1000 deliveries (Morrison 1995). Supraventricular tachycardias have been found to occur in about 1 per 250 to 1 per 1000 children in the general population commonly appearing before the patient is 1 month old (Weindling 1996). The peak incidence for presentation of supraventricular tachycardia in children is under 1 year of age, with most infants being less than 1 month of age at diagnosis (Garson 1981).
Risk Groups or Risk Factors	Important risk factors for the development of respiratory distress syndrome at birth are low gestational age, maternal diabetes, prenatal asphyxia, and male sex. The incidence of respiratory distress syndrome is inversely proportional to the gestational age of the neonate, and rarely occurs in neonates more than 36 weeks' gestation. Approximately 10 to 15% of neonates with birth weights less than 2500g are estimated to develop respiratory distress syndrome (Ishisaka 1996). Risk factors for neonatal tachycardia have not been described.
Potential Mechanisms	Methylphenidate is a catecholaminergic (noradrenergic and dopaminergic) agent and has sympathomimetic properties. Sympathomimetics can induce heart rate and blood pressure increases.
Preventability	Methylphenidate is not recommended for use during pregnancy unless a clinical decision is made that postponing treatment may pose a greater risk to the pregnancy.
Potential Public Impact of Safety Concern	At present, a limited amount of data from the use of methylphenidate in pregnant women is available. Foetal tachycardia and respiratory distress have been reported in spontaneous case reports. Based on the overall use of methylphenidate and the limited reports of neonatal cardiac or respiratory toxicity to date, it is not expected that this risk will have an impact with respect to overall public health.

(Continued)

Table 18.21: Important Potential Risk: Neonatal Cardio-Respiratory Toxicity (Neonatal/Foetal Tachycardia, Respiratory Distress/Apnoea) (Continued)

Regulatory Action Taken	The safety of the use of methylphenidate containing products during pregnancy and lactation was assessed by the CHMP as part of the Article 31 referral procedure and further discussed in the Safety Working Party in December 2008. The core EU SmPC was amended to include the following (Pregnancy, Section 4.6): "Cases of neonatal cardio-respiratory toxicity, specifically foetal tachycardia and respiratory distress have been reported in spontaneous case reports."
Evidence Source	Center for the Evaluation of Risks to Human Reproduction (CERHR) (2005), National Toxicology Program, US Department of health and Human Services), 2005. NTP-CERHR monograph on the potential human reproductive and developmental effects of methylphenidate. NIH Publication No. 05-4473. Council for International Organizations of Medical Sciences (CIOMS) (1999) (Gordon AJ ed). Report of CIOMS Working Groups III and V. Guidelines for preparing core clinical-safety information on drugs 2nd ed. Geneva; 1999. Garson A Jr (1981), Gillette PC, McNamara DG. Supraventricular tachycardia in children: clinical features, response to treatment, and long-term follow-up in 217 patients. J Pediatr 1981;98:875-882. Ishisaka DY (1996). Exogenous surfactant use in neonates. Ann Pharmacother 1996;30(4):389-398. Morrison JJ (1995), Rennie JM, Milton PJ. Neonatal respiratory morbidity and mode of delivery at term: influence of timing of elective caesarean section. Br J Obstet Gynaecol 1995; 102(2): 101-106. Ventura SJ (1998), Martin JA, Curtin SC, Mathews TJ. Report of final natality statistics, 1996. Mon Vital Stat Rep 1998; 46(11 Suppl):1-99. Weindling SN (1996), Saul JP, Walsh EP. Efficacy and risks of medical therapy for supraventricular tachycardia in neonates and infants. Am Heart J 1996; 131(1): 66-72. Whittle W (2006), Chaddha V, Wyatt P, Huppertz B, Kingdom J. Ultrasound detection of placental insufficiency in women with 'unexplained' abnormal maternal serum screening results, Clin Genet 2006;69:97-104.

Table 18.22: Important Potential Risk: Neonatal Effects on Growth (Via Lactation)

	Population From Double-Blind Trials		**Population From All Trials**
Potential Risk: *Neonatal Effects on Growth (via lactation)**	CONCERTA (N=321) N (%)	Placebo (N=318) N (%)	CONCERTA (N=2854) N (%)
Frequency**	0	0	0
Rate per 1000 person-year†	--	--	0.0
95% confidence interval‡	--	--	0.0, 2.6
Seriousness/outcomes§			
Resulted in Death	0	0	0
Was Serious	0	0	0
Discontinued Treatment	0	0	0
Resolved/Recovered	0	0	0
Resolved with Continuing Effects	0	0	0
Not Resolved/Not Yet Recovered/Continuing	0	0	0
Severity§			
Mild	0	0	0
Moderate	0	0	0
Severe	0	0	0

* Reported MedDRA preferred terms include: none.

** A subject is counted only once regardless of the number of events.

† Person-years: Double-blind CONCERTA=12.6, Double-blind Placebo=10.2; Overall CONCERTA=1426.

‡ CI are two-sided 95% exact Poisson

§ Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event), and Severity (most severe).

No adverse events for this important potential risk were reported in clinical trials of CONCERTA. As a result, the causal relationship of relevant adverse events for this potential risk could not be evaluated on the basis of aggregate safety data from clinical trials of CONCERTA.

(Continued)

Table 18.22: Important Potential Risk: Neonatal Effects on Growth (Via Lactation) (Continued)

Postmarketing	To review neonatal effects on growth in postmarketing safety data, a search was conducted of the BRM worldwide database (SCEPTRE) of reports received cumulatively through 31 August 2009 (BRM Ticket number HD0362214) (This search was not limited to cases that were "via Lactation.") It included all spontaneous, postmarketing study, literature, registry, and health-authority reports. All cases were retrieved independent of the reporter's relationship attribution. The search included CONCERTA as a suspect or concomitant medication, without regard to formulation and dosage forms of the product, and retrieved adverse event reports with the MedDRA (Version 12.0) preferred terms: Foetal growth retardation, Foetal malnutrition, Poor weight gain neonatal, Weight decrease neonatal. One case with the MedDRA preferred term Foetal Growth Retardation was identified (20090808424) and reviewed with the matched maternal case. This case involved a foetus in a 21-year-old female with history of nicotine abuse. Maternal smoking during pregnancy is associated with several adverse developmental outcomes in the offspring (Shea 2008). In addition, the "growth retardation of foetus was doubtful, as it could also be that the date of conception was not correct (2 weeks later than former[ly] suspected)." Based on this limited information, applying CIOMS III/IV threshold criteria (CIOMS 1999), no evidence of a drug-related link between CONCERTA and neonatal effects on growth was found.
Nature of the Risk	Methylphenidate has been found in the breast-milk of women treated with methylphenidate. There is one case report of an infant who experienced an unspecified decrease in weight during the period of exposure but recovered and gained weight after the mother discontinued treatment with methylphenidate (Sec 4.6, EU SmPC). Reversible growth impairment was reported in neonatal rats. In neonatal rats who were treated during Postnatal Days 5 to 24 or Postnatal Days 5 to 15 with methylphenidate, growth impairment was observed on Postnatal Days 35 or 55. Growth impairment was not observed in peri-adolescent rats on Postnatal Days 35 to 54 or Postnatal Days 55 and 85. Reversibility of growth impairment in neonatal rats was both rapid and complete (Pizzi 1986, Pizzi 1987). Pregnant rats or rabbits administered methylphenidate during organogenesis did not show any foetal growth related effects at AUC doses of 11.7 (rats) and 3.79 (rabbits) times the maximum human therapeutic dose (Teo 2003). Likewise adult rats administered methylphenidate (up to 40 mg/kg, d,l- methylphenidate) during pregnancy and lactation (Gestation Day 7 - Postnatal Day 20) showed no offspring growth (by measured body weight) related effects (Teo 2002).

(Continued)

Table 18.22: Important Potential Risk: Neonatal Effects on Growth (Via Lactation) (Continued)

Background Incidence / Prevalence	Unknown
Risk Groups or Risk Factors	Unknown
Potential Mechanisms	It has been hypothesised that a persistent, stimulant-induced, increase in hypothalamic dopamine may affect pituitary function, thus slowing growth. Acute administration of methylphenidate increases growth hormone and decreases prolactin, but no consistent changes in plasma levels of these hormones have been documented during chronic treatment in children with ADHD.
Preventability	A decision must be made whether to discontinue breast-feeding or to abstain from methylphenidate treatment considering the benefit of breast feeding for the child and the benefit of therapy for the woman.
Potential Public Impact of Safety Concern	At present, a limited amount of data from the use of methylphenidate in pregnant women is available. Reduction in the rate of growth of neonates has been reported in preclinical juvenile toxicity studies only. Based on the overall use of methylphenidate and the limited reports of neonatal growth retardation in humans to date, it is not expected that this risk will have an impact with respect to overall public health.
Regulatory Action Taken	The safety of the use of methylphenidate containing products during pregnancy and lactation was assessed by the CHMP as part of the Article 31 referral procedure and further discussed in the Safety Working Party in December 2008. The core EU SmPC was amended to include the following (Lactation, Section 4.6): "Methylphenidate has been found in the breast-milk of a woman treated with methylphenidate. There is one case report of an infant who experienced an unspecified decrease in weight during the period of exposure but recovered and gained weight after the mother discontinued treatment with methylphenidate. A risk to the suckling child cannot be excluded."
Evidence Source	Council for International Organizations of Medical Sciences (CIOMS) (1999) (Gordon AJ, ed). Report of CIOMS Working Groups III and V. Guidelines for preparing core clinical-safety information on drugs 2nd ed. Geneva; 1999. Pizzi WJ (1987), Rode EC, Barnhart JE. Differential effects of methylphenidate on the growth of neonatal and adolescent rats. Neurotoxicol Teratol 1987; 9: 107-11. Pizzi WJ (1986), Rode EC, Barnhart JE. Methylphenidate and growth: demonstration of a growth impairment and a growth-rebound phenomenon. Dev Pharmacol Ther 1986;9(5):361-368. Shea AK (2008), Steiner M. Cigarette smoking during pregnancy. Nicotine Tob Res. 2008;10(2):267-278. Teo SK (2003), Stirling DI, Hoberman AM, et al. D-methylphenidate and D,L-methylphenidate are note developmental toxicants in rats and rabbits. Birth Defects Res Part B Dev Reprod Toxicol 2003; 68:162-171. Teo SK (2002), Stirling DI, Thomas SD, Hoberman AM, Christian MS, Khetani VD. The perinatal and postnatal toxicity of D-methylphenidate and D,L-methylphenidate in rats. Reprod Toxicol 2002;16:353-366.

1.6. Identified and Potential Interactions With Other Medicinal Products, Food, and Other Substances

Important identified interactions with other medicinal products are described in Table 19. In humans, methylphenidate is metabolised primarily by de-esterification to α-phenyl-2-piperidine acetic acid (PPAA). After oral administration of radiolabelled methylphenidate in humans, methylphenidate was extensively metabolised and approximately 80% of the radioactivity was excreted in urine in the form of PPAA (Faraj 1974). Since the de-esterification of methylphenidate is not an oxidative process involving liver microsomes, the potential for metabolic drug-drug interactions is limited. There are no data to suggest that the absorption of methylphenidate occurs via a transporter system. Thus, inducers or inhibitors of cytochrome P450 are not expected to have any relevant impact on methylphenidate pharmacokinetics. Conversely, the d- and l-enantiomers of methylphenidate do not relevantly inhibit cytochrome P450 1A2, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A.

There is no food effect with CONCERTA, based on the results of studies in adults (EU MAA 21-121\Mod5.3.3.1\Study C-99-002 and Study C-99-025) and children (EU MAA 21 121\ Mod5.3.3.2\Study C-97-033).

Table 19: Identified Interactions With Other Medicinal Products

Interacting Substance	**Anti-Hypertensive Drugs**
Effect of interaction	The effectiveness of anti-hypertensive drugs may be decreased when taken with methylphenidate. MedDRA terms: blood pressure increased, blood pressure systolic increased, blood pressure diastolic increased, hypertension
Evidence source	EU MAA 21-121\ISS Section 11.0: Vital Signs
Possible mechanisms	Methylphenidate is a catecholaminergic agent (noradrenergic and dopaminergic) and has sympathomimetic properties. Sympathomimetics can induce heart rate and blood pressure increases; an effect that may reduce the effectiveness of anti hypertensive agents.
Potential health risk	Analysis of data from clinical trials of methylphenidate in patients with ADHD data showed that a greater proportion of subjects assigned to methylphenidate experienced an increase from baseline in systolic and diastolic blood pressure of more than 10 mm Hg relative to placebo. The short- and long-term clinical consequences of these cardiovascular effects are not known, but the possibility of clinical complications cannot be excluded as a result of the effects observed in the clinical trial data. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate.
Discussion	Methylphenidate is a sympathomimetic agent that has the propensity to stimulate the sympathetic nervous system, resulting in changes in vital signs, including blood pressure elevation. Drug-induced blood pressure elevation should be distinguished from hypertension. Drug-induced elevation in blood pressure is reversible when the drug is discontinued. Hypertension is a chronic state that persists when medications are withdrawn. Methylphenidate is associated with blood pressure elevations that do not persist when therapy is discontinued.
Interacting substance	**Drugs that elevate blood pressure**
Effect of interaction	Methylphenidate may exacerbate the effect of drugs that elevate blood pressure. The combination of methylphenidate and monoamine oxidase inhibitors may result in a possible hypertensive crisis (Markowitz 1999). MedDRA terms: blood pressure increased, blood pressure systolic increased, blood pressure diastolic increased, hypertension
Evidence source	Markowitz 1999, EU MAA 21-121\ISS Section 11.0: Vital Signs
Possible mechanisms	Methylphenidate is a catecholaminergic agent (noradrenergic and dopaminergic) and has sympathomimetic properties. Sympathomimetics can induce heart rate and blood pressure increases; an effect that may exacerbate the effects of drugs that elevate blood pressure.

(Continued)

Table 19: Identified Interactions With Other Medicinal Products (Continued)

Interacting substance	**Drugs that elevate blood pressure (Continued)**
Potential health risk	See Potential health risk under Antihypertensive drugs. Risk of hypertensive crisis with concomitant use of methylphenidate and monoamine oxidase inhibitors.
Discussion	Caution is advised in patients being treated with methylphenidate with any other drug that can also elevate blood pressure. Methylphenidate is contraindicated in patients being treated (currently or in the preceding 2 weeks) with non-selective, irreversible monoamine oxidase inhibitors.
Interacting substance	**Alcohol**
Effect of interaction	An expected effect of alcohol is that it may exacerbate the adverse central nervous system effects of psychoactive drugs, including methylphenidate.
Evidence source	Markowitz 2000, Patrick 2007
Possible mechanisms	Alcohol may selectively increase circulating plasma concentrations of d-methylphenidate.
Potential health risk	The more pronounced stimulant effects when alcohol is coadministered with methylphenidate may have abuse liability implications. It is advisable for patients to abstain from alcohol during methylphenidate treatment.
Discussion	It is possible that ethanol could reduce the rate of conversion of methylphenidate to ritalinic acid (Markowitz 2000). A metabolic drug-drug interaction resulting in the formation of a new active metabolite, ethylphenidate, has been reported in cases where methylphenidate was coadministered with ethanol (Markowitz 2000). This central nervous system active metabolite may contribute to the catecholamineric effects of methylphenidate in some patients depending upon the dosage of methylphenidate and the amount of alcohol consumed. Ethanol elevates plasma d-methylphenidate C_{max} and area under the concentration–time curve by approximately 40% and 25%, respectively (Patrick 2007).
Interacting substance	**Halogenated anaesthetics**
Effect of interaction	There is a risk of sudden blood pressure increase during surgery. Methylphenidate may exacerbate this effect. MedDRA terms: blood pressure increased, blood pressure systolic increased, blood pressure diastolic increased, hypertension
Evidence source	EU MAA 21-121\ISS Section 11.0: Vital Signs, Ririe 1997

(Continued)

Table 19: Identified Interactions With Other Medicinal Products (Continued)

Interacting substance	**Halogenated anaesthetics (Continued)**
Possible mechanisms	Available data provide little information about the precise nature of the interaction of methylphenidate with anaesthetic agents (Ririe 1997).
Potential health risk	There is a risk of sudden increase in blood pressure during surgery with the use of halogenated anaesthetics; concomitant use of methylphenidate may exacerbate this effect.
Discussion	If surgery is planned, methylphenidate treatment should not be used on the day of surgery.
Interacting substance	**Centrally acting alpha-2 agonists (eg, clonidine)**
Effect of interaction	Serious adverse events including sudden death have been reported with the concomitant use of psychostimulants and clonidine. MedDRA term: sudden death
Evidence source	Cantwell 1997, Fenichel 1995, Tourette's Syndrome Study Group 2002
Possible mechanisms	Available data provide little information about the mechanism of the interaction of methylphenidate with clonidine resulting in adverse cardiovascular effects. Coadministration of methylphenidate and oral clonidine may decrease the plasma concentrations of clonidine. It has been suggested that methylphenidate inhibits absorption of oral clonidine.
Potential health risk	The safety of using methylphenidate in combination with clonidine was evaluated in a placebo-controlled trial in children with ADHD and comorbid tic disorder (Tourette's Syndrome Study Group 2002). Study medications were tolerated well except that sedation was common in subjects receiving clonidine (48%). The report of moderate to severe sedation was less common among subjects treated with methylphenidate in combination with clonidine (21%) than among those receiving clonidine alone (35%). The safety of using methylphenidate with clonidine or other alpha-2. agonists has not otherwise been systematically evaluated.
Discussion	Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established (Cantwell 1997; Fenichel 1995).
Interacting substance	**Dopaminergic drugs**
Effect of interaction	Methylphenidate use with dopaminergic drugs may be associated with pharmacodynamic interactions.
Evidence source	Armenteros 2007, Gunther 2006, Kutcher 2004, Levy 1988, Levy 1996, Seeman 1998, Taylor 2004, Wald 1978
Possible mechanisms	A predominant action of methylphenidate is to increase extracellular dopamine levels. Methylphenidate may be associated with pharmacodynamic interactions when coadministered with direct and indirect dopamine agonists (including dihydrophenylalanine [DOPA] and tricyclic antidepressants) as well as dopamine antagonists (including antipsychotics such as haloperidol).

(Continued)

Table 19: Identified Interactions With Other Medicinal Products (Continued)

Interacting substance	**Dopaminergic drugs (Continued)**
Potential health risk	Stimulant medications exert their therapeutic effect in ADHD by increasing dopamine and norepinephrine in the interneuronal space. Both of these neurotransmitters may have a role in the aetiology of psychiatric symptoms.
Discussion	Current clinical guidelines recommend the use of the atypical antipsychotic, risperidone, in combination with methylphenidate for the management of individual, difficult-to-treat children and adolescents with ADHD. While an International Consensus Statement only suggests using risperidone in addition to methylphenidate for the treatment of ADHD and comorbid disruptive behavioural disorder (Kutcher 2004), the European Clinical Guidelines on Hyperkinetic Disorder also allow for the use of combination therapy for treatment-refractory ADHD (ie, if methylphenidate monotherapy fails) (Taylor 2004). Clinical data have recently become available to document the beneficial effect of augmentation therapy with risperidone in patients with ADHD (and comorbid disruptive behavioural disorder) who fail treatment with stimulants alone, including methylphenidate (Armenteros 2007, Gunther 2006). The data document the relative safety of the combination therapy. Data from human pharmacology studies evaluating the effect of haloperidol on relevant pharmacodynamic measures of methylphenidate treatment do not suggest a direct antagonistic effect. In 2 studies published by Levy et al, haloperidol without methylphenidate resulted in a directionally opposite effect on the continuous performance test in subjects with ADHD (Levy 1988, Levy 1996). The opposing effect of haloperidol on methylphenidate for relevant outcomes may be a result of sedation or motor slowing rather than a direct effect of haloperidol on attention. The outcome measures evaluated in the studies by Levy et al. and Wald et al (ie, errors of commission and omission, reaction time in the continuous performance test, euphoria, speed of speech) may not be directly relevant for the therapeutic effect of methylphenidate in the treatment of ADHD (Levy 1988, Levy 1996, Wald 1978). The role of D2 receptors in the therapeutic effect of methylphenidate, ie, a DAT inhibitor, in ADHD is still being debated. There is preclinical evidence to suggest that D2 receptor density and the functional state of D2 receptors only affect the pharmacological effect of methylphenidate to a limited extent (Seeman 1998).
Interacting substance	**Coumarin anticoagulants**
Effect of interaction	Higher plasma concentrations and, hence, greater effects of coumarin.
Evidence source	Bellward 1969, Garrettson 1969, Hague 1971, Hunninghake 1970
Possible mechanisms	Methylphenidate may inhibit the metabolism of coumarin anticoagulants.
Potential health risk	When starting or stopping treatment with methylphenidate, it may be necessary to adjust the dosage of these drugs already being taken and establish coagulation times.

(Continued)

Table 19: Identified Interactions With Other Medicinal Products (Continued)

Interacting substance	**Coumarin anticoagulants (Continued)**
Discussion	The data are conflicting. A preliminary study in 4 healthy volunteers showed a slight increase in the elimination half-life of ethyl biscoumacetate (Garrettson 1969) when combined with methylphenidate. This effect was not supported in a double-blind interaction study conducted in 12 healthy subjects (Hague 1971). Furthermore, other studies conducted in dogs have also found no effect of methylphenidate on ethyl-biscoumacetate (Bellward 1969) or warfarin (Hunninghake 1970) metabolism.
Interacting substance	**Anticonvulsants (eg, phenobarbital, phenytoin, primodone)**
Effect of interaction	Possible increase in effect of anticonvulsants.
Evidence source	Markowitz 1999
Possible mechanisms	Methylphenidate may inhibit the metabolism of anticonvulsants such as phenobarbital, phenytoin, and primodone.
Potential health risk	When starting or stopping treatment with methylphenidate, it may be necessary to adjust the dosage of these drugs already being taken and establish drug plasma concentrations.
Discussion	Several case reports indicate that methylphenidate inhibits metabolism of phenytoin; however, studies specifically designed to evaluate such an interaction have failed to detect one, and systematic evaluation of this potential interaction has failed to support case reports (Markowitz 1999). Given that these interactions do not occur in all instances, a pharmacogenetic component may be involved.
Interacting substance	**Antidepressants (tricyclic antidepressants and serotonin reuptake inhibitors)**
Effect of interaction	Possible increase in effect of these antidepressants.
Evidence source	Cooper 1973, Findling 1996, Gammon 1993, Markowitz 1999, McGlohn 1995, Stoll 1996, Wharton 1971
Possible mechanisms	Methylphenidate may inhibit the metabolism of tricyclic antidepressants and serotonin reuptake inhibitors, resulting in higher systemic exposure to these drugs. In some patients, coadministration of methylphenidate with tricyclic antidepressants, such as imipramine, increases concentrations of imipramine (Wharton 1971, Cooper 1973, Markowitz 1999). Methylphenidate may also increase concentrations of the N-desmethyl metabolite of desipramine when the 2 are administered in combination (Cooper 1973, Markowitz 1999). Selective serotonin reuptake inhibitors are metabolised by CYP 2D6, and there have been reports of adverse events possibly indicative of a drug interaction in patients receiving sertraline and methylphenidate (McGlohn 1995). Several reports indicate that combinations of selective serotonin reuptake inhibitors with methylphenidate are tolerated.

(Continued)

Table 19: Identified Interactions With Other Medicinal Products (Continued)

Interacting substance	Antidepressants (tricyclic antidepressants and serotonin reuptake inhibitors) (Continued)
Potential health risk	When starting or stopping treatment with methylphenidate, it may be necessary to adjust the dosage of these drugs already being taken and establish drug plasma concentrations.
Discussion	Literature reports on drug interactions with methylphenidate and antidepressants suggested an influence of methylphenidate on the disposition of these drugs, but not an influence of antidepressants on methylphenidate (Markowitz 1999). Many tricyclic antidepressants are metabolised by CYP 2D6. In some patients, coadministration of methylphenidate with tricyclic antidepressants increases concentrations of the antidepressant (Wharton 1971, Cooper 1973, Markowitz 1999). Several reports indicate that combinations of selective serotonin receptor inhibitors with methylphenidate are well tolerated (Stoll 1996). Gammon and Brown (1993) treated patients with a combination of fluoxetine and methylphenidate. Findling (1996) treated 4 patients (11-16 years of age) with methylphenidate (10-40 mg/day) and either fluoxetine or sertraline without any significant adverse events reported.

1.7. Epidemiology of the Indication (Attention Deficit Hyperactivity Disorder) and Important Adverse Events

1.7.1. Incidence, Prevalence, Mortality and Demographic Profile of the Target Population (Attention Deficit Hyperactivity Disorder)

ADHD is a developmental condition of inattention and distractibility, with or without accompanying hyperactivity. In the past, various terms were used to describe this condition, including hyperactive syndrome and, from the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM–III), "minimal brain dysfunction." In the revised DSM-III, this condition was renamed ADHD. In the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (APA DSM-IV-TR), adults or children must have had an onset of symptoms before age 7 years that caused significant social or academic impairment.

According to DSM-IV-TR, the essential feature of ADHD is a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequently displayed and more severe than is typically observed in individuals at a comparable level of development. Some hyperactive-impulsive or inattentive symptoms that cause impairment must have been present before age 7 years, although many individuals are diagnosed after the symptoms have been present for a number of years, especially in the case of individuals with the Predominantly Inattentive Type. Some impairment from the symptoms must be present in at least 2 settings (eg, at home and at school or work). There must be clear evidence of interference with developmentally appropriate social, academic, or

occupational functioning. The disturbance does not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and is not better accounted for by another mental disorder (eg, a Mood Disorder, Anxiety Disorder, Dissociative Disorder, or Personality Disorder).

1.7.1.1. Incidence of ADHD

ADHD is typically chronic in nature with an unclear onset; therefore, prevalence provides a better estimate of the burden of ADHD disease.

1.7.1.2. Prevalence of ADHD

ADHD is one of the most common neurobehavioural disorders of childhood and can persist through adolescence and into adulthood. According to DSM-IV the prevalence of ADHD is estimated at 3% to 7% of school-age children. The reported rates vary depending on the nature of the population sampled and the method of ascertainment. Data on prevalence in adolescence and adulthood are limited. However, community samples of adolescents report prevalence estimates between 1.5% and 6% (Cuffe 2001).

Selected country-specific prevalence of ADHD is provided in Table 20.

Table 20: Selected Country-Specific Prevalence of ADHD

	Age Group (Years)	Prevalence Rate (%)
NORTH AMERICA		
U.S.[a]	8 to 15	8.7
U.S.[b]	4 to 18	7.8
U.S.[c]	7 to 11	5.4
Canada[d]	4 to 16	6
EUROPE		
UK[e]	4 to 16	5
UK[f]	4 to 16	2
France		Unknown
Germany[g]	4 to 16	2 to 4
Italy		Unknown
Spain		Unknown
WORLDWIDE		
Worldwide[h]	18 and under	5.29
Worldwide[i]	school-age children	2 to 18
Worldwide[j]	children	5 to 10

Notes and Sources:

[a] Prevalence of children age 8 to 15 meeting DSM-IV criteria for ADHD (Archives of Pediatrics and Adolescent Medicine; V.161; No.9; 9/07; p857)

[b] Prevalence of ever-diagnosed ADHD in 2003; (The New England Journal of Medicine; V.354; No.25; 6/22/06; p2637)

[c] Estimated prevalence of an ADHD diagnosis in a nationally representative sample (Pediatrics; V.117; No.4; 4/06; p e601)

[d] ADHD prevalence based on DSM-IV criteria (The Lancet; V.351; 2/7/98; p429)

[e] ADHD prevalence based on DSM-IV criteria;

[f] ADHD prevalence based on ICD-10 criteria (The Lancet; V.351; 2/7/98; p429)

[g] ADHD prevalence based on ICD-10 criteria (The Lancet; V.351; 2/7/98; p429)

[h] ADHD/HD worldwide pooled prevalence in a broad systematic review (American Journal of Psychiatry; V.164; No.6; 6/07; p942)

[i] ADHD prevalence estimate in community samples (Morbidity and Mortality Weekly Report; V.54; No.34; 9/2/05; p842)

[j] ADHD prevalence in children (Biological Psychiatry; V.57; 2005; p1215)

1.7.1.3. Mortality Associated With ADHD

No clear correlation with mortality exists in ADHD. However, studies suggest that childhood ADHD is a risk factor for subsequent conduct and substance abuse problems, which may increase the risk of mortality (Barkley 1996).

1.7.1.4. Potential Health Risk of ADHD

The pathology of ADHD is not clear and the health risk from ADHD is primarily psychosocial. However, exact morbidity has not been quantified. A person with ADHD may struggle with impairments in crucial areas of life, including relationships with peers and family members, and performance at school or work. Some studies have demonstrated increases in substance abuse, risk-taking, and criminal behaviours among adolescents and adults who have ADHD (Cuffe 2005). Increases in unintentional injuries and health care utilisation have been noted in some studies of people with ADHD (DiScala 1998; Cuffe 2005).

1.7.1.5. Demographic Profile of Target Population With ADHD

Variation in the **geographic distribution** of ADHD has been observed across studies (See Prevalence Section). The differences in prevalence rates reported across countries may be cultural ("environmental expectations") and due to the heterogeneity of ADHD (ie, the many etiological paths to get to inattention/distractibility/hyperactivity). Furthermore, the International Classification of Diseases, 10th Revision (ICD-10) criteria for ADHD used in Great Britain may be considered stricter than the DSM-IV-TR criteria (Cuffe 2005).

According to DSM-IV-TR, ADHD is a developmental disorder that requires an onset of symptoms before **age** 7 years. It is difficult to establish this diagnosis in children younger than age 4 or 5 years, because their characteristic behaviour is much more variable than that of older children and may include features that are similar to symptoms of ADHD. After childhood, symptoms may persist into adolescence and adulthood, or they may ameliorate or disappear. The percentages in each group are not well established, but as many as 65% of children with ADHD will have ADHD or some residual symptoms of ADHD as adults.

ADHD is more frequently diagnosed in males than in females, with male-to-female ratios ranging from 2:1 to 9:1, depending on the type (ie, the Predominantly Inattentive Type may have a **gender** ratio that is less pronounced) and setting (ie, clinic-referred children are more likely to be male). This male predominance is particularly pronounced in young children, and decreases with increasing age. The predominantly inattentive type of ADHD is found more commonly in girls than in boys. One study reported 92% of girls with ADHD received a diagnosis of primarily inattentive type (Cuffe 2005).

The current literature on **racial and ethnic differences** in psychiatric disorders derives mainly from behaviour and symptom checklist data. There is evidence of possible differences by race and ethnicity in the prevalence of psychiatric disorders in general and ADHD in particular (Cuffe 2005), and cross-cultural differences of psychiatric symptoms. Two reports show that overall Child Behaviour Checklist scores were higher in the United States than in Puerto Rico or the Netherlands. In addition, in the Methods for the Epidemiology of Child and Adolescent Mental Disorders study, the prevalence of ADHD varied dramatically across sites despite the fact that they all used the same methodology. ADHD prevalence ranged from a low of 1.6% in the largely Hispanic Puerto Rico site to a high of 9.4% in the Atlanta, Georgia site (Jensen 1999). Native American children had a lower rate of ADHD in the Great Smoky Mountains Study, but the difference was not statistically significant. On the other hand, there are several studies reporting that black children had higher rates of ADHD symptoms than white children. However, in a study examining the 1998 National Health Interview Survey, white parents

more frequently reported they were told by a health care professional that their child had ADHD (Cuffe 2005).

1.7.2. Comorbidity in the Target Population

Important comorbidities in patients with ADHD are described in Table 21.

Lists of concomitant medications for the identified comorbidities have been prepared using a search of primary published literature, national practice guidelines, governmental communications, electronic medical records, and payer databases. The drugs listed reflect those drugs with documented utilisation for each comorbidity and do not necessarily reflect drugs approved by any specific country for the treatment of the comorbidities listed.

Table 21: Important Comorbidities of Attention Deficit Hyperactivity Disorder

Comorbidity	**Autism**
Incidence of comorbidity	Unknown
Prevalence of comorbidity	According to a study from the U.S., ADHD was diagnosed in 31% of the children with autism. The rate is increased to nearly 55% when subsyndromal cases are included. (Leyfer 2006)
Mortality of comorbidity	Unknown
Coprescribed medicinal products:	Buspirone, clomipramine, clonidine, fluoxetine, fluvoxamine, haloperidol, risperidone, secretin
Comorbidity	**Restless Legs Syndrome (RLS)**
Incidence of comorbidity	Unknown
Prevalence of comorbidity	In clinical samples, up to 44% of subjects with ADHD have been found to have RLS or RLS symptoms, and up to 26% of subjects with RLS have been found to have ADHD or ADHD symptoms. RLS symptoms are usually under diagnosed in ADHD children because the complaint of RLS dysaesthesia in children is usually mild and intermittent. RLS is usually progressive, and it is thus likely that these children will become more symptomatic in the future. (Cortese 2005)
Mortality of comorbidity	Unknown
Coprescribed medicinal products:	Cabergoline, carbidopa (Levodopa), Clonazepam, Pergolide, Pramipexole, Ropinirole, Rotigotine, Tramadol
Comorbidity	**Psychiatric Disorders**
Incidence of comorbidity	Unknown
Prevalence of comorbidity	According to a U.S. study, ADHD patients (age 18 years or younger) were treated for mental disorders nearly 5 times more than the matched controls (28.7% versus 5.9%). Significantly higher proportions of the ADHD patient population were treated for mental health comorbidities such as depression, conduct disorder, and oppositional defiant disorder. In both the ADHD patient and control groups, depression was the most common of the selected conditions; however, the prevalence of this comorbidity was more than 4.5-fold higher in the ADHD cohort (17.9% versus 3.9%). (Swensen 2003)
Mortality of comorbidity	Unknown
Coprescribed medicinal products:	Amitriptyline, Chlorpromazine, Fluphenazine, Loxapine, Phenelzine, Perphenazine, Perphenazine, Risperidone, Thioridazine, Thiothixene, Ziprasidone

(Continued)

Table 21: Important Comorbidities of Attention Deficit Hyperactivity Disorder (Continued)

Comorbidity	**Depression**
Incidence of comorbidity	Unknown
Prevalence of comorbidity	In one series of studies, the lifetime prevalence of severe depression among children with ADHD (280 subjects) was 15% in females and 29% in males compared with 1% to 2% of males and females without ADHD. (Fishman 2007) The available literature contains reports that young people with an ADHD diagnosis are at increased risk for suicidal behaviour, as compared to their population age group. A review of the literature by James et al (James 2004) determined that the rate of completed suicide in males (aged 5 to 24 years) with ADHD was between 32 and 39 per 100,000 patients per year, which is roughly 3 times greater than in the general population. A separate study using a US managed care database (Swensen 2002) determined that patients with an ADHD diagnosis (adults and children) were nearly 3 times more likely to make a suicide attempt (OR=2.9 95% CI: 2.4, 3.5) than age and gender-matched controls.
Mortality of comorbidity	Unknown
Coprescribed medicinal products:	Citalopram Hydrobromide, Venlafaxine Hydrochloride, Escitalopram Oxalate, Isocarboxazid, Paroxetine Hydrochloride, Bupropion Hydrochloride, Sertraline Hydrochloride, Amitriptyline
Comorbidity	**Behaviour Disorders**
Incidence of comorbidity	Unknown
Prevalence of comorbidity	About half of children with ADHD referred to clinics have behaviour disorders as well as ADHD (Cuffe 2005); however, it should be noted that the behaviour disorder might have been partially responsible for the referral. Oppositional Defiant Disorder is one of the most common disorders occurring with ADHD (46%). Conduct Disorder is less common (25%) (Cuffe 2005)
Mortality of comorbidity	Unknown
Coprescribed medicinal products:	Bupropion, Fluoxetine, Phenytoin, Carbamazepine, Valproic Acid, Lithium, Clonidine
Comorbidity	**Obsessive-Compulsive Disorder**
Incidence of comorbidity	Unknown
Prevalence of comorbidity	A recent literature review documents that as many as 30% of children and adolescents with obsessive-compulsive disorder also satisfy diagnostic criteria for ADHD. (Geller 2002)
Mortality of comorbidity	Unknown
Coprescribed medicinal products:	Clomipramine, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Citalopram, Phenelzine, Quetiapine

(Continued)

Table 21: Important Comorbidities of Attention Deficit Hyperactivity Disorder (Continued)

Comorbidity	**Anxiety Disorder**
Incidence of comorbidity	Unknown
Prevalence of comorbidity	In a study of 173 U.S. children (ages 8 to 13 years) with a primary anxiety disorder, ADHD was a comorbid diagnosis in 15.0%. (Kendall 2001)
Mortality of comorbidity	Unknown
Coprescribed medicinal products:	Alprazolam, Amitriptyline; Chlordiazepoxide, Amobarbital, Aprobarbital, Meprobamate, Buspirone, Butabarbital, Chloral Hydrate, Chlordiazepoxide, Clorazepate, Diazepam, Doxepin, Duloxetine, Escitalopram, Hydroxyzine, Lorazepam, Mephobarbital, Meprobamate, Midazolam, Oxazepam, Oxymorphone, Paroxetine, Perphenazine, Prazepam, Prochlorperazine, Sertraline, Thioridazine, Trifluoperazine, Venlafaxine, Citalopram, Clonazepam, Droperidol, Estazolam, Fluoxetine, Flurazepam, Fluvoxamine, Gepirone, Isocarboxazid, Kava Kava (Piper methysticum), Nadolol, Nefazodone, Pagoclone, Phenelzine, Pregabalin, Propranolol, Quazepam, Sertindole, Tranylcypromine, Trazodone, Valerian (Valeriana officinalis)
Comorbidity	**Tic Disorders**
Incidence of comorbidity	Unknown
Prevalence of comorbidity	One study evaluating the comorbidity of ADHD and tic disorders enrolled one hundred twenty-eight male children and adolescents with ADHD and 110 male controls who were comprehensively evaluated at baseline and 4 years later. The overall rate of tic disorders was significantly greater in the children with ADHD vs. controls (43/128 [34%] vs. 7/110 [6%], χ^2_1=26, *P*<.001). The rate of tic disorders in subjects with ADHD did not differ by referral source (26/70 [37%] vs. 17/58 [29%], χ^2_1=0.9, *P*=.35; psychiatric vs. paediatric ascertainment, respectively). Among children who did not have a tic disorder reported at baseline, those with ADHD had a greater probability of having a tic disorder reported only at follow-up (21/106 [20%] vs. 3/106 [3%], χ^2_1=15, *P*<. 001). In addition, the probability of a tic disorder being reported only at follow-up was greatest in the ADHD group that was youngest at baseline (12/36 [33%] aged 6-8 years, 5/38 [13%] aged 9-12 years, 4/32 [13%] aged 13 years or older; χ^2_2=6.3, *P*<.05) (Spencer 1995). It is unclear if the observed tic disorders are related to ADHD, treatment, or more diligent assessment of ADHD subjects.
Mortality of condition	Unknown
Coprescribed medicinal products:	See Tourette's syndrome

(Continued)

Table 21: Important Comorbidities of Attention Deficit Hyperactivity Disorder (Continued)

Comorbidity	**Tourette's Syndrome**
Incidence of comorbidity	Unknown
Prevalence of comorbidity	All children aged 5 to 15 years in the county of Varmland (central Sweden) who had been registered with a diagnosis of Tourette's syndrome from 1 January 1995 through 30 June 1998 were examined with regard to clinical symptoms, severity, and comorbidity. Altogether 58 children with a diagnosis of Tourette's syndrome were found. There was a very high rate of comorbid ADHD in these subjects (64%). (Kadesjo 2000)
Mortality of comorbidity	Unknown
Coprescribed medicinal products:	Haloperidol, Pimozide, Clonidine, Mecamylamine, Nicotine, Pergolide, Risperidone, Ziprasidone
Comorbidity	**Injury**
Incidence of comorbidity	Unknown
Prevalence of comorbidity	The main traits of ADHD - inattention and impulsivity/ hyperactivity - may place a person with ADHD at greater risk for certain types of accidents and injuries. Children and adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD) can have more frequent and severe injuries than peers without ADHD. Research indicates that children with ADHD are significantly more likely to be injured as pedestrians or while riding a bicycle, to receive head injuries, injure more than one part of the body, and be hospitalised for accidental poisoning. Children with ADHD may be admitted to intensive care units or have an injury result in disability more frequently than other children (DiScala 1998).
Mortality of comorbidity	Unknown
Coprescribed medicinal products:	Not applicable

1.7.3. Epidemiology of the Identified/Potential Risk in the Target Population (ADHD) When Unexposed to the Product

The epidemiologies of each important identified or potential risk in patients with ADHD when unexposed to CONCERTA are described in Tables 22.1 and 22.2.

Table 22.1: Epidemiology of Each Identified Risk in Patients With ADHD When Unexposed to CONCERTA

Identified risk	**Hypertension**
Incidence of condition	Unknown
Prevalence of condition	Screening surveys of junior and high school-aged children have found the prevalence of hypertension to be between 1% and 2% (Flynn 2001b). A review of studies performed in referral centres suggests that the frequency of primary hypertension among children is increasing over time (Feld 1988; Arar 1994; Flynn 2001a). The proportion of all hypertension in children that was classified as primary has increased from 16% in 1988 to 23% in 1994, and most recently was measured as 48.6%. There have been no published reports showing an increased prevalence of hypertension for children or adolescents diagnosed with ADHD.
Mortality of condition	Unknown
Identified risk	**Tachycardia**
Incidence of condition	The published epidemiology of these CV events has primarily been assessed for the general population of children and adolescents, without determination of ADHD diagnosis. A study that included 26 US community emergency departments (ED) and 2.3 million ED visits found that primary cardiac arrhythmias in those 18 years of age or younger were an infrequent presentation to the ED. The incidence of clinically significant arrhythmias in these patients was reported as 5.7 per 100,000 emergency department visits. Atrial tachyarrhythmia was the most common presentation in this study population (Sacchetti 1999).
Prevalence of condition	The prevalence of cardiac rhythm disturbances in the general population of children has been estimated from large population-based samples from Japan (Niwa 2004). A sample of 152,322 school children, including 71,855 elementary students (ages 5 to 6 years) and 80,467 junior high students (ages 12 to 13 years), was screened for several types of arrhythmias. Any cardiac rhythm disturbance was found in 1.25% of elementary students and 2.32% of junior high students, with the prevalence higher in males than females (2.0% versus 1.38%).
Mortality of condition	Unknown

(Continued)

Table 22.1: Epidemiology of Each Identified Risk in Patients With ADHD When Unexposed to CONCERTA (Continued)

Identified risk	**Raynaud's Phenomenon**
Incidence of condition	Unknown
Prevalence of condition	There are no data on Raynaud's Phenomenon (RP) specific to the ADHD population. It is unknown if there is a difference between the ADHD population and the general paediatric population with respect to RP. A cross-sectional study in England was conducted to determine the prevalence of RP in children ages 12 to 15 years, and its relationship to age and sex. The subjects were 903 school children in the second to fourth year of secondary education from 28 schools in Northwestern England. 720 children (80%) agreed to participate in the study and completed the questionnaire on the occurrence of RP. Responses from 4 children (2 boys, 2 girls) were not usable; 31 children did not report their age and were excluded from the age-based analysis. Among the total study population, 43 (12.2%) of 352 boys and 64 (17.6%) of 364 girls reported symptoms of RP. For boys versus girls by age, the following percentages were reported: 12 years, 9.8% vs. 11.4%; 13 years, 10.3% vs. 13.6%; 14 years, 14.7% vs. 17.9%; and 15 years, 14.3% vs. 44.0%. A total of 14.9% of the study population reported symptoms consistent with RP. The prevalence was higher in girls than in boys, and increased with increasing age. It is reported more frequently in girls, and, despite the narrow age range studied, was shown to increase with age. (Jones 2003)
Mortality of condition	Unknown
Identified risk	**Hallucinations (Auditory, Skin Sensation, Visual Disturbance)**
Incidence of condition	Not Applicable
Prevalence of condition	There is very little published research on the frequency of psychosis, including hallucinations, in young persons with ADHD. One estimate of the background rate in the general population comes from a study in New Zealand, which reported 14% of 11 year olds have had either delusional beliefs or hallucinatory experiences (Poulton 2000). While no data exist on the co-occurrence of psychosis in ADHD patients, one suggestive finding is that adults with schizophrenia have been found to have an increased prevalence of ADHD features in childhood (Pine 1993)
Mortality of condition	Not Applicable
Identified risk	**Psychosis/Mania**
Incidence of condition	Not Applicable
Prevalence of condition	There is very little published research on the frequency of psychosis, including hallucinations, in young persons with ADHD. One estimate of the background rate in the general population comes from a study in New Zealand, which reported 14% of 11 year olds have had either delusional beliefs or hallucinatory experiences (Poulton 2000). While no data exist on the co-occurrence of psychosis in ADHD patients, one suggestive finding is that adults with schizophrenia have been found to have an increased prevalence of ADHD features in childhood (Pine 1993)
Mortality of condition	Not Applicable

(Continued)

Table 22.1: Epidemiology of Each Identified Risk in Patients With ADHD When Unexposed to CONCERTA (Continued)

Identified risk	**Anorexia**
Incidence of condition	The General Practice Research Database (GPRD) was searched for newly recorded cases of anorexia and bulimia nervosa between 1994 and 2000, inclusive. The incidence of anorexia nervosa per 100,000 population for the year 2000 was reported as follows (females versus males): ages 0 to 9 years, 0 (0 vs. 0); 10 to 19 years, 18.0 (34.6 vs. 2.3); 20 to 39 years, 5.5 (10.5 vs. 0.5); 40 years and older, 2.2 (3.7 vs. 0.6); total 4.7 (8.6 vs. 0.7). Over the period studied, annual incidence rates for diagnosed anorexia nervosa remained stable for females aged 10 to 39 years. The rate in 1988 was 18.5 per 100,000 and in the year 2000 the rate was 20.1 per 100,000, with minimal variation in the intervening years. In 2000 the age- and gender-adjusted incidence of anorexia nervosa diagnosed in primary care was 4.7 per 100,000 population. The incidence rate varied dramatically according to the age gender group. The incidence rate for females was 8.6 per 100,000 compared with 0.7 per 100,000 for males. This translated to a relative risk for females to males of 12:1. The highest incidence, 34.6 per 100,000 population, was found in females aged 10 to 19 years. (Currin 2005)
Prevalence of condition	Unknown
Mortality of condition	Unknown
Identified risk	**Decreased Rate of Growth**
Incidence of condition	Unknown
Prevalence of condition	Population norms of height-for-age in European and US children have been established. These charts have been widely used by paediatricians to assess individual growth (Cole 1994). By definition, a child could be identified as being at a certain percentile for height, given their age. There is no agreed-upon threshold that represents a growth deficit among healthy children. European height and weight growth charts commonly extend from the 3rd to the 97th centile, whereas in North America the extremes are usually the 5th and 95th centiles. There is no good reason for the difference, and neither chart is particularly useful for screening owing to the high false positive rate associated with a cut off based on the lowest centile. However, the data are used to compare specific groups to the population and to determine the value of growth deficits by converting group means to Z-scores. Stunting, or marked growth failure, is defined by the WHO as being greater than 2 standard deviations below the population mean of height-for-age. In a 2000 report from the WHO (WHO 2000), the prevalence of stunting among children was estimated to be 2.1% in the US, 5.6% in Japan, and 33% in developing countries. Note that, by definition, if height-for-age follows a normal distribution, 2.5% of children will be classified as "stunted," simply based on statistical principles, because that is the expected percentage of children beyond 2 standard deviations from the mean. Note also that this seems to be using one standard across all countries, which may or may not be appropriate.

(Continued)

Table 22.1: Epidemiology of Each Identified Risk in Patients With ADHD When Unexposed to CONCERTA (Continued)

Identified risk	Decreased Rate of Growth (Continued)
Prevalence of condition (Continued)	Deficits in height in children with ADHD have been long-standing concerns (Spencer 1998). In general, suppressed height gain in early adolescence has been observed among ADHD children treated with stimulants, in several studies (Spencer 1998). A study of 124 referred boys with ADHD and 109 control subjects found a modest height deficit (2.1 cm) between ADHD subjects and controls (Spencer 1996). This deficit was found to be temporary and not related to stimulant treatment. The study authors, along with previous investigators, concluded that ADHD is associated with temporary height deficits that may resolve by late adolescence, and appear to be mediated by ADHD itself and not its treatment (Spencer 1998). The MTA follow-up study was a longitudinal study of stimulant-treated and stimulant-naïve children (7.0 to 9.9 years of age) with ADHD. The study also included 213 non-diagnosed classmates of the children with ADHD. At entry to the MTA study, the stimulant-naïve cohort was greater than expected based on population norms. At the 36-month assessment, the stimulant-naïve cohort was taller and heavier than population norms (Z-height: 0.541; Z-weight: 0.765). The stimulant-naïve cohort was also taller and heavier than the classmate control group. The study observed that those left untreated had a greater growth rate over the 36-month period as opposed to less than that of the classmate control group or the expectation based on population norms (Swanson 2007).
Mortality of condition	Not applicable

Table 22.2: Epidemiology of Each Potential Risk in Patients With ADHD When Unexposed to CONCERTA

Potential risk	**Migraine**
Incidence of condition	According to data from the UK-based General Practice Research Database (GPRD), the age-specific incidence rates (per 1000 person-years) of medically diagnosed migraine in the general population were reported as follows (with incidence rates for men versus women in parentheses): 1 to 9 years, 1.29 (1.23 vs. 1.35); 10 to 19 years, 6.43 (5.04 vs. 7.89); 20 to 29 years, 4.52 (2.15 vs. 6.77); 30 to 39 years, 4.50 (2.09 vs. 6.83); 40 to 49 years, 4.61 (2.06 vs. 7.11); 50 to 59 years, 3.34 (1.64 vs. 5.01); 60 to 69 years, 2.06 (1.25 vs. 2.82); 70 to 79 years, 1.32 (0.81 vs. 1.70) (Becker 2008). ADHD was not identified as a co-occurring condition among migraine patients.
Prevalence of condition	Not applicable
Mortality of condition	Not applicable
Potential risk	**Repetitive behaviours**
Incidence of condition	The rates of repetitive behaviours among populations with ADHD have not been described in the published literature.
Prevalence of condition	Unknown
Mortality of condition	Not applicable
Potential risk	**QT prolongation**
Incidence of condition	The rates of QT prolongation among populations with ADHD have not been described in the published literature.
Prevalence of condition	Unknown
Mortality of condition	Unknown
Potential risk	**Cyanosis**
Incidence of condition	The rates of cyanosis among populations with ADHD have not been described in the published literature.
Prevalence of condition	Unknown
Mortality of condition	Unknown
Potential risk	**Arrhythmias**
Incidence of condition	A study that included 26 US community emergency departments and 2.3 million ED visits found that primary cardiac arrhythmias in those under 18 years of age was a infrequent presentation to the ED (Sacchetti 1999). The incidence of clinically significant arrhythmias in these patients was reported as 5.7 per 100,000 emergency department visits. Atrial tachyarrhythmia was the most common presentation in this study population.

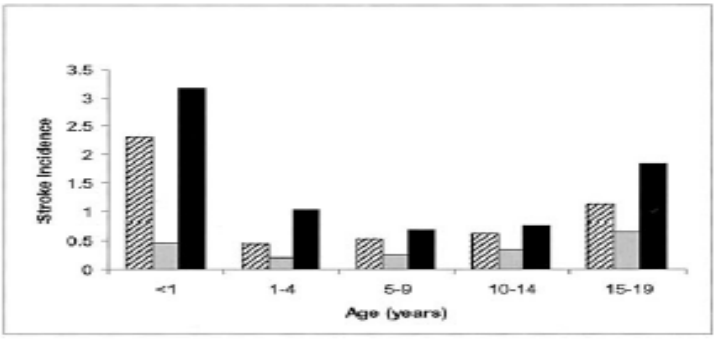
(Continued)

Table 22.2: Epidemiology of Each Potential Risk in Patients With ADHD When Unexposed to CONCERTA (Continued)

Potential risk	**Arrhythmias (continued)**
Prevalence of condition	The prevalence of cardiac rhythm disturbances in the general population of children has been estimated from large population-based samples from Japan (Niwa 2004). A sample of 152,322 school children, including 71,855 elementary students (ages 5 to 6 years) and 80,467 junior high students (ages 12 to 13 years), was screened for several types of arrhythmias. Any cardiac rhythm disturbance was found in 1.25% of elementary students and 2.32% of junior high students, with the prevalence higher in males than females (2.0% versus 1.38%). There have been no published reports of an association between arrhythmias and ADHD among children and adolescents.
Mortality of condition	Unknown
Potential risk	**Sudden death**
Incidence of condition	It is estimated that as many as 14,000 paediatric sudden deaths occur in the US each year (Myerberg 1993). Sparse data on the incidence of sudden death in children exist.
Prevalence of condition	Not applicable
Mortality of condition	Sudden cardiac death is defined as an unexpected natural death from cardiac causes within a short time (≤1 hour) from the onset of symptoms and in a person with no previous history of serious cardiac disease (Atwood 2005).
Potential risk	**Cerebrovascular Disorders**
Incidence of condition	The range of incidence that has been reported for childhood stroke is generally between 2.5 to 3.1 per 100,000 persons per year, with some outliers. Researchers from the University of California at San Francisco examined all hospital admissions for first stroke in the state of California among children 1 month up to 19 years of age (Fullerton 2003). During the years 1991 through 2000, there were 2,278 first admissions for stroke among all children in California. This represented an average annual incidence for all strokes of 2.3 per 100,000 children. According to stroke type, the incidence was 1.2 per 100,000 children for ischemic stroke, and 1.1 per 100,000 children for haemorrhagic stroke. A similar study of childhood stroke was conducted in the Cincinnati metropolitan area that identified possible strokes through hospital admissions, with confirmation through medical charts, autopsy records, and brain imaging studies (Broderick 1993). During a 2-year period, 16 cases fit criteria of a first-ever stroke among those less than 15 years of age, yielding an annual incidence rate of 2.6 per 100,000 children (95% CI: 1.2 to 4.1). The incidence by stroke type was 1.2 per 100,000 children (95% CI: 0.3 to 2.0) for cerebral infarction and 1.5 per 100,000 children (95% CI: 0.4 to 2.3) for haemorrhagic stroke. A study conducted in Dijon, France found a substantially higher incidence of stroke among children under 16 years old (Giroud 1995). Examining the Stroke Registry of Dijon, the authors found 28 cases of childhood stroke during 9 years of follow-up, resulting in an incidence of 13.02 per 100,000 children per year. By stroke type, the incidence rates were 7.91 per 100,000 children for ischemic stroke and 5.11 per 100,000 for haemorrhagic stroke. The larger estimate of incidence found in this study is likely due to the increased sensitivity of a standing registry, specifically designed for ascertainment of stroke. Among other methods, the authors state that the use of computer tomography scan to diagnose all cases may have included minor strokes into their study.

(Continued)

Table 22.2: Epidemiology of Each Potential Risk in Patients With ADHD When Unexposed to CONCERTA (Continued)

Potential risk	Cerebrovascular Disorders (Continued)
Incidence of condition (Continued)	The reported incidence of 2.5 to 3.1 per 100,000 children, aged 19 years and under, is probably an overestimation since it has been previously reported (Schoenberg 1978; Bamford 1988) that approximately 45% of childhood strokes occur before the age of 5 years. None of the studies reviewed reported age-specific rates of stroke in children. However, data from the California study by Fullerton and colleagues (Fullerton 2003) indicate that the incidence of stroke among children ages 5 to 19 years old is likely to be near or slightly under 1.0 per 100,000 person-years.
	
	Figure. Annual stroke incidence (stroke admissions per 100,000 person-years) in California children from 1991 through 2000 by age and stroke subtype. Hatched columns = intracerebral hemorrhage; gray columns = subarachnoid hemorrhage; black columns = ischemic stroke.
	There have been no published reports showing an increased risk of stroke in children or adolescents diagnosed with ADHD.
Prevalence of condition	Not described
Mortality of condition	Between 1979 and 1998, mortality from stroke in children declined 58%, from 0.55 to 0.23 per 100,000 person-years. Mortality from all stroke subtypes declined: ischemic stroke declined 19%, from 0.10 to 0.08 per 100,000 person-years; subarachnoid haemorrhage declined 79%, from 0.24 to 0.05 per 100,000 person-years; and intracerebral haemorrhage declined 54%, from 0.21 to 0.10 per 100,000 person-years. The time trends were significant for each stroke subtype ($p=0.010$ for ischemic stroke, $p<0.0001$ for subarachnoid haemorrhage and intracerebral haemorrhage). The decline in childhood mortality from subarachnoid haemorrhage was greater for blacks than for whites. In 1979, the mortality rate in blacks was 2.1 times that for whites; by 1998, the ratio had decreased to 1.6. For intracerebral haemorrhage, the gap between black and white mortality rates increased from a ratio of 1.8 in 1979 to 2.4 in 1998. For ischemic stroke mortality, the ratio of black to white death rates was 1.7 in 1979 and 1.4 in 1998 (Fullerton 2002).

(Continued)

Table 22.2: Epidemiology of Each Potential Risk in Patients With ADHD When Unexposed to CONCERTA (Continued)

Potential risk	**Aggression**
Incidence of condition	Not Applicable
Prevalence of condition	Acts of aggression or violence are relatively common among school-age children. In the US, the Centers for Disease Control and Prevention (CDC) has found that 33% of high-school students reported being in a physical fight in the past year, and that 4.2% had required medical attention (CDC 2004) The prevalence varied by gender with males (40.5%) more likely than females (25.1%) to have been in a physical fight. US middle school students have also been surveyed by the CDC and asked about any involvement in fights during their lifetime. Sixty-one percent of these US adolescents reported ever being involved in some form of fighting behaviour (threats, physical fighting), and 30% reported ever being involved in at least 1 weapon-related behaviour (Clubb 2001). A relatively high prevalence of fights has also been found in the U.K., where 51% of 8 to 11 year olds reported having at least 1 aggressive fight in the past year (Boulton 1993). ADHD and Conduct Disorder are highly comorbid conditions. An estimated 20% to 40% of children with ADHD will develop conduct disorder, which can be characterised by aggressive behaviour toward people, animals, or property (NIMH 2004) Children with ADHD have been shown to have high impulsivity, which was associated with the initiation of fights (Halperin 1995) An epidemiological study that utilised hospitalization records in Australia found that children and young adolescents (aged 5 to 15 years) with ADHD were 3 times more likely (OR=3.1; 95% CI: 1.31-7.06) to be hospitalised for assault and injuries inflicted by another person (Lam 2005). One study (Guevara 2002) found the odds ratios for the co-morbid conditions of oppositional defiant disorder and conduct disorder to be 17.7 and 5.5 respectively.
Mortality of condition	Not Applicable
Potential risk	**Hostility**
Incidence of condition	The rates of hostility outside of aggressive disorders among ADHD paediatric populations have not been described in the literature.
Prevalence of condition	Unknown
Mortality of condition	Not applicable

(Continued)

Table 22.2: Epidemiology of Each Potential Risk in Patients With ADHD When Unexposed to CONCERTA (Continued)

Potential risk	**Depression**
Incidence of condition	Not applicable
Prevalence of condition	Clinical depression in children and adolescents has been studied much less extensively than in adults. However, several population-based studies have been performed that described the scope of this occurrence. Their consensus is that up to 2.5 percent of primary school-aged children, and up to 8.3 percent of adolescents in the US meet criteria for major depression (Birmaher 1996). Depression is relatively rare in children, but grows to become somewhat common in adolescence. By the end of adolescence, the prevalence of ever having depression is nearly 25% (Kessler 2001). An increased risk for major depression in children and adolescents with ADHD has been consistently reported in the medical literature (Biederman 1998). Epidemiologic studies have reported that comorbid depression may be found in roughly 20% to 30% of ADHD cases (Anderson 1987). The MTA was a NIMH US-sponsored clinical study of 579 children (ages 7-10 years) with ADHD. At baseline assessment, 3.8% of the ADHD subjects were found to have major depression, as measured by parent and teacher responses. This represents an elevated prevalence in comparison to the general population estimate of 2.5% for that age group. The comorbidity of ADHD and depression in children is believed to represent an ADHD subpopulation that is at higher risk for poor psychiatric and social outcomes. Faraone and Biederman discuss the evidence of a familial link between the 2 mental disorders in an article reviewing family studies, which also suggested shared familial risk factors (Faraone 1997). In a 4-year follow-up of 76 children with ADHD and depression, the 2 conditions were found to have independent disease courses. This suggested that depression in ADHD children was actual depression and not demoralization associated with their ADHD. Additionally, clinical research has concluded that the comorbidity of ADHD with affective disorders, such as depression, is not due to their overlapping symptoms (Milberger 1995).
Mortality of condition	Unknown
Potential risk	**Suicidality**
Incidence of condition	In the United States, the annual rate of completed suicide for those ages 10 to 19 years was 4.6 per 100,000 persons (CDC 2004). Within this age group, the occurrence of suicide is related to age. For males, the suicide rate in the prepubertal age group (ages 6-12 years) is approximately 0.45 per 100,000, while the rate for male adolescents (ages 13-19 years) is 9.85 per 100,000. From the CDC Youth Risk Behavior Surveillance System in the US, it was found that 8.8% of 9th to 12th graders reported making a suicide attempt in the past year (CDC 2004), and that 16.9% reported experiencing suicidal ideation in the past year (CDC 2004). However, the predictive relationship between suicidal ideation and attempts to completed suicide may be weak and is controversial (Klein 2006).

(Continued)

Table 22.2: Epidemiology of Each Potential Risk in Patients With ADHD When Unexposed to CONCERTA (Continued)

Potential risk	**Suicidality (Continued)**
Incidence of condition (Continued)	The available literature contains reports that young people with an ADHD diagnosis are at increased risk for suicidal behaviour, as compared to their population age group. A review of the literature by James et al (James 2004) determined that the rate of completed suicide in males (aged 5 to 24 years) with ADHD was between 32 and 39 per 100,000 patients per year, which is roughly 3 times greater than in the general population. A separate study using a US managed care database (Swensen 2002) determined that patients with an ADHD diagnosis (adults and children) were nearly 3 times more likely to make a suicide attempt (OR=2.9 95% CI: 2.4, 3.5) than age and gender-matched controls.
Prevalence of condition	Unknown
Mortality of condition	See incidence
Potential risk	**Tics/Tourette's syndrome/Dystonias**
Incidence of condition	Not Applicable
Prevalence of condition	The prevalence of tic disorders in children varies from 1% to 29% depending on the characteristics of the study population, the diagnostic criteria, and the study design and methods. One study was conducted to find the epidemiological distribution of tic disorders in Swedish school children aged 7 to 15 years. A total population of 4,479 children and their parents were asked to fill in a questionnaire covering both motor and vocal tics. Two hundred and ninety-seven children (190 males, 107 females) were found to have tics. 0.8% had chronic motor tics, and 0.5% had chronic vocal tics. Further, 4.8% of the children had transient tics. All together 6.6% of 7- to 15-year-old children currently had or had experienced some kind of tic disorder during the last year. Prevalence of different tic disorders was higher among younger children and in males, and was highly associated with school dysfunction (Khalifa 2003). One study (Khalifa 2003) was conducted to find the epidemiological distribution of Tourette's syndrome in Swedish school children aged 7 to 15 years. A total population of 4,479 children and their parents were asked to fill in a questionnaire covering vocal tics. Tourette's syndrome, according to DSM-IV criteria, was found in 0.6% of the total population. Prevalence of different tic disorders was higher among younger children and in males, and was highly associated with school dysfunction. The prevalence of Tourette's syndrome was higher than was previously thought but other tic disorders were more common in this childhood population. Another study (Hornsey 2001) on the prevalence of Tourette's syndrome found the condition to be extremely rare, although recent survey indicates motor components of Tourette's syndrome (without speech disorder) may have prevalence of 2-5% in the general population of adolescents.

(Continued)

Table 22.2: Epidemiology of Each Potential Risk in Patients With ADHD When Unexposed to CONCERTA (Continued)

Potential risk	**Tics/Tourette's Syndrome/Dystonias (Continued)**
	There have been few epidemiological studies of dystonia. Most previous studies have provided estimates based on few cases. A European prevalence study was undertaken to provide more precise rates of dystonia by pooling data from 8 European countries. Cases of dystonia from specialist movement disorder (and botulinum toxin) clinics were ascertained by adult neurologists. The crude annual period prevalence rate (1996-1997) for primary dystonia was 152 per million (95% confidence interval 142-162), with focal dystonia having the highest rate of 117 per million (ESDE 2000).
Mortality of condition	Not applicable
Potential risk	**Effect on Final Height**
Incidence of condition	Unknown
Prevalence of condition	See Decreased rate of growth
Mortality of condition	Unknown
Potential risk	**Sexual Maturation (Delayed)**
Incidence of condition	The timing of sexual maturity has been collected on a population level in the US to establish reference data for age at entry into well-established stages. The NHANES III assessed Tanner stage in 4,263 children and adolescents ages 8 to 19 years (Sun 2002). This data provides median age of menarche and median age at entry into Tanner stages 2 through 5. The Spencer et al. (1996) study also assessed pubertal development to see if height deficits in ADHD were potentially related to delays in puberty. The age of onset for Tanner stages was collected and no difference was found between boys with ADHD and control subjects. In a cross-sectional study comparing ADHD girls (6-17 years) with non-ADHD controls, no meaningful associations were identified between ADHD or its treatment and pubertal development (Biederman 2003).
Prevalence of condition	Not applicable
Mortality of condition	Not applicable

(Continued)

Table 22.2: Epidemiology of Each Potential Risk in Patients With ADHD When Unexposed to CONCERTA (Continued)

Potential risk	Carcinogenicity
Incidence of condition	As with adults, childhood cancer is not one disease entity, but rather is a spectrum of different malignancies. Over 50% of childhood cancers are either leukaemias, the most common type being acute lymphocytic leukaemia, or brain and other central nervous system tumours. The overall average annual age-specific rate for cancer in children in Europe in the 1990s was 140 per million, based on 48847 cases. The age-specific rate for the age-range 0-19 years was 157 per million, and the age-specific rate for adolescents was 193 per million (n=7109). In all age groups, incidence was significantly higher in boys than in girls. In adolescents, the highest incidence rates were for lymphomas (European age-specific rate 47.4 per million), followed by carcinomas (38.1), central nervous system tumours (24.6), germ-cell tumours (24.5), and leukaemia (23.4) (Steliarova-Foucher 2004). The overall incidence rates of cancer have been increasing over time in all ages. The difference in age-specific rates between the first and the last decade was significant at all ages, and it was largest at the beginning and end of the age-range. Based on 100596 children with cancer, the average age-specific rate per million was 118 in the 1970s, 124 in the 1980s, and 139 in the 1990s. The average annual change was 1.0% ($p<0.0001$): 0.8% ($p<0.0001$) between the 1970s and 1980s and 1.3% ($p<0.0001$) between the 1980s and 1990s (Steliarova-Foucher 2004).
Prevalence of condition	The most common tumour type in infants was neuroblastoma (1260 [28%]). Leukaemia was most common in the age group of 1 to 4 years (7150 [41%]), and central nervous system tumours in the age group of 5 to 9 years (3748 [28%]). After age 10 years, embryonic tumours, such as retinoblastoma, nephroblastoma (most renal tumours), and hepatoblastoma (most hepatic tumours) almost disappeared, whereas other cancers became more frequent, notably lymphomas, carcinomas, germ-cell tumours, and bone tumours. In adolescents, lymphomas represented 25% (1745) and carcinomas 20% (1404) of the total. On the whole, the most common tumour types in children were leukaemia (ASR 44.8), central nervous system tumours (29.8), and lymphomas (15.5) (Steliarova-Foucher 2004).
Mortality of condition	Overall, 5-year survival of 44438 children diagnosed in the 1990s in Europe was 73%. 5-year survival for 7512 children in the east was 64% (63–65%), and for 36926 children in the west it was 75% (74–75%) ($p<0.0001$). Population-based actuarial survival has increased greatly over the past 30 years. Overall 5-year survival for 20,735 children diagnosed in the 1970s was 44% (44–45%); for 38659 children diagnosed in the 1980s, it was 64% (64–65%), and for 34319 children diagnosed in the 1990s, it was 74% (73-74%). Five-year actuarial survival for the 4004 adolescents diagnosed in the 1970s was 50% (48-51%); for the 6234 adolescents diagnosed in the 1980s, it was 63% (62–64%), and for those 4134 diagnosed in the 1990s, it was 74% (73-76%) (Steliarova-Foucher 2004).

(Continued)

Table 22.2: Epidemiology of Each Potential Risk in Patients With ADHD When Unexposed to CONCERTA (Continued)

Potential risk	**Off-Label Use**
Incidence of condition	Unknown
Prevalence of condition	Unknown
Mortality of condition	Unknown
Potential risk	**Diversion [of Methylphenidate]**
Incidence of condition	Unknown
Prevalence of condition	Data from the MTF Study (McCabe 2004), an annual, nationally representative survey that is based on a multistage probability sample of 8th, 10th, and 12th grade students in the United States were used to examine the prevalence and factors associated with illicit methylphenidate use in a nationally representative sample of 8th, 10th, and 12th grade students. In 2001, the unadjusted prevalence of illicit methylphenidate use in the past year for the entire sample was 4.0% with 5.1% of 12th grade students, 4.8% of 10th grade students and 2.9% of 8th grade students reported non-medical use of methylphenidate in the previous year. After adjusting for other factors, white students were over six times more likely than African-American students to report illicit methylphenidate use. Students in higher-grade levels (10th and 12th grade) and those earning lower grade point averages had an increased likelihood of illicit methylphenidate use. In 2007 (Johnston 2007), 3.8% of 12th grade students, 2.8% of 10th grade students and 2.1% of 8th grade students reported nonmedical use of methylphenidate in the previous year.
Mortality of condition	According to poison control data, Toxic Exposure Surveillance System (TESS), there were over 4900 methylphenidate exposures among those 18 years and younger reported to TESS and 0 deaths (Bronstein 2007) reported in 2006.
Potential risk	**Withdrawal Syndrome**
Incidence of condition	Unknown
Prevalence of condition	Unknown
Mortality of condition	Unknown

(Continued)

Table 22.2: Epidemiology of Each Potential Risk in Patients With ADHD When Unexposed to CONCERTA (Continued)

Potential risk	**Drug Abuse and Drug Dependence**
Incidence of condition	Not Applicable
Prevalence of condition	Studies of ADHD and substance use disorder (SUD) include epidemiologic data of prevalence in patients with ADHD or SUD as the primary diagnosis. In studies of adolescents with SUD, the rates of comorbid ADHD have been noted to range from 23% to 31% (Hovens 1994; DeMilo 1989; Milin 1991) Adults with alcohol or SUD have high rates of childhood (35%-71%) and current (15%-25%) ADHD (Wilens 1995; Goodwin 1975; Levin 1998; Schubiner 2000). Another set of studies has prospectively followed children and adolescents with ADHD to determine what factors contributed the highest risk for developing SUD, including other disruptive behavioural disorders, and what reduced the risk of SUD in children and teens with ADHD. Investigators at the Massachusetts General Hospital conducted 2 large prospective studies that followed boys and girls with ADHD into adolescence and adulthood (Biederman 2006a, Biederman 2006b). They found an earlier onset and higher rates of substance abuse in children with ADHD than in their same-sex peers who did not have ADHD. In all, 13% of girls with ADHD had used illicit substances, and 4% had used alcohol in adolescence (control peers, 3% and 0%, respectively); 26% of boys had used alcohol and 21% reported drug abuse (control peers, 16% and 11%).
Mortality of condition	Unknown
Potential risk	**Lymphocytic Leukaemia**
Incidence of condition	The rates of lymphocytic leukaemia in populations with ADHD have not been described in the published literature. ALL is the most common childhood malignancy, with an annual incidence of 3 to 4 cases per 100,000 children (Bhatia 2002). Approximately two-thirds of all ALL cases are in children. The age specific incidence of ALL per 100,000 in the US has been estimated as follows: under 1 year, 1.8; ages 1-4 years, 7.0; ages 5-9 years, 3.2; ages 10-14 years, 1.8; ages 15-19 years, 1.1 (Redaelli 2005).
Prevalence of condition	Approximately 231,856 people in the US live with or are in remission from leukaemia. The approximate prevalence of ALL as of January 1, 2006 was 58,856 (Horner 2009).
Mortality of condition	Complete remission rates of ALL in children are close to 100% (Redaelli 2005). The overall survival at 5 years by race has been estimated to be 89.3% for Asian, 83.6% for white, 78.1% for Hispanic, and 74.4% for black children (Bhatia 2002). The age-adjusted US mortality rate for children and adults is 0.5 per 100,000 population (Redaelli 2005).

(Continued)

Table 22.2: Epidemiology of Each Potential Risk in Patients With ADHD When Unexposed to CONCERTA (Continued)

Potential risk	**Neonatal Cardio-Respiratory Toxicity (Neonatal/Foetal Tachycardia, Respiratory Distress/Apnoea)**
Incidence of condition	The rates of neonatal cardio-respiratory toxicity in populations with ADHD have not been described in the published literature. Supraventricular tachycardias have been found to occur in about 1 per 250 to 1 per 1000 children in the general population, commonly appearing before the patient is 1 month old (Weindling 1996). The peak incidence for presentation of SVT in children is under 1 year of age, with most infants being less than 1 month of age at diagnosis (Garson 1981). The rate of respiratory distress (RDS) syndrome/hyaline membrane disease among all neonates in the US is 6.6 per 1000 live births (Ventura 1998). In a case series conducted in England, the incidence of respiratory distress syndrome at term was 2.2 per 1000 deliveries (Morrison 1995). The incidence of RDS is inversely proportional to the gestational age of the neonate, and rarely occurs in neonates more than 36 weeks' gestation (Ishisaka 1996).
Prevalence of condition	Unknown
Mortality of condition	The infant mortality rate caused by respiratory distress syndrome in the US was 0.4 per 1000 live births in 1995. Mortality caused by respiratory distress accounted for 5.2% of the infant mortality rate (Lee 1999). Outcomes of neonatal tachycardia are highly dependent on the underlying pathology (Roggen 2008).
Potential risk	**Neonatal Effects on Growth (Via Lactation)**
Incidence of condition	Unknown
Prevalence of condition	Unknown
Mortality of condition	Unknown

1.8. Pharmacological Class Effects

The risks described in Section 1.5 of this document are considered class effects by the CHMP; the identified and potential risks for methylphenidate products for the treatment of ADHD are defined in the Rapporteur's (MHRA) Assessment Report dated 3 December 2008.

1.9. Additional EU Requirements

1.9.1. Potential for Overdose

Analysis of the data concluded that the overdose section of the current SmPC (Annex 2) adequately described the MAH's experience with overdose (SmPC, Section 4.9).

An ad-hoc review of postmarketing cases of overdose from first marketing authorisation (01 August 2000) to 28 February 2007 was conducted. A total of 156 cases of overdose have been reported with CONCERTA. The data presented in these reported cases of CONCERTA overdose supported a causal association in this context between arrhythmia, sinus arrhythmia and heart rate increased when applying the CIOMS III and V threshold criteria for causality assessment. There was insufficient evidence to support a causal association with cardiac arrest, coma, flushing, and hyperpyrexia in the context of

overdose (BRM Report July 2007). A more recent search of the postmarketing database for cases of overdose (Preferred Terms: Accidental overdose, Drug level increased, Drug toxicity, Overdose, Intentional overdose, Multiple drug overdose, Multiple drug overdose intentional) was performed (Cumulative 01 August 2000 to 10 August 2009; BRM Report, PSUR 2009). This assessment is consistent with the previous evaluation.

1.9.2. Potential for Misuse for Illegal Purpose

The physical properties of the OROS tablet significantly reduce the potential to release methylphenidate in quantities sufficient to produce the central nervous system effects that drug abusers find desirable. Additionally, the pharmacokinetic profile of methylphenidate released from the OROS tablet delays the entry of the total dose into the central nervous system making oral abuse or misuse less likely than with immediate-release formulations.

1.9.3. Potential for Off-Label Use

According to IMS covering CONCERTA retail prescriptions in the 4 major European countries where CONCERTA is available (Germany, France, Spain, and United Kingdom), from January 2003 to June 2009, the vast majority (94.0%) of retail prescriptions of CONCERTA were prescribed to children and adolescents between the ages of 6 and 20 years (no split <17 and ≥17 years is feasible). Approximately 78.9% of European CONCERTA prescriptions were prescribed for the treatment of ADHD or ADHD-related symptoms, based on IMS data for the time period from January 2005 to June 2009 (diagnosis data earlier than 2005 are not available). The most common indications for off-label use of CONCERTA in this age category, based upon cumulative IMS data for the time period from January 2005 through June 2009, were conduct disorder, childhood autism, and Asperger's syndrome; conditions known to have a high comorbidity with ADHD.

As part of the Article 31 referral follow-up measures, the Company (with the other MAHs) will provide all available retrospective drug utilisation data using health-related electronic databases in all Member States where methylphenidate is used, to allow an evaluation of changes in usage over time including off-label use. This evaluation will be performed annually for 5 years. These annual evaluations of methylphenidate usage will be submitted for assessment.

The published estimated proportion of off-label use of methylphenidate was 2.0% (Novak 2007). Based on a review of the medical literature, the most significant indications for off-label use were identified and are presented in the postmarketing section of Table 18.16.

1.9.4. Potential for Off-Label Paediatric Use

CONCERTA is indicated for treatment of ADHD in children and adolescents 6 to 17 years of age. Based on 2003 to 2009 retail prescription data in the 4 major EU countries where CONCERTA is available, only 0.4% of all prescriptions were for children below the age of 6 years. Therefore, off-label use in the paediatric population is minimal and not advocated.

As indicated above in section 1.9.3 (Potential for off-label use) the Company will provide all available retrospective drug utilisation data to allow an evaluation of changes in usage over time including off-label use.

1.10. Summary - Ongoing Safety Concerns

Important identified and potential risks (as defined in the Rapporteur's [MHRA] Assessment Report dated 3 December 2008) for which there are specific pharmacovigilance activities (ongoing or proposed) are listed in Table 23.

Table 23: Summary of On-Going Safety Concerns

Important identified risks	Hypertension Tachycardia Raynaud's phenomenon Hallucinations (auditory, skin sensation, visual disturbance) Psychosis/Mania Anorexia Decreased rate of growth
Important potential risks	Migraine Repetitive behaviours QT prolongation Cyanosis Arrhythmias Sudden death Cerebrovascular disorders Aggression Hostility Depression Suicidality Tics/Tourette's syndrome/Dystonias Effect on final height Sexual maturation (delayed) Carcinogenicity Off-label use Diversion Withdrawal syndrome Drug abuse and Drug dependence Lymphocytic leukaemia Neonatal cardio-respiratory toxicity(neonatal/foetal tachycardia, respiratory distress/apnoea) Neonatal effects on growth (via lactation)
Important missing information[a]	

[a] Long-term safety was identified as important missing information in the Rapporteur's (MHRA) Assessment Report dated 3 December 2008.

A description of the planned actions for each of the above ongoing safety concerns is described in Section 3.1.

2. PHARMACOVIGILANCE PLAN

2.1. Routine Pharmacovigilance Practices

2.1.1. Objectives

The objective of the routine pharmacovigilance program conducted by the Benefit Risk Management Department of Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (J&JPRD) is to systematically review postmarketing safety data from multiple sources to detect and evaluate changes suggestive of new safety concerns. Early detection of safety signals enables the MAH to develop and implement appropriate risk management strategies.

Standard pharmacovigilance practices include the following:

- Real-time reviews of single cases.
- Scheduled reviews of aggregate data from SCEPTRE, a component of the BRM Worldwide Safety System to identify relevant changes in reporting frequency or patterns of adverse events.
- Aggregate reviews, at pre-specified intervals, of product quality complaint cases with associated adverse events and lot numbers from SCEPTRE, to identify safety signals related to product quality and manufacturing.
- Data mining, at regular intervals, of regulatory databases such as the United States FDA Adverse Events Reporting System (AERS)/Spontaneous Reporting System (SRS) and the World Health Organisation (WHO) Vigibase, to identify adverse events of interest reported disproportionately for the MAH's products relative to other products in the databases.

Both medically confirmed and medically unconfirmed reports are included in these reviews.

2.1.2. Data Sources

2.1.2.1. SCEPTRE

This database contains adverse event information received by the MAH from multiple sources, including health care professionals, the biomedical and scientific literature, health authorities, and consumers. Serious events reported from clinical trials also are entered into SCEPTRE. This database contains the most complete and current safety information on MAH products. Individual reports are reviewed as the information becomes available, and appropriate follow-up investigation is conducted to collect relevant information.

2.1.2.2. FDA AERS/SRS Database

This regulatory database contains all adverse event information reported to FDA on products approved for marketing in the US. This includes all adverse event reports by manufacturers as specified by US regulations, US spontaneous reports received directly from health care professionals or consumers, and serious and unexpected foreign reports (where the US package insert is the reference safety information used to determine expectedness). This database is used unless otherwise specified for screening at defined intervals to detect disproportionalities. The publicly released version of the FDA database currently has a lag-time of 3 to 6 months. Adverse event case narratives are not directly available to the MAH but may be ordered separately (as MedWatch reports).

2.1.2.3. WHO Vigibase

This is the largest regulatory database and contains all adverse event reports from national health authorities of member countries. The top five contributors by volume of reports are the United States, United Kingdom, Germany, Australia, and Canada. This is the standard database screened at defined intervals using data mining tools for products marketed exclusively outside of the United States unless otherwise specified. No case narratives are available for Vigibase cases.

2.1.3. Surveillance Methods

- Standardised and validated reports detect interval changes in reporting frequency, relative reporting, and reporting patterns of MAH drugs contained in the SCEPTRE database.
- An intra-lot disproportionality approach is used to identify lot-related adverse event reports for MAH drugs contained in SCEPTRE.
- Statistical methods such as proportional reporting ratio (PRR) and empirical Bayes geometric mean (EBGM) scores detect adverse events that are reported disproportionately with the company product as compared to all other drugs in the FDA AERS/SRS database or WHO Vigibase.
- Case series are constructed to characterise the event(s) under scrutiny utilising SCEPTRE and standard descriptive epidemiological methods including case definition.
- Interpretation of the findings incorporates statistically based methods and clinical medical judgment.

2.1.4. Operational Plan

Routine surveillance includes the following steps:

- The timing of surveillance reviews generally is synchronised with preparation of Periodic Safety Update Reports (PSURs).
- Signals identified during surveillance review are further evaluated in topic review reports.

- Findings are discussed with the Postmarketing Safety Expert and other functional groups within BRM, and recommendations are made for further evaluation and/or action. If the original signal is not confirmed as a safety issue, ongoing routine surveillance may be the recommended action. If the safety signal is consistent with a safety issue, further evaluation/actions may include, but are not limited to, clinical or epidemiological studies or revision of the company core data sheet.
- Lot-related findings are communicated to the appropriate Complaint Vigilance Department of the MAH.

2.2. Summary of Safety Concerns and Planned Pharmacovigilance Actions

Each safety concern and the pharmacovigilance actions planned in response to the safety concern are summarised in Table 24.

Table 24: Summary of Safety Concerns and Planned Pharmacovigilance Actions

Safety Concern	Planned Action
Important Identified Risks	
Hypertension Tachycardia	• Routine pharmacovigilance • Follow up on FDA pharmacoepidemiologic study (ongoing)[a]
Raynaud's phenomenon Hallucinations (auditory, skin sensation, visual disturbance) Psychosis/Mania Anorexia	• Ongoing monitoring with routine pharmacovigilance practices as described in Section 2.1. No additional surveillance activities are needed at this time to monitor risk (see Section 3).
Decreased rate of growth	• Routine pharmacovigilance • Follow up MTA Study (ongoing)[a] • Investigator-initiated study in adolescents (ongoing)[a]
Important Potential Risks	
Migraine Repetitive behaviours QT prolongation Cyanosis Arrhythmias Aggression Hostility Depression Tics/Tourette's syndrome/Dystonias Withdrawal syndrome Lymphocytic leukaemia Neonatal cardio-respiratory toxicity(neonatal/foetal tachycardia, respiratory distress/apnoea) Neonatal effects on growth (via lactation)	• Ongoing monitoring with routine pharmacovigilance practices as described in Section 2.1. No additional surveillance activities are needed at this time to monitor risk (see Section 3).
Sudden death Cerebrovascular disorders	• Routine pharmacovigilance • Enhanced pharmacovigilance (additional surveillance for sudden death and Cerebrovascular disorders through the use of a questionnaire) (ongoing)[a] • Follow up on FDA pharmacoepidemiologic study (ongoing)[a]
Suicidality	• Routine pharmacovigilance • Enhanced pharmacovigilance (additional surveillance for suicidality through the use of a questionnaire) (ongoing)[a] • Determine the feasibility of a meta-analysis of the risk of suicidality (feasibility report submitted to MHRA for assessment on 31 July 2009)[a]
Effect on final height	• Routine pharmacovigilance • Follow up MTA Study (ongoing)[a]
Sexual maturation (delayed)	• Routine pharmacovigilance • Investigator-initiated study in adolescents (ongoing) [a] • Follow up MTA Study (ongoing)[a]

(Continued)

Table 24: Summary of Safety Concerns and Planned Pharmacovigilance Actions (Continued)

Carcinogenicity	• Routine pharmacovigilance • Enhanced pharmacovigilance (additional surveillance for carcinogenicity through the use of a questionnaire) (ongoing)[a] • Evaluation of cytogenicity studies (CRIT124D2201 and NCT00341029) submitted to the MHRA and CHMP members by a MAH on behalf of all MAHs of methylphenidate-containing products on 30 March 2009.
Off-label use	• Routine pharmacovigilance • IMS prescription data drug utilisation survey (DUS) (ongoing)[a]
Diversion	• Routine pharmacovigilance • Monitoring supply of controlled substances follows National regulations [a]
Drug abuse and Drug dependence	• Routine pharmacovigilance
Important missing information	
Long-term safety[b]	• Routine pharmacovigilance was described in Section 2.1. • Determine the feasibility of a long-term safety study with outcomes for adverse cognitive and psychiatric effects in corporation with other MAHs (ongoing)

[a] See Section 2.3 for further information.
[b] Identified in the Rapporteur's (MHRA) Assessment Report dated 3 December 2008.

2.3. Detailed Action Plan for Specific Safety Concerns

The identified and potential safety concerns listed in Section 2.2 will be monitored through routine pharmacovigilance activities as described in Section 2.1. This section provides detailed information on the action plan for Specific Safety Concerns that will extend beyond routine pharmacovigilance. A list of the Specific Safety Concerns along with an overview of the detailed action plan is provided in Table 25.

Table 25: Detailed Action Plan for Specific Safety Concerns

Safety Concerns	**Sudden Death, Cerebrovascular Disorders, Suicidality, Carcinogenicity**
Actions proposed	Enhanced pharmacovigilance through the use of a questionnaire (follow up for sudden death, cerebrovascular disorders, suicidality, carcinogenicity) has been implemented and is ongoing
Objective of proposed action	• To complement passive surveillance by providing more comprehensive and robust data on these specific events of interest • To compare the reporting rates for these events over time • To help define the likelihood of a relationship between CONCERTA use and the above safety concerns
Rationale for proposed action	The above safety concerns have been identified as potential risks for methylphenidate
Further measures which may be adopted and the decision criteria for initiating such measures	• Labelling changes to inform health care practitioners and patients • Additional risk minimisation activity (education tool) for severe risks with a significant impact on patient safety
Milestones for evaluation and reporting including justification for choice of milestones	Individual serious adverse events processed and reported to health authorities in accordance with regulatory requirements
Titles of protocols	Not applicable
Safety Concerns	**Hypertension, Tachycardia, Sudden Death, Cerebrovascular Disorders**
Action proposed	Follow up on FDA pharmacoepidemiologic study (This is an ongoing study. Data collection is scheduled for completion by the end of 2009.)
Objective of proposed action	• To obtain long-term safety data on CONCERTA use and the risk of cardiovascular disorders including tachycardia, sudden death and cerebrovascular disorders • To explore a potential relationship between the use of ADHD drugs and serious cardiovascular adverse events
Rationale for proposed action	The above safety concerns have been identified as either identified or potential risks for methylphenidate

(Continued)

Table 25: Detailed Action Plan for Specific Safety Concerns (Continued)

Safety Concerns	**Hypertension, Tachycardia, Sudden Death, Cerebrovascular Disorders (Continued)**
Further measures which may be adopted and the decision criteria for initiating such measures	• Labelling changes to inform health care practitioners and patients • Additional risk minimisation activity (educational tool) for severe risks with a significant impact on patient safety
Milestones for evaluation and reporting including justification for choice of milestones	To be determined
Titles of protocols	Not applicable
Safety Concerns	**Decreased Rate of Growth, Effect on Final Height, Sexual Maturation (Delayed)**
Action proposed	Follow up MTA Study (This is an ongoing study. No data are yet available from subjects followed up over 8 years for either effects on growth or sexual maturation.
Objective of proposed action	To obtain more precise information and long-term follow up on the effects on growth, final height, and sexual maturation.
Rationale for proposed action	The above safety concerns have been identified as identified or potential risks for methylphenidate
Further measures which may be adopted and the decision criteria for initiating such measures	• Labelling changes to inform health care practitioners and patients • Additional risk minimisation activity (educational tool) for severe risks with a significant impact on patient safety
Milestones for evaluation and reporting including justification for choice of milestones	To be determined
Titles of protocols	Not applicable
Safety Concerns	**Decreased Rate of Growth, Sexual Maturation (Delayed)**
Action proposed	Investigator-initiated study in adolescents/Smoking cessation study (This study is ongoing. Results to be provided upon completion.)
Objective of proposed action	To obtain more precise information and long-term follow up on the effects on growth and sexual maturation compared with population norms.
Rationale for proposed action	The above safety concerns have been identified as identified or potential risks for methylphenidate

(Continued)

Table 25: Detailed Action Plan for Specific Safety Concerns (Continued)

Safety Concerns	**Decreased Rate of Growth, Sexual Maturation (Delayed) (Continued)**
Further measures which may be adopted and the decision criteria for initiating such measures	• Labelling changes to inform health care practitioners and patients • Additional risk minimisation activity (educational tool) for severe risks with a significant impact on patient safety
Milestones for evaluation and reporting including justification for choice of milestones	To be determined
Titles of protocols	Not applicable
Safety Concern	**Suicidality**
Action proposed	A report of the feasibility assessment to conduct a meta-analysis of the risk of suicidality
Objective of proposed action	To evaluate the risk of suicidal behaviour and suicidal ideation associated with the use of methylphenidate in children and adolescents with ADHD on the basis of clinical trial data of methylphenidate that is currently available to the MAHs.
Rationale for proposed action	Suicidality has been identified as a potential risk for methylphenidate
Further measures which may be adopted and the decision criteria for initiating such measures	• Labelling changes to inform health care practitioners and patients • Additional risk minimisation activity (educational plan) for severe risk with a significant impact on patient safety
Milestones for evaluation and reporting including justification for choice of milestones	Submitted to MHRA on 31 July 2009.
Titles of protocols	Not applicable
Safety Concern	**Carcinogenicity**
Action proposed	Evaluation of cytogenicity studies (CRIT124D2201 and NCT00341029) submitted to the MHRA and CHMP members by a MAH on behalf of all MAHs of methylphenidate-containing products on 30 March 2009.
Objective of proposed action	To provide additional information on whether methylphenidate produces cytogenetic abnormalities in paediatric patients.
Rationale for proposed action	Carcinogenicity has been identified as a potential risk for methylphenidate
Further measures which may be adopted and the decision criteria for initiating such measures	• Labelling changes to inform health care practitioners and patients

(Continued)

Table 25: Detailed Action Plan for Specific Safety Concerns (Continued)

Safety Concern	**Carcinogenicity (Continued)**
Milestones for evaluation and reporting including justification for choice of milestones	Submitted to the MHRA and CHMP by a MAH on behalf of all MAHs of methylphenidate-containing products on 30 March 2009.
Titles of protocols	Not applicable
Safety Concern	**Off-Label Use**
Action proposed	Drug utilisation study based on IMS prescription data
Objective of proposed action	The MAHs committed to provide all available data on an annual review basis for the next 5 years in all Member States where methylphenidate is used to allow an evaluation of changes in usage over time.
Rationale for proposed action	The above safety concerns have been identified as potential risks for methylphenidate
Further measures which may be adopted and the decision criteria for initiating such measures	• Labelling changes to inform health care practitioners and patients • Additional risk minimisation activity (educational tool) for severe risk with a significant impact on patient safety
Milestones for evaluation and reporting including justification for choice of milestones	The MAHs to submit a report presenting retrospective data from a drug utilisation study for 2008 in Q4 2009.
Titles of protocols	Not applicable
Safety Concern	**Diversion**
Action proposed	Monitoring supply of controlled substances follows national regulations
Objective of proposed action	To monitor the supply of CONCERTA in accordance with national regulations in order to identify diversion of product.
Rationale for proposed action	The above safety concerns have been identified as potential risks for methylphenidate
Further measures which may be adopted and the decision criteria for initiating such measures	• Labelling changes to inform health care practitioners and patients • Educational activities and additional risk minimisation activities for severe risks with a significant impact on patient safety
Milestones for evaluation and reporting including justification for choice of milestones	Not applicable (monitoring supply of controlled substances follows national regulations)
Titles of protocols	Not applicable

(Continued)

Table 25: Detailed Action Plan for Specific Safety Concerns (Continued)

Safety Concern	Long-Term Safety
Action proposed	Detailed feasibility assessment for a scientifically valid, well-designed, and suitably powered long-term safety study as specified in the Letter of Undertaking dated 19 January 2009.
Objective of proposed action	Long-term safety study to evaluate adverse cognitive outcomes and adverse psychiatric outcomes (eg, mood disorders, hostility, and psychotic disorders).
Rationale for proposed action	Long-term safety has been identified as important missing information for methylphenidate
Further measures which may be adopted and the decision criteria for initiating such measures	• Labelling changes to inform health care practitioners and patients • Additional risk minimisation activity (educational tool)
Milestones for evaluation and reporting including justification for choice of milestones	The MAHs to submit a report on the feasibility of a long-term study in Q3 2009. The MAHs are preparing to submit Q4 2009.
Titles of protocols	Not applicable

2.4. Overview of Study Protocols for the Pharmacovigilance Plan

No study protocols are planned.

2.5. Details of Updates to the EU-RMP

This document is considered the second version of the EU RMP for CONCERTA. A history of the development of this document is provided in this section.

On 26 January 2007, the MHRA, the Reference Member State for CONCERTA XL (referred to as CONCERTA throughout this document), forwarded the request from the European PhVWP for the development of a European RMP for all methylphenidate-containing products. The following 6 specific areas of concern were to be addressed in the RMP: cardiovascular adverse events, cerebrovascular adverse events, psychiatric adverse events, effects of long–term treatment, effects on growth, and carcinogenicity. The focus and content of the first draft of the RMP for CONCERTA dated 30 April 2007 exclusively addressed these PhVWP-specified areas.

On 15 November 2007, the CHMP issued a list of outstanding issues related to the Article 31 referral for all authorised medicinal products containing methylphenidate. As part of this request the MAHs were asked to develop a core RMP. Initial discussions took place between J&JPRD, Novartis, and UCB to coordinate the response to the letter from CHMP dated 15 November 2007. Given the time restrictions for responding by the deadline and taking into consideration the time required to organise the legal framework to allow

competing companies to collaborate, the MAHs were unable to provide a joint position on the core RMP at that time. However, on behalf of the EU MAHs for CONCERTA* Prolonged Release Tablets, J&JPRD amended the following sections of the RMP for CONCERTA (document dated 23 January 2008) in line with the 15 November 2007 letter from CHMP: Safety Specification (Sections 1.5, 1.7 and 1.10), Pharmacovigilance Plan (Sections 2.2 to 2.4 and 2.6), Evaluation of the Need for Risk Minimisation (Section 3.1), Risk Minimisation Plan (Section 4), and Summary of the EU Risk Management Plan (Section 5).

On 30 May 2008, CHMP issued its second list of outstanding issues related to the Article 31 referral for all authorised medicinal products containing methylphenidate. This referral requested submission of a core RMP that evaluated the list of identified and potential risks.

The Company submitted an updated RMP for CONCERTA in October 2008 which addressed each of the identified and potential risks identified by CHMP.

In the Rapporteur's (MHRA) Assessment Report dated 3 December 2008, the core table of risks was updated to include the following 3 potential risks:

- Lymphocytic leukaemia
- Neo-natal cardio-respiratory toxicity (neonatal/foetal tachycardia, respiratory distress/apnoea
- Neonatal effects on growth (via lactation)

In the May 2009 European Commission decision for the referral procedure, the conditions of the Marketing Authorisation requested that the MAHs include, in the core safety specification, the final core table of identified and potential risks as requested by the CHMP. It also requested the evaluation of newly identified or potential risks, or new new/important information on existing identified or potential risks on an ongoing basis.

This RMP addresses the requests from the CHMP opinion as ratified by the European Commission after conclusion of the Article 31 Referral. (Note that the list of identified and potential risks ratified by the European Commission in the Final Assessment Report dated 22 January 2009 differs from the list of identified

* Janssen-Cilag Pharma GmbH, Janssen-Cilag N.V./S.A., Johnson & Johnson D.O.O., Janssen-Cilag S.A., Janssen-Cilag Oy, Janssen-Cilag Ltd, Janssen-Cilag Farmacêutica Lda., Janssen-Pharmaceutica N.V., Janssen-Cilag AB, Janssen-Cilag GmbH, Janssen-Cilag Pharmaceutical SACI, Janssen-Cilag BV, Janssen-Cilag AS, Janssen-Cilag International N.V.

and potential risks provided in the Rapporteur's (MHRA) Assessment Report dated 3 December 2008. In response to an inquiry from the Company, the MHRA advised that the RMP follow those of the Assessment Report dated 3 December 2008.)

2.6. Summary of Outstanding Actions, Including Milestones

The present list of actions is provided in Table 26.

Table 26: Present List of Actions to be Completed (Ongoing and Planned) With Milestones and Timelines

Actions[a]	Milestones/ Exposure[b]	Milestones/ Calendar Time[b]	Status
Enhanced pharmacovigilance through the use of a questionnaire			Ongoing
Follow-up FDA pharmacoepidemiologic study			Ongoing
Follow-up MTA Study			Ongoing
Investigator-initiated/Smoking cessation study in adolescents			Ongoing
Meta-analysis of the risk of suicidality (feasibility report)		31 Jul 2009	Submitted
Evaluation of cytogenicity studies (CRIT124D2201 and NCT00341029)		30 Mar 2009	Submitted
Drug utilisation analysis based on IMS prescription data	2008 Data	Q4 09	Ongoing
Long-term safety study (feasibility report)		Q3 09 (MAHs to submit Q4 09)	Proposed

[a] The identified and/or potential risks for which these actions are ongoing or proposed are listed in Table 25 (links actions with applicable risks). Long-term safety was identified by the CHMP as important missing information.

[b] If not listed, milestones to be determined.

PART II

3. EVALUATION OF THE NEED FOR RISK MINIMISATION ACTIVITIES

The MAH believes that the current contraindications, warnings and precautions within the proposed harmonised EU SmPC (Annex 2) for CONCERTA adequately inform prescribers and patients about the benefit-risk of CONCERTA. In addition, the MAH has not identified any evidence to support new risks associated with CONCERTA that necessitates new risk minimisation activities. However, the CHMP requested that MAHs of methylphenidate produce a risk minimisation tool (an education tool) that is discussed in Section 4.

3.1. Planned Actions for Each Safety Concern

Table 27 summarises the planned actions for each of the identified and potential risks identified by the CHMP.

Table 27: Planned Actions for Each Safety Concern

Safety Concern (Identified and Potential Risks)	Routine Risk Minimisation Activities Sufficient?	If Yes, Provide Description of Routine Activity and Justification
Hypertension/ Tachycardia *(Identified risks)*	[a] (See comment in table footnote on last page)	Pre-treatment screening for blood pressure and heart rate and need for ongoing monitoring at each adjustment of dose and then at least at every 6 months (Sec 4.2, SmPC). Contraindicates use in patients with severe hypertension and patients with pre-existing cardiovascular disorders such as angina (Sec 4.3, SmPC) (hypertension only) Warning to monitor blood pressure and pulse (centile chart) at each adjustment of dose and then at least 6-monthly (Sec 4.4, SmPC) Interaction wording between methylphenidate and vasopressor agents, antihypertensive drugs and non-selective, irreversible monoamine oxidasers (Sec 4.5, SmPC) (hypertension only) Hypertension and tachycardia are listed as ADRs (Sec 4.8, SmPC)
Raynaud's phenomenon *(Identified risk)*	Yes	Raynaud's phenomenon is listed as an ADR (Sec 4.8, SmPC)
Hallucinations (auditory, skin sensation, visual disturbance) Psychosis/Mania *(Indentified risks)* Aggression Hostility Tics/Tourette's syndrome/ Dystonias *(Potential risks)*	[a]	Pre-treatment screening for psychiatric disorders and ongoing monitoring at each adjustment of dose and at least 6-monthly intervals for development of *de novo* or worsening of pre-existing psychiatric disorders (Sec 4.2, SmPC) Contraindicates use in patients with diagnosis or history of psychotic symptoms (visual/tactile/auditory hallucinations and delusions), severe mood disorders, schizophrenia and psychopathic/borderline personality disorder, and severe and episodic (Type I) Bipolar (affective) Disorder (that is not well controlled). (Sec 4.3, SmPC) Warning to monitor development or worsening of psychiatric disorders, aggression or hostility and motor or verbal tics/Tourette's syndrome is advised at each adjustment of dose and then at least at 6-monthly intervals. There is additional precautionary language concerning monitoring of aggression or hostility, psychotic symptoms or mania and motor or vocal tics with long-term use (more than 12 months) of methylphenidate (Sec 4.4, SmPC) Hallucinations, psychotic disorders, mania, aggression, tics, and "worsening of pre-existing tics of Tourette's syndrome" are listed as ADRs (Sec 4.8, SmPC)

(Continued)

Table 27: Planned Actions for Each Safety Concern (Continued)

Safety Concern (Identified and Potential Risks)	Routine Risk Minimisation Activities Sufficient?	If Yes, Provide Description of Routine Activity and Justification
Anorexia *(Identified risk)*	[a]	Contraindication for use in patients who are diagnosed or have a history of anorexia nervosa/anorexic disorders (Sec 4.3, SmPC) Monitoring of weight and appetite required at ongoing monitoring (Sec 4.2 SmPC) and patients not gaining weight as expected are advised to have treatment interrupted (Sec 4.4, SmPC) Anorexia is listed as an ADR (Sec 4.8, SmPC)
Decreased rate of growth *(Identified risk)*	[a]	Pre-treatment screening calls for prescribers to accurately record pre-treatment height and weight on growth chart, and for ongoing monitoring this is to happen at least 6-monthly intervals (Sec 4.2, SmPC) Warning that moderately reduced weight and growth retardation have been reported with long-term use and that height, weight and appetite should be monitored at least 6-monthly intervals (Sec 4.4, SmPC). Also, patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted (Sec 4.4, SmPC) Growth retardation during prolonged use in children" is listed as an ADR (Sec 4.8, SmPC)
Migraine Repetitive behaviours *(Potential risks)*	Yes	Migraine and Repetitive behaviour are listed as ADRs (Sec 4.8, SmPC)
QT prolongation Cyanosis Sexual maturation (delayed) *(Potential risks)*	Yes	No regulatory action required
Arrhythmias *(Potential risk)*	[a]	Contraindicates use in patients with potentially life-threatening arrhythmias (Sec 4.3, SmPC) Precautionary text regarding malignant arrhythmias and palpitations that patients who are being considered for treatment should have a careful history (including assessment for a family history of malignant arrhythmia) and physical examination to assess for the presence of cardiac disease (Sec 4.4, SmPC) Arrhythmia is listed as an ADR (Sec 4.8, SmPC)

(Continued)

Table 27: Planned Actions for Each Safety Concern (Continued)

Safety Concern (Identified and Potential Risks)	Routine Risk Minimisation Activities Sufficient?	If Yes, Provide Description of Routine Activity and Justification
Sudden death *(Potential risk)*	[a]	Contraindicates use in patients with pre-existing cardiovascular disorders such as angina and potentially life-threatening arrhythmias (Sec 4.3, SmPC) Precautionary language for patients with pre-existing structural cardiac abnormalities or other serious cardiac disorders including cardiomyopathy and serious heart rhythm abnormalities (Sec 4.4, SmPC) Risk of sudden death with misuse (Sec 4.4, SmPC) and concomitant use with clonidine (Sec 4.5, SmPC) "Sudden cardiac death" is listed as an ADR (Sec 4.8, SmPC)
Cerebrovascular disorders *(Potential risk)*	[a]	Contraindicates use in patients with pre-existing cerebrovascular disorders, cerebral aneurysm, vascular abnormalities including vasculitis or stroke (Sec 4.3, SmPC) Precautionary text for patients with additional risk factors such as cardiovascular disease/concomitant medications that elevate blood pressure should be assessed at every visit for neurological signs and symptoms after initiating treatment with methylphenidate (Sec 4.4, SmPC) Precautionary text for cerebral vasculitis which can develop as a very rare idiosyncratic reaction to methylphenidate (Sec 4.4, SmPC) "Cerebrovascular disorders (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion)" is listed as an ADR (Sec 4.8, SmPC)
Depression Suicidality *(Potential risks)*	[a]	Contraindicates use in patients with a diagnosis or history of suicidal tendencies and severe depression (Sec 4.3, SmPC) Warning under 'suicidal tendency' sub-heading to immediately evaluate patients with emergent suicidal ideation and consideration of discontinuation of methylphenidate (Sec 4.4, SmPC) Warning under 'Forms of bipolar disorder' to screen for comorbid depressive symptoms and family history of suicide prior to initiating treatment in patients with comorbid bipolar disorder (Sec 4.4, SmPC) Warning under 'Long-term use' sub-heading to monitor for development of *de novo* or worsening of psychiatric disorders including depression and also possible need for supervision during withdrawal from abusive use as severe depression may occur ('Withdrawal' section 4.4). Depression, Suicidal ideation, and "Suicidal attempt (including completed suicide)" are listed as ADRs (Sec 4.8, EU SmPC)

(Continued)

Table 27: Planned Actions for Each Safety Concern (Continued)

Effect on final height *(Potential risk)*	Yes	Pre-treatment screening calls for prescribers to accurately record pre-treatment height and weight on growth chart, and for ongoing monitoring this is to happen at least 6-monthly intervals (Sec 4.2, SmPC). Warning that the effects of methylphenidate on final height and final weight are currently unknown and being studied (Sec 4.4, SmPC). Growth should be monitored during methylphenidate treatment: height, weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart. Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.
Carcinogenicity *(Potential risk)*	Yes	Preclinical information on carcinogenicity is provided in Section 5.3 of SmPC.
Off-label use *(Potential risk)*	[a]	States that safety and efficacy of CONCERTA in children under 6 years of age has not been established and should not be used in this population (Sec 4.2, SmPC). Clarifies that safety and efficacy has not been established in adults and the elderly, in addition to children less than 6 years of age (Sec 4.2, SmPC). Not indicated for fatigue (Sec 4.4, SmPC)
Diversion *(Potential risk)*	[a]	The SmPC Sections 4.2 and 4.4, advise that patients should be monitored for the risk of diversion and misuse of methylphenidate.
Withdrawal syndrome *(Potential risk)*	[a]	Precautionary text under the withdrawal subheading (Sec 4.4): Careful supervision is required during drug withdrawal, as this may unmask depression as well as chronic over-activity. Some patients may require long-term follow up. Careful supervision is required during withdrawal from abusive use since severe depression may occur.
Drug abuse and Drug dependence *(Potential risk)*	[a]	States that patients should be monitored for the risk of diversion, misuse and abuse of methylphenidate (Sec 4.2 and Sec 4.4 SmPC). Additional precautionary text in Sec 4.2, SmPC.) "Cases of abuse and dependence have been described, more often with immediate release formulations" is listed as an ADR (Sec 4.8, EU SmPC)
Lymphocytic leukaemia *(Potential risk)*	Yes	No regulatory action required
Neonatal cardio-respiratory toxicity(neonatal/ foetal tachycardia, respiratory distress/apnoea) *(Potential risk)*	Yes	The SmPC includes the following (pregnancy, Sec 4.6): "Cases of neonatal cardio-respiratory toxicity, specifically foetal tachycardia and respiratory distress have been reported in spontaneous case reports."

(Continued)

Table 27: Planned Actions for Each Safety Concern (Continued)

Neonatal effects on growth (via lactation) *(Potential risk)*	Yes	The core EU SmPC was amended to include the following (lactation, section 4.6): "Methylphenidate has been found in the breast-milk of a woman treated with methylphenidate. There is one case report of an infant who experienced an unspecified decrease in weight during the period of exposure but recovered and gained weight after the mother discontinued treatment with methylphenidate. A risk to the suckling child cannot be excluded."
Long-term use[b]	[a]	Section 4.4, Long-term use (more than 12 months). The long-term safety profile of methylphenidate is not fully known. Patients on long-term therapy (ie, over 12 months) must have careful monitoring according to the guidance above (ongoing monitoring) for cardiovascular status, growth, appetite, development of de novo or worsening of pre-existing psychiatric disorders. Psychiatric disorders to monitor for include (but are not limited to) tics, depression, irritability, lack of spontaneity, withdrawal, and excessive perseveration.

[a] The CHMP has requested that the MAHs of methylphenidate-containing products for ADHD prepare an educational tool (physician's guide to prescribing and checklists described in Table 28); however, this material will be developed for all of the MAHs by a third party and the exact content will be determined.

[b] Identified as an area of important missing information for all MAHs of methylphenidate in the defined in the Rapporteur's (MHRA) Assessment Report dated 3 December 2008 (see Section 1.5).

A copy of the proposed CONCERTA EU SmPC and package leaflet highlighting the changes listed in the above table are provided with this response in Annex 2.

3.2. Potential for Medication Errors

The Company is not aware of any relevant evidence that medication errors are related to the safety concerns highlighted by the CHMP.

4. RISK MINIMISATION PLAN

The CHMP requests that all MAHs of methylphenidate produce the following risk minimisation tools with information from the Clinical Particulars section of the agreed upon SmPC (Annex 2):

- Physician's guide to prescribing, and
- Checklists for actions before prescribing and for ongoing monitoring for prescribers and, if possible, caregivers.

J&JPRD in coordination with 4 of the other largest MAHs holders of methylphenidate (Novartis, Shire, Medice, and Laboratorios Rubio) are working to produce such an educational programme. It has been agreed that it would be appropriate for the MAHs to work with an independent group to produce the educational tool. In this way, the educational tools will be applicable to all methylphenidate products, rather than company or brand specific. Table 28 provides information on the educational tools.

Table 28: Additional Risk Minimisation Measures Planned (Educational Tools)

Safety Concerns: This educational tool will address safety concerns listed in Table 29.

Routine Risk Minimisation Activities

For each important identified and potential risk, current labelling and/or proposed labelling changes are provided in Table 29. The risks specifically addressed by this Educational Tool are identified in the column titled "Proposed Risk Minimisation Activities" of Table 29; these risks are identified by the notation of "educational tool" in this column.

Additional Risk Management Activity: Educational Tools

(The CHMP has requested that the MAHs of methylphenidate containing products for ADHD prepare educational material. As described in this table, the educational tools are being developed by a third party (ScopeMedical) with input from MAHs.)

Objective and Rationale

To educate physicians on the use methylphenidate according to the safety guidance given in the safety sections of the core SmPC as requested in the Article 31 referral.

This will be achieved by providing core educational tools to aid healthcare providers in ensuring they are well informed and able to use methylphenidate according to the most recent safety information and guidance provided in the SmPC.

Proposed Actions:

The **scope** of this project will be strictly medical education. To ensure this, all content is being developed by a third party (ScopeMedical), with input from MAHs and, in line with the core safety elements in the EU Methylphenidate SmPC. ScopeMedical also advises MAHs on the format and web-based technology to be used for distribution of the educational tools.

The **key messages** of this educational tool are as follows:

- Alignment with label regarding diagnosis (DSM-IV criteria), medical history, and comorbidities assessments at baseline for contraindications and values to be monitored, as well as tool for documentation. The goal is to evaluate if the patient is an appropriate candidate for a methylphenidate prescription and characteristics to document before prescription.
- Monitoring during treatment related to safety aspects in the core SmPC including blood pressure, heart rate, height and body weight, and occurrence or worsening of pre-existing psychiatric symptoms, tics, or seizures. Also, the educational tool will address recommended periods off medication.

The educational tools will be submitted to Health Authorities for assessment prior to inclusion onto a live website.

Only the active ingredient methylphenidate will be mentioned (no brand names). The focus of the educational tool is the appropriate treatment according to the SmPC for methylphenidate. Safety guidance will be given in line with the SmPC for methylphenidate and assist healthcare providers in prescribing methylphenidate.

The education tool will be **distributed** via a Web site. The MAHs will request the medical communication agency to develop an independent Web site. MAHs view this Web site only as a carrier to distribute the developed tools providing guidance on the safe use of methylphenidate and not a platform to give broad education on ADHD. The Web site will include the objectives with a welcome message. The user will have the ability to download the patient baseline and monitoring tool, the SmPC. In addition, the Web site will include a legal notice and privacy policy statement. The Web site design will be independent of any company branding but will carry a link to the European Network on Hyperkinetic Disorders group. The content of the Web site will be available in the 23 official EU languages. The information on the Web site will be available for download and incorporation within individual patient dossiers.

(Continued)

Table 28: Additional Risk Minimisation Measures Planned (Educational Tools) (Continued)

Awareness and promotion of the Web site will be accomplished by links to the MAH's Web sites and professional communities. The URL will be mentioned during company specific medical educational events on ADHD (symposia etc.) and on materials. It is proposed that the URL be mentioned on each MAH SmPC. The Web site will be accessible to all medical professionals. The use of an independent third party rather than a pharmaceutical company will mean that no login or password is required. The target audience is the healthcare providers. Patients will have access to the educational messages within the Patient Information Leaflet, which is automatically provided with their medication should treatment with methylphenidate be prescribed.

Criteria Used to Verify Success

Audit of the Web site will comprise usefulness of the Web site and the number of times visited. This information will be generated via questions available on the Web site for completion by the user.

Proposed Review Period To be determined.

5. SUMMARY OF THE EU RISK MANAGEMENT PLAN

Table 29 provides an overall summary of the risk management plan.

Table 29: Overall Summary of the Risk Management Plan

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)[a]	Proposed Risk Minimisation Activities (Routine and Additional)[b]
Hypertension/ Tachycardia *(Identified risks)*	Routine pharmacovigilance Follow-up on FDA pharmacoepidemiologic study (ongoing)	Labelling: SmPC: Posology/Admin (Sec 4.2) SmPC: Contraindications (Sec 4.3) SmPC: Warnings (Sec 4.4) SmPC: Interactions (Sec 4.5) SmPC Undesirable Effects (Sec 4.8) Educational tool[c]
Raynaud's phenomenon *(Identified risk)*	Routine pharmacovigilance	Labelling: SmPC: Undesirable Effects (Sec 4.8)
Hallucinations (auditory, skin sensation, visual disturbance) Psychosis/Mania *(Identified risks)*	Routine pharmacovigilance	Labelling: SmPC: Posology/Admin (Sec 4.2) SmPC: Contraindications (Sec 4.3) SmPC: Warnings (Sec 4.4) SmPC Undesirable Effects (Sec 4.8) Educational tool[c]
Aggression *(Potential risk)*	Routine pharmacovigilance	Labelling: SmPC: Posology/Admin (Sec 4.2) SmPC: Warnings (Sec 4.4) SmPC Undesirable Effects (Sec 4.8) Educational tool[c]
Hostility Tics/Tourette's syndrome/Dystonias *(Potential risks)*	Routine pharmacovigilance	Labelling: SmPC: Warnings (Sec 4.4) SmPC Undesirable Effects (Sec 4.8), except hostility and dystonia Educational tool[c]
Anorexia *(Identified risk)*	Routine pharmacovigilance	Labelling: SmPC: Contraindication (Sec 4.3) SmPC: Warning (Sec 4.4) SmPC Undesirable Effects (Sec 4.8) Educational tool[c]
Decreased rate of growth *(Identified risk)*	Routine pharmacovigilance Follow-up MTA study (ongoing) Investigator-initiated study in adolescents (ongoing)	Labelling: SmPC: Posology/Admin (Sec 4.2) SmPC: Warnings (Sec 4.4) SmPC Undesirable Effects (Sec 4.8) Educational tool[c]
Migraine Repetitive behaviours *(Potential risks)*	Routine pharmacovigilance	Labelling: SmPC: Undesirable effects (Sec 4.8)
QT prolongation Cyanosis *(Potential risks)*	Routine pharmacovigilance	

(Continued)

Table 29: Overall Summary of the Risk Management Plan (Continued)

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)[a]	Proposed Risk Minimisation Activities (Routine and Additional)[b]
Arrhythmias *(Potential risk)*	Routine pharmacovigilance	Labelling: SmPC: Contraindications (Sec 4.3) SmPC: Warning (Sec 4.4) SmPC Undesirable Effects (Sec 4.8) Educational tool[c]
Sudden death *(Potential risk)*	Routine pharmacovigilance Enhanced pharmacovigilance (ongoing) Follow-up on FDA pharmacoepidemiologic study (ongoing)	Labelling: SmPC: Contraindications (Sec4.3) SmPC: Warnings (Sec 4.4) SmPC: Interactions (Sec 4.5) SmPC Undesirable Effects (Sec 4.8) Educational tool[c]
Cerebrovascular disorders *(Potential risk)*	Routine pharmacovigilance Enhanced pharmacovigilance (ongoing) Follow-up on FDA pharmacoepidemiologic study (ongoing)	Labelling: SmPC: Contraindications (Sec4.3) SmPC: Warnings (Sec 4.4) SmPC Undesirable Effects (Sec 4.8) Educational tool[c]
Depression *(Potential risk)*	Routine pharmacovigilance	Labelling: SmPC: Contraindication (Sec 4.3) SmPC: Warning (Sec 4.4) SmPC Undesirable Effects (Sec 4.8) Educational tool[c]
Suicidality *(Potential risk)*	Routine pharmacovigilance Enhanced pharmacovigilance (ongoing) Feasibility regarding meta-analysis of the risk of suicidality	Labelling: SmPC: Contraindication (Sec 4.3) SmPC: Warning (Sec 4.4) SmPC Undesirable Effects (Sec 4.8) Educational tool[c]
Effect on final height *(Potential risk)*	Routine pharmacovigilance Follow-up MTA study (ongoing)	Labelling: SmPC: Posology/Admin (Sec 4.2) SmPC: Warnings (Sec 4.4)
Sexual maturation (delayed) *(Potential risk)*	Routine pharmacovigilance Investigator-initiated study in adolescents (ongoing) Follow up MTA Study (ongoing)	
Carcinogenicity *(Potential risk)*	Routine pharmacovigilance Enhanced pharmacovigilance (ongoing) Evaluation of cytogenicity studies - submitted to the MHRA products	Labelling: SmPC: Preclinical safety data (Sec 5.3)

(Continued)

Table 29: Overall Summary of the Risk Management Plan (Continued)

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)[a]	Proposed Risk Minimisation Activities (Routine and Additional)[b]
Off-label use *(Potential risk)*	Routine pharmacovigilance IMS prescription data drug utilisation survey (DUS)	Labelling: SmPC: Posology/Admin (Sec 4.2) Educational tool[c]
Diversion *(Potential risk)*	Routine pharmacovigilance Monitoring supply of controlled substances follows National regulations	Labelling: SmPC: Posology/Admin (Sec 4.2) SmPC: Warning (Sec 4.4) Educational tool[c]
Withdrawal syndrome *(Potential risk)*	Routine pharmacovigilance	Labelling: SmPC: Warning (Sec 4.4) Educational tool[c]
Drug abuse and Drug dependence *(Potential risk)*	Routine pharmacovigilance	Labelling: SmPC: Posology/Admin (Sec 4.2) SmPC: Warning (Sec 4.4) Educational tool[c]
Lymphocytic leukaemia *(Potential risk)*	Routine pharmacovigilance	
Neonatal cardio-respiratory toxicity (neonatal/foetal tachycardia, respiratory distress/apnoea) *(Potential risk)*	Routine pharmacovigilance	Labelling: SmPC: Warning (Sec 4.6)
Neonatal effects on growth (via lactation) *(Potential risk)*	Routine pharmacovigilance	Labelling: SmPC: Warning (Sec 4.6)
Long-term safety[d]	Routine pharmacovigilance Determine the feasibility of a long-term safety study in corporation with other MAHs (ongoing)	Labelling: SmPC: Warnings (Sec 4.4) Educational tool[c]

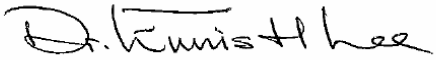
[a] Details of the routine pharmacovigilance activities are found in Section 2.1. Details of the additional pharmacovigilance activities are found in Table 25.

[b] Details of the routine risk minimisation activities (current labelling and proposed labelling changes) are provided in Table 27. (The SmPC is available in Annex 2.) Details of the additional risk minimisation activities (educational tool) are provided in Table 28; the exact content of the education tool is to be determined.

[c] The CHMP has requested that the MAHs of methylphenidate-containing products for ADHD prepare an educational tool (described in Table 28). The educational tools are being developed by a third party (ScopeMedical) with input from MAHs.)

[d] Identified as an area of important missing information for all MAHs of methylphenidate in the defined in the Rapporteur's (MHRA) Assessment Report dated 3 December 2008.

6. CONTACT PERSON FOR THIS EU-RMP

Names	Dr. Ennis Lee
Position	Vice President, Qualified Person for Pharmacovigilance (QPPV)
Qualifications	BSc, MB BS, FFPM
Signature	

7. REFERENCES

American Academy of Pediatrics (AAP) (2000). Clinical Practice Guideline: Diagnosis and Evaluation of the Child With Attention-Deficit/Hyperactivity Disorder. Pediatrics 2000;105:1158-1170.

American Psychiatric Association (APA) (1994). Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). 4th ed. Washington, DC, 1994.

Anderson JC (1987), Williams S, McGee R, Silva PA. DSM-III disorders in preadolescent children. Prevalence in large sample from the general population. Arch Gen Psych 1987;44(1)69-76.

Arar MY (1994), Hogg RJ, Arant BS Jr, Seikaly MG. Etiology of sustained hypertension in children in the southwestern United States. Pediatr Nephrol 1994;8:186-189.

Armenteros JL (2007), Lewis JE, Davalos M. Risperidone augmentation for treatment-resistant aggression in attention-deficit/hyperactivity disorder: a placebo-controlled pilot study. J Am Acad Child Adolesc Psychiatry 2007;46(5):558-565.

Atwood C (2005), Eisenberg MS, Herlitz J, Rea TD. Incidence of EMS-treated out-of-hospital cardiac arrest in Europe. Resuscitation 2005;67(1):75-80.

Bamford J (1988), Sandercock P, Dennis M, et al. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project 1981-86. 1. Methodology, demography and incident cases of first-ever stroke. J Neurol Neurosurg Psychiatry 1988;51:1373-1380.

Barkley RA (1996), Murphy KR, Kwasnik D. Motor vehicle driving competencies and risks in teens and young adults with attention deficit hyperactivity disorder. Pediatrics 1996;98(6 Pt 1):1089-1095.

Barzman DH (2008). Findling RL. Pharmacological treatment of pathologic aggression in children. Int Rev Psychiatry 2008;20:151-157.

Bastecky J (1996). Methylphenidate (Ritalin) in the treatment of acute drug poisoning. Ceska a Slovenska Psychiatrie 1996:92(Suppl 1):68-69.

Becker C (2008), Brobert GP, Almqvist PM, et al. Migraine incidence, comorbidity and health resource utilization in the UK. Cephalalgia 2008;28:57.

Bellward G (1969), Read III JM, Garrettson LK. Further studies of the inhibition of drug metabolism by methylphenidate. Fed Proc 1969;28:418.

Belson M (2007), Kingsley B, Holmes A. Risk factors for acute leukemia in children: a review. Environ Health Perspect 2007;115:138-45.

Ben-Itzhak R (2008). Giladi N. Gruendlinger L. Hausdorff JM. Can methylphenidate reduce fall risk in community-living older adults? A double-blind, single-dose cross-over study. J Am Geriatr Soc 2008;56(4):695-700.

Benefit Risk Management Report (2007). Postmarketing reports of overdose with CONCERTA® (OROS® methylphenidate hydrochloride): cumulative summary through 28 February 2007. Document No. EDMS-USRA-10489006; J&JPRD 31 July 2007).

Benefit Risk Management Report (2008). Postmarketing reports with fatal outcome with CONCERTA® (OROS® methylphenidate): cumulative summary through September 30 2007. Document ID No. EDMS-USRA 10665441; J&JPRD (Jan 2008).

Benefit Risk Management Report (2005). Response to Swissmedic request for information regarding CONCERTA® (OROS® methylphenidate hydrochloride) and cytogenetic abnormalities. Document No. EDMS-USRA-9503507; J&JPRD (05 May 2005).

Benefit Risk Management Report (PSUR 2007). Periodic Safety Update Report. OROS® methylphenidate HCl (From 01 Aug 2006 to 10 August 2007). Document ID No. EDMS-USRA-10519290:2.0. J&JPRD (26 Sep 2007).

Benefit Risk Management Report (PSUR 2008). Periodic Safety Update Report. OROS® methylphenidate HCl (From 11Aug2007-10Aug2008). Document ID No. EDMS-USRA-10859695:2.0. J&JPRD (25 September 2008).

Benefit Risk Management Report (PSUR 2009). Periodic Safety Update Report. OROS® methylphenidate HCl (From 11Aug2008-10Aug2009). Document ID No. EDMS-USRA-EDMS-USRA-11227189. J&JPRD (25 September 2009).

Bhatia S (2002), Sather HN, Heerema NA, et al. Racial and ethnic differences in survival of children with acute lymphoblastic leukemia. Blood 2002;100(6):1957-1964.

Biederman J (2003), Faraone SV, Monuteaux MC, Plunkett EA, Gifford J, Spencer T. Growth deficits and Attention–Deficit/Hyperactivity Disorder revisited: Impact of gender, development and treatment. Pediatrics 2003;111(5):1010-1016.

Biederman J (1998), Mick E, Faraone SV. Depression in attention deficit hyperactivity disorder (ADHD) children: “True” depression or demoralization? J Affective Disorder 1998;47:113-122.

Biederman J (2006a), Monuteaux MC, Mick E, et al. Psychopathology in females with attention-deficit/hyperactivity disorder: a controlled, five-year prospective study. Biol Psychiatry. 2006;60:1098-1105.

Biederman J (2006b), Monuteaux MC, Mick E, et al. Young adult outcome of attention deficit hyperactivity disorder: a controlled 10-year follow-up study. Psychol Med. 2006;36:167-179.

Birmaher B (1996), Ryan ND, Williamson DE, et al. Childhood and adolescent depression: a review of the past 10 years. Part I. J Am Acad Child Adolesc Psychiatry 1996;35(11):1427-1439.

Boulton MJ (1993). Proximate causes of aggressive fighting in middle school children. Br J Educ Psychol 1993;63(2):231-244.

Breitbart W (2007), Alici-Evcimen Y. Update on psychotropic medications for cancer-related fatigue. J Natl Compr Cancer Netw 2007;5:1081-1091.

Broderick J (1993), Talbot GT, Prenger E, Leach A, Brott T. Stroke in children within a major metropolitan area: the surprising importance of intracerebral hemorrhage. J Child Neurol 1993;8(3):250-255.

Bronstein AC (2007), Spyker DA, Cantilena LR, Green J, Rumack BH, Heard SE. 2006 Annual Report of the American Association of Poison Control Centers National Poison Data System (NPDS), Clinical Toxicology 2007;45:815-917.

Buhagiar K (2007), Cassar J. Methylphenidate augmentation of fluvoxamine for treatment-resistant depression: a case report and review literature. Turk Psikiyatri Dergisi 2007;18:179-183.

Cantwell DP (1997), Swanson J, Connor DF. Case study: adverse response to clonidine. J Am Acad Child Adolesc Psychiatry 1997;36(4):539-544.

Center for the Evaluation of Risks to Human Reproduction (CERHR) (2005) National Toxicology Program, US Department of health and Human Services, 2005. NTP-CERHR monograph on the potential human reproductive and developmental effects of methylphenidate. NIH Publication No. 05-4473.

Centers for Disease Control and Prevention (CDC) (2004). Miniño AM, Arias E, Kochanek KD, Murphy SL, Smith BL. Deaths: final data for 2000. National Vital Statistics Reports, 50(15). Hyattsville, MD: National Center for Health Statistics, 2002. Surveillance Summaries, 21 May 2004. MMWR 2004:53 (No.SS-2).

Chatterjee-Chakrabarty S (2005), Miller BT, Collins TJ, Nagamani M. Adverse effects of methylphenidate on the reproductive axis of adolescent female rats. Fertil Steril 2005; 84 (Suppl 2):1131-1138.

Clinical Study Report 01-146 (2003). An Evaluation of the Safety and Efficacy of CONCERTA® (up to 72 mg daily) in Adolescents with Attention Deficit Hyperactivity Disorder (ADHD). Document ID No. EDMS-PSDB-6282931; Ortho McNeil (August 2003).

Clinical Study Report 12-001 (2003). Multi-dose pharmacokinetics of CONCERTA® (methylphenidate HCl) in healthy adolescents with ADHD. McNeil (August 2003).

Clinical Study Report 12-101 (2004). A Multicenter Randomized Parallel-Group Study Evaluating Treatment Outcomes of CONCERTA® (Extended-Release Methylphenidate) and Strattera™ (Atomoxetine) in Children With Attention-Deficit/Hyperactivity Disorder. Document ID No. EDMS-PSDB-6248555; Ortho McNeil (20 Aug 2004).

Clinical Study Report C-97-025 (1999). Comparative Crossover Study of OROS® (methylphenidate HCl), Ritalin®, and Placebo in Children with ADHD. Alza (May 1999).

Clinical Study Report C-97-033-03 (1999). Bioavailability of OROS® (methylphenidate HCl) qd under various breakfast conditions relative to Ritalin® tid in children with ADHD. Alza (March 1999)

Clinical Study Report C-98-003 (1999). Screening, Efficacy, and Safety Study Evaluating OROS® (methylphenidate HCl), Ritalin, and Placebo in Children with ADHD. Alza (June 1999).

Clinical Study Report C-98-005 (1999). Multicenter Study Comparing the Efficacy and Safety of OROS® (methylphenidate HCl), Ritalin and Placebo in Children with ADHD. Alza (June 1999).

Clinical Study Report C-98-007-02 (1999). Initiation of OROS® (methylphenidate HCl) treatment in children with ADHD. Alza (June 1999).

Clinical Study Report C-98-012 (2003). Long-term Safety and Effectiveness of OROS® (methylphenidate HCl) in Children with ADHD (Part I and Part II). Document No. EDMS-PSDB-7023276; Alza (February 2003).

Clinical Study Report C-99-018 (2003). Open-Label Study to Evaluate Patient Use and Safety of OROS® (methylphenidate HCl) in Patients with ADHD in a Community Setting. Document No. EDMS-PSDB-7020870; Alza (April 2003).

Clinical Study Report C-2000-045 (2005). A Multicentre, Open-Label Study to Evaluate Safe and Effective Doses of Methylphenidate HCl Extended-Release Tables (Concerta®) in Children with Attention Deficit Hyperactivity Disorder (ADHD) Transferring From Treatment With Methylphenidate HCl Immediate-Release Tablets (MPH-IR). Document ID No. EDMS-PSDB-5074809; Janssen-Cilag EMEA (13 July 2005).

Clinical Study Report CON-CAN-1 (2005). A Randomized, Controlled, Effectiveness Trial of OROS-Methylphenidate compared to Usual Care with Immediate-Release-Methylphenidate in Attention-Deficit-Hyperactivity-Disorder. Document No. EDMS-PSDB-7020285; Janssen-Ortho Inc., Canada (20 Sep 2005).

Clinical Study Report CON-CAN-2 (2005). A 6-Month Open-Label Extension Trial of Concerta® or Usual Clinical Care with Immediate Release Methylphenidate (IR MPH) in Children Aged 6-13 Years with Attention Deficit Hyperactivity Disorder (ADHD). Document No. EDMS-PSDB-7020296; Janssen-Ortho Inc., Canada (20 Sep 2005).

Clubb PA (2001), Browne DC, Humphrey AD, Schoenbach V, Meyer B, Jackson M; RSVPP Steering Committee. Violent behaviors in early adolescent minority youth: results from a "middle school youth risk behavior survey". Matern Child Health J 2001;5(4):225-235.

Cole TJ (1994). Do growth chart centiles need a face lift? BMJ 1994;308(6929): 641-642.

Comings DE (1990), Himes JA, Comings BG. An epidemiologic study of Tourette's Syndrome in a single school district; 1990. J Clin Psychiatry 51(11):463-469.

Cooper TB (1973), Simpson GM. Concomitant imipramine and methylphenidate administration: a case report. Am J Psychiatry 1973;130(6):721.

Cortese S (2005), Konofal E, Lecendreux M, et al. Restless legs syndrome and attention-deficit/hyperactivity disorder: a review of the literature. Sleep 2005;28(8):1007-1013.

Council for International Organizations of Medical Sciences (CIOMS) (1999) (Gordon AJ ed). Report of CIOMS Working Groups III and V. Guidelines for preparing core clinical-safety information on drugs 2nd ed. Geneva; 1999.

Cuffe SP (2001), McKeown RE, Jackson KL, Addy CL, Abramson R, Garrison CZ. Prevalence of attention-deficit/hyperactivity disorder in a community sample of older adolescents. J Am Acad Child Adolesc Psychiatry 2001;40(9):1037-1044.

Cuffe SP (2005), Moore CG, McKeown RE. Prevalence and correlates of ADHD symptoms in the national health interview survey. J Atten Disord 2005;9(2):392-401.

Currin L (2005), Schmidt U, Treasure J, Jick H. Time trends in eating disorder incidence. Br J Psychiatry 2005;186:132-135.

Curtin C (2005), Bandini LG, Perrin EC, Tybor DJ, Must A. Prevalence of overweight in children and adolescents with attention deficit hyperactivity disorder and autism spectrum disorders: a chart review. BMC Pediatr 2005;5:48.

DeMilo L (1989). Psychiatric syndromes in adolescent substance abusers. Am J Psychiatry 1989;146:1212-1214.

DiScala C (1998), Lescohier I, Barthel M, Li G. Injuries to children with attention deficit hyperactivity disorder. Pediatrics 1998;102(6):1415-1421.

Donoghue AJ (2005), Nadkarni V, Berg RA, Osmond MH, Wells G, Nesbitt L, Stiell IG; CanAm Pediatric Cardiac Arrest Investigators. Out-of-hospital pediatric cardiac arrest: an epidemiologic review and assessment of current knowledge. Ann Emerg Med 2005;46(6):512-522.

Dunnick JK (1995), Hailey JR. Experimental studies on the long-term effects of methylphenidate hydrochloride. Toxicol 1995;103:77-84.

El-Zein RA (2005), Abdel-Rahman SZ, Hay MJ, et al. Cytogenetic effects in children treated with methylphenidate. Cancer Lett 2005;230(2):1-8.

Epidemiological Study of Dystonia in Europe Collaborative Group (ESDE) (2000). A prevalence study of primary dystonia in eight European countries. J Neurol 2000;247(10):787-792.

Faraj BA (1974), Israili ZH, Perel ML. Metabolism and disposition of methylphenidate-^{14}C: Studies in man and animals. J Pharmacol Exp Ther 1974;191:535-547.

Faraone SV (1997), Biederman J. Do attention deficit hyperactivity disorder and major depression share familial risk factors? J Nerv Ment Dis 1997;185(9):533-541.

Feld LG (1988), Springate JE. Hypertension in children. Curr Probl Pediatr 1988;18:317-373.

Fenichel RR (1995). Combining methylphenidate and clonidine: the role of post-marketing surveillance. J Child Adolesc Psychopharmacol 1995;5(3):155-156.

Feron FJM (2005), Hendrikson JGH, van Kroonenburgh MJPG, et al. Dopamine transporter in attention-deficit hyperactivity disorder normalizes after cessation of methylphenidate. Pediatr Neurol 2005;33:179-183.

Findling RI (1996). Open-label treatment of comorbid depression and attentional disorders with co-administration of serotonin reuptake inhibitors and psychostimulants in children, adolescents, and adults: a case series. J Child Adolesc Psychopharmacol 1996;6(3):165-175.

Fishman PA (2007), Stang PE, Hogue SL. Impact of comorbid attention deficit disorder on the direct medical costs of treating adults with depression in managed care. J Clin Psychiatry 2007;68(2):248-253.

Flapper BC (2008), Schoemaker MM. Effects of methylphenidate on quality of life in children with both developmental coordination disorder and ADHD. Dev Med Child Neurol 2008;50:294-299.

Flynn JT (2001a). Characteristics of children with primary hypertension referred to a tertiary center. Am J Hypertens 2001;14:239A.

Flynn JT (2001b). What's new in pediatric hypertension? Curr Hypertens Rep 2001;3:503-510 B7.

Fone KCF (2005), Nutt DJ. Stimulants: use and abuse in the treatment of attention deficit hyperactivity disorder. Curr Opin Pharmacol 2005;5:87-93.

Freeman GB (1998), Reichelderfer D, Athey PM, et al. Toxicity evaluation of methylphenidate hydrochloride in transgenic mice. Toxicol Sci 1998;42:72.

Fullerton HJ (2002), Chetkovich DM, Wu YW, Smith WS, Johnston SC. Deaths from stroke in US children, 1979 to 1998. Neurology 2002;59(1):34-39.

Fullerton HJ (2003), Wu YW, Zhao S, Johnston SC. Risk of stroke in children: Ethnic and gender disparities. Neurology 2003;61(2):189-194.

Gadow KD (2007), Sverd J, Nolan EE, Sprafkin J, Schneider J. Immediate-release methylphenidate for ADHD in children with comorbid chronic multiple tic disorder. J Am Acad Child Adolesc Psychiatry 2007;46(7):840-848.

Galloway SM (1987), Armstrong MJ, Colman S, et al. Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: evaluations of 108 chemicals. Environ Mol Mutagen 1987;10(Suppl 10):1-175.

Gammon GD (1993), Brown TE. Fluoxetine and methylphenidate combination for treatment of attention deficit disorder and comorbid depressive disorder. J Child Adolesc Psychopharmacol 1993;3:1-10.

Garrettson LK (1969), Perel JM, Dayton PG. Methylphenidate interaction with both anticonvulsants and ethyl biscoumacetate. JAMA 1969;207:2053-2056.

Garson A Jr (1981), Gillette PC, McNamara DG. Supraventricular tachycardia in children: clinical features, response to treatment, and long-term follow-up in 217 patients. J Pediatr 1981;98:875-882.

Geller DA (2002), Biederman J, Faraone SV, et al. Attention-deficit/hyperactivity disorder in children and adolescents with obsessive-compulsive disorder: fact or artifact? J Am Acad Child Adolesc Psychiatry 2002;41(1):52-8.

Giroud M (1995), Lemesle M, Gouyon JB, Nivelon JL, Milan C, Dumas R. Cerebrovascular disease in children under 16 years of age in the city of Dijon, France: a study of incidence and clinical features from 1985 to 1993. J Clin Epidemiol 1995;48(11):1343-1348.

Goodwin DW (1975), Schulsinger F, Hermansen L, Guze SB, Winokur G. Alcoholism and the hyperactive child syndrome. J Nerv Ment Dis. 1975;160:349-353.

Goraya TY (2000), Jacobsen SJ, Belau PG, et al. Validation of death certificate diagnosis of out-of-hospital coronary heart disease deaths in Olmsted County, Minnesota. Mayo Clinic Proc 2000;75:681-687.

Guevara J (2002), Lozano P, Wickizer T, Mell L, Gephart H. Psychotropic medication use in a population of children who have attention-deficit/hyperactivity disorder. Pediatrics 2002;109(5):733-739.

Gunther T (2006), Herpertz-Dahlmann B, Jolles J, Konrad K. The influence of risperidone on attentional functions in children and adolescents with attention-deficit/hyperactivity disorder and co-morbid disruptive behavior disorder. J Child Adolesc Psychopharmacol 2006;16(6):725-735.

Haas DC (2004), Sheehe PR. Dextroamphetamine pilot crossover trials and n of 1 trials in patients with chronic tension-type and migraine headache. Headache 2004;44:1029-1037.

Hague DE (1971), Smith ME, Ryan JR, et al. The effect of methylphenidate and prolintane on the metabolism of ethylbiscoumacetate. Clin Pharmacol Ther 1971;12:259-262.

Halperin JM (1995), Newcorn JH, Matier K, Bedi G, Hall S, Sharma V. Impulsivity and the initiation of fights in children with disruptive behavior disorders. J Child Psychol Psychiatry 1995;36(7):1199-1211.

Hanna A (2006), Sledge G, Mayer ML, et al. A phase II study of methylphenidate for the treatment of fatigue. Support Care Cancer 2006;14:210-215.

Hedley AA (2004), Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999-2002. JAMA 2004;291(23):2847-2850.

Holtkamp K (2004), Konrad K, Muller B, et al. Overweight and obesity in children with Attention-Deficit/Hyperactivity Disorder. Int J Obes Relat Metab Disord 2004;28(5):685-689.

Homsi J (2001), Nelson KA, Sarhill N et al., A phase II study of methylphenidate for depression in advanced cancer, Am J Hosp Palliat Care 2001;18:403–407.

Horner MJ (2009), Ries LAG, Krapcho M, Neyman N, et al (eds). SEER Cancer Statistics Review, 1975-2006, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2006/, based on November 2008 SEER data submission, posted to the SEER web site, 2009.

Hornsey H (2001), Banerjee S, Zeitlin H, Robertson M. Prevalence of Tourette's syndrome in 13-14 year olds in mainstream schools. J Child Psychol Psychiatry 2001;42(8):1035-1039.

Hovens JG (1994), Cantwell DP, Kiriakos R. Psychiatric comorbidity in hospitalized adolescent substance abusers. J Am Acad Child Adolesc Psychiatry 1994;33:476-483.

Hunninghake D (1970). Studies of inhibition of drug metabolism by methylphenidate. Fed Proc 1970;29;345.

Ilgenli TF (2007), Congologlu A, Ozturk C, et al. Acute effect of methylphenidate on QT dispersion in children with attention deficit disorder. Adv Ther 2007;24:182-188.

Ishisaka DY (1996). Exogenous surfactant use in neonates. Ann Pharmacother 1996;30(4):389-398.

James A (2004), Lai FH, Dahl C. Attention deficit hyperactivity disorder and suicide: a review of possible associations. Acta Psychiatr Scand 2004;110:408-415.

Jensen PS (2007), Arnold LE, Swanson JM, et al. 3-Year Follow-up of the NIMH MTA Study. J Am Acad Child Adolesc Psychiatry 2007;46(8);989-1002.

Jensen PS (2001), Hinshaw SP, Kraemer HC, et al. ADHD comorbidity findings from the MTA study: comparing comorbid subgroups. J Am Acad Child Adolesc Psychiatry 2001;40(2):147-158.

Jensen PS (1999), Kettle L, Roper MT, et al. Are stimulants overprescribed? Treatment of ADHD in four U.S. communities. J Am Acad Child Adolesc Psychiatry 1999;38(7):797-804.

Jensen R (2008), Stovner LJ. Epidemiology and comorbidity of headache. Lancet Neurol 2008;7:354-361.

Johnston LD (2007), O'Malley PM, Bachman JG, Schulenberg JE. Overall, illicit drug use by American teens continues gradual decline in 2007. University of Michigan News Service: Ann Arbor, MI. [Online]. Available: www.monitoringthefuture.org; accessed 16 Jan 2008.

Jones GT (2003), Herrick AL, Woodham SE, Baildam EM, Macfarlane GJ, Silman AJ. Occurrence of Raynaud's phenomenon in children ages 12-15 years: prevalence and association with other common symptoms. Arthritis Rheum 2003;48(12): 3518-3521.

Kadesjo B (2000), Gillberg C. Tourette's disorder: epidemiology and comorbidity in primary school children. J Am Acad Child Adolesc Psychiatry 2000;39(5):548-555.

Kendall PC (2001), Brady EU, Verduin TL. Comorbidity in childhood anxiety disorders and treatment outcome. J Am Acad Child Adolesc Psychiatry 2001;40(7):787-794.

Kessler RC (2001), Avenevoli S, Merikangas KR. Mood disorders in children and adolescents: An epidemiologic perspective. Biol Psychiatry 2001;49:1002-1014.

Khalifa N (2003), von Knorring AL. Prevalence of tic disorders and Tourette's syndrome in a Swedish school population. Dev Med Child Neurol 2003;45(5):315-319.

Klein D (2006). The flawed basis for FDA post-marketing safety decisions: The example of anti-depressants and children. Neuropsychopharmacol 2006;31:689-699.

Kurlan R (1994), Whitmore D, Irvine C, McDermott MP, Como PG. Tourette's syndrome in a special education population: A pilot study involving a single school district. Neurology 1994;44(4)699-702.

Kurscheidt JC (2008), Peiler P, Behnken A, et al. Acute effects of methylphenidate on neuropsychological parameters in adults with ADHD: possible relevance for therapy. J Neural Transm 2008;115:357-362.

Kutcher S (2004), Aman M, Brooks SJ, et al. International consensus statement on attention-deficit/hyperactivity disorder (ADHD) and disruptive behaviour disorders (DBDs): clinical implications and treatment practice suggestions. Eur Neuropsychopharmacol 2004;14(1):11-28.

Lam LT (2005). Attention deficit disorder and hospitalization owing to intra- and interpersonal violence among children and young adolescents. J Adolesc Health 2005;36(1):19-24.

Laval G (2008), Paris A. Methylphenidate in palliative care in cancer patient: a double-blind randomised trial versus placebo. Bull Cancer 2008;95:241-246.

Lavretsky H (2006), Park S, Siddarth P, et al. Methylphenidate enhanced antidepressant response to citalopram in the elderly: a double-blind, placebo-controlled pilot trial. Am J Geriatr Psychiatry 2006;14:181-185.

Lee K (1999), Khoshnood B, Wall SN, et al. Trend in mortality from respiratory distress syndrome in the United States, 1970-1995. J Pediatr 1999;134(4):434-440.

Levin FR (1998), Evans S, Kleber HD. Prevalence of adult attention-deficit/hyperactivity disorder among cocaine abusers seeking treatment. Drug Alcohol Depend 1998;52:15-25.

Levy F (1988), Hobbes G. The action of stimulant medication in attention deficit disorder with hyperactivity: dopaminergic, noradrenergic, or both? J Am Acad Child Adolesc Psychiatry 1988;27(6):802-805.

Levy F (1996), Hobbes G. Does haloperidol block methylphenidate? Motivation or attention? Psychopharmacology 1996;126(1):70-74.

Leyfer OT (2006), Folstein SE, Bacalman S. Comorbid psychiatric disorders in children with autism: interview development and rates of disorders. J Autism Dev Disord 2006;36(7):849-861.

Liberthson R (1996). Sudden death from cardiac causes in children and young adults. NEJM 1996:334(16);1039-1044.

Lynch JK (2002), Hirtz D, DeVeber G, et al. Report of the National Institute of Neurological Disorders and Stroke Workshop on Perinatal and Childhood Stroke. Pediatrics 2002;109(1):116-123.

Mannuzza S (2008), Klein RG, Truong NL. Age of methylphenidate treatment initiation in children with ADHD and later substance abuse: prospective follow-up into adulthood. Am J Psychiatry 2008;165:604-609.

Mantani A (2008), Fujikawa T, Ohmori N, Yamawaki S. Methylphenidate in the treatment of geriatric patients with vascular depression: a retrospective chart review. Am J Geriatric Psychiatry 2008;16(4):336-337.

Markowitz JS (2000), DeVane CL, Boulton DW, Nahas Z, Risch SC, Diamond F, Patrick KS. Ethylphenidate formation in human subjects after the administration of a single dose of methylphenidate and ethanol. Drug Metab Dispos 2000;28:620-624.

Markowitz JS (1999), Morrison SD, DeVane CL. Drug interactions with psychostimulants. Int J Clin Psychopharmacology. 1999;14(1):1-18.

Masi G (2008), Milone A, Manfredi A, Pari C, Paziente A, Millepiedi S. Conduct disorder in referred children and adolescents: clinical and therapeutic issues. Compr Psychiatry 2008;49:146-153.

Mason A (1998), Barnerjee S, Eapen V, Zeitlin H, Robertson MM. The prevalence of Tourette's syndrome in a mainstream school population. Dev Med Child Neurol 1998;4(5):292-296.

McCabe SE (2004), Teter CJ, Boyd CJ, Guthrie SK. Prevalence and correlates of illicit methylphenidate use among 8th, 10th, and 12th grade students in the United States, 2001. J Adolesc Health 2004;35(6):501-504.

McCarthy J (2007). Children with autism spectrum disorders and intellectual disability. Curr Opin Psychiatry 2007;20:472-476.

McGlohn SE (1995), Bostwick JM. Sertraline with methylphenidate in an ICU patient. Psychosomatics 1995;36(6):584-585.

Mendonca DA (2007), Menezes K, Jog MS. Methylphenidate improves fatigue scores in Parkinson disease: a randomized controlled trial. Movement Disorders 2007;22:2070-2076.

Meyers CA (1998), Weitzner MA, Valentine AD, et al. Methylphenidate therapy improves cognition, mood, and function of brain tumor patients. J Clin Oncol 1998;16:2522–2527.

Milberger S (1995), Biederman J, Faraone SV, Murphy J, Tsuang MT. Attention deficit hyperactivity disorder and comorbid disorders: Issues of overlapping symptoms. Am J of Psychiatry 1995;152(12):1793-1799.

Milin R (1991), Halikas JA, Meller JE, Morse C. Psychopathology among substance abusing juvenile offenders. J Am Acad Child Adolesc Psychiatry 1991;30:569-574.

Mirsalis J (1983), Tyson K, Beck J, et al. Induction of unscheduled DNA synthesis (UDS) in hepatocytes following in vitro and in vivo treatment. Environ Mutagen 1983;5:482.

Moller JH (1998), ed. Surgery of Congenital Heart Disease Pediatric Cardiac Care Consortium 1984-1995. Prevalence and incidence of cardiac malformations. Armonk, NY: Futura Publishing Company, 1998:20. Vol. 6.

Morita T (2000), Otani H, Tsunoda J, et al. Successful palliation of hypoactive delirium due to multi-organ failure by oral methylphenidate. Support Care Cancer 2000:8:134–137.

Morrison JJ (1995), Rennie JM, Milton PJ. Neonatal respiratory morbidity and mode of delivery at term: influence of timing of elective caesarean section. Br J Obstet Gynaecol 1995; 102(2): 101-106.

Mortelmans K (1986), Haworth S, Lawlor T, Speck W, Tainer B, Zeiger E. Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals. Environ Mutagen 1986;8(Suppl 7):1-119.

Murray CJL (1996), Lopez AD. Global health statistics: a compendium of incidence, prevalence, and mortality estimates for over 200 conditions, World Health Organization, Harvard University Press, 1996.

Myerburg RJ (1993), Kessler KM, Castellanos A. Sudden cardiac death: epidemiology, transient risk, and intervention assessment. Ann Intern Med 1993;119(12):1187-1197.

National Institute of Mental Health (NIMH) (2004). Bethesda (MD): US Department of Health and Human Services; 2004 Attention Deficit Hyperactivity Disorder. http://www.nimh.nih.gov/publicat/ NIMHadhdpub.pdf. Accessed on April 24 2007.

National Toxicology Program (NTP) (1995). Toxicology and Carcinogenesis Studies of Methylphenidate Hydrochloride (CAS No. 298-59-9) in F344/N Rats and B6C3F1 Mice (Feed Studies). NTP TR No. 439, NIH Publication No. 95-3355. Research Triangle Park, NC: US Dept of Health & Human Services, Public Health Service, National Institutes of Health 1995.

National Toxicology Program (NTP) (1997). Toxicity Evaluation of Methylphenidate HCl (CAS No, 298-59-9) in Transgenic Mice. Research Triangle Park, NC: US Dept of Health & Human Services, Public Health Service, National Institutes of Health 1997.

Nelson JC (2007). Augmentation strategies in the treatment of major depressive disorder. Recent findings and current status of augmentation strategies. CNS Spectr 2007;12(Suppl 22):6-9.

Niwa K (2004), Warita N, Sunami Y, Shimura A, Tateno S, Sugita K. Prevalence of arrhythmias and conduction disturbances in large population-based samples of children. Cardiol Young 2004;14(1):68-74.

Ng B (2008). Methylphenidate and depression. J Clin Psychopharmacol 2008;28:116-117; author reply 117-8.

Nonclinical Study Report 98-5607-054 (1999). In Vivo Mouse Micronucleus Assay of Methylphenidate Hydrochloride by Acute Oral Dosing in CD-1 Mice. Alza (01 June 1999).

Nonclinical Study Report FBM 05-4548 (2006). Effect of methylphenidate hydrochloride on cardiovascular system in unrestricted conscious dogs. Kobuchisawa Laboratories, Fuji Biomedix Co., Ltd. (22 Feb 2006).

Nonclinical Study Report FBM 05-9739 (2006). Effects of methylphenidate hydrochloride on the action potential in isolated guinea pig papillary muscle. Kobuchisawa Laboratories, Fuji Biomedix Co., Ltd (25 Feb 2006).

Nonclinical Study Report FBM 05-9740 (2006). Effects of methylphenidate hydrochloride on the membrane K + current (I kr) in hERG-transfected HEK293 cells in unrestricted conscious dogs. Kobuchisawa Laboratories, Fuji Biomedix Co., Ltd. (25 Feb 2006).

Nonclinical Study Report TR-02-5607-001 (2004). A juvenile oral toxicity study of methylphenidate HCl in rats. Alza (June 2004).

Novak SP (2007), Kroutil LA, Williams RL, Van Brunt DL. The nonmedical use of prescription ADHD medications: results from a national Internet panel. Substance Abuse Treatment, Prevention, & Policy 2007;2:32.

Oestreicher N (2007), Friedman GD, Jiang SF, Chan J, Quesenberry C Jr, Habel LA. Methylphenidate use in children and risk of cancer at 18 sites: results of surveillance analyses. Pharmacoepidemiol Drug Saf 2007;16(12):1268-1272.

Ogden CL (2002), Kuczmarski RJ, Flegal KM, et al. Centers for Disease Control and Prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. Pediatrics 2002;109(1):45-60.

Palumbo D (2004), Spencer T, Lynch J, Co-Chien H, Faraone SV. Emergence of tics in children with ADHD: impact of once-daily OROS methylphenidate therapy. J Child Adolesc Psychopharmacol 2004;14(2):185-194.

Patkar AA (2006), Masand PS, Pae C-U, et al. A randomized, double-blind, placebo-controlled trial of augmentation with an extended release formulation of methylphenidate in outpatients with treatment-resistant depression. J Clin Psychopharmacol 2006;26:653-656.

Patrick KS (2007), Straughn AB, Minhinnett RR et al. Influence of ethanol and gender on methylphenidate pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther 2007;81(3):346-353.

Pavlovskaya M (2007), Hochstein S, Keren O, Mordvinov E, Groswasser Z. Methylphenidate effect on hemispheric attentional imbalance in patients with traumatic brain injury: a psychophysical study. Brain Injury 2007;21:489-497.

Pine DS (1993), Klein RG, Lindy DC, Marshall RD. Attention-deficit hyperactivity disorder and comorbid psychosis: a review and two clinical presentations. J Clin Psychiatry 1993;54(4):140-145.

Pizzi WJ (1987), Rode EC, Barnhart JE. Differential effects of methylphenidate on the growth of neonatal and adolescent rats. Neurotoxicol Teratol 1987; 9: 107-11.

Pizzi WJ (1986), Rode EC, Barnhart JE. Methylphenidate and growth: demonstration of a growth impairment and a growth-rebound phenomenon. Dev Pharmacol Ther 1986;9(5):361-368.

Pollak L (2007), Dobronevsky Y, Prohorov T, Bahunker S, Rabey JM. Low dose methylphenidate improves freezing in advanced Parkinson's disease during off-state. J Neural Transm 2007;72 (Suppl):145-148.

Ponsa I (2009), Ramos-Quiroga JA, Ribases M et al. Absence of cytogenetic effects in children and adults with attention-deficit/hyperactivity disorder treated with methylphenidate. Mutation Research 2009; 666:44–49.

Poulton R (2000), Caspi A, Moffitt TE, Cannon M, Murray R, Harrington H. Children's self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. Arch Gen Psychiatry 2000;57(11):1053-1058.

Pui CH (2008), Robison LL, Look AT. Acute lymphoblastic leukaemia. Lancet 2008;371:1030-1043.

Redaelli A (2005), Laskin BL, Stephens JM, Botteman MF, Pashos CL. A systematic literature review of the clinical and epidemiological burden of acute lymphoblastic leukaemia (ALL). Eur J Cancer Care 2005;14(1):53-62.

Ririe DG (1997), Ririe KL, Sethna NF, Fox L. Unexpected interaction of methylphenidate (Ritalin) with anaesthetic agents. Paediatr Anaesth 1997;7(1):69-72.

Robinson MD (1995), Anastasio GD, Little JM, et al. Ritalin for nicotine withdrawal: Nesbitt's paradox revisited. Addictive Behaviors 1995;20(4):481-490.

Roffman JL (1997), Raskin LA. Stereotyped behavior: Effects of d-amphetamine and methylphenidate in the young rat. Pharmacol Biochem Behav 1997; 58:1095-1102.

Roggen A (2008), Pavlovic M, Pfammatter JP. Frequency of spontaneous ventricular tachycardia in a pediatric population. Am J Cardiol 2008;101(6):852-854.

Rosenthal GR (1998). Prevalence of congenital heart disease. In: Chapter 48 of the Science & Practice of Pediatric Cardiology. 2nd ed. Baltimore, MD: Williams and Wilkins; 1998:1083-1105.

Rudd CJ (1983), Mitchell AD, Spalding J. L5178Y mouse lymphoma cell mutagenesis assay of coded chemicals incorporating analyses of the colony size distributions. Environ Mutagen 1983;5:419.

Sacchetti A (1999), Moyer V, Baricella R, Cameron J, Moakes ME. Primary cardiacarrhythmias in children. Pediatr Emerg Care 1999;15 (2):95-98.

Schoenberg BS (1978), Mellinger JF, Schoenberg DG. Cerebrovascular disease in infants and children: a study of incidence, clinical features, and survival. Neurology 1978;28:763-768.

Schubiner H (2000), Tzelepis A, Milberger S, et al. Prevalence of attention-deficit/hyperactivity disorder and conduct disorder among substance abusers. J Clin Psychiatry 2000;61:244-251.

Seeman P (1998), Madras BK. Anti-hyperactivity medication: methylphenidate and amphetamine. Mol Psychiatry 1998; 3(5):386-396.

Shea AK (2008), Steiner M. Cigarette smoking during pregnancy. Nicotine Tob Res. 2008;10(2):267-278.

Singh NN (1985), Millichamp CJ. Pharmacological treatment of self-injurious behavior in mentally retarded persons. J Autism Dev Disord 1985;15:257-267.

Spencer T (1995), Biederman J, Harding M, Wilens T, Faraone S. The relationship between tic disorders and Tourette's syndrome revisited. J Am Acad Child Adolesc Psychiatry 1995;34(9):1133-1139.

Spencer T (1998), Biederman J, Wilens T. Growth deficits in children with attention deficit hyperactivity disorder. Pediatrics 1998;102:501-506.

Spencer TJ (1996), Biederman J, Harding M, O'Donnell D, Faraone SV, Wilens TE. Growth deficits in ADHD children revisited: evidence for disorder-associated growth delays? J Am Acad Child Adolesc Psychiatry 1996;35(11):1460-1469.

Steliarova-Foucher E (2004), Stiller C, Kaatsch P, et al. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCIS project): an epidemiological study. Lancet 2004;364(9451):2097-2105.

Stoll AL (1996), Pillay SS, Diamond L, et al. Methylphenidate augmentation of serotonin selective reuptake inhibitors: a case series. J Clin Psychiatry 1996;57:72-76.

Stopper H (2008), Walitza S, Warnke A, Gerlach M. Brief review of available evidence concerning the potential induction of genomic damage by methylphenidate. J Neural Transm 2008;115:331-334.

Sun SS (2002), Schubert CM, Chumlea WC, et al. National estimates of the timing of sexual maturation and racial differences among US children. Pediatrics 2002;110(5):911-919.

Suter LG (2005), Murabito JM, Felson DT, Fraenkel L. The incidence and natural history of Raynaud's phenomenon in the community. Arthritis Rheum 2005;52(4):1259-1263.

Swanson JM (2007), Elliott GR, Greenhill LL, et al. Effects of stimulant medication on growth rates across 3 years in the MTA follow-up. J Am Acad Child Adolesc Psychiatry 2007;46(8):1015-1027.

Swensen AR (2002), Allen AJ, Kreusi M, et al. Increased risk of self-injury and suicide risk for patients with attention deficit/hyperactivity disorder. Eur Neuropsychopharmacol 2002;12:S421.

Swensen AR (2003), Birnbaum HG, Secnik K, Marynchenko M, Greenberg P, Claxton A. Attention-deficit/hyperactivity disorder: increased costs for patients and their families. J Am Acad Child Adolesc Psychiatry 2003;42(12):1415-1423.

Syed RH (2008), Moore TL. Methylphenidate and dextroamphetamine-induced peripheral vasculopathy. J Clin Rheumatol 2008;14:30-33.

Tauscher-Wisniewski S (2006). Aggression in attention-deficit/hyperactivity disorder children: diagnostic or comorbid symptom? Expert Rev Neurotherapeutics 2006;6:197-199.

Taylor E (2004), Dopfner M, Sergeant J, et al. European clinical guidelines for hyperkinetic disorder -- first upgrade. Eur Child Adolesc Psychiatry 2004; 13(Suppl 1):I7-30.

Teo SK (2003), Stirling DI, Hoberman AM, et al. D-methylphenidate and D,L-methylphenidate are note developmental toxicants in rats and rabbits. Birth Defects Res Part B Dev Reprod Toxicol 2003; 68:162-171.

Teo SK (2002), Stirling DI, Thomas SD, et al. The perinatal and postnatal toxicity of D-methylphenidate and D,L-methylphenidate in rats. Reprod Toxicol 2002;16:353-366.

Tourette's Syndrome Study Group (2002). Treatment of ADHD in children with tics: A randomised controlled trial. Neurology 2002; 58:527-536.

Tucker JD (2009), Suter W, Petibone DM et al. Cytogenetic assessment of methylphenidate treatment in pediatric patients treated for attention deficit hyperactivity disorder. Mutation Research 2009; 677:53-58.

Valdizan Uson JR (2008), Idiazabal Alecha MA. Diagnostic and treatment challenges of chronic fatigue syndrome: role of immediate-release methylphenidate. Neurotherapeutics 2008;8(6):917-927.

Van Harten PN (1999), Hoek HW, Kahn RS. Acute dystonia induced by drug treatment. BMJ 1999;319(7210):623-626.

Ventura SJ (1998), Martin JA, Curtin SC, Mathews TJ. Report of final natality statistics, 1996. Mon Vital Stat Rep 1998; 46(11 Suppl):1-99.

Vetter VL (2008), Elia J, Erickson C, et al. Cardiovascular monitoring of children and adolescents with heart disease receiving stimulant drugs. Circulation 2008;117:2407-2423.

Vitiello B (2008). Understanding the risk of using medications for attention deficit hyperactivity disorder with respect to physical growth and cardiovascular function. Child Adolesc Psychiatric Clin N Am 2008;17:459-474.

Wakamatsu A (2009), Nomura S, Tate Y, Shimizu S, Harada Y. Effects of methylphenidate hydrochloride on the cardiovascular system in vivo and in vitro: A safety pharmacology study. J Pharmacol Toxicol Methods 2009;59(3):128-134.

Wald D (1978), Ebstein RP, Belmaker RH. Haloperidol and lithium blocking of the mood response to intravenous methylphenidate. Psychopharmacology 1978;57(1):83-87.

Walitza S (2009), Kampf K, Artamonov N, et al. No elevated genomic damage in children and adolescents with attention deficit/hyperactivity disorder after methylphenidate therapy. Toxicol Lett 2009;184(1):38-43.

Walitza S (2007), Werner B, Romanos M, et al. Does methylphenidate cause a cytogenetic effect in children with attention deficit hyperactivity disorder? Environ Health Perspect 2007;115:936-940.

Waschbusch DA (2007), Carrey N, Willoughby MT, King S, Andrade BF. Effects of methylphenidate and behavior modification on the social and academic behavior of children with disruptive behavior disorders: the moderating role of callous/unemotional traits. J Clin Child Adolesc Psychol 2007;36:629-644.

Weindling SN (1996), Saul JP, Walsh EP. Efficacy and risks of medical therapy for supraventricular tachycardia in neonates and infants. Am Heart J 1996; 131(1): 66-72.

Wharton RN (1971), Perel JM, Dayton PG, Malitz S. A potential clinical use of methylphenidate with tricyclic antidepressants. Am J Psychiatry 1971;127(12):55-61.

Whittle W (2006), Chaddha V, Wyatt P, Huppertz B, Kingdom J. Ultrasound detection of placental insufficiency in women with 'unexplained' abnormal maternal serum screening results, Clin Genet 2006;69:97-104.

Wilens T (1995), Spencer T, Biederman J. Are attention-deficit/hyperactivity disorder and the psychoactive substance use disorders really related? Harv Rev Psychiatry 1995;3:260-262.

Wilens TE (2003), Faraone SV, Biederman J, Gunawardene S. Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. Pediatrics 2003;111:179-185.

Wilens TE (2008). Pharmacotherapy of ADHD in adults. CNS Spectr 2008;13:11-13.

Williams AN (2000). Childhood stroke-beyond re-inventing the wheel. Eur J Paediatr Neurology 2000;4:103-107.

Wilwerding MB (1995), Loprinzi CL, Mailliard JA, et al. A randomized, crossover evaluation of methylphenidate in cancer patients receiving strong narcotics. Support Care Cancer 1995;3:135-138.

Witt KL (2008), Shelby MD, Itchon-Ramos N, et al. Methylphenidate and amphetamine do not induce cytogenetic damage in lymphocytes of children with ADHD. J Am Acad Child Adolesc Psychiatry 2008:47:1375-1383.

World Health Organization (WHO) (2000) Global Database on Child Growth and Malnutrition. Geneva: WHO, 2000.

Young KD (2004), Gausche-Hill M, McClung CD, Lewis RJ. A prospective, population-based study of the epidemiology and outcome of out-of-hospital pediatric cardiopulmonary arrest. Pediatrics 2004;114(1):157-164.

ANNEX 1

MEDICINAL PRODUCT CODE (FROM EUDRAVIGILANCE)

European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

Interface between European Risk Management Plan (EU-RMP) and EudraVigilance

AS REFERRED TO IN

ANNEX 1 OF

"ANNEX C: TEMPLATE FOR EU RISK MANAGEMENT PLAN (EU-RMP)"

VER. 1.0.0

MEDICINAL PRODUCT

CONCERTA®

ACTIVE SUBSTANCE(S)

METHYLPHENIDATE HYDROCHLORIDE

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

1. TABLE OF CONTENTS

1. TABLE OF CONTENTS 2
2. INTRODUCTION 3
3. STARTING UP 4
4. SENDER 6
5. MEDDRA VERSION 7
6. MEDICINAL PRODUCT 8
7. INDICATIONS 10
8. IDENTIFIED RISKS 12
9. POTENTIAL RISKS 21
10. IDENTIFIED INTERACTIONS 40
11. POTENTIAL INTERACTIONS 49

2. INTRODUCTION

This document should be completed as described below and submitted in electronic format at the same time as the EU Risk Management Plan in accordance to requirements detailed in the 'Guideline on Risk Management Systems for Medicinal Products for Human Use' (EMEA/CHMP/96268/2005). The information provided in this document should be consistent with the data provided in the EU Risk Management Plan. The purpose of this document is to allow for the monitoring of identified and potential risks in relation to suspected adverse reactions reported to EudraVigilance in line with Regulation No. 726/2004, Directive 2001/83/EC as amended and Volume 9A of 'The Rules Governing Medicinal Products in the European Union' of the Notice to Marketing Authorisation Holders. An updated version of this electronic document should be submitted each time an update of the EU Risk Management Plan is provided.

All the fields of this electronic document should be populated with one term only except for the free text fields where several terms are allowed.

The completed document should be sent in Word and PDF format to h-eurmp-evinterface@emea.europa.eu or by physical media (CD-ROM) to:

EudraVigilance

Post-Authorisation of Medicines for Human Use
Pharmacovigilance and Post-Authorisation Safety and Efficacy

European Medicines Agency (EMEA)
7 Westferry Circus, Canary Wharf
London E14 4HB - United Kingdom

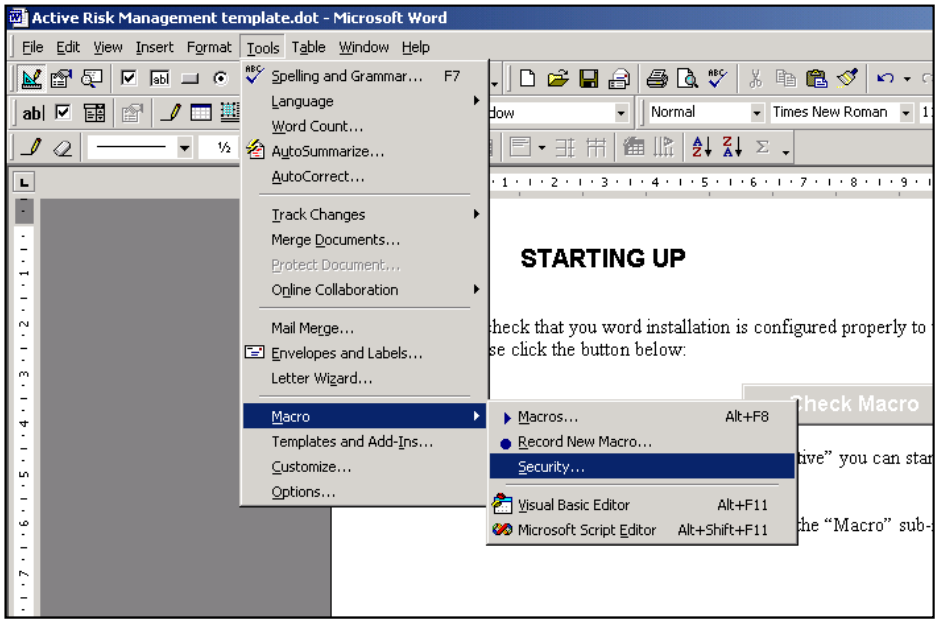
3. STARTING UP

Click on the button below in order to check that your installation is properly configured to work with Microsoft Word Macros.

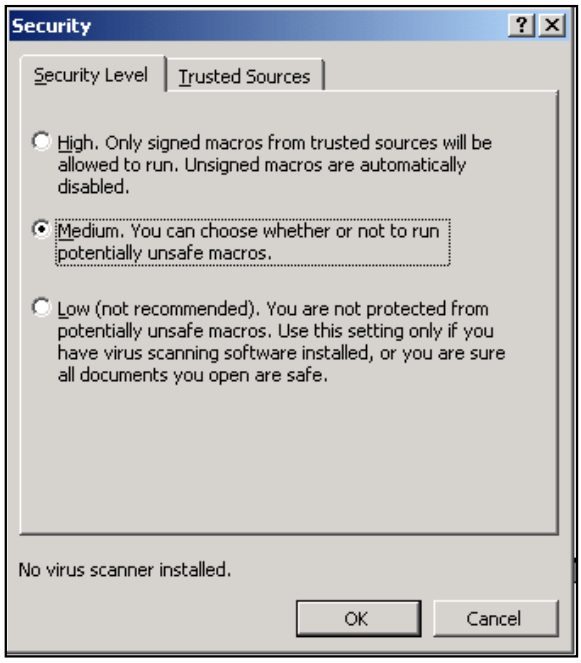
Check Macro

If you get a message box saying “Macros Active!” you can start to work with the document otherwise follow the steps indicated below:

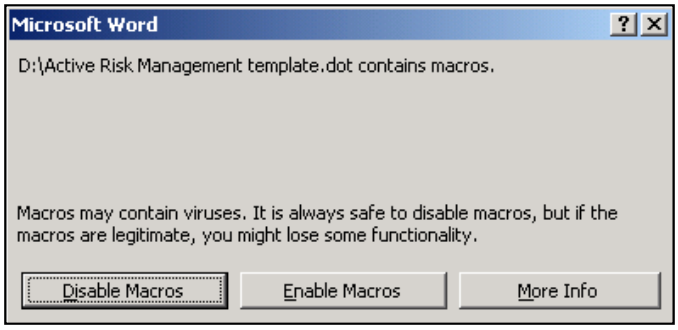
1. Open the “Tools” menu and within the “Macro” sub-menu select “Security…”



2. Select the option Medium.



3. Close all the open Word documents and Microsoft Word
4. Double click on the “Active Risk Management template”
5. While the word document opens, click “Enable Macros” in the dialog window.



4. SENDER

Enter the information regarding your organisation in line with the information you provide(d) when you register(ed) for the electronic reporting of Individual Case Safety Reports (ICSRs) to EudraVigilance. Your organization ID should be identical with the identifier of your organization chosen in the frame of the EudraVigilance registration process. Ensure that the details for the qualified person responsible for pharmacovigilance match with the registration information in EudraVigilance.

The version date of this document is the date of submission of this document in electronic format to the EMEA as outlined in chapter 2.

Organisation Name	Janssen-Cilag International N.V.
Organisation ID (if available)	JNJFOC
Qualified Person	Ennis Lee, BSc, MB, BS, FFPM
e-Mail Address	elee@its.jnj.com
Telephone Number	44-1494-6588220
Mailing Address	50-100 Holmers Farm Way High Wycombe Buckinghamshire HP124DP United Kingdom
Version Date	
Next PSUR Date (if available)	27 Sept 2009

5. MEDDRA VERSION

The MedDRA versions allowed in this document are the previous and current MedDRA version released by the MedDRA Maintenance and Support Service Organisation (MedDRA MSSO). Only one MedDRA version should be used throughout the document.

MedDRA Version (Used for this document)	12.0

6. MEDICINAL PRODUCT

- Specify the medicinal product name in the 'Product Name' field.

Product Name	CONCERTA

- The 'Substance Name' section should be repeated for each active substance contained in the medicinal product. To do so, click on the Add Substance button to enter the active substances as necessary (e.g. multiple substances medicinal product). In order to remove a selected substance, use the button Remove Substance.

Substance Name	CAS Number (where applicable)	
Methylphenidate Hydrochloride	**298-59-9**	

- The 'Medicinal Product Presentations' section should be repeated for each pharmaceutical form of the medicinal product. To do so, click on the Add Presentation button. You can use the button Remove Presentation to remove a selected presentation. To enter additional active substances (e.g. multiple substances medicinal product) use the Add Substance button, after selecting a field from the substance table that you want to extend. To delete a selected substance use the button Remove Substance after selecting a field from the substance that you want to delete.

Medicinal Product Presentations

Pharmaceutical form	Extended- release tablets

Substance Name	**Strength**	**Unit**	
Methylphenidate Hydrochloride	18	mg	Extended-release tablets
Methylphenidate Hydrochloride	27	mg	Extended-release tablets
Methylphenidate Hydrochloride	36	mg	Extended-release tablets
Methylphenidate Hydrochloride	54	mg	Extended-release tablets

7. INDICATIONS

This chapter should reflect the indications as specified in the EU Risk Management Plan. In the table below, the 'Medicinal Product Indications' section should be repeated when indications are different between target populations (e.g. for medicinal product(s) authorised for indication(s) A(X) in adults, adolescents and children for indication(s) A(X) and authorised for indication(s) B(X) for adults only). Several target populations may be selected at the same time.

The indications should be entered as free text and as MedDRA term with corresponding MedDRA code. Several indications may be entered in the section 'Indication (free text)' and the most suitable MedDRA terms and codes should be provided in the MedDRA term fields to match each indication (all MedDRA levels are permitted).

To add a new 'Medicinal Product Indications' section you should click on the Add Indication button. In case you need to remove a 'Medicinal Product Indications' section you should click on Remove Indication button after selecting a field from this section. Several MedDRA terms from different MedDRA levels can be selected. Use the Add Term or Remove Term buttons to add or remove MedDRA terms.

Medicinal Product Indications	
Indication (Free text)	CONCERTA is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).
Target Population	☐Preterm Newborn Infants ☐Term Newborn Infants (0 D – 28 D) ☐Infants and toddlers (28 D – 24 M) ☒Children (2 Y – 12Y) ☒Adolescent (12 Y – 16/18 Y) ☒Adult (18 Y – 65 Y) ☐Elderly (>= 65 Y) ☒Male ☒Female ☐Pregnancy ☐Lactating
Target Population (Free text)	Children and adolescents aged 6 to 17 and adults aged 18 to 65 who met DSM-IV criteria for ADHD. CONCERTA should be used as a part of a comprehensive treatment program where remedial measures alone prove insufficient. A comprehensive treatment program for the treatment of ADHD may include other measures (psychological, educational, social) for patients with this disorder. Diagnosis must be made according to DSM-IV criteria or the guidelines in ICD-10 and should be based on a complete history and evaluation of the patient.

MedDRA Level	MedDRA Code	MedDRA Term	
PT	10003736	Attention deficit/hyperactivity disorder	

8. IDENTIFIED RISKS

This chapter should reflect the identified risks as specified in the EU Risk Management Plan.

In the table below, the 'Identified Risks for the Medicinal Product' section should be repeated when identified risks are different between target populations (e.g. for medicinal products with identified risk(s) A(X) in adults, adolescents and children and identified risk(s) B(X) in elderly). Several target populations may be selected at the same time.

The identified risks should be entered as free text and as MedDRA term with corresponding MedDRA code. Several identified risks may be entered in the section 'Identified Risk (free text)' and the most suitable MedDRA terms and codes should be provided in the MedDRA term fields to match each identified risk (all MedDRA levels are permitted).

To add a new 'Identified Risks for the Medicinal Product' section, you should click on the Add Identified Risk button. In case you need to remove an 'Identified Risks for the Medicinal Product' section you should click on Remove Identified Risk button after selecting a field from this section. Several MedDRA terms from different MedDRA levels can be selected. Use the Add Term or Remove Term buttons to add or remove MedDRA terms.

Identified Risks for the Medicinal Product

Identified Risk (Free text)	Hypertension
Target Population	☐Preterm Newborn Infants ☐Term Newborn Infants (0 – 28 D) ☐Infants and toddlers (28 D – 24 M) ☒Children (2 Y – 12Y) ☒Adolescent (12 Y – 16/18 Y) ☒Adult (18 Y – 65 Y) ☐Elderly (>= 65 Y) ☒Male ☒Female ☐Pregnancy ☐Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term
PT	10020772	Hypertension
PT	10000358	Accelerated hypertension
PT	10005728	Blood pressure abnormal
PT	10005730	Blood pressure ambulatory abnormal
PT	10005732	Blood pressure ambulatory increased
PT	10005736	Blood pressure diastolic abnormal
PT	10005739	Blood pressure diastolic increased
PT	10005746	Blood pressure fluctuation
PT	10005748	Blood pressure immeasurable
PT	10051128	Blood pressure inadequately controlled
PT	10005750	Blood pressure increased
PT	10063926	Blood pressure management
PT	10053354	Blood pressure orthostatic abnormal
PT	10053355	Blood pressure orthostatic increased

PT	10005757	Blood pressure systolic abnormal		
PT	10005760	Blood pressure systolic increased		
PT	10050701	Congenital pulmonary hypertension		
PT	10010968	Cor pulmonale		
PT	10010969	Cor pulmonale acute		
PT	10010970	Cor pulmonale chronic		
PT	10012758	Diastolic hypertension		
PT	10014129	Eclampsia		
PT	10058554	Eisenmenger's syndrome		
PT	10057615	Endocrine hypertension		
PT	10015488	Essential hypertension		
PT	10049058	HELLP syndrome		
PT	10020564	Hyperadrenocorticism		
PT	10059238	Hypertensive angiopathy		
PT	10020801	Hypertensive cardiomegaly		
PT	10058222	Hypertensive cardiomyopathy		
PT	10020802	Hypertensive crisis		
PT	10058179	Hypertensive emergency		
PT	10020803	Hypertensive encephalopathy		
PT	10020823	Hypertensive heart disease		
PT	10055171	Hypertensive nephropathy		
PT	10023533	Labile blood pressure		
PT	10049079	Labile hypertension		
PT	10052313	Liddle's syndrome		
PT	10025600	Malignant hypertension		

PT	10025603	Malignant hypertensive heart disease		
PT	10026674	Malignant renal hypertension		
PT	10026924	Maternal hypertension affecting foetus		
PT	10052066	Metabolic syndrome		
PT	10033771	Paradoxical pressor response		
PT	10036485	Pre-eclampsia		
PT	10036563	Pregnancy induced hypertension		
PT	10062886	Procedural hypertension		
PT	10063561	Pulmonary artery wall hypertrophy		
PT	10037400	Pulmonary hypertension		
PT	10048007	Withdrawal hypertension		
PT	10038464	Renal hypertension		
PT	10038562	Renovascular hypertension		
PT	10038926	Retinopathy hypertensive		
PT	10062553	Scleroderma renal crisis		
PT	10039834	Secondary hypertension		
PT	10042957	Systolic hypertension.		

Identified Risks for the Medicinal Product

Identified Risk (Free text)	Tachycardia
Target Population	☐Preterm Newborn Infants ☐Term Newborn Infants (0 – 28 D) ☐Infants and toddlers (28 D – 24 M) ☒Children (2 Y – 12Y) ☒Adolescent (12 Y – 16/18 Y) ☒Adult (18 Y – 65 Y) ☐Elderly (>= 65 Y) ☒Male ☒Female ☐Pregnancy ☐Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
PT	10003668	Atrial tachycardia	
PT	10049775	Neonatal tachycardia	
PT	10040752	Sinus tachycardia	
PT	10042604	Supraventricular tachycardia	
PT	10043071	Tachycardia	
PT	10043079	Tachycardia paroxysmal	
PT	10047302	Ventricular tachycardia	

Identified Risks for the Medicinal Product

Identified Risk (Free text)	Raynaud's phenomenon
Target Population	☐ Preterm Newborn Infants ☐ Term Newborn Infants (0 – 28 D) ☒ Infants and toddlers (28 D – 24 M) ☒ Children (2 Y – 12Y) ☒ Adolescent (12 Y – 16/18 Y) ☒ Adult (18 Y – 65 Y) ☐ Elderly (>= 65 Y) ☒ Male ☒ Female ☐ Pregnancy ☐ Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
PT	10037912	Raynaud's phenomenon	
PT	10047139	Vasoconstriction	
PT	10054880	Vascular insufficiency	
PT	10033546	Pallor	
PT	10034568	Peripheral coldness	
PT	10034576	Peripheral ischaemia	

Identified Risks for the Medicinal Product

Identified Risk (Free text)	Hallucinations (auditory, skin sensation, visual disturbance)
Target Population	☐Preterm Newborn Infants ☐Term Newborn Infants (0 – 28 D) ☐Infants and toddlers (28 D – 24 M) ☒Children (2 Y – 12Y) ☒Adolescent (12 Y – 16/18 Y) ☒Adult (18 Y – 65 Y) ☐Elderly (>= 65 Y) ☒Male ☒Female ☐Pregnancy ☐Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
PT	10019079	Hallucinations, mixed	
PT	10019063	Hallucination	
PT	10019070	Hallucination, auditory	
PT	10019071	Hallucination, gustatory	
PT	10019072	Hallucination, olfactory	
PT	10062824	Hallucination, synaesthetic	
PT	10019074	Hallucination, tactile	
PT	10019075	Hallucination, visual	
PT	10020927	Hypnagogic hallucination	
PT	10020928	Hypnopompic hallucination	
PT	10062684	Somatic hallucination	

Identified Risks for the Medicinal Product

Identified Risk (Free text)	Psychosis/mania
Target Population	☐Preterm Newborn Infants ☐Term Newborn Infants (0 – 28 D) ☐Infants and toddlers (28 D – 24 M) ☒Children (2 Y – 12Y) ☒Adolescent (12 Y – 16/18 Y) ☒Adult (18 Y – 65 Y) ☐Elderly (>= 65 Y) ☒Male ☒Female ☐Pregnancy ☐Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
SMQ	20000117	Psychosis and psychotic disorders	

Identified Risks for the Medicinal Product

Identified Risk (Free text)	Anorexia
Target Population	☐Preterm Newborn Infants ☐Term Newborn Infants (0 – 28 D) ☐Infants and toddlers (28 D – 24 M) ☒Children (2 Y – 12Y) ☒Adolescent (12 Y – 16/18 Y) ☒Adult (18 Y – 65 Y) ☐Elderly (>= 65 Y) ☒Male ☒Female ☐Pregnancy ☐Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
PT	10002646	Anorexia	
PT	10061428	Decreased appetite	
PT	10063743	Hypophagia	
PT	10048828	Underweight	
PT	10047897	Weight gain poor	
PT	10060961	Appetite disorder	
PT	10000159	Abnormal loss of weight	

9. POTENTIAL RISKS

This chapter should reflect the potential risks as specified in the EU Risk Management Plan.

In the table below, the 'Potential Risks for the Medicinal Product' section should be repeated when potential risks are different between target populations (e.g. for medicinal products with potential risk(s) A(X) in adults, adolescents and children and potential risk(s) B(X) in elderly). Several target populations may be selected at the same time.

The potential risks should be entered as free text and as MedDRA term with corresponding MedDRA code. Several potential risks may be entered in the section 'Potential Risks (free text)' and the most suitable MedDRA terms and codes should be provided in the MedDRA term fields to match each potential risk (all MedDRA levels are permitted).

To add a new 'Potential Risks for the Medicinal Product' section, you should click on the Add Potential Risk button. In case you need to remove a 'Potential Risks for the Medicinal Product' section you should click on Remove Potential Risk button after selecting a field from this section. Several MedDRA terms from different MedDRA levels can be selected. Use the Add Term or Remove Term buttons to add or remove MedDRA terms.

Potential Risks for the Medicinal Product

Potential Risk (Free text)	Migraine
Target Population	☐ Preterm Newborn Infants ☐ Term Newborn Infants (0 – 28 D) ☐ Infants and toddlers (28 D – 24 M) ☒ Children (2 Y – 12 Y) ☒ Adolescent (12 Y – 16/18 Y) ☒ Adult (18 Y – 65 Y) ☐ Elderly (>= 65 Y) ☒ Male ☒ Female ☐ Pregnancy ☐ Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
PT	10027599	Migraine	
PT	10050258	Basilar migraine	
PT	10056236	Complicated migraine	
PT	10067039	Familial hemiplegic migraine	
PT	10027607	Migraine with aura	
PT	10052787	Migraine without aura	
PT	10050122	Ophthalmoplegic migraine	
PT	10052784	Retinal migraine	
PT	10052945	Status migrainosus	

Potential Risks for the Medicinal Product	

Potential Risk (Free text)	Repetitive behaviours
Target Population	☐ Preterm Newborn Infants ☐ Term Newborn Infants (0 – 28 D) ☐ Infants and toddlers (28 D – 24 M) ☒ Children (2 Y – 12 Y) ☒ Adolescent (12 Y – 16/18 Y) ☒ Adult (18 Y – 65 Y) ☐ Elderly (>= 65 Y) ☒ Male ☒ Female ☐ Pregnancy ☐ Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
PT	10029898	Obsessive-compulsive disorder	
LLT	10042009	Stereotyped repetitive movements	
PT	10066241	Compulsive lip biting	
PT	10034703	Perseveration	

Potential Risks for the Medicinal Product

Potential Risk (Free text)	QT prolongation
Target Population	☐ Preterm Newborn Infants ☐ Term Newborn Infants (0 – 28 D) ☐ Infants and toddlers (28 D – 24 M) ☒ Children (2 Y – 12 Y) ☒ Adolescent (12 Y – 16/18 Y) ☒ Adult (18 Y – 65 Y) ☐ Elderly (>= 65 Y) ☒ Male ☒ Female ☐ Pregnancy ☐ Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
SMQ (Narrow)	20000001	Torsade de pointes/QT prolongation (SMQ)	

Potential Risks for the Medicinal Product

Potential Risk (Free text)	Cyanosis
Target Population	☐ Preterm Newborn Infants ☐ Term Newborn Infants (0 – 28 D) ☐ Infants and toddlers (28 D – 24 M) ☒ Children (2 Y – 12 Y) ☒ Adolescent (12 Y – 16/18 Y) ☒ Adult (18 Y – 65 Y) ☐ Elderly (>= 65 Y) ☒ Male ☒ Female ☐ Pregnancy ☐ Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
PT	10011704	Cyanosis Central	
PT	10011703	Cyanosis	

Potential Risk (Free text)	Arrhythmias
Target Population	☐Preterm Newborn Infants ☐Term Newborn Infants (0 – 28 D) ☐Infants and toddlers (28 D – 24 M) ☒Children (2 Y – 12 Y) ☒Adolescent (12 Y – 16/18 Y) ☒Adult (18 Y – 65 Y) ☐Elderly (>= 65 Y) ☒Male ☒Female ☐Pregnancy ☐Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
SMQ	20000049	Cardiac arrhythmias	

Potential Risks for the Medicinal Product

Potential Risk (Free text)	Sudden death
Target Population	☐ Preterm Newborn Infants ☐ Term Newborn Infants (0 – 28 D) ☐ Infants and toddlers (28 D – 24 M) ☒ Children (2 Y – 12 Y) ☒ Adolescent (12 Y – 16/18 Y) ☒ Adult (18 Y – 65 Y) ☐ Elderly (>= 65 Y) ☒ Male ☒ Female ☐ Pregnancy ☐ Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
PT	10042434	Sudden death	
PT	10049418	Sudden cardiac death	
PT	10042440	Sudden infant death syndrome	

Potential Risks for the Medicinal Product

Potential Risk (Free text)	Cerebrovascular disorders
Target Population	☐ Preterm Newborn Infants ☐ Term Newborn Infants (0 – 28 D) ☐ Infants and toddlers (28 D – 24 M) ☒ Children (2 Y – 12 Y) ☒ Adolescent (12 Y – 16/18 Y) ☒ Adult (18 Y – 65 Y) ☐ Elderly (>= 65 Y) ☒ Male ☒ Female ☐ Pregnancy ☐ Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
SMQ	20000060	Cerebrovascular disorders	

Potential Risks for the Medicinal Product

Potential Risk (Free text)	Aggression
Target Population	☐ Preterm Newborn Infants ☐ Term Newborn Infants (0 – 28 D) ☐ Infants and toddlers (28 D – 24 M) ☒ Children (2 Y – 12 Y) ☒ Adolescent (12 Y – 16/18 Y) ☒ Adult (18 Y – 65 Y) ☐ Elderly (>= 65 Y) ☒ Male ☒ Female ☐ Pregnancy ☐ Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
SMQ	20000142	Hostility/aggression	

Potential Risks for the Medicinal Product

Potential Risk (Free text)	Hostility
Target Population	☐ Preterm Newborn Infants ☐ Term Newborn Infants (0 – 28 D) ☐ Infants and toddlers (28 D – 24 M) ☒ Children (2 Y – 12 Y) ☒ Adolescent (12 Y – 16/18 Y) ☒ Adult (18 Y – 65 Y) ☐ Elderly (>= 65 Y) ☒ Male ☒ Female ☐ Pregnancy ☐ Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
SMQ	20000142	Hostility/aggression	

Potential Risks for the Medicinal Product

Potential Risk (Free text)	Depression
Target Population	☐ Preterm Newborn Infants ☐ Term Newborn Infants (0 – 28 D) ☐ Infants and toddlers (28 D – 24 M) ☒ Children (2 Y – 12 Y) ☒ Adolescent (12 Y – 16/18 Y) ☒ Adult (18 Y – 65 Y) ☐ Elderly (>= 65 Y) ☒ Male ☒ Female ☐ Pregnancy ☐ Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
SMQ	20000035	Depression and suicide/self-injury	

Potential Risks for the Medicinal Product

Potential Risk (Free text)	Suicidality
Target Population	☐ Preterm Newborn Infants ☐ Term Newborn Infants (0 – 28 D) ☐ Infants and toddlers (28 D – 24 M) ☒ Children (2 Y – 12 Y) ☒ Adolescent (12 Y – 16/18 Y) ☒ Adult (18 Y – 65 Y) ☐ Elderly (>= 65 Y) ☒ Male ☒ Female ☐ Pregnancy ☐ Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
SMQ	20000035	Depression and suicide/self-injury	

Potential Risks for the Medicinal Product

Potential Risk (Free text)	Tics/Tourette's syndrome/Dystonias
Target Population	☐ Preterm Newborn Infants ☐ Term Newborn Infants (0 – 28 D) ☐ Infants and toddlers (28 D – 24 M) ☒ Children (2 Y – 12 Y) ☒ Adolescent (12 Y – 16/18 Y) ☒ Adult (18 Y – 65 Y) ☐ Elderly (>= 65 Y) ☒ Male ☒ Female ☐ Pregnancy ☐ Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
PT	10044126	Tourette's disorder	
LLT	10043849	Tics	
SMQ	20000098	Dystonia	

Potential Risks for the Medicinal Product

Potential Risk (Free text)	Carcinogenicity
Target Population	☐ Preterm Newborn Infants ☐ Term Newborn Infants (0 – 28 D) ☐ Infants and toddlers (28 D – 24 M) ☒ Children (2 Y – 12 Y) ☒ Adolescent (12 Y – 16/18 Y) ☒ Adult (18 Y – 65 Y) ☐ Elderly (>= 65 Y) ☒ Male ☒ Female ☐ Pregnancy ☐ Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
SOC	10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	

Potential Risks for the Medicinal Product

Potential Risk (Free text)	Diversion
Target Population	☐ Preterm Newborn Infants ☐ Term Newborn Infants (0 – 28 D) ☐ Infants and toddlers (28 D – 24 M) ☒ Children (2 Y – 12 Y) ☒ Adolescent (12 Y – 16/18 Y) ☒ Adult (18 Y – 65 Y) ☐ Elderly (>= 65 Y) ☒ Male ☒ Female ☐ Pregnancy ☐ Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
PT	10066053	Diversion	

Potential Risks for the Medicinal Product

Potential Risk (Free text)	Withdrawal syndrome
Target Population	☐Preterm Newborn Infants ☐Term Newborn Infants (0 – 28 D) ☐Infants and toddlers (28 D – 24 M) ☒Children (2 Y – 12 Y) ☒Adolescent (12 Y – 16/18 Y) ☒Adult (18 Y – 65 Y) ☐Elderly (>= 65 Y) ☒Male ☒Female ☐Pregnancy ☐Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
SMQ	20000102	Drug Withdrawal	

Potential Risks for the Medicinal Product

Potential Risk (Free text)	Drug Abuse and Drug Dependence
Target Population	☐Preterm Newborn Infants ☐Term Newborn Infants (0 – 28 D) ☐Infants and toddlers (28 D – 24 M) ☐Children (2 Y – 12 Y) ☒Adolescent (12 Y – 16/18 Y) ☒Adult (18 Y – 65 Y) ☐Elderly (>= 65 Y) ☒Male ☒Female ☐Pregnancy ☐Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
PT	10061111	Drug abuser	
PT	10012335	Dependence	
PT	10013663	Drug dependence	
PT	10013675	Drug dependence antepartum	
PT	10013676	Drug dependence, postpartum	
PT	10053243	Polysubstance dependence	
PT	10065679	Intentional drug misuse	
PT	10022523	Intentional overdose	
PT	10062764	Multiple drug overdose intentional	

Potential Risks for the Medicinal Product

Potential Risk (Free text)	Lymphocytic leukaemia
Target Population	☐ Preterm Newborn Infants ☐ Term Newborn Infants (0 – 28 D) ☐ Infants and toddlers (28 D – 24 M) ☒ Children (2 Y – 12 Y) ☒ Adolescent (12 Y – 16/18 Y) ☒ Adult (18 Y – 65 Y) ☐ Elderly (>= 65 Y) ☒ Male ☒ Female ☐ Pregnancy ☐ Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
PT	10000846	Acute lymphocytic leukaemia	
PT	10000847	Acute lymphocytic leukaemia (in remission)	
PT	10063620	Acute lymphocytic leukaemia recurrent	
PT	10008958	Chronic lymphocytic leukaemia	
PT	10008959	Chronic lymphocytic leukaemia (in remission)	
PT	10008961	Chronic lymphocytic leukaemia recurrent	
PT	10008962	Chronic lymphocytic leukaemia refractory	
PT	10008963	Chronic lymphocytic leukaemia stage 0	
PT	10008964	Chronic lymphocytic leukaemia stage 1	
PT	10008965	Chronic lymphocytic leukaemia stage 2	
PT	10008966	Chronic lymphocytic leukaemia stage 3	
PT	10008967	Chronic lymphocytic leukaemia stage 4	
PT	10058717	Chronic lymphocytic leukaemia transformation	

PT	10025270	Lymphocytic leukaemia		
PT	10036888	Prolymphocytic leukaemia		
PT	10042970	T-cell chronic lymphocytic leukaemia		
PT	10042985	T-cell prolymphocytic leukaemia		
PT	10042970	T-cell chronic lymphocytic leukaemia		

10. IDENTIFIED INTERACTIONS

This chapter should reflect the identified interactions as specified in the EU Risk Management Plan. In the table below, the 'Identified Interactions for the Medicinal Product' section should be repeated for each identified interaction, specified at the substance or the class level.

To add a new 'Identified Interaction for the Medicinal Product' section, you should click on the Add Identified Interaction button. In case you need to remove an 'Identified Interaction for the Medicinal Product' section, you should click on Remove Identified Interaction button after selecting a field from this section.

The 'Identified Interaction for the Medicinal Product' sub-section should be repeated when identified risks are different between target populations (e.g. for a medicinal product with identified risk(s) A(X) in adults, adolescents and children and identified risk(s) B(X) in elderly). Several target populations may be selected at same time. The identified risks should be specified as free text. Several identified risks may be entered in the section 'Identified Risks (free text)' and the most suitable MedDRA terms and codes should be provided in the MedDRA term fields to match each identified risk (all MedDRA levels are permitted). To add a new 'Identified Interaction for the Medicinal Product' sub-section, you should click on the Add Identified Risk button. In case you need to remove an 'Identified Interaction for the Medicinal Product' sub-section, you should click on Remove Identified Risk button after selecting a field from the section. Several MedDRA terms from different MedDRA levels can be selected. Use the Add Term or Remove Term button to add or remove MedDRA terms.

Identified Interactions for the Medicinal Product

Substance Name/Class	ATC Code (where applicable)	
Anti-Hypertensive Drugs: Angiotensin-converting enzyme inhibitors, ß-blockers, calcium antagonists, diuretics, angiotensin II receptor antagonists	C02, C03, C07, C08, C09	

Identified Interaction for the Medicinal Product

Identified Risk (Free text)	Methylphenidate is a sympathomimetic agent that has the propensity to stimulate the sympathetic nervous system, resulting in changes in vital signs, including blood pressure elevation.
Target Population	☐ Preterm Newborn Infants ☐ Term Newborn Infants (0 – 28 D) ☐ Infants and toddlers (28 D – 24 M) ☐ Children (2 Y – 12 Y) ☒ Adolescent (12 Y – 16/18 Y) ☒ Adult (18 Y – 65 Y) ☐ Elderly (>= 65 Y) ☒ Male ☒ Female ☐ Pregnancy ☐ Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
PT	10020772	Hypertension	
PT	10005750	Blood pressure increased	
PT	10005760	Blood pressure systolic increased	
PT	10005739	Blood pressure diastolic increased	

Identified Interactions for the Medicinal Product

Substance Name/Class	ATC Code (where applicable)	
Alcohol-Ethanol	V03AB16	

Identified Interaction for the Medicinal Product

Identified Risk (Free text)	Ethanol elevates plasma d-methylphenidate C_{max} and area under the concentration–time curve by approximately 40% and 25%, respectively.
Target Population	☐ Preterm Newborn Infants ☐ Term Newborn Infants (0 – 28 D) ☐ Infants and toddlers (28 D – 24 M) ☐ Children (2 Y – 12 Y) ☒ Adolescent (12 Y – 16/18 Y) ☒ Adult (18 Y – 65 Y) ☐ Elderly (>= 65 Y) ☒ Male ☒ Female ☐ Pregnancy ☐ Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
PT	10013685	Drug effect prolonged	
PT	10061132	Drug level above	
PT	10013722	Drug level increased	
PT	10048652	Enzyme induction	
PT	10048653	Enzyme inhibition	
HLT	10022528	Interactions	

Identified Interactions for the Medicinal Product

Substance Name/Class	ATC Code (where applicable)	
Halogenated anaesthetics: halothane, enflurane, isoflurane and desflurane	N01AB01, N01AB04, N01AB06, N01AB07	

Identified Interaction for the Medicinal Product

Identified Risk (Free text)	There is a risk of sudden blood pressure increase during surgery. Methylphenidate may exacerbate this effect.
Target Population	☐ Preterm Newborn Infants ☐ Term Newborn Infants (0 – 28 D) ☐ Infants and toddlers (28 D – 24 M) ☐ Children (2 Y – 12 Y) ☐ Adolescent (12 Y – 16/18 Y) ☒ Adult (18 Y – 65 Y) ☐ Elderly (>= 65 Y) ☒ Male ☒ Female ☐ Pregnancy ☐ Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
PT	10020772	Hypertension	
PT	10005750	Blood pressure increased	
PT	10005760	Blood pressure systolic increased	
PT	10005739	Blood pressure diastolic increased	

Identified Interactions for the Medicinal Product

Substance Name/Class	ATC Code (where applicable)	
Centrally acting alpha-2 agonists (e.g., clonidine)	S01EA04	

Identified Interaction for the Medicinal Product

Identified Risk (Free text)	Serious adverse events including sudden death have been reported with the concomitant use of psychostimulants and clonidine
Target Population	☐ Preterm Newborn Infants ☐ Term Newborn Infants (0 – 28 D) ☐ Infants and toddlers (28 D – 24 M) ☒ Children (2 Y – 12 Y) ☒ Adolescent (12 Y – 16/18 Y) ☒ Adult (18 Y – 65 Y) ☐ Elderly (>= 65 Y) ☒ Male ☒ Female ☐ Pregnancy ☐ Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
PT	10042434	Sudden death	
PT	10049418	Sudden cardiac death	
PT	10042440	Sudden infant death syndrome	

Identified Interactions for the Medicinal Product

Substance Name/Class	ATC Code (where applicable)	
Dopaminergic drugs	N04B	

Identified Interaction for the Medicinal Product

Identified Risk (Free text)	Methylphenidate increased extracellular dopamine levels and may be associated with pharmacodynamic interactions when coadministered with dopamine agonists as well as dopamine antagonists.
Target Population	☐ Preterm Newborn Infants ☐ Term Newborn Infants (0 – 28 D) ☐ Infants and toddlers (28 D – 24 M) ☒ Children (2 Y – 12 Y) ☒ Adolescent (12 Y – 16/18 Y) ☒ Adult (18 Y – 65 Y) ☐ Elderly (>= 65 Y) ☒ Male ☒ Female ☐ Pregnancy ☐ Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
PT	10013685	Drug effect prolonged	
PT	10061132	Drug level above	
PT	10013722	Drug level increased	
PT	10048652	Enzyme induction	
PT	10048653	Enzyme inhibition	
HLT	10022528	Interactions	

Identified Interactions for the Medicinal Product

Substance Name/Class	ATC Code (where applicable)	
Coumarin anticoagulants	B01	

Identified Interaction for the Medicinal Product

Identified Risk (Free text)	Higher plasma concentrations and, hence, greater effects of coumarin.
Target Population	☐ Preterm Newborn Infants ☐ Term Newborn Infants (0 – 28 D) ☐ Infants and toddlers (28 D – 24 M) ☒ Children (2 Y – 12 Y) ☒ Adolescent (12 Y – 16/18 Y) ☒ Adult (18 Y – 65 Y) ☐ Elderly (>= 65 Y) ☒ Male ☒ Female ☐ Pregnancy ☐ Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
HLGT	10064477	Coagulopathies and bleeding diatheses	
PT	10013685	Drug effect prolonged	
PT	10061132	Drug level above	
PT	10013722	Drug level increased	
PT	10048652	Enzyme induction	
PT	10048653	Enzyme inhibition	
HLT	10022528	Interactions	

Identified Interactions for the Medicinal Product

Substance Name/Class	ATC Code (where applicable)	
Anticonvulsants	N03	

Identified Interaction for the Medicinal Product

Identified Risk (Free text)	Possible increase in effect of anticonvulsants.
Target Population	☐ Preterm Newborn Infants ☐ Term Newborn Infants (0 – 28 D) ☐ Infants and toddlers (28 D – 24 M) ☒ Children (2 Y – 12 Y) ☒ Adolescent (12 Y – 16/18 Y) ☒ Adult (18 Y – 65 Y) ☐ Elderly (>= 65 Y) ☒ Male ☒ Female ☐ Pregnancy ☐ Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
PT	10013685	Drug effect prolonged	
PT	10061132	Drug level above	
PT	10013722	Drug level increased	
PT	10048652	Enzyme induction	
PT	10048653	Enzyme inhibition	
HLT	10022528	Interactions	

Identified Interactions for the Medicinal Product

Substance Name/Class	ATC Code (where applicable)	
Antidepressants: Tricyclic antidepressants:amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, and trimipramine) Slective serotonin reuptake inhibitors (SSRIs) (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline)	N06AA N06AB	

Identified Interaction for the Medicinal Product

Identified Risk (Free text)	Possible increase in effect of these antidepressants.
Target Population	☐ Preterm Newborn Infants ☐ Term Newborn Infants (0 – 28 D) ☒ Infants and toddlers (28 D – 24 M) ☒ Children (2 Y – 12 Y) ☒ Adolescent (12 Y – 16/18 Y) ☒ Adult (18 Y – 65 Y) ☐ Elderly (>= 65 Y) ☒ Male ☒ Female ☐ Pregnancy ☐ Lactating
Target Population (Free text)	

MedDRA Level	MedDRA Code	MedDRA Term	
SMQ (Narrow)	20000079	Convulsions	
PT	10040108	Serotonin syndrome	
PT	10013685	Drug effect prolonged	
PT	10061132	Drug level above	
PT	10013722	Drug level increased	
PT	10048652	Enzyme induction	
PT	10048653	Enzyme inhibition	
HLT	10022528	Interactions	

11. POTENTIAL INTERACTIONS

This chapter should reflect the potential interactions as specified in the EU Risk Management Plan. In the table below, the 'Potential Interactions for the Medicinal Product' section should be repeated for each potential interaction, specified at the substance or the class level.

To add a new 'Potential Interaction for the Medicinal Product' section, you should click on the Add Potential Interaction button. In case you need to remove a 'Potential Interaction for the Medicinal Product' section, you should click on Remove Potential Interaction button after selecting a field from this section.

The 'Potential Interaction for the Medicinal Product' sub-section should be repeated when potential risks are different between target populations (e.g. for a medicinal product with potential risk(s) A(X) in adults, adolescents and children and potential risk(s) B(X) in elderly). Several target populations may be selected at same time. The potential risks should be specified as free text. Several potential risks may be entered in the section 'Potential Risks (free text)' and the most suitable MedDRA terms and codes should be provided in the MedDRA term fields to match each potential risk (all MedDRA levels are permitted). To add a new 'Potential Interaction for the Medicinal Product' sub-section, you should click on the Add Potential Risk button. In case you need to remove a 'Identified Interaction for the Medicinal Product' sub-section, you should click on Remove Potential Risk button after selecting a field from the section. Several MedDRA terms from different MedDRA levels can be selected. Use the Add Term or Remove Term button to add or remove MedDRA terms.

Potential Interactions for the Medicinal Product- Not Reported	

ANNEX 2

SUMMARY OF PRODUCT CHARACTERISTICS

CONCERTA (Methylphenidate HCl)
Module 1.3.1 Product Information

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CONCERTA XL 18 mg prolonged-release tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 18 mg of methylphenidate hydrochloride.

Excipients: contains 6.49 mg of lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release Tablet.
Capsule-shaped yellow tablet with “alza 18” printed on one side in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Attention-Deficit/Hyperactivity Disorder (ADHD)

CONCERTA XL is indicated as part of a comprehensive treatment programme for Attention Deficit Hyperactivity Disorder (ADHD) in children aged 6 years of age and over when remedial measures alone prove insufficient. Treatment must be under the supervision of a specialist in childhood behavioural disorders. Diagnosis should be made according to DSM-IV criteria or the guidelines in ICD-10 and should be based on a complete history and evaluation of the patient. Diagnosis cannot be made solely on the presence of one or more symptom.

The specific aetiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use of medical and specialised psychological, educational, and social resources.

A comprehensive treatment programme typically includes psychological, educational and social measures as well as pharmacotherapy and is aimed at stabilising children with a behavioural syndrome characterised by symptoms which may include chronic history of short attention span, distractibility, emotional lability, impulsivity, moderate to severe hyperactivity, minor neurological signs and abnormal EEG. Learning may or may not be impaired.

CONCERTA XL treatment is not indicated in all children with ADHD and the decision to use the drug must be based on a very thorough assessment of the severity and chronicity of the child’s symptoms in relation to the child’s age.

Appropriate educational placement is essential, and psychosocial intervention is generally necessary. Where remedial measures alone prove insufficient, the decision to prescribe a stimulant must be based on rigorous assessment of the severity of the child's symptoms. The use of methylphenidate should always be used in this way according to the licensed indication and according to prescribing / diagnostic guidelines.

4.2 Posology and method of administration

Treatment must be initiated under the supervision of a specialist in childhood and/or adolescent behavioural disorders.

CONCERTA XL must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed (see section 4.4).

CONCERTA XL may be administered with or without food (see section 5.2).

CONCERTA XL is taken once daily in the morning.

Pre-treatment screening:
Prior to prescribing, it is necessary to conduct a baseline evaluation of a patient's cardiovascular status including blood pressure and heart rate. A comprehensive history should document concomitant medications, past and present co-morbid medical and psychiatric disorders or symptoms, family history of sudden cardiac/unexplained death and accurate recording of pre-treatment height and weight on a growth chart (see sections 4.3 and 4.4)

Ongoing monitoring:
Growth, psychiatric and cardiovascular status should be continuously monitored (see also section 4.4).

- Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and then at least every 6 months;
- Height, weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart;
- Development of *de novo* or worsening of pre-existing psychiatric disorders should be monitored at every adjustment of dose and then at least every 6 months and at every visit.

Patients should be monitored for the risk of diversion, misuse and abuse of methylphenidate.

Dose titration
Careful dose titration is necessary at the start of treatment with CONCERTA XL. Dose titration should be started at the lowest possible dose.

Other strengths of this medicinal product and other methylphenidate-containing products may be available.

Dosage may be adjusted in 18 mg increments In general, dosage adjustment may proceed at approximately weekly intervals.

The maximum daily dosage of CONCERTA XLis 54 mg.

Patients New to Methylphenidate: Clinical experience with CONCERTA XL is limited in these patients (see section 5.1). CONCERTA XL may not be indicated in all children with ADHD syndrome. Lower doses of short-acting methylphenidate formulations may be considered sufficient to treat patients new to methylphenidate. Careful dose titration by the physician in charge is required in order to avoid unnecessarily high doses of methylphenidate. The recommended starting dose of CONCERTA XL for patients who are not currently taking methylphenidate, or for patients who are on stimulants other than methylphenidate, is 18 mg once daily.

Patients Currently Using Methylphenidate: The recommended dose of CONCERTA XL for patients who are currently taking methylphenidate three times daily at doses of 15 to 45 mg/day is provided in Table 1. Dosing recommendations are based on current dose regimen and clinical judgement.

TABLE 1
Recommended Dose Conversion from
Other Methylphenidate Regimens, where available, to CONCERTA XL

Previous Methylphenidate Daily Dose	**Recommended CONCERTA XL Dose**
5 mg Methylphenidate three times daily	18 mg once daily
10 mg Methylphenidate three times daily	36 mg once daily
15 mg Methylphenidate three times daily	54 mg once daily

If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

Long-term (more than 12 months) use in children and adolescents
The safety and efficacy of long-term use of methylphenidate has not been systematically evaluated in controlled trials. Methylphenidate treatment should not and need not, be indefinite. Methylphenidate treatment is usually discontinued during or after puberty. The physician who elects to use methylphenidate for extended periods (over 12 months) in children and adolescents with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that methylphenidate is de-challenged at least once yearly to assess the child's condition (preferable during times of school holidays). Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Dose reduction and discontinuation

Treatment must be stopped if the symptoms do not improve after appropriate dosage adjustment over a one-month period. If paradoxical aggravation of symptoms or other serious adverse events occur, the dosage should be reduced or discontinued.

Adults
Methylphenidate is not licensed for use in adults in ADHD. Safety and efficacy have not been established in this age group

Elderly
Methylphenidate should not be used in the elderly. Safety and efficacy has not been established in this age group.

Children under 6 years of age
Methylphenidate should not be used in children under the age of 6 years. Safety and efficacy in this age group has not been established.

4.3 Contraindications

- Known sensitivity to methylphenidate or any of the excipients
- Glaucoma
- Phaeochromocytoma
- During treatment with non-selective, irreversible monoamine oxidase (MAO) inhibitors, or within a minimum of 14 days of discontinuing those drugs, due to the risk of hypertensive crisis (see section 4.5)
- Hyperthyroidism or Thyrotoxicosis
- Diagnosis or history of severe depression, anorexia nervosa/anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder
- Diagnosis or history of severe and episodic (Type I) Bipolar (affective) Disorder (that is not well-controlled)
- Pre-existing cardiovascular disorders including severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies (disorders caused by the dysfunction of ion channels).
- Pre-existing cerebrovascular disorders cerebral aneurysm, vascular abnormalities including vasculitis or stroke

4.4 Special warnings and precautions for use

Methylphenidate treatment is not indicated in all children with ADHD and the decision to use the drug must be based on a very thorough assessment of the severity and chronicity of the child's symptoms in relation to the child's age.

Long-term use (more than 12 months) in children and adolescents
The safety and efficacy of long-term use of methylphenidate has not been systematically evaluated in controlled trials. Methylphenidate treatment should not and need not, be indefinite. Methylphenidate treatment is usually discontinued during or after puberty. Patients on long-term therapy (i.e. over 12 months) must have careful ongoing monitoring according to the guidance in sections 4.2 and 4.4. for cardiovascular status, growth, appetite, development of *de novo* or worsening of pre-existing psychiatric disorders. Psychiatric disorders to monitor for are described below, and include (but are not limited to) motor or vocal tics, aggressive or hostile behaviour, agitation, anxiety, depression, psychosis, mania, delusions, irritability, lack of spontaneity, withdrawal and excessive perseveration.

The physician who elects to use methylphenidate for extended periods (over 12 months) in children and adolescents with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that methylphenidate is de-challenged at least once yearly to assess the child's condition (preferably during times of school holidays). Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Use in adults
Methylphenidate is not licensed for use in adults with ADHD. Safety and efficacy have not been established in this age group.

Use in the elderly
Methylphenidate should not be used in the elderly. Safety and efficacy has not been established in this age group.

Use in children under 6 years of age
Methylphenidate should not be used in children under the age of 6 years. Safety and efficacy in this age group has not been established.

Cardiovascular status
Patients who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden cardiac or unexplained death or malignant arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further specialist cardiac evaluation if initial findings suggest such history or disease. Patients who develop symptoms such as palpitations, exertional chest pain, unexplained syncope, dyspnoea or other symptoms suggestive of cardiac disease during methylphenidate treatment should undergo a prompt specialist cardiac evaluation.

Analyses of data from clinical trials of methylphenidate in children and adolescents with ADHD showed that patients using methylphenidate may commonly experience changes in diastolic and systolic blood pressure of over 10 mmHg relative to controls. The short- and long-term clinical consequences of these

cardiovascular effects in children and adolescents are not known, but the possibility of clinical complications cannot be excluded as a result of the effects observed in the clinical trial data. **Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate.** See section 4.3 for conditions in which methylphenidate treatment in contraindicated.

Cardiovascular status should be carefully monitored. Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and then at least every 6 months.

The use of methylphenidate is contraindicated in certain pre-existing cardiovascular disorders **unless specialist paediatric cardiac advice has been obtained (see section 4.3).**

Sudden death and pre-existing structural cardiac abnormalities or other serious cardiac disorders

Sudden death has been reported in association with the use of stimulants of the central nervous system at usual doses in children, some of whom had structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone may carry an increased risk of sudden death, stimulant products are not recommended in children or adolescents with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant medicine.

Misuse and Cardiovascular Events
Misuse of stimulants of the central nervous system may be associated with sudden death and other serious cardiovascular adverse events.

Cerebrovascular disorders
See section 4.3 for cerebrovascular conditions in which methylphenidate treatment is contraindicated. Patients with additional risk factors (such as a history of cardiovascular disease, concomitant medications that elevate blood pressure) should be assessed at every visit for neurological signs and symptoms after initiating treatment with methylphenidate.

Cerebral vasculitis appears to be a very rare idiosyncratic reaction to methylphenidate exposure. There is little evidence to suggest that patients at higher risk can be identified and the initial onset of symptoms may be the first indication of an underlying clinical problem. Early diagnosis, based on a high index of suspicion, may allow the prompt withdrawal of methylphenidate and early treatment. The diagnosis should therefore be considered in any patient who develops new neurological symptoms that are consistent with cerebral ischemia during methylphenidate therapy. These symptoms could include severe headache, numbness, weakness, paralysis, and impairment of coordination, vision, speech, language or memory.

Treatment with methylphenidate is not contraindicated in patients with hemiplegic cerebral palsy.

Psychiatric disorders
Co-morbidity of psychiatric disorders in ADHD is common and should be taken into account when prescribing stimulant products. In the case of emergent psychiatric symptoms or exacerbation of pre-existing psychiatric disorders, methylphenidate should not be given unless the benefits outweigh the risks to the patient.

Development or worsening of psychiatric disorders should be monitored at every adjustment of dose, then at least every 6 months, and at every visit; discontinuation of treatment may be appropriate.

Exacerbation of pre-existing psychotic or manic symptoms
In psychotic patients, administration of methylphenidate may exacerbate symptoms of behavioural disturbance and thought disorder.

Emergence of new psychotic or manic symptoms
Treatment-emergent psychotic symptoms (visual/tactile/auditory hallucinations and delusions) or mania in children and adolescents without prior history of psychotic illness or mania can be caused by methylphenidate at usual doses. If manic or psychotic symptoms occur, consideration should be given to a possible causal role for methylphenidate, and discontinuation of treatment may be appropriate.

Aggressive or hostile behaviour
The emergence or worsening of aggression or hostility can be caused by treatment with stimulants. Patients treated with methylphenidate should be closely monitored for the emergence or worsening of aggressive behaviour or hostility at treatment initiation, at every dose adjustment and then at least every 6 months and every visit. Physicians should evaluate the need for adjustment of the treatment regimen in patients experiencing behaviour changes.

Suicidal tendency
Patients with emergent suicidal ideation or behaviour during treatment for ADHD should be evaluated immediately by their physician. Consideration should be given to the exacerbation of an underlying psychiatric condition and to a possible causal role of methylphenidate treatment. Treatment of an underlying psychiatric condition may be necessary and consideration should be given to a possible discontinuation of methylphenidate.

Tics
Methylphenidate is associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported. Family history should be assessed and clinical evaluation for tics or Tourette's syndrome in children should precede use of methylphenidate. Patients should be regularly monitored for the emergence or worsening of tics during treatment with methylphenidate. **Monitoring should be at every adjustment of dose and then at least every 6 months or every visit.**

Anxiety, agitation or tension
Methylphenidate is associated with the worsening of pre-existing anxiety, agitation or tension. Clinical evaluation for anxiety, agitation or tension should precede use of methylphenidate and patients should be **regularly monitored for the emergence or worsening of these symptoms during treatment, at every adjustment of dose and then at least every 6 month or every visit.**

Forms of bipolar disorder
Particular care should be taken in using methylphenidate to treat ADHD in patients with comorbid bipolar disorder (including untreated Type I Bipolar Disorder or other forms of bipolar disorder) because of concern for possible precipitation of a mixed/manic episode in such patients. Prior to initiating treatment with methylphenidate, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. **Close ongoing monitoring is essential in these patients (see above 'Psychiatric Disorders' and section 4.2) . Patients should be monitored for symptoms at every adjustment of dose, then at least every 6 months and at every visit.**

Growth
Moderately reduced weight gain and growth retardation have been reported with the long-term use of methylphenidate in children.

The effects of methylphenidate on final height and final weight are currently unknown and being studied.

Growth should be monitored during methylphenidate treatment: height, weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart. Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Seizures
Methylphenidate should be used with caution in patients with epilepsy. Methylphenidate may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and rarely in patients without a history of convulsions and no EEG abnormalities. If seizure frequency increases or new-onset seizures occur, methylphenidate should be discontinued.

Abuse, misuse and diversion
Patients should be carefully monitored for the risk of diversion, misuse and abuse of methylphenidate.

Methylphenidate should be used with caution in patients with known drug or alcohol dependency because of a potential for abuse, misuse or diversion.

Chronic abuse of methylphenidate can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes can occur, especially in response to parenteral abuse.

Patient age, the presence of risk factors for substance use disorder (such as co-morbid oppositional-defiant or conduct disorder and bipolar disorder), previous or current substance abuse should all be taken into account when deciding on a course of treatment for ADHD. Caution is called for in emotionally unstable patients, such as those with a history of drug or alcohol dependence, because such patients may increase the dosage on their own initiative.

For some high-risk substance abuse patients, methylphenidate or other stimulants may not be suitable and non-stimulant treatment should be considered.

Withdrawal
Careful supervision is required during drug withdrawal, since this may unmask depression as well as chronic over-activity. Some patients may require long-term follow up.

Careful supervision is required during withdrawal from abusive use since severe depression may occur.

Fatigue
Methylphenidate should not be used for the prevention or treatment of normal fatigue states.

Excipients: galactose intolerance
This medicinal product contains lactose: patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Choice of methylphenidate formulation
The choice of formulation of methylphenidate-containing product will have to be decided by the treating specialist on an individual basis and depends on the intended duration of effect.

Drug screening
This product contains methylphenidate which may induce a false positive laboratory test for amphetamines, particularly with immunoassay screen test.

Renal or hepatic insufficiency
There is no experience with the use of methylphenidate in patients with renal or hepatic insufficiency.

Haematological effects
The long-term safety of treatment with methylphenidate is not fully known. In the event of leukopenia, thrombocytopenia, anaemia or other alterations, including those indicative of serious renal or hepatic disorders, discontinuation of treatment should be considered.

Potential for gastrointestinal obstruction
Because the CONCERTA XL tablet is nondeformable and does not appreciably change in shape in the gastrointestinal (GI) tract, it should not ordinarily be

administered to patients with pre-existing severe GI narrowing (pathologic or iatrogenic) or in patients with dysphagia or significant difficulty in swallowing tablets. There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in nondeformable prolonged-release formulations.

Due to the prolonged-release design of the tablet, CONCERTA XL should only be used in patients who are able to swallow the tablet whole. Patients should be informed that CONCERTA XL must be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interaction
It is not known how methylphenidate may effect plasma concentrations of concomitantly administered drugs. Therefore, caution is recommended at combining methylphenidate with other drugs, especially those with a narrow therapeutic window.

Methylphenidate is not metabolised by cytochrome P450 to a clinically relevant extent. Inducers or inhibitors of cytochrome P450 are not expected to have any relevant impact on methylphenidate pharmacokinetics. Conversely, the d- and l-enantiomers of methylphenidate do not relevantly inhibit cytochrome P450 1A2, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A.

However, there are reports indicating that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (eg, phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). When starting or stopping treatment with methylphenidate, it may be necessary to adjust the dosage of these drugs already being taken and establish drug plasma concentrations (or for coumarin, coagulation times).

Pharmacodynamic interactions
Anti-hypertensive drugs
Methylphenidate may decrease the effectiveness of drugs used to treat hypertension.

Use with drugs that elevate blood pressure
Caution is advised in patients being treated with methylphenidate with any other drug that can also elevate blood pressure (see also sections on cardiovascular and cerebrovascular conditions in Section 4.4).

Because of possible hypertensive crisis, methylphenidate is contraindicated in patients being treated (currently or within the preceding 2 weeks) with non-selective, irreversible MAO-inhibitors (see section 4.3).

Use with alcohol

Alcohol may exacerbate the adverse CNS effect of psychoactive drugs, including methylphenidate. It is therefore advisable for patients to abstain from alcohol during treatment.

Use with halogenated anaesthetics
There is a risk of sudden blood pressure increase during surgery. If surgery is planned, methylphenidate treatment should not be used on the day of surgery.

Use with centrally acting alpha-2 agonists (e.g. clonidine)
Serious adverse events, including sudden death, have been reported in concomitant use with clonidine. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

Use with domapinergic drugs
Caution is recommended when administering methylphenidate with dopaminergic drugs, including antipsychotics. Because a predominant action of methylphenidate is to increase extracelluar dopamine levels, methylphenidate may be associated with pharmacodynamic interactions when co-administered with direct and indirect dopamine agonists (including DOPA and tricyclic antidepressants) or with dopamine antagonists including antipsychotics.

4.6 Pregnancy and lactation

Pregnancy
There is a limited amount of data from the use of methylphenidate in pregnant women.

Cases of neonatal cardiorespiratory toxicity, specifically foetal tachycardia and respiratory distress have been reported in spontaneous case reports.

Studies in animals have shown evidence of reproductive toxicity at maternally toxic doses (see section 5.3).

Methylphenidate is not recommended for use during pregnancy unless a clinical decision is made that postponing treatment may pose a greater risk to the pregnancy.

Lactation
Methylphenidate has been found in the breast-milk of a woman treated with methylphenidate.

There is one case report of an infant who experienced an unspecified decrease in weight during the period of exposure but recovered and gained weight after the mother discontinued treatment with methylphenidate. A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from methylphenidate therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

Methylphenidate can cause dizziness, drowsiness and visual disturbances including difficulties with accommodation, diplopia and blurred vision. It may have a moderate influence on the ability to drive and use machines. Patients should be warned of these possible effects and advised that if affected, they should avoid potentially hazardous activities such as driving or operating machinery.

4.8 Undesirable effects

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and post-market spontaneous reports with CONCERTA XL and those, which have been reported with other methylphenidate hydrochloride formulations. If the ADRs with CONCERTA XL and the methylphenidate formulation frequencies were different, the highest frequency of both databases was used.

Frequency estimate:
very common (≥ 1/10)
common (≥ 1/100 to < 1/10)
uncommon (≥ 1/1000 to <1/100)
rare (≥ 1/10,000 to <1/1000)
very rare (<1/10,000)
not known (cannot be estimated from the available data).

System Organ Class	Adverse Drug Reaction Frequency					
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Infections and infestations		Nasopharyngitis				
Blood and lymphatic system disorders					Anaemia, Leucopenia, Thrombocytopenia, Thrombo-cytopenic purpura	Pancytopenia
Immune system disorders			Hypersensitivity reactions such as Angioneurotic oedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias,			

CONCERTA (Methylphenidate HCl)
Module 1.3.1 Product Information

System Organ Class	Adverse Drug Reaction					
	Frequency					
	Very common	Common	Uncommon	Rare	Very rare	Not known
			Pruritus, Rashes, and Eruptions			
Metabolism and nutritional disorders*		Anorexia, Decreased appetite, Moderately reduced weight and height gain during prolonged use in children*				
Psychiatric disorders*	Insomnia, Nervousness	Anorexia, Affect lability, Aggression*, Agitation*, Anxiety*, Depression*, Irritability, Abnormal behaviour	Psychotic disorders*, Auditory, visual and tactile hallucinations*, Anger, Suicidal ideation*, Mood altered, Mood swings, Restlessness, Tearfulness, Tics*, Worsening of pre-existing tics of Tourette's syndrome*, Hypervigilance, Sleep disorder	Mania*, Disorientation, Libido disorder	Suicidal attempt (including completed suicide)*, Transient depressed mood*, Abnormal thinking, Apathy, Repetitive behaviours, Over-focussing	Delusions*, Thought disturbances*, Confusional state, dependence. Cases of abuse and dependence have been described, more often with immediate release formulations
Nervous system disorders	Headache	Dizziness, Dyskinesia, Psychomotor hyperactivity, Somnolence	Sedation, Tremor		Convulsions, Choreo-athetoid movements, Reversible ischaemic neurological deficit, Neuroleptic malignant syndrome (NMS; Reports were poorly documented and in most cases, patients were also receiving other drugs, so the role of methylphenidate is unclear).	Cerebrovascular disorders* (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), Grand mal convulsions*, Migraine
Eye disorders			Diplopia, Blurred vision	Difficulties in visual		

CONCERTA (Methylphenidate HCl)
Module 1.3.1 Product Information

System Organ Class	Adverse Drug Reaction					
	Frequency					
	Very common	Common	Uncommon	Rare	Very rare	Not known
				accommodation, Mydriasis, Visual disturbance		
Cardiac disorders*		Arrhythmia, Tachycardia, Palpitations	Chest pain	Angina pectoris	Cardiac arrest; Myocardial infarction	Supraventricular tachycardia, Bradycardia, Ventricular extrasystoles, Extrasystoles
Vascular disorders*		Hypertension			Cerebral arteritis and/or occlusion, Peripheral coldness, Raynaud's phenomenon	
Respiratory, thoracic and mediastinal disorders		Cough, Pharyngolaryngeal pain	Dyspnoea			
Gastrointestinal disorders		Abdominal pain, Diarrhoea, Nausea, Stomach discomfort, Vomiting, Dry mouth	Constipation			
Hepatobiliary disorders			Hepatic enzyme elevations		Abnormal liver function, including hepatic coma	
Skin and subcutaneous tissue disorders		Alopecia, Pruritis, Rash, Urticaria	Angioneurotic oedema, Bullous conditions, Exfoliative conditions	Hyperhidrosis, Macular rash; Erythema	Erythema multiforme, Exfoliative dermatitis, Fixed drug eruption	
Musculoskeletal, connective tissue and bone disorders		Arthralgia	Myalgia, Muscle twitching		Muscle cramps	
Renal and urinary disorders			Haematuria			
Reproductive system and breast disorders				Gynaecomastia		

System Organ Class	Adverse Drug Reaction Frequency					
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
General disorders and administration site conditions		Pyrexia, Growth retardation during prolonged use in children*	Chest pain, Fatigue		Sudden cardiac death*	Chest discomfort, Hyperpyrexia
Investigations		Changes in blood pressure and heart rate (usually an increase)*, Weight decreased*	Cardiac murmur*, Hepatic enzyme increased		Blood alkaline phosphatase increased, Blood bilirubin increased, Platelet count decreased, White blood cell count abnormal	

*see Section 4.4

4.9 Overdose

When treating patients with overdose, allowances must be made for the delayed release of methylphenidate from this formulation.

Signs and Symptoms

Acute overdose, mainly due to overstimulation of the central and sympathetic nervous systems, may result in vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Treatment

There is no specific antidote to methylphenidate overdosage.

Treatment consists of appropriate supportive measures.

The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. If the signs and symptoms are not too severe and the patient is conscious, gastric contents may be evacuated by induction of vomiting or gastric lavage. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. In the presence of severe intoxication, a carefully titrated dose of a benzodiazepine be given before performing gastric lavage.

Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal haemodialysis for overdose of methylphenidate has not been established.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psychoanaleptics, psychostimulants and nootropics, centrally acting sympathomimetics: ATC code: N06BA04

Methylphenidate HCl is a mild central nervous system (CNS) stimulant. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Methylphenidate is thought to block the reuptake of noradrenaline and dopamine into the presynaptic neurone and increase the release of these monoamines into the extraneuronal space. Methylphenidate is a racemic mixture comprised of the d- and l-isomers. The d-isomer is more pharmacologically active than the l-isomer.

In the pivotal clinical studies, CONCERTA XL was assessed in 321 patients already stabilised with immediate release preparations (IR) of methylphenidate and in 95 patients not previously treated with IR preparations of methylphenidate.

Clinical studies showed that the effects of CONCERTA XL were maintained until 12 hours after dosing when the product was taken once daily in the morning.

5.2 Pharmacokinetic properties

Absorption
Methylphenidate is readily absorbed. Following oral administration of CONCERTA XL to adults the drug overcoat dissolves, providing an initial maximum drug concentration at about 1 to 2 hours. The methylphenidate contained in the two internal drug layers is gradually released over the next several hours. Peak plasma concentrations are achieved at about 6 to 8 hours, after which plasma levels of methylphenidate gradually decrease. CONCERTA XL taken once daily minimises the fluctuations between peak and trough concentrations associated with immediate-release methylphenidate three times daily. The extent of absorption of CONCERTA XL once daily is generally comparable to conventional immediate release preparations.

Following the administration of CONCERTA XL 18 mg once daily in 36 adults, the mean pharmacokinetic parameters were: C_{max} 3.7 ± 1.0 (ng/mL), T_{max} 6.8 ± 1.8 (h), AUC_{inf} 41.8 ± 13.9 (ng.h/mL), and $t_{½}$ 3.5 ± 0.4 (h).

No differences in the pharmacokinetics of CONCERTA XL were noted following single and repeated once daily dosing, indicating no significant drug accumulation. The AUC and $t_{1/2}$ following repeated once daily dosing are similar to those following the first dose of CONCERTA XL 18 mg.

Following administration of CONCERTA XL in single doses of 18, 36, and 54 mg/day to adults, C_{max} and $AUC_{(0\text{-}inf)}$ of methylphenidate were proportional to dose.

Distribution
Plasma methylphenidate concentrations in adults decline biexponentially following oral administration. The half-life of methylphenidate in adults following oral administration of CONCERTA XL was approximately 3.5 h. The rate of protein binding of methylphenidate and of its metabolites is approximately 15%. The apparent volume of distribution of methylphenidate is approximately 13 litres/kg.

Metabolism
In humans, methylphenidate is metabolised primarily by de-esterification to alpha-phenyl-piperidine acetic acid (PPA, approximately 50 fold the level of the unchanged substance) which has little or no pharmacologic activity. In adults the metabolism of CONCERTA XL once daily as evaluated by metabolism to PPA is similar to that of methylphenidate three times daily. The metabolism of single and repeated once daily doses of CONCERTA XL is similar.

Excretion
The elimination half-life of methylphenidate in adults following administration of CONCERTA XL was approximately 3.5 hours. After oral administration, about 90% of the dose is excreted in urine and 1 to 3% in faeces, as metabolites within 48 to 96 hours. Small quantities of unchanged methylphenidate are recovered in urine (less than 1%). The main urinary metabolite is alpha-phenyl-piperidine acetic acid (60-90%).

After oral dosing of radiolabelled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPA, accounting for approximately 80% of the dose.

Food Effects
In patients, there were no differences in either the pharmacokinetics or the pharmacodynamic performance of CONCERTA XL when administered after a high fat breakfast on an empty stomach.

Special Populations
Gender
In healthy adults, the mean dose-adjusted $AUC_{(0\text{-}inf)}$ values for CONCERTA XL were 36.7 ng.h/mL in men and 37.1 ng.h/mL in women, with no differences noted between the two groups.

Race
In healthy adults receiving CONCERTA XL, dose-adjusted $AUC_{(0\text{-}inf)}$ was consistent across ethnic groups; however, the sample size may have been insufficient to detect ethnic variations in pharmacokinetics.

Age
The pharmacokinetics of CONCERTA XL has not been studied in children younger than 6 years of age. In children 7-12 years of age, the pharmacokinetics of

CONCERTA XL after 18, 36 and 54 mg were (mean±SD): C_{max} 6.0±1.3, 11.3±2.6, and 15.0±3.8 ng/mL, respectively, T_{max} 9.4±0.02, 8.1±1.1, 9.1±2.5 h, respectively, and $AUC_{0-11.5}$ 50.4±7.8, 87.7±18.2, 121.5±37.3 ng.h/mL, respectively.

Renal Insufficiency
There is no experience with the use of CONCERTA XL in patients with renal insufficiency. After oral administration of radiolabelled methylphenidate in humans, methylphenidate was extensively metabolised and approximately 80% of the radioactivity was excreted in the urine in the form of PPA. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of CONCERTA XL.

Hepatic Insufficiency
There is no experience with the use of CONCERTA XL in patients with hepatic insufficiency.

5.3 Preclinical safety data

Carcinogenicity
In life-time rat and mouse carcinogenicity studies, increased numbers of malignant liver tumours were noted in male mice only. The significance of this finding to humans is unknown.

Methylphenidate did not affect reproductive performance or fertility at low multiples of the clinical dose.

Pregnancy-embryonal/foetal development
Methylphenidate is not considered to be teratogenic in rats and rabbits. Foetal toxicity (i.e. total litter loss) and maternal toxicity was noted in rats at maternally toxic doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Butylhydroxytoluene (E321)
Cellulose acetate 398-10
Hypromellose 3cp
Phosphoric acid concentrated
Poloxamer 188
Polyethylene oxides 200K and 7000K
Povidone K29-32
Sodium chloride
Stearic acid
Succinic acid
Black iron oxide (E172)
Ferric oxide yellow (E172)

Film Coat:
Ferric oxide yellow (E172)
Hypromellose 15cp
Lactose monohydrate
Stearic acid
Titanium dioxide (E171)
Triacetin

Clear Coat:
Carnauba wax
Hypromellose 6cp
Macrogol 400

Printing Ink:
Black iron oxide (E172)
Hypromellose 6cp
Isopropyl alcohol
Propylene glycol
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Keep the bottle tightly closed. Do not store above 30ºC.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottle with a child-resistant polypropylene closure with one or two desiccants enclosed.

28 or 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

CONCERTA (Methylphenidate HCl)
Module 1.3.1 Product Information

7. MARKETING AUTHORISATION HOLDER

<To be completed nationally>

8. MARKETING AUTHORISATION NUMBER

<To be completed nationally>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: <To be completed nationally>

Date of last renewal: <To be completed nationally>

10. DATE OF REVISION OF THE TEXT

<To be completed nationally>

ANNEX 3

TABLE OF STUDIES

Clinical Trial Programme

Study No[a] Sponsor Principal Investigator (Country/Countries)	Start Date Completion Date	Study Description/Design Phase	Study Treatments Study Drugs/Dosing Regimen		Duration	Study Population E=enrolled C=completed RC[b]
Efficacy and Safety Controlled Clinical Studies						
C-97-025 ALZA Pelham US	23 Jan 1998 28 May 1998	Double-blind, double-dummy, randomised, placebo- and active-controlled, cross-over comparison study to evaluate the safety and efficacy of CONCERTA in children with ADHD Phase 2/3	CONCERTA Ritalin® Placebo	18, 36, 54 mg qd 5, 10, 15 mg tid (CONCERTA and Ritalin: 1 week at each dose until efficacy reached) tid	Total of 21 days	E: 70 C: 68 RC:68
C-98-003 ALZA Swanson/Wigal US	27 Sep 1998 22 Jan 2009	Double-blind, double-dummy, randomised, placebo- and active-controlled, 3-way cross-over study to evaluate the safety and efficacy of CONCERTA in children with ADHD Phase 2/3	CONCERTA Ritalin Placebo	18, 36, 54 mg qd 5, 10, 15 mg tid (CONCERTA and Ritalin: 1 week at each dose until efficacy reached) tid	Total of 21 days	E: 64 C: 61 RC:62
C-98-005 ALZA Multicentre US	Oct 1998 Dec 1998	Double-blind, double-dummy, randomised, placebo- and active-controlled, parallel group study to evaluate the safety and efficacy of CONCERTA in children with ADHD Phase 3	CONCERTA Ritalin Placebo	18, 36, 54 mg qd 5, 10, 15 mg tid (CONCERTA and Ritalin: 1 week at each dose until efficacy reached) tid	Total of 28 days	E: 312 C: 206 RC:104
01-146 **McNeil** Multicentre US	1 Apr 2002 16 Oct 2002	4-phase study (screening, open-label titration/run-in, randomised double-blind, open-label follow up) to evaluate the safety and efficacy of CONCERTA in adolescents with ADHD Phase 3b	CONCERTA	OL Run-In: 18, 36, 54, 72 mg qd (Starting dose 18 mg qd; 1 week at each dose until efficacy reached – individualised dose.) DB: Randomised to individualized dose of CONCERTA or matching placebo OL: Individualized dose of CONCERTA	Run-In: 1 to 4 weeks DB: 2 weeks OL: 8 weeks	OL: E: 220 RC: 220 DB: E: 177 RC: 87 OL: E: 171 C: 135 RC: 171

(Continued)

Clinical Trial Programme (Continued)

Study No[a] Sponsor Principal Investigator (Country/Countries)	Start Date Completion Date	Study Description/Design Phase	Study Treatments Study Drugs/Dosing Regimen	Duration	Study Population E=enrolled C=completed RC[b]
Efficacy and Safety Uncontrolled Clinical Studies					
C-98-007-002 **ALZA** Multicentre US	27 Sep 1998 5 Dec 1998	Open-label, nonrandomised, dose-escalation study in children with ADHD Phase 3	CONCERTA 18, 36, 54 mg qd (1 week at each dose until efficacy reached)	1 to 28 days	E: 111 C: 106 RC:110
C-98-012 ALZA Multicentre US	June 1998 Dec 2000	Open-label, nonrandomisedstudy to evaluate the long-term safety and effectiveness of CONCERTA in children with ADHD Phase 3	CONCERTA <u>Part 1</u>: 18, 36, or 54 qd Determined by participation in preceding ALZA study (flexible dosing) <u>Part 2</u>: Received same daily dose at that taken at the end of Part 1 (flexible dosing)	<u>Part 1</u>: Up to 1 year <u>Part 2</u>: Up to 27 months	<u>Part 1</u>: E: 436 C:289, RC:432 <u>Part 2</u> E: 278, C: 229, RC:278[c]
C-99-018-00 **ALZA** Multicentre US	8 Jan 00 to 9 Feb 01	Open-label, nonrandomised study to evaluate safety, effectiveness, and clinical use of CONCERTA in patients with ADHD in a community setting Phase 3b	CONCERTA 18, 36, 54 mg qd (flexible dosing) (Starting dose: no prior MPH: 18 mg qd prior MPH use: 18, 36, or 54 mg qd per predefined conversion schedule)	9 months	E: 1082[d] C: 737 RC:1082
12-101 **McNeil** Multicentre US	4 Jul 2003 30 Nov 2003	Open-label, parallel group study to evaluate treatment outcomes of CONCERTA and Strattera™ in children with ADHD Phase 4	CONCERTA 18 to 36 mg qd Starting dose: 18 mg qd Strattera Starting dose: 0.5 mg/kg/day Both CONCERTA and Strattera: Physicians determined the need for titration to the next higher dose level at subsequent visits	21 days	E:1322[d] C[e] RC:850

(Continued)

Clinical Trial Programme (Continued)

Study No[a] Sponsor Principal Investigator (Country/Countries)	Start Date Completion Date	Study Description/Design Phase	Study Treatments Study Drugs/Dosing Regimen	Duration	Study Population E=enrolled C=completed RC[b]
Efficacy and Safety Uncontrolled Clinical Studies (Continued)					
CON-CAN-1 **Janssen-Ortho Canada** Multicentre Canada	Dec 2002 Feb 2004	Open-label, randomised study to evaluate the effectiveness of CONCERTA versus usual clinical care with IR MPH in children with ADHD Phase 3	CONCERTA IR MPH	18, 27, 36, 54 mg qd 5 or 10 mg bid or tid per MD prescription (Titrated to a clinically effective dose of either study medication over 4 weeks and maintained on that dose for an additional 4 weeks.)	8 weeks	Analyzed: 145 RC: 72[c]
CON-CAN-2 **Janssen-Ortho Canada** Multicentre Canada	Jun 2003 Aug 2004	Open-label, 1-arm extension study of CON-CAN-1 Phase 3	CONCERTA IR MPH	18, 27, 36, or 54 mg qd 5 or 10 mg bid or tid per MD prescription (At study initiation, subjects continued taking the medication to which they were randomised to in CON-CAN-2 or switched to the other treatment arm.)	6 months	E: 119[d,f] RC: 116[c]
C-2000-045 **Janssen-Cilag Europe** Multicentre UK and Germany	Nov 2001 Nov 2003	Open-label, dose-adjustment study to evaluate safe and effective doses of CONCERTA in children with ADHD transferring from treatment with IR MPH Phase 3b	CONCERTA	18, 36, 54 mg qd (Starting dose based on predefined conversion schedule. Dose could be adjusted within the 18 to 54 mg ranges.)	21 days with an option to continue up to 12 months	E: 105[d] C: 101 (21 days) 56 (12 months) RC: 105

[a] Johnson & Johnson Pharmaceutical Research & Development (J&JPRD) is a global organization that includes, but is not limited to Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Janssen-Cilag International N.V., McNeil Pediatrics Division of McNeil-PPC, Inc.; ALZA Corporation, Janssen-Ortho Inc., and McNeil Consumer and Specialty Pharmaceuticals Division of McNeil-PPC, Inc.

[b] RC = The number of subjects that received CONCERTA.

[c] Studies C-98-007-002, CON-CAN-1, CON-CAN-2: the number of subjects receiving CONCERTA that is available in the dataset for the respective study.

[d] Studies C-99-018-00, 12-101, CON-CAN-2, C-2000-045: the number of subjects available for analysis that is available in the dataset for the respective study.

[e] Study 12-101: subject completion was not recorded.

[f] Study CON-CAN-2: The study report lists 109 analyzed subjects; Efficacy Results section clarifies that 54 subjects were on CONCERTA in CON-CAN-1 and 55 subjects on IR MPH in CON-CAN-1 switched to CONCERTA in CON-CAN-2.

Key: ADHD = Attention Deficit Hyperactivity Disorder; IR=immediate-release; MPH=methylphenidate; UK = United Kingdom; US = United States

ANNEX 4

EUROPEAN COMMISSION DECISION – ANNEX III AND ANNEX IV

Annex 4.1

European Commission Decision – Annex III

ANNEX III

AMENDMENTS TO THE SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

…[ ]…

Attention-Deficit/Hyperactivity Disorder (ADHD)

Methylphenidate is indicated as part of a comprehensive treatment programme for attention-deficit / hyperactivity disorder (ADHD) in children aged 6 years of age and over when remedial measures alone prove insufficient. Treatment must be under the supervision of a specialist in childhood behavioural disorders. Diagnosis should be made according to DSM-IV criteria or the guidelines in ICD-10 and should be based on a complete history and evaluation of the patient. Diagnosis cannot be made solely on the presence of one or more symptom.

The specific aetiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use of medical and specialised psychological, educational, and social resources.

A comprehensive treatment programme typically includes psychological, educational and social measures as well as pharmacotherapy and is aimed at stabilising children with a behavioural syndrome characterised by symptoms which may include chronic history of short attention span, distractibility, emotional lability, impulsivity, moderate to severe hyperactivity, minor neurological signs and abnormal EEG. Learning may or may not be impaired.

Methylphenidate treatment is not indicated in all children with ADHD and the decision to use the drug must be based on a very thorough assessment of the severity and chronicity of the child's symptoms in relation to the child's age.

Appropriate educational placement is essential, and psychosocial intervention is generally necessary. Where remedial measures alone prove insufficient, the decision to prescribe a stimulant must be based on rigorous assessment of the severity of the child's symptoms. The use of methylphenidate should always be used in this way according to the licensed indication and according to prescribing / diagnostic guidelines.

4.2 Posology and method of administration

…[ ]…

Treatment must be initiated under the supervision of a specialist in childhood and/or adolescent behavioural disorders.

Pre-treatment screening:
Prior to prescribing, it is necessary to conduct a baseline evaluation of a patient's cardiovascular status including blood pressure and heart rate. A comprehensive history should document concomitant medications, past and present co-morbid medical and psychiatric disorders or symptoms, family history of sudden cardiac/unexplained death and accurate recording of pre-treatment height and weight on a growth chart (see sections 4.3 and 4.4)

Ongoing monitoring:
Growth, psychiatric and cardiovascular status should be continuously monitored (see also Section 4.4).

- Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and then at least every 6 months;

- height, weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart;

- development of *de novo* or worsening of pre-existing psychiatric disorders should be monitored at every adjustment of dose and then least every 6 months and at every visit.

Patients should be monitored for the risk of diversion, misuse and abuse of methylphenidate.

Dose titration
Careful dose titration is necessary at the start of treatment with methylphenidate. Dose titration should be started at the lowest possible dose.

Other strengths of this medicinal product and other methylphenidate-containing products may be available.

{The MA Holder should describe the dose conversion (between formulations) and the dose titration steps that are relevant to the formulation and strength of their own methylphenidate product, in each methylphenidate SPC in the EU}

The maximum daily dosage of methylphenidate is *{to be completed nationally}*.

Long-term (more than 12 months) use in children and adolescents
The safety and efficacy of long term use of methylphenidate has not been systematically evaluated in controlled trials. Methylphenidate treatment should not and need not, be indefinite. Methylphenidate treatment is usually discontinued during or after puberty. The physician who elects to use methylphenidate for extended periods (over 12 months) in children and adolescents with ADHD should periodically re-evaluate the long term usefulness of the drug for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that methylphenidate is de-challenged at least once yearly to assess the child's condition (preferable during times of school holidays). Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Dose reduction and discontinuation
Treatment must be stopped if the symptoms do not improve after appropriate dosage adjustment over a one-month period. If paradoxical aggravation of symptoms or other serious adverse events occur, the dosage should be reduced or discontinued.

Adults
Methylphenidate is not licensed for use in adults in ADHD. Safety and efficacy have not been established in this age group

Elderly
Methylphenidate should not be used in the elderly. Safety and efficacy has not been established in this age group.

Children under 6 years of age
Methylphenidate should not be used in children under the age of 6 years. Safety and efficacy in this age group has not been established.

4.3 Contraindications

…[ ]…

Known sensitivity to methylphenidate or any of the excipients

- Glaucoma
- Phaeochromocytoma
- During treatment with non-selective, irreversible monoamine oxidase (MAO) inhibitors, or within a minimum of 14 days of discontinuing those drugs, due to risk of hypertensive crisis (see section 4.5)
- Hyperthyroidism or Thyrotoxicosis
- Diagnosis or history of severe depression, anorexia nervosa/anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder.
- Diagnosis or history of severe and episodic (Type I) Bipolar (affective) Disorder (that is not well-controlled)
- pre-existing cardiovascular disorders including severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies (disorders caused by the dysfunction of ion channels).
- pre-existing cerebrovascular disorders cerebral aneurysm, vascular abnormalities including vasculitis or stroke

4.4 Special warnings and precautions for use

…[ ]…

Methylphenidate treatment is not indicated in all children with ADHD and the decision to use the drug must be based on a very thorough assessment of the severity and chronicity of the child's symptoms in relation to the child's age.

Long-term use (more than 12 months) in children and adolescents

The safety and efficacy of long term use of methylphenidate has not been systematically evaluated in controlled trials. Methylphenidate treatment should not and need not, be indefinite. Methylphenidate treatment is usually discontinued during or after puberty. Patients on long-term therapy (i.e. over 12 months) must have careful ongoing monitoring according to the guidance in sections 4.2 and 4.4. for cardiovascular status, growth, appetite, development of *de novo* or worsening of pre-existing psychiatric disorders. Psychiatric disorders to monitor for are described below, and include (but are not limited to) motor or vocal tics, aggressive or hostile behaviour, agitation, anxiety, depression, psychosis, mania, delusions, irritability, lack of spontaneity, withdrawal and excessive perseveration.

The physician who elects to use methylphenidate for extended periods (over 12 months) in children and adolescents with ADHD should periodically re-evaluate the long term usefulness of the drug for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that methylphenidate is de-challenged at least once yearly to

assess the child's condition (preferably during times of school holidays). Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Use in adults
Methylphenidate is not licensed for use in adults with ADHD. Safety and efficacy have not been established in this age group

Use in the elderly
Methylphenidate should not be used in the elderly. Safety and efficacy has not been established in this age group.

Use in children under 6 years of age
Methylphenidate should not be used in children under the age of 6 years. Safety and efficacy in this age group has not been established.

Cardiovascular status
Patients who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden cardiac or unexplained death or malignant arrhythmia,) and physical exam to assess for the presence of cardiac disease, and should receive further specialist cardiac evaluation if initial findings suggest such history or disease. Patients who develop symptoms such as palpitations, exertional chest pain, unexplained syncope, dyspnoea or other symptoms suggestive of cardiac disease during methylphenidate treatment should undergo a prompt specialist cardiac evaluation.

Analyses of data from clinical trials of methylphenidate in children and adolescents with ADHD showed that patients using methylphenidate may commonly experience changes in diastolic and systolic blood pressure of over 10 mmHg relative to controls. The short- and long-term clinical consequences of these cardiovascular effects in children and adolescents are not known, but the possibility of clinical complications cannot be excluded as a result of the effects observed in the clinical trial data. **Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate.** See section 4.3 for conditions in which methylphenidate treatment in contraindicated.

Cardiovascular status should be carefully monitored. Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and then at least every 6 months.

The use of methylphenidate is contraindicated in certain pre-existing cardiovascular disorders **unless specialist paediatric cardiac advice has been obtained (see Section 4.3 'Contraindications').**

Sudden death and pre-existing cardiac structural abnormalities or other serious cardiac disorders
Sudden death has been reported in association with the use of stimulants of the central nervous system at usual doses in children, some of whom had cardiac structural abnormalities or other serious heart problems. Although some serious heart problems alone may carry an increased risk of sudden death, stimulant products are not recommended in children or adolescents with known cardiac structural abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant medicine.

Misuse and Cardiovascular Events
Misuse of stimulants of the central nervous system may be associated with sudden death and other serious cardiovascular adverse events.

Cerebrovascular disorders
See section 4.3 for cerebrovascular conditions in which methylphenidate treatment in contraindicated. Patients with additional risk factors (such as a history of cardiovascular disease, concomitant

medications that elevate blood pressure) should be assessed at every visit for neurological signs and symptoms after initiating treatment with methylphenidate.

Cerebral vasculitis appears to be a very rare idiosyncratic reaction to methylphenidate exposure. There is little evidence to suggest that patients at higher risk can be identified and the initial onset of symptoms may be the first indication of an underlying clinical problem. Early diagnosis, based on a high index of suspicion, may allow the prompt withdrawal of methylphenidate and early treatment. The diagnosis should therefore be considered in any patient who develops new neurological symptoms that are consistent with cerebral ischemia during methylphenidate therapy. These symptoms could include severe headache, numbness, weakness, paralysis, and impairment of coordination, vision, speech, language or memory..

Treatment with methylphenidate is not contraindicated in patients with hemiplegic cerebral palsy

Psychiatric disorders
Co-morbidity of psychiatric disorders in ADHD is common and should be taken into account when prescribing stimulant products. In the case of emergent psychiatric symptoms or exacerbation of pre-existing psychiatric disorders, methylphenidate should not be given unless the benefits outweigh the risks to the patient.

Development or worsening of psychiatric disorders should be monitored at every adjustment of dose, then at least every 6 months, and at every visit; discontinuation of treatment may be appropriate.

Exacerbation of pre-existing Psychotic or manic symptoms
In psychotic patients, administration of methylphenidate may exacerbate symptoms of behavioural disturbance and thought disorder.

Emergence of new psychotic or manic symptoms
Treatment-emergent psychotic symptoms (visual/tactile/auditory hallucinations and delusions) or mania in children and adolescents without prior history of psychotic illness or mania can be caused by methylphenidate at usual doses. If manic or psychotic symptoms occur, consideration should be given to a possible causal role for methylphenidate, and discontinuation of treatment may be appropriate.

Aggressive or hostile behaviour
The emergence or worsening of aggression or hostility can be caused by treatment with stimulants. Patients treated with methylphenidate should be closely monitored for the emergence or worsening of aggressive behaviour or hostility at treatment initiation, at every dose adjustment and then at least every 6 months and every visit. Physicians should evaluate the need for adjustment of the treatment regimen in patients experiencing behaviour changes.

Suicidal tendency
Patients with emergent suicidal ideation or behaviour during treatment for ADHD should be evaluated immediately by their physician. Consideration should be given to the exacerbation of an underlying psychiatric condition and to a possible causal role of methylphenidate treatment. Treatment of an underlying psychiatric condition may be necessary and consideration should be given to a possible discontinuation of methylphenidate.

Tics
Methylphenidate is associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported. Family history should be assessed and clinical evaluation for tics or Tourette's syndrome in children should precede use of methylphenidate. Patients should be regularly monitored for the emergence or worsening of tics during treatment with methylphenidate. **Monitoring should be at every adjustment of dose and then at least every 6 months or every visit.**

Anxiety, agitation or tension
Methylphenidate is associated with the worsening of pre-existing anxiety, agitation or tension. Clinical evaluation for anxiety, agitation or tension should precede use of methylphenidate and patients should be **regularly monitored for the emergence or worsening of these symptoms during treatment, at every adjustment of dose and then at least every 6 month or every visit.**

Forms of bipolar disorder
Particular care should be taken in using methylphenidate to treat ADHD in patients with comorbid bipolar disorder (including untreated Type I Bipolar Disorder or other forms of bipolar disorder) because of concern for possible precipitation of a mixed/manic episode in such patients. Prior to initiating treatment with methylphenidate, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. **Close ongoing monitoring is essential in these patients (see above 'Psychiatric Disorders' and section 4.2) . Patients should be monitored for symptoms at every adjustment of dose, then at least every 6 months and at every visit.**

Growth
Moderately reduced weight gain and growth retardation have been reported with the long-term use of methylphenidate in children.

The effects of methylphenidate on final height and final weight are currently unknown and being studied.

Growth should be monitored during methylphenidate treatment: height, weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart. Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Seizures
Methylphenidate should be used with caution in patients with epilepsy. Methylphenidate may lower the convulsive threshold in patient with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and rarely in patients without a history of convulsions and no EEG abnormalities. If seizure frequency increases or new-onset seizures occur, methylphenidate should be discontinued.

Abuse, misuse and diversion
Patients should be carefully monitored for the risk of diversion, misuse and abuse of methylphenidate

Methylphenidate should be used with caution in patients with known drug or alcohol dependency because of a potential for abuse, misuse or diversion.

Chronic abuse of methylphenidate can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes can occur, especially in response to parenteral abuse.

Patient age, the presence of risk factors for substance use disorder (such as co-morbid oppositional-defiant or conduct disorder and bipolar disorder), previous or current substance abuse should all be taken into account when deciding on a course of treatment for ADHD. Caution is called for in emotionally unstable patients, such as those with a history of drug or alcohol dependence, because such patients may increase the dosage on their own initiative.

For some high-risk substance abuse patients, methylphenidate or other stimulants may not be suitable and non-stimulant treatment should be considered.

Withdrawal
Careful supervision is required during drug withdrawal, since this may unmask depression as well as chronic over-activity. Some patients may require long-term follow up.

Careful supervision is required during withdrawal from abusive use since severe depression may occur.

Fatigue
Methylphenidate should not be used for the prevention or treatment of normal fatigue states.

Excipients: galactose/sucrose intolerance
This medicinal product contains lactose: patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicinal product contains sucrose: patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine

Choice of methylphenidate formulation
The choice of formulation of methylphenidate-containing product will have to be decided by the treating specialist on an individual basis and depends on the intended duration of effect.

Drug screening
This product contains methylphenidate which may induce a false positive laboratory test for amphetamines, particularly with immunoassay screen test.

Renal or hepatic insufficiency
There is no experience with the use of methylphenidate in patients with renal or hepatic insufficiency.

Haematological effects
The long-term safety of treatment with methylphenidate is not fully known. In the event of Leukopenia, thrombocytopenia, anaemia or other alterations, including those indicative of serious renal or hepatic disorders, discontinuation of treatment should be considered.

Potential for gastrointestinal obstruction
{This wording should be including only in SPCs where it is appropriate, – see wording below :}

Because the *{Invented name}* tablet is nondeformable and does not appreciably change in shape in the gastrointestinal (GI) tract, it should not ordinarily be administered to patients with pre-existing severe GI narrowing (pathologic or iatrogenic) or in patients with dysphagia or significant difficulty in swallowing tablets. There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in nondeformable prolonged-release formulations.

Due to the prolonged-release design of the tablet, *{Invented name}* should only be used in patients who are able to swallow the tablet whole. Patients should be informed that *{Invented name}* must be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interaction

…[ ]…

It is not known how methylphenidate may effect plasma concentrations of concomitantly administered drugs. Therefore, caution is recommended at combining methylphenidate with other drugs, especially those with a narrow therapeutic window.

Methylphenidate is not metabolised by cytochrome P450 to a clinically relevant extent. Inducers or inhibitors of cytochrome P450 are not expected to have any relevant impact on methylphenidate pharmacokinetics. Conversely, the d- and l- enantiomers of methylphenidate do not relevantly inhibit cytochrome P450 1A2, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A.

However, there are reports indicating that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g. phenobarbitol, phenytoin, primodone) and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). When starting or stopping treatment with methylphenidate, it may be necessary to adjust the dosage of these drugs already being taken and establish drug plasma concentrations (or for coumarin, coagulation times).

Pharmacodynamic interactions

…[ ]…

Anti-hypertensive drugs
Methylphenidate may decrease the effectiveness of drugs used to treat hypertension.

Use with drugs that elevate blood pressure
Caution is advised in patients being treated with methylphenidate with any other drug that can also elevate blood pressure (see also sections on cardiovascular and cerebrovascular conditions in Section 4.4 Warnings and Precautions for use)

Because of possible hypertensive crisis, methylphenidate is contraindicated in patients being treated (currently or within the preceding 2 weeks) with non-selective, irreversible MAO-inhibitors (see section 4.3 Contraindications).

Use with alcohol
Alcohol may exacerbate the adverse CNS effects of psychoactive drugs, including methylphenidate. It is therefore advisable for patients to abstain from alcohol during treatment.

Use with halogenated anaesthetics
There is a risk of sudden blood pressure increase during surgery. If surgery is planned, methylphenidate treatment should not be used on the day of surgery.

Use with centrally acting alpha-2 agonists (e.g. clonidine)
Serious, adverse events, including sudden death, have been reported in concomitant use with clonidine. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

Use with domapinergic drugs
Caution is recommended when administering methylphenidate with dopaminergic drugs, including antipsychotics. Because a predominant action of methylphenidate is to increase extracelluar dopamine levels, methylphenidate may be associated with pharmacodynamic interactions when co-administered with direct and indirect dopamine agonists (including DOPA and tricyclic antidepressants) or with dopamine antagonists including antipsychotics.

4.6 Pregnancy and lactation

Pregnancy
There is a limited amount of data from the use of methylphenidate in pregnant women.

Cases of neonatal cardiorespiratory toxicity, specifically fetal tachycardia and respiratory distress have been reported in spontaneous case reports.

Studies in animals have only shown evidence of reproductive toxicity at maternally toxic doses. (See section 5.3)

Methylphenidate is not recommended for use during pregnancy unless a clinical decision is made that postponing treatment may pose a greater risk to the pregnancy.

Lactation
Methylphenidate has been found in the breast-milk of a woman treated with methylphenidate

There is one case report of an infant who experienced an unspecified decrease in weight during the period of exposure but recovered and gained weight after the mother discontinued treatment with methylphenidate. A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from methylphenidate therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

…[ ]…

Methylphenidate can cause dizziness, drowsiness and visual disturbances including difficulties with accommodation, diplopia and blurred vision. It may have a moderate influence on the ability to drive and use machines. Patients should be warned of these possible effects and advised that if affected, they should avoid potentially hazardous activities such as driving or operating machinery.

4.8 Undesirable effects

…[ ]…

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and post-market spontaneous reports with *{invented name}* and those, which have been reported with other methylphenidate hydrochloride formulations. If the ADRs with *{invented name}* and the methylphenidate formulation frequencies were different, the highest frequency of both databases was used.

Frequency estimate:
very common (≥ 1/10)
common (≥ 1/100 to < 1/10)
uncommon (≥ 1/1000 to <1/100)
rare (≥ 1/10,000 to <1/1000)
very rare (<1/10,000)
not known (cannot be estimated from the available data).

Infections and infestations
Common: Nasopharyngitis

Blood and lymphatic disorders
Very rare: Anaemia, leukopenia, thrombocytopenia, thrombocytopenic purpura
Unknown: Pancytopenia

Immune system disorders
Uncommon: hypersensitivity reactions such as angioneurotic oedema, anaphylactic reactions, auricular swelling, bullous conditions, exfoliative conditions, urticarias, pruritis, rashes and eruptions

Metabolism and nutritional disorders*
Common: anorexia, decreased appetite, moderately reduced weight and height gain during prolonged use in children*

Psychiatric disorders*
Very common: insomnia, nervousness
Common: anorexia, affect lability, aggression*, agitation*, anxiety*, depression*, irritability, abnormal behaviour
Uncommon: psychotic disorders*, auditory, visual, and tactile hallucinations*, anger, suicidal ideation*, mood altered, mood swings, restlessness, tearfulness, tics*, worsening of pre-existing tics or Tourette's syndrome*, hypervigilance, sleep disorder
Rare: mania*, disorientation, libido disorder
Very rare: suicidal attempt (including completed suicide)*, transient depressed mood*, abnormal thinking, apathy, repetitive behaviours, over-focussing,
Not known: delusions*, thought disturbances*, confusional state, dependence.

Cases of abuse and dependence have been described, more often with immediate release formulations (frequency not known)

Nervous system disorders
Very common: headache
Common: dizziness, dyskinesia, psychomotor hyperactivity, somnolence
Uncommon: sedation, tremor
Very rare: convulsions, choreo-athetoid movements, reversible ischaemic neurological deficit
Neuroleptic malignant syndrome (NMS; Reports were poorly documents and in most of cases, patients were also receiving other drugs, so the role of methylphenidate is unclear).
Not known: cerebrovascular disorders* (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), grand mal convulsions*, migraine

Eye disorders
Uncommon: diplopia, blurred vision,
Rare: difficulties in visual accommodation, mydriasis, visual disturbance

Cardiac disorders*
Common: arrhythmia, tachycardia palpitations
Uncommon: chest pain
Rare: angina pectoris
Very rare: cardiac arrest, myocardial infarction
Not known: supraventricular tachycardia, bradycardia, ventricular extrasystoles, extrasystoles

Vascular disorders*
Common: hypertension
Uncommon:
Very rare: cerebral arteritis and/or occlusion, peripheral coldness, Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders
Common: cough, pharyngolaryngeal pain

Uncommon: dyspnoea

Gastrointestinal disorders
Common: abdominal pain, diarrhoea, nausea, stomach discomfort, and vomiting – *{for inclusion in SPCs for non-modified release formulations}: "*these usually occur at the beginning of treatment and may be alleviated by concomitant food intake", Dry mouth.
Uncommon: constipation

Hepatobiliary disorders
Uncommon: hepatic enzyme elevations
Very rare: abnormal liver function, including hepatic coma

Skin and subcutaneous tissue disorders
Common: alopecia, pruritus, rash, urticaria
Uncommon: angioneurotic oedema, bullous conditions, exfoliative conditions
Rare: hyperhidrosis, macular rash, erythema
Very rare: erythema multiforme, exfoliative dermatitis, fixed drug eruption

Musculoskeletal, connective tissue and bone disorders
Common: arthralgia
Uncommon: myalgia, muscle twitching
Very rare: muscle cramps

Renal and urinary disorders
Uncommon: haematuria

Reproductive system and breast disorders
Rare: Gynaecomastia

General disorders and administration site conditions
Common: pyrexia, growth retardation during prolonged use in children*
Uncommon: chest pain, fatigue
Very rare: sudden cardiac death*
Not known: chest discomfort, hyperpyrexia

Investigations
Common: changes in blood pressure and heart rate (usually an increase)*, weight decreased*
Uncommon: cardiac murmur*, hepatic enzyme increased
Very rare: blood alkaline phosphatase increased, blood bilirubin increased, platelet count decreased, white blood count abnormal

*See Section 4.4 'Special warnings and precautions for use'

4.9 Overdose

…[ ]…

When treating patients with overdose, allowances must be made for the delayed release of methylphenidate from methylphenidate.

Signs and symptoms
Acute overdose, mainly due to overstimulation of the central and sympathetic nervous systems, may result in vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia,

tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis and dryness of mucous membranes.

Treatment
There is no specific antidote to methylphenidate overdosage.

Treatment consists of appropriate supportive measures.

The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. If the signs and symptoms are not too severe and the patient is conscious, gastric contents may be evacuated by induction of vomiting or gastric lavage. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. In the presence of severe intoxication, a carefully titrated dose of a benzodiazepine be given before performing gastric lavage.

Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal haemodialysis for overdose of methylphenidate has not been established.

Section 5.3 Preclinical safety data

…[ ]…

Carcinogenicity
In life-time rat and mouse carcinogenicity studies, increased numbers of malignant liver tumours were noted in male mice only. The significance of this finding to humans is unknown.

Methylphenidate did not affect reproductive performance or fertility at low multiples of the clinical dose.

Pregnancy-embryonal/foetal development
Methylphenidate is not considered to be teratogenic in rats and rabbits. Foetal toxicity (i.e. total litter loss) and maternal toxicity was noted in rats at maternally toxic doses.

PACKAGE LEAFLET

1. WHAT METHYLPHENIDATE IS AND WHAT IT IS USED FOR

…[ ]…

Methylphenidate is used to treat attention deficit hyperactivity disorder (ADHD) in adolescents and children 6 years of age and over when other non pharmaceutical measures alone have proven insufficient.

Methyphenidate should be used together with other forms of treatment, as part of a comprehensive treatment programme. A comprehensive treatment programme typically includes psychological, educational and social measures as well as pharmacotherapy and is aimed at stabilising children with ADHD with symptoms that may include chronic history of short attention span, distractibility, emotional lability, impulsivity, moderate to severe hyperactivity, minor neurological signs and abnormal electoencephalograpy (EEG). Learning may or may not be impaired. Diagnosis cannot be made solely on the presence of one or more symptom. Adequate diagnosis requires the use of medical and specialised psychological, educational, and social resources.

Methylphenidate must only be initiated by, and used under the supervision of, a specialist in childhood and/or adolescent behavioural disorders

Methylphenidate treatment is not indicated in all children with ADHD and the decision to use the drug must be based on a very thorough assessment of the severity and chronicity of the child's symptoms in relation to the child's age. The use of methylphenidate should always be used in this way according to the licensed indication and according to prescribing / diagnostic guidelines.

…[ ]…

2. Before you take methylphenidate

…[ ]…

Do not take methylphenidate if you or your child

- are allergic (hypersensitive) to methylphenidate or any of the other ingredients of methylphenidate.
- have glaucoma (increased pressure in the eye)
- have phaeochromocytoma (a tumour of the adrenal gland)
- are taking medicines known as monoamine oxidase inhibitors (MAOIs) for depression, or have taken MAOIs in the last 14 days
- have thyroid problems
- suffer from anorexia nervosa or anorexic disorders
- suffer from depression, mood disorders, mania, or have suicidal thoughts
- suffer from psychotic symptoms or schizophrenia or psychopathic/borderline personality disorder.
- have a diagnosis or history of severe and episodic (Type I) Bipolar (affective) Disorder
- has heart problems such as a history of a heart attack, irregular heartbeat, pain and discomfort in the chest, heart failure, heart disease or significant problems with the structure or function of the heart that were present at birth.
- have a very high blood pressure or narrowing of the vessels, possibly resulting in pain in the arms and legs
- has experienced a cerebrovascular disorder such as stroke, cerebral aneurysm, or vascular abnormalities including cerebral vasculitis

Methylphenidate is not licensed for use in adults with ADHD.

Methylphenidate should not be given to children under 6 years of age or the elderly as the safety and benefits of use in these age groups have not been established.

Take special care with methylphenidate and tell a doctor if you or your child

- Has been told to take these tablets for longer than 12 months (see section 3 below, on long-term use)
- Is entering puberty (teenage years)
- Is about to stop taking methylphenidate as your doctor may want to monitor your child for depression
- has a heart disease or other serious heart problem
- has had seizures (convulsions, epilepsy) or abnormal EEGs (electroencephalograms brain scans)
- has high blood pressure.
- has liver or kidney problems.
- if you or your child has psychiatric disorders .
- has motion or verbal tics (hard-to-control, repeated twitching of any parts of the body or repeated sounds and words)
- is seeing, hearing or feeling things that are not there (hallucinations)
- believes things that are not true (delusions)
- feels unusually suspicious (paranoia)
- experiences mood swings such as racing or impulsive thoughts followed by feeling irritable or emotionally and socially withdrawn
- has suicidal thoughts or actions
- feels depressed or guilty
- feels agitated, anxious or tense
- experiences new or worsening aggressive or hostile behaviour

Tell the doctor before treatment if any of the above conditions or symptoms applies to you or your child.

Checks that your doctor will make before treatment with methylphenidate begins:

In order for your doctor to decide if methylphenidate is the correct medicine for you or your child, your doctor will discuss the following with you:

- about any medications you or your child is taking
- about any other medical conditions (such as heart conditions) you, your child or you family may have.
- whether there is a family history of sudden unexplained death in the family.
- how you or your child are feeling e.g. are you feeling emotional, having strange thoughts or if you have had any of these feelings in the past.
- about any mental health/psychiatric/behavioural problems you or your child or other family members have or have had in the past. Your doctor will specifically discuss wether you or your child is at risk for bipolar (affective) disorder, which will involve checking psychiatric history, inlcuding a family history of suicide, bipolar disorder and depression.
- to measure you or your child's height and weight, heart rate and blood pressure and will record these on a chart
- whether there is a family history of tics

It is important that you provide all information so your doctor can decide if methylphenidate is the correct medicine for you or your child. Your doctor may decide you or your child need other medical tests before you or your child take this medicine.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

If you or your child is taking other medicines, methylphenidate may affect how well other medicines work or may cause side effects. If you or your child is taking any of the following medicines, check with the doctor before taking methylphenidate:

- Non-selective, irreversible, monoamine oxidase (MAO) inhibitors (used to treat depression)
- Vasopressor agents (drugs which may increase blood pressure)
- Medicines used to reduce the blood pressure, for example clonidine, guanethidine, verapamil propranolol, etc.
- Some cough and cold remedies which contain ingredients that can affect blood pressure, so it is important to check with your pharmacist when you buy any of these products.
- Medicines for depression, including amitriptyline, imipramine and fluoxetine, paroxetine
- Medicines for epilepsy (anticonvulsants) (e.g. phenobarbital, phenytoin, primidone, etc)
- medicines that thin the blood to prevent blood clots (blood thinners, e.g. warfarin)
- dopaminergic drugs, including antipsychotics

If surgery is planned using a halogenated anaesthetic (a certain type of anaesthetic), you or your child should not take methylphenidate on the day of surgery, due to the risk of a sudden rise in blood pressure during surgery.

Drug testing
This medicine may give a positive result when testing for drug use.

If you are in any doubt about whether any medicines you or your child is taking are included in the list above, ask your doctor or pharmacist before taking

methylphenidate.

{For inclusion in the PL of non-modified release formulations of methylphenidate:}
"Taking methylphenidate with food and drink
Taking methylphenidate with food may help relieve stomach pains, feeling sick or vomitting."

Taking methylphenidate with alcohol
You or your child must not drink alcohol while taking this medicine as alcohol may make this medicine's side effects worse. Remember that some foods and medicines contain alcohol.

Pregnancy and breast-feeding
Tell your doctor or pharmacist before using methylphenidate if you or your child is:
- sexually active. Your doctor will discuss contraception with you.
- pregnant or think you may be pregnant. Your doctor will decide whether you or your daughter should use methylphenidate.
- breast-feeding or planning to breast-feed. There is limited information that suggests that methylphenidate is passed into human breast milk. Therefore, your doctor will decide whether you or your daughter should breast-feed while using methylphenidate.

Driving or using machines
Dizziness, drowsiness and visual disturbances may occur when taking methylphenidate. If such side-effects occur it may be dangerous to perform any hazardous activities, such as driving, operating machinery, riding a bike or climbing trees until you are certain that you or your child will not be affected.

Important information about some of the ingredients of methylphenidate
{To be completed nationally, as appropriate]

…[ ]…
3. HOW TO <TAKE> <USE> methylphenidate
…[ ]…

Before you start treatment, at every change of dose and then at least every 6 months or every visit your doctor will conduct various tests to make sure that methylphenidate is still acceptabley safe and beneficial. These will include:

- Measuring blood pressure and heart rate and recording these on a chart, each time your dose in changed and then at least every six months or at every visit.
- Measuring height, weight and appetite recording these on a chart, each time your dose in changed and then at least every six months or at every visit.
- Assessing psychiatric symptoms, each time your dose in changed and then at least every six months or at every visit.

Dose titration
Careful dose titration is necessary at the start of treatment with methylphenidate. Dose titration should be started at the lowest possible dose.

<Always <take> <use> methylphenidate exactly as your doctor has told you. You should check with your <doctor> <or> <pharmacist> if you are not sure.> <The usual dose is...>

If you or your child do not feel better with this medicine, your doctor may decide a different treatment is needed. Tell the doctor if there is no improvement in your childs condition after 1 month of treatment with methylphenidate.

Long-term treatment

Methylphenidate treatment does not need to be indefinite. If methylphenidate is taken for more than a year, your doctor should stop your treatment with methylphenidate for a short time once a year to see if the medicine is still needed. You or your child may continue to see a benefit when methylphenidate is either temporarily or permanently stopped. This may happen during school holidays.

Patients on long-term therapy (i.e. over 12 months) must have careful ongoing monitoring, especially for . or cardiovascular status, growth, appetite, development of *de novo* or worsening of pre-existing psychiatric symptoms

Abuse
Your child should be monitored for the risk of diversion, misuse and abuse of methylphenidate. Longstanding abuse of methylphenidate can lead to marked tolerance, psychological dependence, abnormal behaviour, psychotic episodes. This medicine is intended solely for you or for your child. It must only be prescribed by a doctor and must therefore not be passed on to anyone else. It may harm other people, even if they have the same symptoms as your child

If you <take> <use> more methylphenidate than you should
If you or your child takes too many tablets, contact the doctor or nearest hospital casualty department immediately and tell them how many tablets have been taken.

Signs of overdose may include: vomiting, agitation, shaking, increased uncontrolled movements, muscle twitching, fits (may be followed by coma), feeling of extreme happiness, confusion (severe confusion), hallucinations (seeing, feeling or hearing things that are not real), sweating, flushing, headache, high fever, changes in heart beat (slow, fast or irregular), high blood pressure, dilated pupils and dry nose and mouth.

If you forget to <take> <use> methylphenidate

<you or your child should take the next dose when it is due. Never take a double dose to make up for a forgotten <tablet> <dose> <…>.>

If you stop <taking> <using> methylphenidate

Administration of the tablets should not stop abruptly. You should closely follow the advise of your doctor. Careful supervision is required during withdrawal as this may unmask depression, as well as chronic over-activity.

<If you have any further questions on the use of this product, ask your <doctor> <or> <pharmacist>.>

4. POSSIBLE SIDE EFFECTS

Like all medicines, methylphenidate can cause side effects, although not everybody gets them.

The likelihood of having a side effect is as follows:

Very common (more than 1 out of 10 persons)
Common (more than 1 out of 100 persons and less than 1 out of 10 persons)
Uncommon (more than 1 out of 1,000 persons and less than 1 out of 100 persons)
Rare (more than 1 out of 10,000 persons and less than 1 out of 1,000 persons)
Very rare (less than 1 out of 10,000 persons)
Not known (cannot be estimated from the available data).

The most common side effects are nervousness, sleeplessness and headache.

Some side effects could be **serious**. If you suffer from or have any worries about any of the the side effects below, **tell your doctor or pharmacist:**

- severe changes in mood or personality
- mania
- psychotic disorders, including visual, tactile or auditory hallucinations or delusions
- palpitations, unexplained fainting chest pain, shortness of breath (these can sometimes be signs of cardiac disease)
- paralysis or impairment of movement and vision, difficulties in speech (could be symptoms of cerebral vasculitis).

Effects on growth and maturation
When used for a long period of time, methylphenidate may cause reduced growth (weight gain and/or height) in some children. Your doctor will therefore carefully be watching you or your child's height and weight. as well as how well you or your child is eating. If you or your child is not growing or gaining weight as expected, then you or your child's treatment with methylphenidate may be stopped for a short time

Other side effects include:

Infections and infestations
Common: Nasopharyngitis

Blood and lymphatic disorders
Very rare: Anaemia, leukopenia, thrombocytopenia, thrombocytopenic purpura
Unknown: Pancytopenia

Immune system disorders
Uncommon: hypersensitivity reactions such as angioneurotic oedema, anaphylactic reactions, auricular swelling, bullous conditions, exfoliative conditions, urticarias, pruritis, rashes and eruptions

Metabolism and nutritional disorders*
Common: anorexia, decreased appetite, moderately reduced weight and height gain during prolonged use in children*

Psychiatric disorders*
Very common: insomnia, nervousness
Common: anorexia, affect lability, aggression*, agitation*, anxiety*, depression*, irritability, abnormal behaviour
Uncommon: psychotic disorders*, auditory, visual, and tactile hallucinations*, anger, suicidal ideation*, mood altered, mood swings, restlessness, tearfulness, tics*, worsening of pre-existing tics or Tourette's syndrome*, hypervigilance, sleep disorder
Rare: mania*, disorientation, libido disorder
Very rare: suicidal attempt (including completed suicide)*, transient depressed mood*, abnormal thinking, apathy, repetitive behaviours, over-focussing,
Not known: delusions*, thought disturbances*, confusional state

Nervous system disorders
Very common: headache
Common: dizziness, dyskinesia, psychomotor hyperactivity, somnolence
Uncommon: sedation, tremor
Very rare: convulsions, choreo-athetoid movements, reversible ischaemic neurological deficit
Neuroleptic malignant syndrome (NMS; Reports were poorly documents and in most of cases, patients were also receiving other drugs, so the role of methylphenidate is unclear).
Not known: cerebrovascular disorders* (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), grand mal convulsions*, migraine

Eye disorders
Uncommon: diplopia, blurred vision,
Rare: difficulties in visual accommodation, mydriasis, visual disturbance

Cardiac disorders*
Common: arrhythmia, tachycardia palpitations
Uncommon: chest pain
Rare: angina pectoris
Very rare: cardiac arrest, myocardial infarction
Not known: supraventricular tachycardia, bradycardia, ventricular extrasystoles, extrasystoles

Vascular disorders*
Common: hypertension
Uncommon:
Very rare: cerebral arteritis and/or occlusion, peripheral coldness, Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders
Common: cough, pharyngolaryngeal pain
Uncommon: dyspnoea

Gastrointestinal disorders
Common: abdominal pain, diarrhoea, nausea, stomach discomfort, and vomiting – *{for inclusion in PL for non-modified release formulations :}* "these usually occur at the beginning of treatment and may be alleviated by concomitant food intake", Dry mouth.
Uncommon: constipation

Hepatobiliary disorders
Uncommon: hepatic enzyme elevations
Very rare: abnormal liver function, including hepatic coma

Skin and subcutaneous tissue disorders
Common: alopecia, pruritus, rash, urticaria
Uncommon: angioneurotic oedema, bullous conditions, exfoliative conditions
Rare: hyperhidrosis, macular rash, erythema
Very rare: erythema multiforme, exfoliative dermatitis, fixed drug eruption

Musculoskeletal, connective tissue and bone disorders
Common: arthralgia
Uncommon: myalgia, muscle twitching
Very rare: muscle cramps

Renal and urinary disorders
Uncommon: haematuria

Reproductive system and breast disorders
Rare: Gynaecomastia

General disorders and administration site conditions
Common: pyrexia, growth retardation during prolonged use in children*
Uncommon: chest pain, fatigue
Very rare: sudden cardiac death*
Not known: chest discomfort, hyperpyrexia

Investigations

Common: changes in blood pressure and heart rate (usually an increase)*****, weight decreased*****
Uncommon: cardiac murmur*****, hepatic enzyme increased
Very rare: blood alkaline phosphatase increased, blood bilirubin increased, platelet count decreased, white blood count abnormal

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

…[ ]…

Annex 4.2

European Commission Decision – Annex IV

ANNEX IV

CONDITIONS OF THE MARKETING AUTHORISATION

CONDITIONS OF THE MARKETING AUTHORISATIONS

National Competent Authorities, coordinated by the Reference Member State where applicable, shall ensure that the following conditions are fulfilled by the Marketing Authorisation Holders:

Product Information

Package Leaflet
The MAHs should harmonise the relevant wording of the Package Leaflet by reflecting the changes proposed in the SPC. The PL wording agreed by the CHMP should be revised to improve patient readability, and will then be user-tested.

Cardiovascular and Cerebrovascular effects

Study designed to:

1) assess the relationship between use of medications for ADHD and the risk of serious cardiovascular disease in children and youth, aged 2-24 years;
2) assess the relationship between use of medications for ADHD and the risk of serious cardiovascular disease in adults, aged 25-64 years; and,
3) perform additional analyses that are relevant to decision makers such as clinicians, state Medicaid programs, and parents/patients.

The MAHs will evaluate the final report of the study, when published, and will update the Core RMP, and where appropriate the Core SPC/PL, to reflect the findings.

Cytogenicity

Study CRIT124D2201 *"An open label, behavioural treatment controlled evaluation of the effects of extended release methylphenidate (Ritalin LA) on the frequency of cytogenetic abnormalities in children 6-12 years old with attention deficit hyperactivity disorder".* The Core RMP, and where appropriate the Core SPC/PL, should be updated to reflect the findings of this study.

Study NCT 00341029 "*Measurement of Cytogenetic Endpoints in Lymphocytes of Children Diagnosed With Attention Deficit/Hyperactivity Disorder (ADHD) and Treated With Methylphenidate or Adderall"*, carried out by US National Institute of Environmental Health Sciences in collaboration with FDA. The MAHs will evaluate the final report of the study, when published, and will update the RMP, and where appropriate the SPC/PL, to reflect the findings:

Growth, Development and Sexual Maturation

MTA Study. "*Effects of stimulant medication on growth in the MTA (Multimodal Treatment Study of ADHD)"* follow-up, carried out by the MTA Cooperative Group. The MAHs will evaluate the final report of the study, when published, and will update the RMP, and where appropriate the SPC/PL, to reflect the findings.

Study on sexual maturation: a 2-year, long-term, open-label, prospective investigator initiated study in the US on 150 adolescents (12-17 years) with ADHD, to determine whether treatment with methylphenidate will prevent smoking in this population. Although the study focuses on smoking prevention, Tanner staging examinations will occur every 6 months during the 2-year follow-up and will monitor each subject's pubertal development to demonstrate whether methylphenidate has any effect on adolescent growth and development compared to population norms. The MAHs will make available the final report of the study, when published, and will update the RMP, and where appropriate the SPC/PL, to reflect the findings.

Psychiatric effects

The MAHs will investigate the feasibility of carrying out a meta-analysis of the risk of suicidality associated with the use of methylphenidate in children and adolescents with ADHD on the basis of the clinical trial data of methylphenidate that is currently available to the MAHs.

If the analysis on the basis of the currently available data is deemed feasible, the MAHs will make the resources available to support the analysis and update the RMP to reflect its findings.

Long Term Use effects

The MAHs committed to provide a detailed feasibility assessment for a scientifically valid, well-designed and suitably powered long-term safety study to examine specific endpoints for the following outcomes:

i) adverse cognitive outcomes
ii) adverse psychiatric outcomes (e.g. mood disorders, hostility and psychotic disorders)

The MAHs will consider including predominantly EU-based data, and the feasibility assessment will also comment on what non-EU sources of data could be used as an alternative. If the feasibility assessment shows that a scientifically valid, well-designed and suitably powered study is viable, then the MAHs commit to provide a detailed protocol. The proposed follow-up duration of at least 5 years for individual subjects will be considered. Within the 5-year follow-up, particular emphasis will be placed on assessing the effects of a cumulative exposure of at least 18 months. Because this is a non-interventional study, the MAH's will have no control over actual prescribing practices. The proposed patient enrolment age will be as young as possible consistent with the age restrictions of the label (i.e. children aged 6 years or more). The preferred design would be a prospective, cohort study. The MAHs agree to evaluate suitable comparator groups.

Drug utilisation studies, including evaluation of Off-Label Use/ Abuse

The MAHs commit to provide all available retrospective data on an annual review basis for the next five years in all Member States where methylphenidate is used, to allow an evaluation of changes in usage over time. Where possible, measures of usage including variables such as information on total amount used, patient age, gender, indication dose, duration of use, treatment continuity, co-morbidities, concomitant medications, data on patterns of use, physician specialty will be used. This commitment will be reviewed after 5 years.

In the Member States that are covered by the IMS database, the MAHs will also evaluate off-label use of methylphenidate. The MAHs will also consider alternative methods for completing the review of usage (where possible) and off-label use in the Member States that are not currently covered by multi-national (EU-wide) databases such as IMS.

Educational tools
The MAHs will produce fully harmonised Risk Minimisation tools that contain all of the important information from the Clinical Particulars section of the Core SPC. :

- Physicians guide to prescribing
- Checklists for actions before prescribing, and for ongoing monitoring for prescribers and, if possible, carers

PSURs

The MAHs will harmonise the PSUR reporting schedule for methylphenidate-containing products and submit once yearly PSURs for their respective products for the next 3 years, after which the reporting frequency will be reviewed. The synchronisation of the PSUR submission will facilitate a common assessment and harmonised response by the National Competent Authorities on updates of the SPC / PL and RMP.

Risk Management Plans

The MAHs should include, in the core safety specification, the final core table of identified and potential risks as requested by the CHMP.

The MAHs should evaluate newly identified or potential risks, or new new/important information on existing identified or potential risks, in the RMP on an ongoing basis