Johnson & Johnson Pharmaceutical Research & Development,
a Division of Janssen-Cilag Ltd

Risk Management Plan
CONCERTA® (methylphenidate hydrochloride)

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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
DISC-IV	Diagnostic Interview Schedule for Children Version-IV
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
IR	immediate release
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
PPA	[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 (IR) 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 methylphenidate of up to 12 hours, a

PRODUCT DETAILS (CONTINUED)

Brief description of product (chemical class, mode of action etc) (Cont)	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. CONCERTA has additionally been authorised for use in adults (up to 65 years of age) with ADHD in a number of countries including the United States (US) (27 June 2008), Canada (15 April 2008), and Australia (21 January 2009).	
Indication(s)	CONCERTA is indicated as part of a comprehensive treatment programme for ADHD in children (over 6 years of age) when remedial measures along prove insufficient.	
Dosage	Dosage may be adjusted in 18 mg increments to a maximum of 54 mg/day. CONCERTA is 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 behavioural disorders in children or adolescents. 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 1 side in black ink Capsule-shaped grey tablet with "alza 27" printed on 1 side in black ink Capsule-shaped white tablet with "alza 36" printed on 1 side in black ink Capsule-shaped brownish-red tablet with "alza 54" printed on 1 side in black ink **Strengths** Available in 18-mg, 36-mg, and 54-mg tablet strengths. A 27-mg tablet strength is registered in the United Kingdom and authorised via mutual recognition in 14 other member states (Austria, Belgium, Finland, France, Germany, Greece, Iceland, Ireland, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden).	
Data lock point for EU Risk Management Plan (RMP)	Preclinical/clinical study/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, 31 Aug 2009, Jun 2010, and Sep 2010.	Version 3

PART I

1. SAFETY SPECIFICATION

The reference safety information for CONCERTA is provided in the Summary of Product Characteristics (SmPC) in 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), as part of the methylphenidate Article 31 referral, 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/m^2 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/m^2 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/m^2 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 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 clinical trials 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	Trial Number (references)	Trial 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	946/946[a]	5-17
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] Adult subjects (n=136) from C-99-018 were removed. Also, adults from C-99-018 were not included in the exposure or risk (descriptive statistics, clinical database) tables.

A limitation inherent to a clinical database is its limited number of patients studied. In total, 2,718 paediatric patients with ADHD have been studied, versus an estimated postmarketing exposure of 9.8 million patient years (Section 1.2.1.2).

The duration of exposure in controlled trials in paediatric patients was up to 4 weeks only, although the duration of open-label exposure was as long as 27 months, which is greater than the average treatment duration in clinical practice (Section 1.2.1.2). Certain postmarketing trials 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 trial exposure comes close to the naturalistic postmarketing exposure to the drug as covered by pharmacovigilance, while safety documentation in the trials is much more precise. Trial C-99-018 evaluated subjects in a community setting over an extended period of time (9 months). Trial 01-146 allowed doses up to 72 mg/day in adolescents.

Exposure to CONCERTA in the paediatric trials is presented by ethnic origin and gender in Table 6.

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

	Male		Female	
	Persons	**Person (years)**	**Persons**	**Person (years)**
CONCERTA (N=321)				
Black/African	17	0.8	4	0.1
White or Caucasian	213	8.1	54	2.4
Other/Unknown	26	1.0	7	0.3

The duration of exposure may include days on which subjects did not take medication.
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1.2.1.2. Exposure in All Clinical Trials Including Open Extensions

Exposure tables include the open-label Trials C–98–007-02, C-98-012, C–99-018, 01-146, 12-101, CON-CAN-1, CON–CAN–2, and C-2000-045 in addition to the double-blind trials mentioned in the previous section. A total of 2,718 subjects were exposed in all clinical paediatric trials.

Exposure to CONCERTA in all paediatric clinical trials is presented by duration in Table 7.

Table 7: Clinical Trial Exposure for All Clinical Trial Populations by Duration in Paediatric Trials

Duration of Exposure	**Persons**	**Person (years)**
Concerta (N=2718)		
Cumulative exposure < 1 months	977	47.2
Cumulative exposure < 3 months	1347	105.0
Cumulative exposure < 6 months	1584	189.3
Cumulative exposure < 12 months	2449	814.9
Cumulative exposure < 24 months	2685	1176.3
Cumulative exposure < 30 months	2718	1245.1

The duration of exposure may include days on which subjects did not take medication.
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Exposure to CONCERTA in all paediatric clinical trials is presented by dose in Table 8.

Table 8: Clinical Trial Exposure for All Clinical Trial Populations by Dose in Paediatric Trials

	Persons	**Person (years)**
Concerta (N=1864)		
18 mg	1075	175.1
27 mg	75	8.0
36 mg	1400	533.0
54 mg	963	470.5
72 mg	95	12.4

The duration of exposure may include days on which subjects did not take medication.
Length of exposure by dose is missing for 850 subjects from Trial 12-101 and 4 subjects from Trial 01-146.
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1.2.1. Exposure in Clinical Trials

1.2.1.1. Exposure in Randomised Blinded Trials

The controlled paediatric trials were C97-025, C-98-003, C-98–005, and 01-146.

Exposure to CONCERTA in the paediatric trials is presented by duration in Table 3.

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

Duration of Exposure	Persons	Person (years)
CONCERTA (N=321)		
Cumulative exposure < 2 weeks	213	5.1
Cumulative exposure < 4 weeks	321	12.7

The duration of exposure may include days on which subjects did not take medication.
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Exposure to CONCERTA in the paediatric trials is presented by dose in Table 4.

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

	Persons	Person (years)
CONCERTA (N=321)		
18 mg	68	3.2
36 mg	138	5.2
54 mg	82	3.2
72 mg	33	1.1

The duration of exposure may include days on which subjects did not take medication.
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Exposure to CONCERTA in the paediatric trials is presented by age group and gender in Table 5.

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

	Male		Female	
	Persons	Person (years)	Persons	Person (years)
CONCERTA (N=321)				
≤ 17	252	9.7	62	2.7
≥ 18	4	0.1	3	0.1

The duration of exposure may include days on which subjects did not take medication.
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Exposure to CONCERTA in all paediatric clinical trials is presented by age group and gender in Table 9.

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

	Male		Female	
	Persons	**Person (years)**	**Persons**	**Person (years)**
Concerta (N=2715)				
≤ 17	2131	1012.6	573	230.5
≥ 18	7	1.2	4	0.7

The duration of exposure may include days on which subjects did not take medication.
Age data was missing for 2 subjects and gender is missing for 1 subject.
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Exposure to CONCERTA in all paediatric clinical trials is presented by ethnic origin and gender in Table 10.

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

	Male		Female	
	Persons	**Person (years)**	**Persons**	**Person (years)**
Concerta (N=2610)				
Black/African	199	56.3	49	15.2
White or Caucasian	1675	826.5	474	196.4
Other/Unknown	173	72.7	40	11.7

The duration of exposure may include days on which subjects did not take medication.
Race data is missing for 108 subjects and gender is missing for 1 subject.
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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 IR 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 trials of CONCERTA in special populations in patients 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

1.3. Populations Not Studied in the Preauthorisation Phase

Tables 16.1 and 16.2 summarise the populations not studied in the preauthorisation phase.

Table 16.1: Important Exclusion Criteria Across Paediatric Trials[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 trial)[c]

Adult subjects (The upper limit for most trials was 12 to 18 years; C-98-018 included adults up to 66 years; however, adult subjects were removed from the paediatric tables) [SmPC (Annex 2)]

Adolescent women of either childbearing potential (after they reached menarche – early trials) or adolescent or adult women who were pregnant or nursing (later trials) [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 Paediatric Trials [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 trial)[c] (Continued)
Medications in addition to methylphenidate for ADHD during the trial (implied, if not specifically listed, in most trials). Trial 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 (Trial 98-018)
Monoamine oxidase inhibitor or who had taken a monoamine oxidase inhibitor in the 14 days before initiation of trial 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 trial 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 trials listed, unless otherwise specified.

[b] Exclusion criteria related to trial 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 trial; and subjects who were known to be non-responders to methylphenidate.

[c] Trials (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=946, 5-17 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 Paediatric Trials[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 trial)[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 trial period – C-2000-045)

[a] The following minor exclusion criteria not included above: criteria regarding participation in previous trials (C-98-005); exclusion due to family members in trial (C-98-005, 01-146); previous trial participation (01-146, CON-CAN-1); related to those persons involved in trial 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] Trials (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=946, 5-17 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. Missing Information on Long-Term Effects of CONCERTA

1.3.1.1. Long-Term Cardiovascular Effects

Currently available long-term safety data for cardiovascular effects specifically arrhythmias, sudden death, and ischaemic cardiac events are not complete and do not extensively characterise these important potential risks.

1.3.1.2. Long-Term Cerebrovascular Effects

Currently available long-term safety data for cerebrovascular effects are not complete and do not extensively characterise this important potential risk.

1.3.1.3. Long-Term Psychiatric Effects

1.3.1.3.1. Psychiatric Effects and Attention-Deficit/Hyperactivity Disorder

It is well established that ADHD co-occurs with other psychiatric disorders, including disruptive behavioural disorders such as oppositional defiant disorder, conduct disorder; and mood disorders such as depression and bipolar disorder; and anxiety disorders (Spencer 2007). In both children and adults diagnosed with ADHD, the very high level of associated psychiatric comorbidity puts those with "pure" ADHD (ie, ADHD only) in a

distinct minority. For example, the Multi-Modal Treatment Study of Children with ADHD (MTA) conducted in the US and involving 579 children aged 7 to 10 years assessed psychiatric comorbidities including mood, anxiety, and disruptive behavioural disorders and concluded that fewer than one-third (31.8%) of patients were diagnosed with only ADHD (Jensen 2001).

Studies have shown that oppositional defiant disorder and ADHD co-occur in between 40% and 60% of all cases (Elia 2008, Wilens 2002), and that a substantial number of those will later develop conduct disorder in adolescence (Faraone 1997b, Biederman 1991). The MTA study including 579 children with ADHD found that 14.0% had a mood/anxiety disorder, 29.5% had oppositional defiant disorder or conduct disorder, and 24.7% had a mood/anxiety disorder plus oppositional defiant disorder or conduct disorder (Jensen 2001). This high level of comorbidity has been confirmed in culturally and regionally diverse epidemiologic samples as well as in clinical samples and is preceding pharmacological treatment (Biederman 1991, Rhode 2005, Ralston 2004, Steinhausen 2006).

Minor depression was found in 21.6% of 342 children and adolescents with ADHD (Elia 2008). In a study of 140 children with ADHD, the prevalence of comorbid major depression was 29% and antisocial disorders, such as conduct disorder, occurred in 11% of these children, both significantly more prevalent than in children without ADHD (Spencer 2007, Biederman 1996). Bipolar disorder was reported in 26% of 165 preschool children with ADHD, and in 18% of 381 school age children with ADHD by Wilens, et al (2002) in a study of children referred for psychiatric evaluation at a US site.

Anxiety disorder has been found to co-exist in up to about 25% of cases in epidemiological and clinical samples (Biederman 1991). Generalised anxiety disorder was found in 15.2% of 342 children with ADHD (Elia 2008). Conduct disorder together with ADHD has been reported to range from 30% to 50% (Biederman 1991). In a large study conducted in 10 European countries it was shown that ADHD is associated with multiple co-existing psychiatric problems, behavioral problems, poorer psychosocial functioning, and had important clinical consequences in terms of greater severity of ADHD (Ralston 2004, Steinhausen 2006).

1.3.1.3.2. Previous Studies Investigating Potential Long-Term Effects of Methylphenidate Exposure on Psychiatric Outcomes

Seven studies that provide evidence regarding the long-term effects of methylphenidate use on psychiatric outcomes in children were identified through a literature search. Six observational studies were conducted in the US (Molina 2009, Mannuzza 2008, Hechtmann 2004, Wilens 2003b, Gadow 1999, Charles 1979) and one observational

study in Canada (Cherland and Fitzpatrick, 1999). Limitations of the published studies include: lack of a comparator group not exposed to methylphenidate (Hechtmann 2004, Wilens 2003b, Cherland and Fitzpatrick 1999, Gadow 1999), relatively small numbers of subjects (Hechtmann 2004, Gadow 1999, Charles 1979), and/or limited follow-up time; only Molina, et al (2009) had a follow-up time of more than 5 years. It has to be considered that the study of Molina and colleagues (2009) started with a fixed randomised schedule over 14 months and, therefore, cannot be considered to be a purely observational study.

Despite their limitations, these studies consistently show no evidence of worsening of psychiatric symptoms during treatment with methylphenidate. In contrast, they even point in the direction of an improvement of behavioural symptoms over time. This lends further support to a positive benefit-risk assessment of long-term treatment of children and adolescents with ADHD with methylphenidate under conditions of routine clinical care.

The recent publication by Molina, et al (2009) extends the results of the prospective MTA study from the previously reported 3-year data to include assessments at 6 and 8 years from the first exposure to methylphenidate. Children were randomly assigned in an open-label, controlled study to receive 1 of 4 treatment approaches for 14 months, and thereafter were basically treated according to routine clinical practice without fixed assignment. The results of the 8-year follow up evaluation suggest that there may be a beneficial effect on the course of comorbid psychiatric disorders over time. In addition, although given the limitations of the study with strict treatment approaches for the first 14 months only, it might be difficult to conclude that the beneficial effects seen years later in the study is entirely due to methylphenidate treatment. However, the data available are strongly supportive for the absence of harm due to methylphenidate treatment. In addition, treatment response was not influenced by presence of psychiatric co-morbid conditions at baseline.

Also, a prospective observational follow-up study by Biederman et al (2008) presented findings that revealed no evidence that stimulant treatment is associated with the risk for subsequent substance use in children and adolescents when they reach young adulthood.

In summary, the results of the long-term observational data are in line with the patterns known from clinical trials and substantiate the absence of an adverse psychiatric outcome of methylphenidate treatment and support a positive benefit risk assessment of treatment in children with ADHD.

1.3.2. 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.

1.3.3. Adult and Geriatric Patients

There is no approval in the EU for use of CONCERTA in the adult population. However, 3 placebo-controlled trials (1 trial included an open-label extension) and 3 open-label trials (1 trial included a randomised withdrawal phase) in adults with ADHD have been completed. One additional trial (C-99-018) in the paediatric submission included adult subjects up to, and including, the age of 65 years.

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

1.3.4. 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.

1.3.5. 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.

1.3.6. 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 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 of the SmPC.

1.3.7. 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.

1.3.8. Populations With Genetic Polymorphism

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

1.3.9. Patients With Cardiovascular Risk Factors

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

1.3.10. Effect of Gender

Of the 2,715 patients in paediatric clinical trials of CONCERTA where gender and age were collected, 78.7% were male and 21.3% were female (Table 9). No important differences in the safety profile of CONCERTA between male and female patients were observed.

1.3.11. Effect of Ethnicity

Of the 2,610 patients in paediatric clinical trials of CONCERTA where ethnicity was collected, 82.3% were white, 9.5% were black or African-American, and 8.2% 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 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 tablet strength is registered in the United Kingdom and authorised via mutual recognition in 14 other member states (Austria, Belgium, Finland, France, Germany, Greece, Iceland, Ireland, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden). 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), and Australia (21 January 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 MAHs 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).

This RMP update addresses the PSUR Reference Member State's (P-RMS, MHRA) RMP Final Assessment Report of the Core Risk Management Plan (RMP-FAR) for methylphenidate issued on 23 September 2010.

A number of pharmacovigilance and risk minimisation activities are currently being conducted by the Company in order to fulfil the conditions of its Marketing Authorisations as adopted by the CHMP (Annex IV of the EC decision; Annex 4). Details regarding the additional pharmacovigilance activities (ie, Evaluation of cytogenicity reports, MTA follow-up, and the FDA/AHRQ/Vanderbilt study; plans for

conduct of the meta-analysis for suicidality, the drug utilisation study, and the evaluation of the feasibility of a long-term safety study) are provided in Table 25. Details regarding the additional risk minimisation activity, the educational tool, are provided in Table 28. Routine risk minimization actitivites include a recent update to Sections 4.8 of the SmPC (Annex 2) to make minor amendments to the frequencies of several ADRs. Assessment of the 2009 PSUR work-share procedure for methylphenidate, ongoing at the time of writing this RMP, proposed changes to the core safety profile for methylphenidate at Sections 4.4 and 4.9. Also, at the request of the EU Member States, the Company (with the other MAHs) harmonised the PSUR reporting schedule for methylphenidate-containing products in 2009. The data lock point for all EU methylphenidate PSURs including CONCERTA is 10 October. PSURs will be submitted annually through 2010.

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 Version 2 and in Version 3 (this document) 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. The Company also conducted a review of the risks for CONCERTA in adults with ADHD 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 listed in the CHMP's Referral 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 list of identified and potential risks were also modified per the P-RMS's (MHRA) Assessment Report dated 23 September 2010: aggression and depression were designated as identified risks (formerly potential risks) and ischaemic cardiac events was designated a new potential risk (not previously included in the CONCERTA RMP).

The identified risks listed below represent the current list of identified risks in the Core Table of Risks for methylphenidate. Aggression and depression were designated as identified risks (formerly potential risks) per the recent Rapporteur's Assessment Report.

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

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 clinical trials and postmarketing surveillance. These identified risks are characterised in Tables 17.1 to 17.9. Postmarketing data is only provided for those terms not identified as ADRs from the CONCERTA clinical trials database.

The potential risks listed below represent the current list of potential risks in the Core Table of Risks for methylphenidate. No additional potential risks are proposed, other than Ischaemic cardiac events per the recent Rapporteur's Assessment Report.

- Migraine
- Repetitive behaviours
- QT prolongation
- Cyanosis
- Arrhythmias
- Sudden death
- Ischaemic cardiac events
- Cerebrovascular disorders

- Hostility
- 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

Of these potential risks, a causal relationship with CONCERTA was established for Tics. The potential risks are characterised in Tables 18.1 to 18.21. Postmarketing data are provided for those terms not identified as ADRs from the CONCERTA clinical trials database.

As requested in the P-RMS's (MHRA) Assessment Report dated 23 September 2010, figures are provided for select identified and potential risks that display the onset and duration of the respective risk based on data from clinical trials of 3 months or greater duration.

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 discussed in Section 1.3.1 (including long-term cardiovascular, cerebrovascular, and psychiatric risks) and 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.

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

Table 17.1: Important Identified Risk: Hypertension

Identified Risk: Hypertension*	**All Randomised, Blinded Trials Population (N=321) N (%)**	**All Clinical Trials Population (N=2718) N (%)**
Frequency**		
Concerta	1 (0.3)	19 (0.7)
vs	Vs	
Placebo (N=318)	0 (0.0)	
Odds Ratio		
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	1
Discontinued Treatment	0	4
Resolved/Recovered/Recovered From AE	1	8
Recovered With Residual Effects	0	1
Continuing/Not Yet Recovered	0	3
Severity****		
Mild	0	17
Moderate	1	1
Severe	0	1

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).
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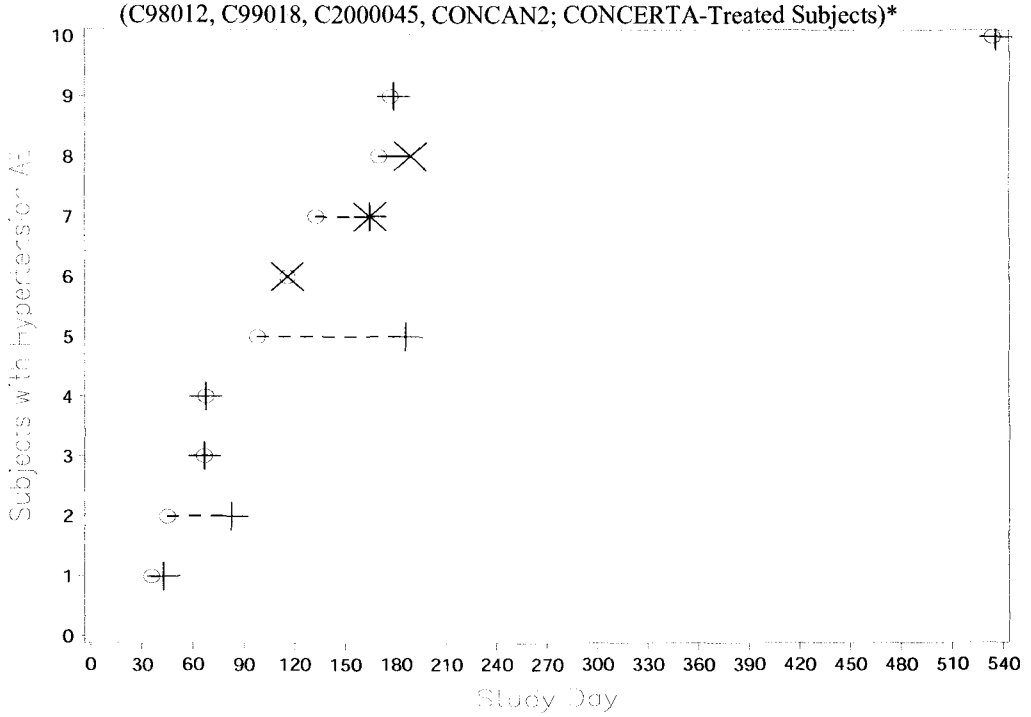
On the basis of the review of aggregate safety data from clinical trials of CONCERTA, a causal relationship was established for Hypertension and Blood pressure increased. A causal relationship was not established for any other adverse event that may be relevant for this important identified risk.

(Continued)

Table 17.1: Important Identified Risk: Hypertension (Continued)

Onset and Duration of Hypertension: Open-Label Trials of at Least 3 Months Duration (C98012, C99018, C2000045, CONCAN2; CONCERTA-Treated Subjects)*



Day	0	30	60	90	120	150	180	210	240
N (%)	1583 (100)	1484 (94)	1386 (88)	1308 (83)	1255 (79)	1232 (78)	1152 (73)	1070 (68)	1034 (65)

Day	270	300	330	360	390	420	450	480	510	540
N	809 (51)	396 (25)	345 (22)	296 (19)	274 (17)	269 (17)	265 (17)	261 (16)	256 (16)	252 (16)

* For Trial C2000045, only subjects who remained in the trial beyond 21 days and who consequently could have been exposed to trial drug for a period up to 12 months were included in the analysis.

Mild
Moderate
Severe
\- Persisting
\+ Resolved
X Drug Withdrawn

(Continued)

Table 17.1: Important Identified Risk: Hypertension (Continued)

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).
Background Incidence /Prevalence	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%. One study showed that more than one-fourth of the world's adult population (totalling nearly 1 billion) had hypertension in 2000, and that this proportion is projected to increase to 29% (1.56 billion) by 2025 (Kearney 2005). There have been no known published reports showing an increased prevalence of hypertension in children, adolescents, or adults diagnosed with ADHD.
Risk Groups or Risk Factors	In assessing the background risk (independent of drug) for cardiovascular events, including hypertension, it is important to identify whether subjects 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 patients 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.

(Continued)

Table 17.1: Important Identified Risk: Hypertension (Continued)

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 patients with severe hypertension according to EU SmPC.
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 states that the report of the FDA/AHRQ/Vanderbilt University study should be evaluated, when available; Table 25 provides details regarding this pharmacovigilance activity. Methylphenidate is contraindicated in patients with severe hypertension (Annex 2, SmPC, Section 4.3). 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 (SmPC, Section 4.3).

(Continued)

Table 17.1: Important Identified Risk: Hypertension (Continued)

Regulatory Action Taken (Continued)	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." Also, in Section 4.4 of the SmPC, under cardiovascular status, the text notes that "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." Hypertension is listed as an ADR in Section 4.8 of the EU SmPC based on clinical trial data in paediatric patients; the frequency of common is based on clinical trial data in paediatric patients and postmarketing spontaneous reports in both paediatric and adult patients.
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. Kearney PM (2005), Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet 2005;365(9455):217-223.

Table 17.2: Important Identified Risk: Tachycardia

Identified Risk: Tachycardia*	**All Randomised, Blinded Trials Population (N=321) N (%)**	**All Clinical Trials Population (N=2718) N (%)**
Frequency**		
Concerta	0	7 (0.3)
vs		
Placebo (N=318)	0	
Odds Ratio		
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	1
Resolved/Recovered/Recovered From AE	0	5
Recovered With Residual Effects	0	0
Continuing/Not Yet Recovered	0	2
Severity****		
Mild	0	2
Moderate	0	4
Severe	0	1

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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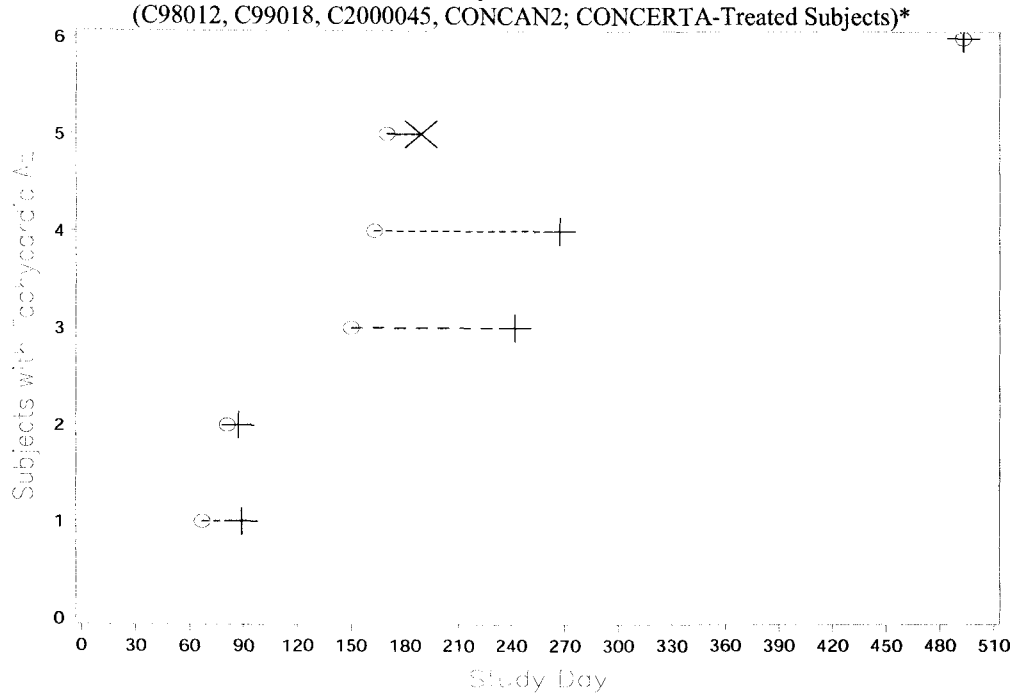
On the basis of the review of aggregate safety data from clinical trials of CONCERTA, a causal relationship was established for Tachycardia. A causal relationship was not established for any other adverse event that may be relevant for this important identified risk.

(Continued)

Table 17.2: Important Identified Risk: Tachycardia (Continued)

Onset and Duration of Tachycardia: Open-Label Trials of at Least 3 Months Duration (C98012, C99018, C2000045, CONCAN2; CONCERTA-Treated Subjects)*



Day	0	30	60	90	120	150	180	210	240
N (%)	1583 (100)	1484 (94)	1386 (88)	1308 (83)	1255 (79)	1232 (78)	1152 (73)	1070 (68)	1034 (65)

Day	270	300	330	360	390	420	450	480	510
N	809 (51)	396 (25)	345 (22)	296 (19)	274 (17)	269 (17)	265 (17)	261 (16)	256 (16)

* For Trial C2000045, only subjects who remained in the trial beyond 21 days and who consequently could have been exposed to trial drug for a period up to 12 months were included in the analysis.



(Continued)

Table 17.2: Important Identified Risk: Tachycardia (Continued)

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 comorbid 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.
Background Incidence/ Prevalence	There have been no published reports of an association between arrhythmias and ADHD. 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 1999). The incidence of clinically significant arrhythmias in these patients was reported as 5.7 per 100,000 ED visits. Atrial tachyarrhythmias were the most common presentation in this study population. A community-based study in the US reported the prevalence of paroxysmal supraventricular tachycardia per 1,000 persons as follows (males vs females, and both sexes, respectively): less than 65 years, 0.95 versus 2.37, 1.65; 65 years or over, 9.69 versus 3.65, 6.16; and all ages, 1.94 versus 2.56, 2.25 (Orejarena, 1998).
Risk Group or Risk Factors	In assessing the background risk (independent of drug) for cardiovascular events, it is important to identify whether patients 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. The rate of tachycardia among adults with ADHD has not been described in the published literature.
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 prescribers. 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 patients 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	Annex IV of the May 2009 EC Decision states that the report of the FDA/AHRQ/Vanderbilt University study should be evaluated, when available; Table 25 provides details regarding this pharmacovigilance activity. The EU SmPC for CONCERTA (Annex 2) contraindicates use in patients with pre-existing cardiovascular disorders such as angina and potentially life-threatening 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 based on clinical trial data in paediatric patients with a frequency of common based on clinical trial data in paediatric patients and postmarketing spontaneous reports in both paediatric and adult patients.
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. Orejarena LA (1998), Vidaillet H Jr, DeStefano F, Nordstrom DL, Vierkant RA, Smith PN, Hayes JJ. Paroxysmal supraventricular tachycardia in the general population. J Am Coll Cardiol 1998;31(1):150-157. 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

Identified Risk: Raynaud's Phenomenon*	**All Randomised, Blinded Trials Population (N=321) N (%)**	**All Clinical Trials Population (N=2718) N (%)**
Frequency**		
Concerta	0	1 (0.0)
vs		
Placebo (N=318)	0	
Odds Ratio		
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	0
Resolved/Recovered/Recovered From AE	0	1
Recovered With Residual Effects	0	0
Continuing/Not Yet Recovered	0	0
Severity****		
Mild	0	0
Moderate	0	1
Severe	0	0

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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

(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 Terms	**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 patients taking methylphenidate. Raynaud's phenomenon is a drug induced vascular effect on the digits and is reversible when the drug is discontinued.

(Continued)

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

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). Recent studies aiming to determine Raynaud's phenomenon prevalence showed variable data depending on the diagnostic criteria, the survey technique (sampling design and interview and examination procedures), and the characteristics of the studied population in various geographical regions. Thus, the prevalence of Raynaud's phenomenon estimated in different studies fluctuates between 4% and 20%. Among women the frequency of Raynaud's phenomenon varies between 4% and 15% to 20%. There is also variance in the prevalence of Raynaud's phenomenon in men, although it is found with lower frequency among men compared with women (Voulgari 2000).

(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, adolescents, or adults 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 was a single report of Raynaud's phenomenon in the clinical trials database. A recent report of "possible Raynaud's" in both the hands and feet of a teenage boy occurred after the dosage of CONCERTA was increased from 54 to 90 mg/day over a 3-month period (Yu 2010). 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, per postmarketing data, and Peripheral coldness, per the Article 31 referral, are listed as ADRs in Section 4.8 of the CONCERTA EU SmPC with a frequency of very rare based on clinical trial data in paediatric patients and postmarketing spontaneous reports in both paediatric and adult patients.
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. Voulgari PV (2000), Alamanos Y, Papazisi D, Christou K, Papanikolaou C, Drosos AA. Prevalence of Raynaud's phenomenon in a healthy Greek population. Ann Rheum Dis 2000;59(3):206-210. Yu ZJ (2010), Parker-Kotler C, Tran K, Weller RA, Weller EB. Peripheral vasculopathy associated with psychostimulant treatment in children with attention-deficit/hyperactivity disorder. Curr Psychiatry Rep 2010;12:111–115.

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

Identified Risk: Hallucinations (Auditory, Skin Sensation, Visual Disturbance)*	**All Randomised, Blinded Trials Population (N=321) N (%)**	**All Clinical Trials Population (N=2718) N (%)**
Frequency**		
Concerta	0	3 (0.1)
vs		
Placebo (N=318)	0	
Odds Ratio		
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	1
Discontinued Treatment	0	1
Resolved/Recovered/Recovered From AE	0	2
Recovered With Residual Effects	0	0
Continuing/Not Yet Recovered	0	1
Severity****		
Mild	0	1
Moderate	0	2
Severe	0	0

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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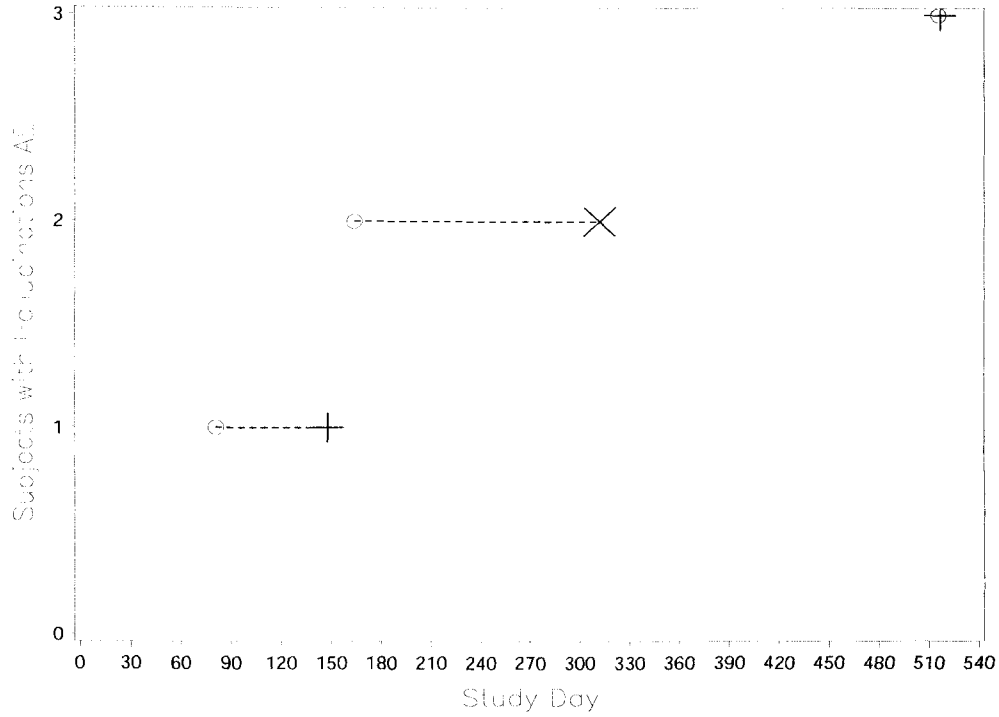
On the basis of the review of aggregate safety data from clinical trials of CONCERTA, a causal relationship was not established for any of the adverse events that may be relevant for this important identified risk.

(Continued)

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

Onset and Duration of Hallucinations: Open-Label Trials of at Least 3 Months Duration (C98012, C99018, C2000045, CONCAN2; CONCERTA-Treated Subjects)*



Day	0	30	60	90	120	150	180	210	240
N (%)	1583 (100)	1484 (94)	1386 (88)	1308 (83)	1255 (79)	1232 (78)	1152 (73)	1070 (68)	1034 (65)

Day	270	300	330	360	390	420	450	480	510	540
N	809 (51)	396 (25)	345 (22)	296 (19)	274 (17)	269 (17)	265 (17)	261 (16)	256 (16)	252 (16)

* For Trial C2000045, only subjects who remained in the trial beyond 21 days and who consequently could have been exposed to trial drug for a period up to 12 months were included in the analysis.

(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 events in patients 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-year-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 comorbid psychiatric disorders (oppositional-defiant disorder, major depression, anxiety, mania, psychosis). The rate of hallucinations among adults with ADHD has not been described in the published literature.
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 comorbid 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 patients 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 consideration of discontinuation of treatment with methylphenidate should treatment-emergent psychotic symptoms (visual/tactile/auditory hallucinations) occur. 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. Hallucination is listed as a single ADR, based on postmarketing data, in Section 4.8 of the CONCERTA EU SmPC with a frequency of uncommon based on clinical trial data in paediatric patients and postmarketing spontaneous reports in both paediatric and adult patients.
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

Identified Risk: Psychosis/Mania*	**All Randomised, Blinded Trials Population (N=321) N (%)**	**All Clinical Trials Population (N=2718) N (%)**
Frequency**		
Concerta	1 (0.3)	76 (2.8)
vs	Vs	
Placebo (N=318)	0 (0.0)	
Odds Ratio		
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	5
Discontinued Treatment	0	15
Resolved/Recovered/Recovered From AE	1	45
Recovered With Residual Effects	0	1
Continuing/Not Yet Recovered	0	25
Severity****		
Mild	0	32
Moderate	1	34
Severe	0	9

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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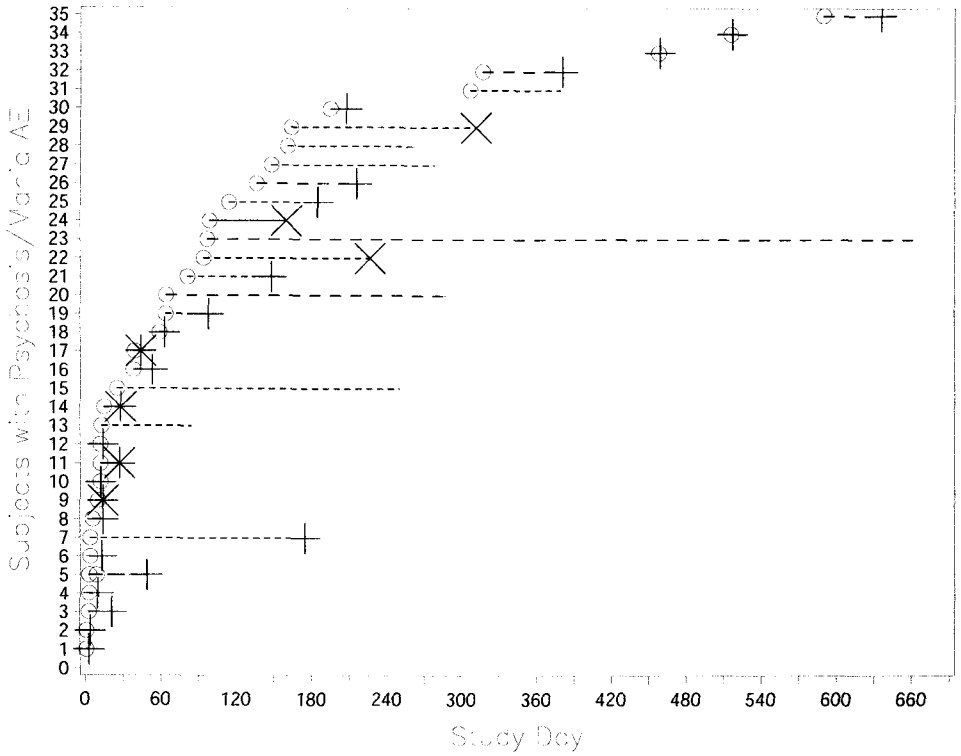
On the basis of the review of aggregate safety data from clinical trials of CONCERTA, a causal relationship was not established for any of the adverse events that may be relevant for this important identified risk.

(Continued)

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

Onset and Duration of Psychosis/Mania: Open-Label Trials of at Least 3 Months Duration (C98012, C99018, C2000045, CONCAN2; CONCERTA-Treated Subjects)*



Day	0	30	60	90	120	150	180	210	240	270	300	330
N (%)	1583 (100)	1484 (94)	1386 (88)	1308 (83)	1255 (79)	1232 (78)	1152 (73)	1070 (68)	1034 (65)	809 (51)	396 (25)	345 (22)

Day	360	390	420	450	480	510	540	570	600	630	660	690
N	296 (19)	274 (17)	269 (17)	265 (17)	261 (16)	256 (16)	252 (16)	244 (15)	242 (15)	214 (14)	132 (8)	86 (5)

* For Trial C2000045, only subjects who remained in the trial beyond 21 days and who consequently could have been exposed to trial drug for a period up to 12 months were included in the analysis.

---------- Mild
---------- Moderate
———— Severe
\- Persisting
\+ Resolved
X Drug Withdrawn

(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 patients 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 events in patients with ADHD with no previous history of psychosis/mania as a mental illness. These psychotic and manic symptoms 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-year-old adolescents in the general paediatric population had either delusional beliefs or hallucinatory experiences. A prospective 8-year follow-up of adolescents (mean age 16.8 [SD 1.0] years) initially enrolled as children in the MTA study found too few reports of psychosis and mania (and hypomania) for reliable statistical analysis; prevalence (≥1 of these conditions) was 2.0% for those receiving medication management, 0.9% for those receiving behavioural therapy, and 2.9% for those receiving combined management (Molina 2009).

(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 comorbid psychiatric disorders (oppositional-defiant disorder, major depression, anxiety, mania, psychosis). The rate of psychosis/mania among adults with ADHD has not been described in the published literature.
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 comorbid 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 in patients 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 disorders is included in Section 4.2. Posology and method of administration. Psychotic disorders is listed as an ADR in Section 4.8 of the EU SmPC. (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 listed as an ADR in Section 4.8 of the SmPC based on postmarketing data. The frequencies of uncommon and rare assigned to Psychotic disorders and Mania, respectively, are based on clinical trial data in paediatric patients and postmarketing spontaneous reports in both paediatric and adult patients.

(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). Molina BSG (2009), Hinshaw SP, Swanson JM, et al. MTA at 8 years: Prospective follow-up of children treated for combined-type ADHD in a multisite study. J Am Acad Child Adolesc Psychiatry 2009;48(5):484-500. 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

Identified Risk: Anorexia*	**All Randomised, Blinded Trials Population (N=321) N (%)**	**All Clinical Trials Population (N=2718) N (%)**
Frequency**		
Concerta	6 (1.9)	293 (10.8)
vs	Vs	
Placebo (N=318)	0 (0.0)	
Odds Ratio		
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	26
Resolved/Recovered/Recovered From AE	2	131
Recovered With Residual Effects	0	5
Continuing/Not Yet Recovered	4	121
Severity****		
Mild	5	176
Moderate	1	107
Severe	0	6

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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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. Among adult women with ADHD, in one study 85% of 126 women with ADHD reported having a history of anorexia. Rates among men were not statistically different from a non-ADHD control group (Cumyn 2009).
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.

(Continued)

Table 17.6: Important Identified Risk: Anorexia (Continued)

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 and Decreased appetite are listed as ADRs in Section 4.8 of the EU SmPC based on clinical trial data in paediatric patients; the frequency of common based on clinical trial data in paediatric patients and postmarketing spontaneous reports in both paediatric and adult patients.
Evidence Source	Cumyn L (2009), French L, Hechtman L. Comorbidity in adults with attention-deficit hyperactivity disorder. Can J Psychiatry 2009;54(10):673-683. 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

Identified Risk: Decreased Rate of Growth*	**All Randomized, Blinded Trials Population (N=321) N (%)**	**All Clinical Trials Population (N=2718) N (%)**
Frequency**		
Concerta	0	0
vs		
Placebo (N=318)	0	
Odds Ratio		
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	0
Resolved/Recovered/Recovered From AE	0	0
Recovered With Residual Effects	0	0
Continuing/Not Yet Recovered	0	0
Severity****		
Mild	0	0
Moderate	0	0
Severe	0	0

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of Concerta to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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

(Continued)

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

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.

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). Data from the 3-year follow up on the Multimodal Treatment Study of ADHD (MTA) study indicate that there is some risk for children and adolescents taking methylphenidate; although it is not yet known if that represents a reversible issue at a particular age or if it affects final height (Swanson 2007). Data from a 10-year prospective study of height and weight in children with ADHD (approximately 22 years of age at follow up) found no evidence that ADHD was associated with differential trajectories of height over time or differences at follow-up in any growth outcome, as well as no evidence that stimulant treatment was associated with differences in growth (Biederman 2010).
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).

(Continued)

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

Background Incidence / Prevalence (Continued)	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. At entry to the MTA study, the height and weight of stimulant-naive children at baseline was greater than expected based on population norms. At the 36-month assessment, the stimulant-naive control group that did not receive medication was taller and heavier than population norms (z height: 0.541; z weight: 0.765), while the 2 medicated groups that received about 1,000 days of treatment over 3 years of the MTA follow-up were slightly above or below expected relative size based on norms (newly medicated: z height 0.073 and z weight 0.293; consistently medicated: z height -0.120 and z weight 0.156). The study observed that those children and adolescents left untreated had a greater growth rate over the 36-month period compared to that of the classmate control group or the expectation based on population norms. Subjects who received treatment showed stimulant-related decreases in growth rates for up to 3 years without evidence of growth rebound after discontinuation of stimulant medication within the 3-year period (Swanson 2007).
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).

(Continued)

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

Risk Groups or Risk Factors (Continued)	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 children and adolescents with ADHD (Jensen 2007). 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 body weight 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 normalisation 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 the May 2009 EC Decision states that follow-up reports from the MTA study and data from an investigator-initiated study (IIS, a 2-year smoking prevention study in adolescents) should be evaluated, when available; Table 25 provides details regarding this pharmacovigilance activity. 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 recorded 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 based on the Article 31 referral of methylphenidate-containing products with a frequency of common based on clinical trial data in paediatric patients and postmarketing spontaneous reports in both paediatric and adult patients.

(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). Biederman J (2010), Spencer TJ, Monuteaux MC, Faraone SV. A naturalistic 10-year prospective study of height and weight in children with attention-deficit hyperactivity disorder grown up: sex and treatment effects. J Pediatr 2010;157:635-640. 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 17.8: Important Identified Risk: Aggression

Identified Risk: Aggression*	**All Randomised, Blinded Trials Population (N=321) N (%)**	**All Clinical Trials Population (N=2718) N (%)**
Frequency**		
Concerta	3 (0.9)	192 (7.1)
vs	Vs	
Placebo (N=318)	7 (2.2)	
Odds Ratio	0.4	
95% confidence interval***	0.1 to 1.9	
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	9
Discontinued Treatment	0	50
Resolved/Recovered/Recovered From AE	0	119
Recovered With Residual Effects	0	3
Continuing/Not Yet Recovered	1	51
Severity****		
Mild	1	60
Moderate	2	108
Severe	0	21

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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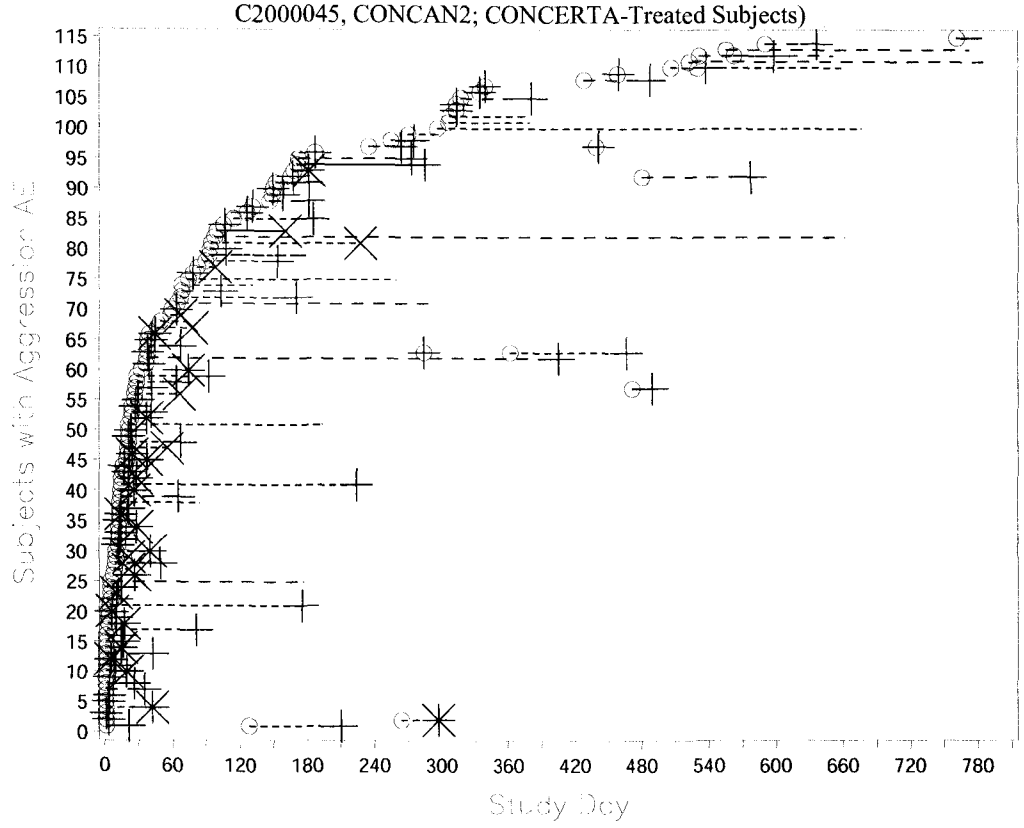
On the basis of the review of aggregate safety data from clinical trials of CONCERTA, a causal relationship was established for Anger. A causal relationship was not established for any other adverse event that may be relevant for this important potential risk.

(Continued)

Table 17.8: Important Identified Risk: Aggression (Continued)

Onset and Duration of Aggression: Open-Label Trials of at Least 3 Months (C98012, C99018, C2000045, CONCAN2; CONCERTA-Treated Subjects)



Day	0	30	60	90	120	150	180	210	240	270	300	330	360
N (%)	1583 (100)	1484 (94)	1386 (88)	1308 (83)	1255 (79)	1232 (78)	1152 (73)	1070 (68)	1034 (65)	809 (51)	396 (25)	345 (22)	296 (19)

Day	390	420	450	480	510	540	570	600	630	660	690	720	750	780	810
N	274 (17)	269 (17)	265 (17)	261 (16)	256 (16)	252 (16)	244 (15)	242 (15)	214 (14)	132 (8)	86 (5)	60 (4)	37 (2)	17 (1)	10 (1)

* For Trial C2000045, only subjects who remained in the trial beyond 21 days and who consequently could have been exposed to trial drug for a period up to 12 months were included in the analysis.

---------- Mild
---------- Moderate
_____ Severe
\- Persisting
\+ Resolved
X Drug Withdrawn

(Continued)

Table 17.8: Important Identified Risk: Aggression (Continued)

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.

Nature of the Risk	Aggression is a common comorbid symptom in patients with ADHD. Nevertheless, underlying aggression can be exacerbated by methylphenidate treatment. Aggressive behaviour has also been reported in patients with ADHD with stimulant treatment, when previous aggressive behaviour did not exist.
Background Incidence/Prevalence	The incidence of psychiatric events in the population of children and adolescents ages 5 to 17 years is the first measure of the underlying background rate for a specific population of interest (paediatric/adolescent 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). 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). At baseline in the MTA study, 14.7% of children with ADHD suffered from conduct disorder. At the 14-month follow-up, the prevalence decreased to 7.2%, with no significant differences observed between treatment groups (Hechtman 2005). Similarly, at the 6-year follow up no significant differences were observed for mean scores of aggression and conduct based on DSM-IV symptoms of conduct disorder between treated or untreated groups (Molina 2009). Rates of aggression and hostility among adults with ADHD have not been described in the published literature.

(Continued)

Table 17.8: Important Identified Risk: Aggression (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 comorbid 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 comorbid 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, in children with ADHD relative to the general population of children (Guervara 2002). Rates of aggression among adults with ADHD have not been described in the published literature.
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.
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.

(Continued)

Table 17.8: Important Identified Risk: Aggression (Continued)

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). Anger, based on clinical trial data in paediatric patients, and Aggression, based on postmarketing data, are listed as ADRs in Section 4.8 of the EU SmPC; the frequencies of uncommon and common, respectively, are based on clinical trial data in paediatric patients and postmarketing spontaneous reports in both paediatric and adult patients.
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. Hechtman L (2005), Etcovitch J, Platt R, et al. Does multimodal treatment of ADHD decrease other diagnoses? Clin Neurosci Res 2005; 5(5): 273-282. Molina BSG (2009), Hinshaw SP, Swanson JM, et al. MTA at 8 years: Prospective follow-up of children treated for combined-type ADHD in a multisite study. J Am Acad Child Adolesc Psychiatry 2009;48(5):484-500. 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 17.9: Important Identified Risk: Depression

Identified Risk: Depression*	**All Randomised, Blinded Trials Population (N=321) N (%)**	**All Clinical Trials Population (N=2718) N (%)**
Frequency**		
Concerta	4 (1.2)	226 (8.3)
vs	Vs	
Placebo (N=318)	4 (1.3)	
Odds Ratio	1.0	
95% confidence interval***	0.2 to 5.4	
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	4
Discontinued Treatment	1	44
Resolved/Recovered/Recovered From AE	2	114
Recovered With Residual Effects	0	3
Continuing/Not Yet Recovered	1	87
Severity****		
Mild	3	108
Moderate	1	98
Severe	0	18

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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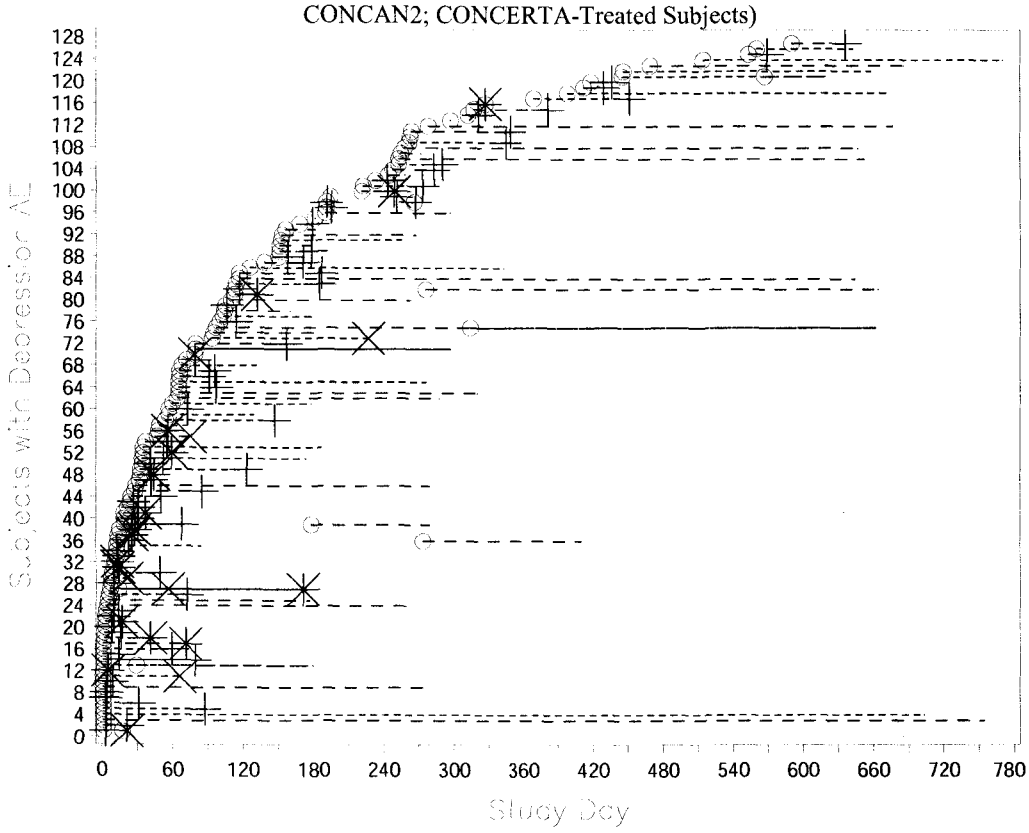
On the basis of the review of aggregate safety data from clinical trials of CONCERTA, a causal relationship was established for Depression. A causal relationship was not established for any other adverse event that may be relevant for this important potential risk.

(Continued)

Table 17.9: Important Identified Risk: Depression (Continued)

Onset and Duration of Depression: Open-Label Trials of at Least 3 Months (C98012, C99018, C2000045, CONCAN2; CONCERTA-Treated Subjects)



Day	0	30	60	90	120	150	180	210	240	270	300	330	360
N (%)	1583 (100)	1484 (94)	1386 (88)	1308 (83)	1255 (79)	1232 (78)	1152 (73)	1070 (68)	1034 (65)	809 (51)	396 (25)	345 (22)	296 (19)

Day	390	420	450	480	510	540	570	600	630	660	690	720	750	780
N	274 (17)	269 (17)	265 (17)	261 (16)	256 (16)	252 (16)	244 (15)	242 (15)	214 (14)	132 (8)	86 (5)	60 (4)	37 (2)	17 (1)

* For Trial C2000045, only subjects who remained in the trial beyond 21 days and who consequently could have been exposed to trial drug for a period up to 12 months were included in the analysis.

Mild
Moderate
Severe
\- Persisting
\+ Resolved
X Drug Withdrawn

(Continued)

Table 17.9: Important Identified Risk: Depression (Continued)

Nature of Risk	Patients with ADHD are known to have an increased prevalence of affective disorders, including major depression, compared with those without ADHD. The depressive symptoms observed in patients with ADHD being treated with methylphenidate are similar in nature and severity to the depressive symptoms observed in those 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. Patients 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.
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 2 conditions were found to have independent disease courses (Milberger 1995). This suggested that depression in children with ADHD 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). Among adults, the lifetime prevalence of severe depression was 36% in females and 27% in males with ADHD (128 subjects) compared with 4% to 6% among males and females without ADHD (Fishman 2007). These estimates were without regard to treatment status. At the 14-month follow up of the MTA study, there were no statistically significant differences of mood disorders among treatment groups (Hechtman 2005). At the 6-year follow-up of adolescents (mean age 14.9 [SD 1.0] years) in the MTA study, the incidence of Diagnostic Interview Schedule for Children Version-IV (DISC-IV) diagnoses of anxiety or depression were lower in those who received behavioural therapy (Beh, 4.3%) versus those who received medical management (MedMgt, 19.1%) and combined management (Comb, 16.4%) (Molina 2009). There were 4 statistically significant contrasts: Comb + MedMgt >Beh + usual community care (CC) (p=0.0050); Beh <CC (p=0.0064); Comb >Beh (p=0.0027); and Comb + Beh <MedMgt + CC (p=0.0132). However, the differences between groups were not statistically significant at the 8-year follow up.

(Continued)

Table 17.9: Important Identified Risk: Depression (Continued)

Risk Groups or Risk Factors	When assessing the background risk (independent of drug), depression in patients with ADHD 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 patients 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 patients with ADHD is not substantially higher than what is expected in an ADHD population. Based on the available evidence, no impact on public health of methylphenidate-induced depression is expected.
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). 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). 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, based on clinical trial data in paediatric patients, and Transient depressed mood, based on the Article 31 referral, are listed as ADRs in Section 4.8 of the EU SmPC; the frequencies of common and very rare, respectively, are based on clinical trial data in paediatric patients and postmarketing spontaneous reports in both paediatric and adult patients.

(Continued)

Table 17.9: Important Identified Risk: Depression (Continued)

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. Hechtman L (2005), Etcovitch J, Platt R, et al. Does multimodal treatment of ADHD decrease other diagnoses? Clin Neurosci Res 2005; 5(5): 273-282. 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. Molina BSG (2009), Hinshaw SP, Swanson JM, et al. MTA at 8 years: Prospective follow-up of children treated for combined-type ADHD in a multisite study. J Am Acad Child Adolesc Psychiatry 2009;48(5):484-500.

Table 18.1: Important Potential Risk: Migraine

Potential Risk: Migraine*	**All Randomised, Blinded Trials Population (N=321) N (%)**	**All Clinical Trials Population (N=2718) N (%)**
Frequency**		
Concerta	0	10 (0.4)
vs		
Placebo (N=318)	0	
Odds Ratio		
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	0
Resolved/Recovered/Recovered From AE	0	8
Recovered With Residual Effects	0	0
Continuing/Not Yet Recovered	0	2
Severity****		
Mild	0	1
Moderate	0	7
Severe	0	2

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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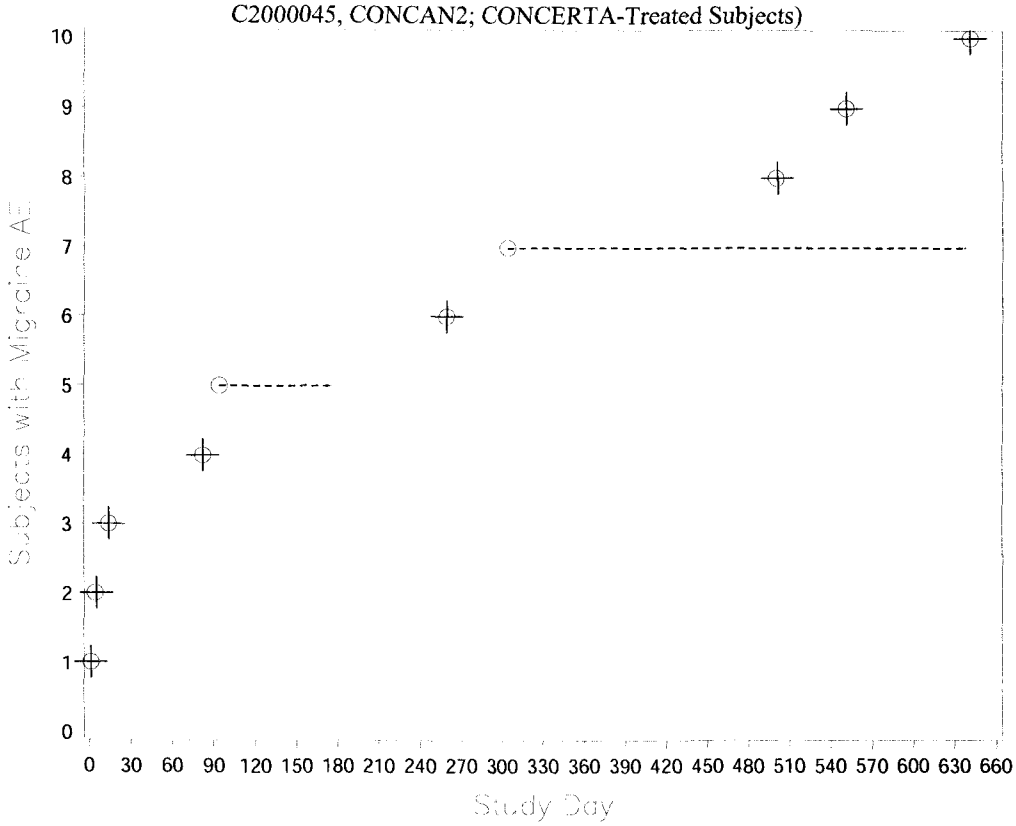
On the basis of the review of aggregate safety data from clinical trials of CONCERTA, a causal relationship was not established for any of the adverse events that may be relevant for this important potential risk.

(Continued)

Table 18.1: Important Potential Risk: Migraine (Continued)

Onset and Duration of Migraine: Open-Label Trials of at Least 3 Months (C98012, C99018, C2000045, CONCAN2; CONCERTA-Treated Subjects)



Day	0	30	60	90	120	150	180	210	240	270	300	330	360
N (%)	1583 (100)	1484 (94)	1386 (88)	1308 (83)	1255 (79)	1232 (78)	1152 (73)	1070 (68)	1034 (65)	809 (51)	396 (25)	345 (22)	296 (19)

Day	390	420	450	480	510	540	570	600	630	660
N	274 (17)	269 (17)	265 (17)	261 (16)	256 (16)	252 (16)	244 (15)	242 (15)	214 (14)	132 (8)

* For Trial C2000045, only subjects who remained in the trial beyond 21 days and who consequently could have been exposed to trial drug for a period up to 12 months were included in the analysis.

Mild
Moderate
Severe
\- Persisting
\+ Resolved
X Drug Withdrawn

(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. The American Migraine Prevalence and Prevention study estimates the 1-year prevalence of migraine as follows in females versus males, by age: ages 12 to 17 years, 6.4% versus 4.0%; ages 18 to 29 years, 17.3% versus 5%; ages 30 to 39 years, 24.4% versus 7.4%; ages 40 to 49 years, 22.2% versus 6.5%; ages 50 to 59 years, 16.0% versus 5.0%; and ages 60 and older, 5.0% versus 1.6% (Lipton 2007). ADHD was not identified as a co-occurring condition among migraine patients. A cross-sectional study of 1,856 children aged 5 to 11 years reported an overall prevalence of migraine of 3.8% and a prevalence of ADHD of 6.1%. The prevalence of ADHD was not statistically different by headache category. However, the prevalence of hyperactivity-impulsivity symptoms was 23.7% in children with migraine compared to 8.1% in children without headache. The authors conclude that migraine is not comorbid to ADHD; however, it may be comorbid to hyperactive-impulsive behaviours (Arruda 2010).

(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.) The frequency of not known assigned to Migraine is based on clinical trial data in paediatric patients and postmarketing spontaneous reports in both paediatric and adult patients.

(Continued)

Table 18.1: Important Potential Risk: Migraine (Continued)

Evidence Source	Arruda MA (2010), Guidetti V, Galli F, Albuquerque RC, Bigal ME. Migraine, tension-type headache, and attention-deficit/hyperactivity disorder in childhood: a population-based study. Postgrad Med. 2010; 122(5):18-26. 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. Lipton RB (2007), Bigal ME, Diamond M. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology 2007;68:343-349.

Table 18.2: Important Potential Risk: Repetitive Behaviours

Potential Risk: Repetitive Behaviours*	**All Randomised, Blinded Trials Population (N=321) N (%)**	**All Clinical Trials Population (N=2718) N (%)**
Frequency**		
Concerta	1 (0.3)	6 (0.2)
vs	Vs	
Placebo (N=318)	0 (0.0)	
Odds Ratio		
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	2
Resolved/Recovered/Recovered From AE	0	2
Recovered With Residual Effects	0	0
Continuing/Not Yet Recovered	0	3
Severity****		
Mild	0	4
Moderate	1	2
Severe	0	0

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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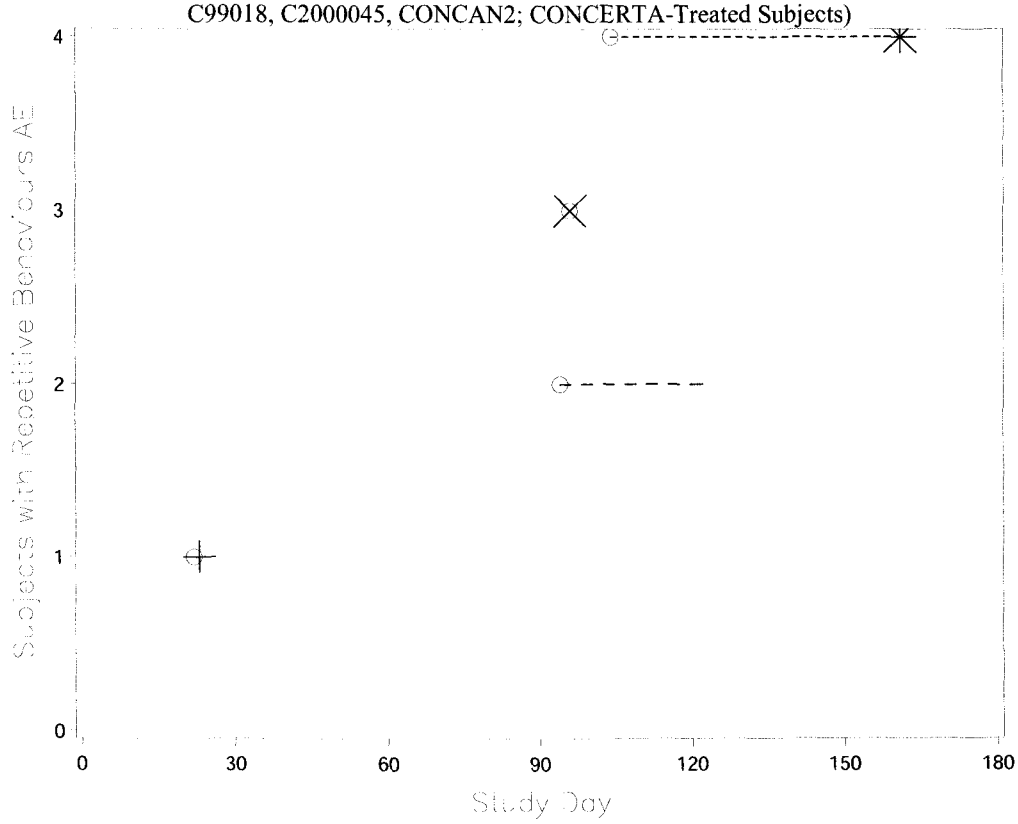
On the basis of the review of aggregate safety data from clinical trials of CONCERTA, a causal relationship was not established for any of the adverse events that may be relevant for this important potential risk.

(Continued)

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

Onset and Duration of Repetitive Behaviours: Open-Label Trials of at Least 3 Months (C98012, C99018, C2000045, CONCAN2; CONCERTA-Treated Subjects)



Day	0	30	60	90	120	150	180
N (%)	1583 (100)	1484 (94)	1386 (88)	1308 (83)	1255 (79)	1232 (78)	1152 (73)

* For Trial C2000045, only subjects who remained in the trial beyond 21 days and who consequently could have been exposed to trial drug for a period up to 12 months were included in the analysis.

- - - - - - - - - - Mild
. . . . . Moderate
———— Severe
\- Persisting
\+ Resolved
X Drug Withdrawn

(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 patients 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). (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.) The frequency of very rare assigned to Repetitive behaviours is based on clinical trial data in paediatric patients and postmarketing spontaneous reports in both paediatric and adult patients.
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

Potential Risk: QT Prolongation*	**All Randomized, Blinded Trials Population (N=321) N (%)**	**All Clinical Trials Population (N=2718) N (%)**
Frequency**		
Concerta	0	0
vs		
Placebo (N=318)	0	
Odds Ratio		
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	0
Resolved/Recovered/Recovered From AE	0	0
Recovered With Residual Effects	0	0
Continuing/Not Yet Recovered	0	0
Severity****		
Mild	0	0
Moderate	0	0
Severe	0	0

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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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 18.3: 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	**Nonserious[a]**	**Serious[a]**
Electrocardiogram QT prolonged	1	18

[a] 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 patients 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 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 the 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

Potential Risk: Cyanosis*	**All Randomized, Blinded Trials Population (N=321) N (%)**	**All Clinical Trials Population (N=2718) N (%)**
Frequency**		
Concerta	0	0
vs		
Placebo (N=318)	0	
Odds Ratio		
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	0
Resolved/Recovered/Recovered From AE	0	0
Recovered With Residual Effects	0	0
Continuing/Not Yet Recovered	0	0
Severity****		
Mild	0	0
Moderate	0	0
Severe	0	0

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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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 patients with ADHD.
Risk Groups or Risk Factors	There are no published reports on risk groups or risk factors for cyanosis among patients 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

Potential Risk: Arrhythmias*	**All Randomised, Blinded Trials Population (N=321) N (%)**	**All Clinical Trials Population (N=2718) N (%)**
Frequency**		
Concerta	0	21 (0.8)
vs		
Placebo (N=318)	0	
Odds Ratio		
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	3
Resolved/Recovered/Recovered From AE	0	16
Recovered With Residual Effects	0	0
Continuing/Not Yet Recovered	0	4
Severity****		
Mild	0	11
Moderate	0	8
Severe	0	2

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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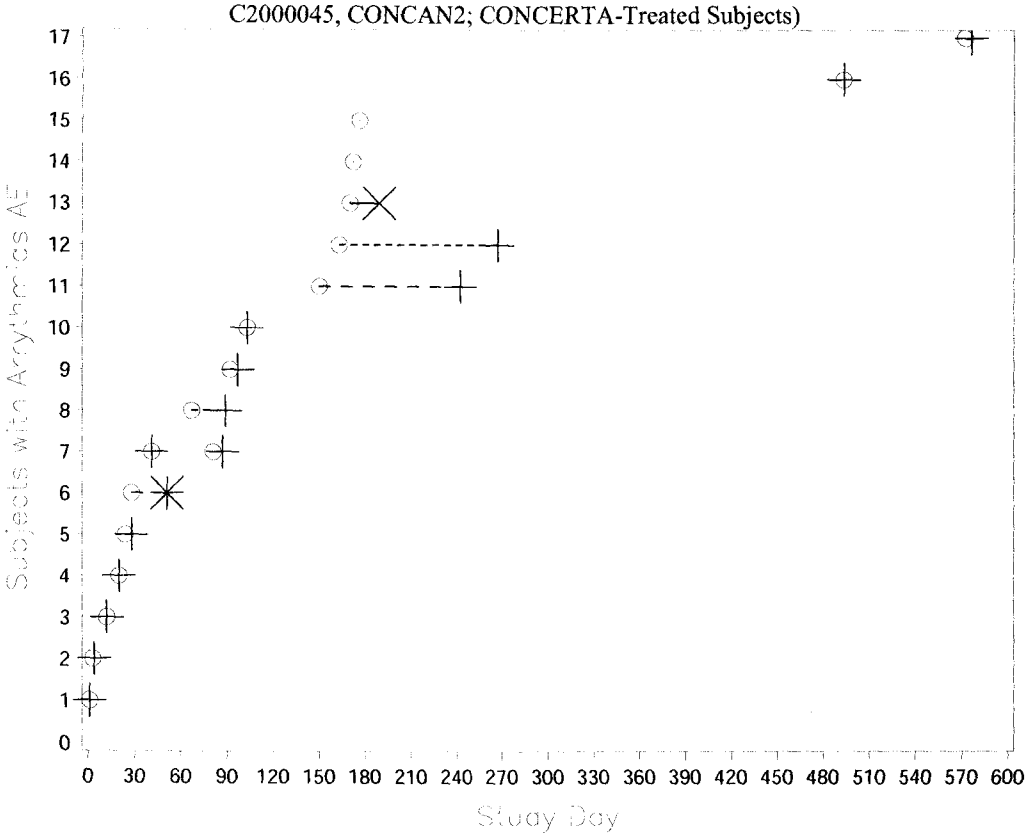
On the basis of the review of aggregate safety data from clinical trials of CONCERTA, a causal relationship was not established for any of the adverse events that may be relevant for this important potential risk.

(Continued)

Table 18.5: Important Potential Risk: Arrhythmias (Continued)

Onset and Duration of Arrhythmias: Open-Label Trials of at Least 3 Months (C98012, C99018, C2000045, CONCAN2; CONCERTA-Treated Subjects)



Day	0	30	60	90	120	150	180	210	240	270
N (%)	1583 (100)	1484 (94)	1386 (88)	1308 (83)	1255 (79)	1232 (78)	1152 (73)	1070 (68)	1034 (65)	809 (51)

Day	300	330	360	390	420	450	480	510	540	570	600
N	396 (25)	345 (22)	296 (19)	274 (17)	269 (17)	265 (17)	261 (16)	256 (16)	252 (16)	244 915)	242 (15)

* For Trial C2000045, only subjects who remained in the trial beyond 21 days and who consequently could have been exposed to trial drug for a period up to 12 months were included in the analysis.

---------- Mild
---------- Moderate
———————— Severe
\- Persisting
\+ Resolved
X Drug Withdrawn

(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 rate of cardiac arrhythmia among children and adults with ADHD has not been described in the published literature. The incidence of atrial fibrillation and flutter in the general population ranges from 20.58 per 100,000 persons per year among males 15 to 44 years of age to 1077.39 per 100,000 persons per year for males ≥85 years of age. In females, corresponding rates are 6.64 per 100,000 persons per year and 1203.7 per 100,000 persons per year, respectively. The incidence of out-of-hospital treated ventricular fibrillation is estimated to be 7.7 per 100,000 persons per year (95% CI: 4.7-11.9) (AHA 2009). The worldwide prevalence of atrial fibrillation ranges from 1.6% to 2%. In persons over the age of 65 years with cardiovascular disease, prevalence approaches 10% (Brignole 2000). 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.
Risk Groups or Risk Factors	Risk factors for cardiac arrhythmias among patients 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 states that the report of the FDA/AHRQ/Vanderbilt University study should be evaluated, when available; Table 25 provides details regarding this pharmacovigilance activity. 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 . . . during methylphenidate treatment should undergo a prompt specialist cardiac evaluation." Arrhythmia is listed as an ADR in Section 4.8 of the EU SmPC. (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.) The frequency of common assigned to Arrhythmia is based on clinical trial data in paediatric patients and postmarketing spontaneous reports in both paediatric and adult patients. Also Extrasystoles and Ventricular extrasystoles are listed as ADRs in Section 4.8 with a frequency of not known based on clinical trial data in paediatric patients and postmarketing spontaneous reports in both paediatric and adult patients.

(Continued)

Table 18.5: Important Potential Risk: Arrhythmias (Continued)

Evidence Source	American Heart Association (AHA) (2009). Heart Disease and Stroke Statistics 2009 Update: A Report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009;199:e21-e181. 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). Brignole M (2000). Ablate and pace: palliating the symptoms? Am J Cardiology 2000;86(Suppl 9A):4k. 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

Potential Risk: Sudden Death*	**All Randomized, Blinded Trials Population (N=321) N (%)**	**All Clinical Trials Population (N=2718) N (%)**
Frequency**		
Concerta	0	0
vs		
Placebo (N=318)	0	
Odds Ratio		
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	0
Resolved/Recovered/Recovered From AE	0	0
Recovered With Residual Effects	0	0
Continuing/Not Yet Recovered	0	0
Severity****		
Mild	0	0
Moderate	0	0
Severe	0	0

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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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 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.

The incidence of sudden death varies largely as a function of coronary artery disease prevalence. In the adult population, the incidence of sudden death is 0.1% to 0.2% per year. The global incidence is underestimated because many sudden deaths are not witnessed. Although cardiac causes are the leading cause of sudden death, especially coronary artery disease, the exact incidences of the other causes, particularly causes of non-cardiac origin are not well estimated because sudden death cases are not systematically autopsied (de la Grandmaison 2002).

(Continued)

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

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 patients with structural cardiac abnormalities may be at a greater risk of sudden death when treated with methylphenidate. The association between stimulant use and sudden death in children and adolescents aged 7 to 19 years was assessed using a case-control study in the US (Gould 2009). A total of 564 cases of sudden death and a matched group of 564 cases of motor vehicle traffic fatalities (children or adolescents were passengers) were identified using mortality data from state vital statistics records between 1985 and 1996. The primary exposure measure was the presence of amphetamine, dextroamphetamine, methamphetamine, or methylphenidate. A significant association of stimulant use with sudden death was observed based on exact conditional logistic regression (odds ratio, 7.4; 95% CI: 1.4, 74.9). A recent retrospective study in the UK did not find an association between an increase in the risk of sudden death and the use of stimulants or atomoxetine (McCarthy 2009). Children, adolescents, and young adults aged 2 to 21 years with a prescription for methylphenidate, dexamphetamine, or atomoxetine were identified using the UK General Practice Research Database between 1 January 1993 and 30 June 2006. Patients were followed from the date of first prescription to the first of the following events: death, transfer, age >21 years, or the end of the study. Seven deaths were reported from this cohort of 18,637 patient-years. For the 6 patients for whom the cause of death was known, none were considered to be sudden death.
Potential Mechanisms	The precise mechanism of sudden death in patients 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).
Preventability	Early detection and management of cardiovascular risk factors by health care professionals.

(Continued)

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

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 patients with structural cardiac abnormalities. Although some structural cardiac abnormalities alone may carry an increased risk of sudden death, stimulant products are not recommended in patients 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 and adults, some of whom had structural cardiac abnormalities or other serious heart problems.
Regulatory Action Taken	Enhanced pharmacovigilance through the use of a questionnaire (follow up for sudden death) has been implemented; Table 25 provides details regarding this pharmacovigilance activity. Annex IV of the May 2009 EC Decision states that the report of the FDA/AHRQ/Vanderbilt University study should be evaluated, when available; Table 25 provides details regarding this pharmacovigilance activity. 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. Additionally precautionary language is included in Section 4.4, Special warnings and precautions for use, under "Sudden death and pre-existing structural cardiac abnormalities or other serious cardiac disorders". There is also additional wording in Section 4.4 in the "Cardiovascular status" sub-heading: "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...)."

(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 (Section 4.4, SmPC) and concomitant use with clonidine (Section 4.5, SmPC). "Sudden cardiac death" is listed as an ADR in Section 4.8 of the EU SmPC. (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.) The frequency of very rare assigned to Sudden cardiac death is based on clinical trial data in paediatric patients and postmarketing data in both paediatric and adult patients.
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). de la Grandmaison GL (2002), Durigon M. Sudden adult death: a medico-legal series of 77 cases between 1995 and 2000. Med Sci Law 2002;42(3):225-232. 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. Gould MS (2009), Walsh BT, Munfakh JL, et al. Sudden death and use of stimulant medications in youths. Am J Psychiatry 2009;166:992-1001. 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)

Evidence Source (Continued)	McCarthy S (2009), Cranswick N, Potts L, Taylor E, Wong ICK. Mortality associated with attention-deficit hyperactivity disorder (ADHD) drug treatment: A retrospective cohort study of children, adolescents and young adults using the General Practice Research Database. Drug Saf 2009;32(11):1089-1096. 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: Ischaemic Cardiac Events

Potential Risk: Ischaemic Cardiac Events*	**All Randomized, Blinded Trials Population (N=321) N (%)**	**All Clinical Trials Population (N=2718) N (%)**
Frequency**		
Concerta	0	0
vs		
Placebo (N=318)	0	
Odds Ratio		
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	0
Resolved/Recovered/Recovered From AE	0	0
Recovered With Residual Effects	0	0
Continuing/Not Yet Recovered	0	0
Severity****		
Mild	0	0
Moderate	0	0
Severe	0	0

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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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 18.7: Important Potential Risk: Ischaemic cardiac events (Continued)

Postmarketing

A summary of Ischaemic cardiac 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: Ischaemic cardiac events

	Number of Events 01 August 2000 to 10 August 2009	
Preferred Term	**Nonserious[a]**	**Serious[a]**
Angina Pectoris	5	5
Coronary artery disease	0	1
Myocardial infarction	0	6
Myocardial ischaemia	0	1

[a] At event level

Source: Source: Benefit Risk Management (BRM) Period Safety Update Report 11 August 2008 to 10 August 2009. This search of the worldwide postmarketing safety database for Cardiac Disorders events was conducted using 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

"Angina pectoris" is listed as an ADR based on postmarketing data.

Nature of the Risk	There have only been a few case reports of ischaemic cardiac events reported in children and adolescents with ADHD being treated with methylphenidate (George 2005). Many of these cases are poorly documented. To date, the nature of ischaemic cardiac events that may occur while children are being treated with methylphenidate appears similar to the events that have been reported in otherwise healthy children (Lane and Ben-Shachar 2007). There have been no unique characteristics identified for those events that were reported in children taking methylphenidate.
Background Incidence / Prevalence	The rates of ischaemic cardiac events in untreated ADHD patients have not been described in the published literature. In the general population, ischaemic cardiac events in adolescents are rare. Approximately 0.25% of paediatric emergency department visits are due to chest pain, and less than 5% of chest pain episodes are linked to a cardiac etiology. A small number of case reports describing myocardial ischemia without predisposing risk factors in adolescents have been reported sporadically (Cava 2004). In adults, the annual incidence of hospital admission for acute cardiac ischaemia in Europe is 1,900 per million population (Widimsky 2010), and in the US an estimated 935,000 new and recurrent events are estimated to occur annually (Lloyd-Jones 2010).
Risk Groups or Risk Factors	Risk factors for ischaemic cardiac events include physical inactivity, smoking, high blood cholesterol and other lipids, high blood pressure, diet, overweight and obesity, and diabetes mellitus (Lloyd-Jones 2010). Risk factors in children include a history of familial hypercholesterolemia and a family history of early coronary heart disease (Dadfarmay 2009).

(Continued)

Table 18.7: Important Potential Risk: Ischaemic cardiac events (Continued)

Potential Mechanisms	Potential mechanisms for stimulant-induced ischaemic cardiac events include tachycardia, catecholamine-induced coronary vasospasm, and cardiomyopathy (George 2005, Thompson 2010). There is little evidence to support any of these mechanisms in the cases that have been reported 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. CONCERTA should not be prescribed for children or adolescents with pre-existing cardiovascular disorders, including angina and myocardial infarction, according to the EU SmPC.
Potential Public Impact of Safety Concern	The risk of ischaemic cardiac events increases with age but they may very rarely also occur in children. Ischaemic heart disease in the young may create a long-term burden for the victims, their families, and society. 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 states that the report of the FDA/AHRQ/Vanderbilt University study should be evaluated, when available; Table 25 provides details regarding this pharmacovigilance activity. The EU SmPC for CONCERTA (Annex 2) contraindicates use in patients with pre-existing cardiovascular disorders including arterial occlusive disease, angina, and myocardial infarction. Precautionary language in the EU SmPC, Section 4.4 (under the sub-heading cardiovascular status) states that "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." "Angina pectoris" is listed as an ADR, based on postmarketing data, in Section 4.8 of the CONCERTA EU SmPC with a frequency of rare based on clinical trial data in paediatric patients and postmarketing spontaneous reports in both paediatric and adult patients. "Myocardial infarction" is listed as an ADR in Section 4.8 of the CONCERTA EU SmPC based on the Article 31 referral of methylphenidate-containing products with a frequency of very rare based on clinical trial data in paediatric patients and postmarketing spontaneous reports in both paediatric and adult patients.

(Continued)

Table 18.7: Important Potential Risk: Ischaemic cardiac events (Continued)

Evidence Source	Cava J (2004), Sayger PL. Chest pain in children and adolescents. Pediatr Clin N Am 2004;51:1553-1568. Dadfarmay S (2009), Dixon J. A case of acute cardiomyopathy and pericarditis associated with methylphenidate. Cardiovasc Toxicol 2009;9(1):49-52. George AK (2005), Kunwar AR, Awashati A. Acute myocardial infarction in a young male on methylphenidate, bupropion, and erythromycin. J Child Adolesc Psychopharmacol 2005;15:693-695. Lane JR (2007), Ben-Sachar G. Myocardial infarction in healthy adolescents. Pediatrics 2007;120:e938-943. Lloyd-Jones D (2010), Adams RJ, Brown TM, et al. Heart disease and stroke statistics - 2010 updated. A report from the American Heart Association. Circulation 2010;121:e46-e215. Thompson J (2010), Thompson JR. Acute myocardial infarction related to methylphenidate for adult attention deficit disorder. J Emerg Med 2010;38:18-21. Widimsky P (2010), Wijns W, Fajadet j, et al, et al. Reperfusion therapy for ST elevation acute myocardial infarction in Europe: description of the current situation in 30 countries. Eur Heart J 2010; 31:943-957.

Table 18.8: Important Potential Risk: Cerebrovascular Disorders

Potential Risk: Cerebrovascular Disorders*	**All Randomized, Blinded Trials Population (N=321) N (%)**	**All Clinical Trials Population (N=2718) N (%)**
Frequency**		
Concerta	0	0
vs		
Placebo (N=318)	0	
Odds Ratio		
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	0
Resolved/Recovered/Recovered From AE	0	0
Recovered With Residual Effects	0	0
Continuing/Not Yet Recovered	0	0
Severity****		
Mild	0	0
Moderate	0	0
Severe	0	0

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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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 18.8: Important Potential Risk: Cerebrovascular Disorders (Continued)

Nature of the Risk	There have only been a few cases of cerebrovascular events recorded in patients 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 patients. 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 patients taking methylphenidate have not been identified.

Background Incidence / Prevalence

In relation to readily available national information, data from the Canadian Paediatric Ischaemic Stroke Registry reveals the incidence of ischaemic 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).

Estimated stroke incidence rates (per 100,000) for men and women, respectively, in selected European countries have been reported as follows (Truelsen 2006):

Estimated Incidence of Stroke (per 100,000) for Men and Women in Selected European Countries

Age range (years)	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75-84**	**≥85**
France (men,women)	19, 9	37, 18	131, 49	253, 109	630, 364	1105, 837	1325, 1113
Germany (men,women)	14, 9	28, 17	131, 60	316, 152	899, 588	1696, 1395	2096, 1857
Italy (men,women)	14, 8	27, 16	124, 63	295, 154	918, 585	1946, 1569	2521, 2214
Spain (men,women)	12, 8	24, 15	132, 57	298, 143	804, 498	1413, 1207	1682, 1647
UK (men,women)	16, 9	32, 18	129, 94	301, 209	845, 652	1512, 1453	1809, 1925

(Continued)

Table 18.8: Important Potential Risk: Cerebrovascular Disorders (Continued)

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.
Preventability(Continued)	CONCERTA should not be prescribed for patients 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	Stroke in patients with ADHD and especially 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.

(Continued)

Table 18.8: Important Potential Risk: Cerebrovascular Disorders (Continued)

Regulatory Action Taken	Enhanced pharmacovigilance through the use of a questionnaire (follow up for cerebrovascular disorders) has been implemented; Table 25 provides details regarding this pharmacovigilance activity. Annex IV of the May 2009 EC Decision states that the report of the FDA/AHRQ/Vanderbilt University study should be evaluated, when available; Table 25 provides details regarding this pharmacovigilance activity. The EU SmPC for CONCERTA (Annex 2) 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). (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.) The frequency of not known assigned to this ADR is based on clinical trial data in paediatric patients and postmarketing spontaneous reports in both paediatric and adult patients.

(Continued)

Table 18.8: 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. Truelsen T (2006), Piechowski-Jozwiak B, Bonita R, Mathers C, Bogousslavsky J, Boysen G. Stroke incidence and prevalence in Europe: a review of available data. Eur J Neurol 2006;13(6):581-598. Williams AN (2000). Childhood stroke-beyond re-inventing the wheel. Europ J Paediatr Neurol 2000;4:103-107.

Table 18.9: Important Potential Risk: Hostility

Potential Risk: Hostility*	**All Randomised, Blinded Trials Population (N=321) N (%)**	**All Clinical Trials Population (N=2718) N (%)**
Frequency**		
Concerta	1 (0.3)	24 (0.9)
vs	Vs	
Placebo (N=318)	0 (0.0)	
Odds Ratio		
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	1
Resolved/Recovered/Recovered From AE	0	21
Recovered With Residual Effects	0	1
Continuing/Not Yet Recovered	0	1
Severity****		
Mild	0	11
Moderate	1	12
Severe	0	1

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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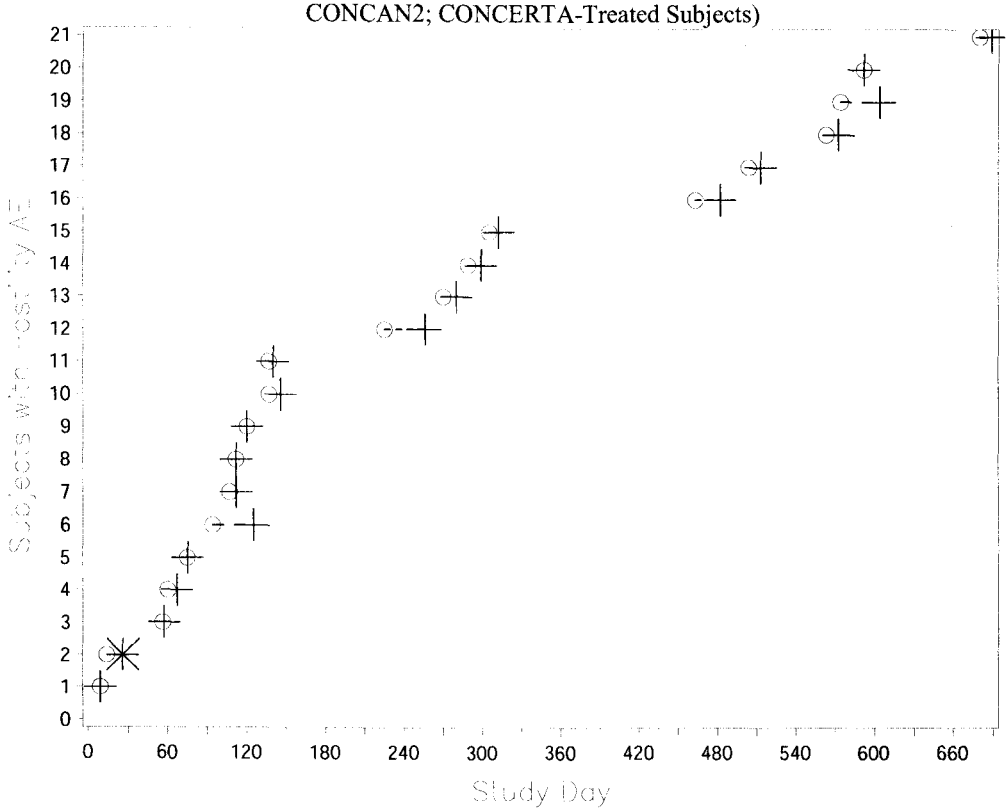
On the basis of the review of aggregate safety data from clinical trials of CONCERTA, a causal relationship was not established for any of the adverse events that may be relevant for this important potential risk.

(Continued)

Table 18.9: Important Potential Risk: Hostility (Continued)

Onset and Duration of Hostility: Open-Label Trials of at Least 3 Months (C98012, C99018, C2000045, CONCAN2; CONCERTA-Treated Subjects)



Day	0	30	60	90	120	150	180	210	240	270	300	330
N (%)	1583 (100)	1484 (94)	1386 (88)	1308 (83)	1255 (79)	1232 (78)	1152 (73)	1070 (68)	1034 (65)	809 (51)	396 (25)	345 (22)

Day	360	390	420	450	480	510	540	570	600	630	660	690
N	296 (19)	274 (17)	269 (17)	265 (17)	261 (16)	256 (16)	252 (16)	244 (15)	242 (15)	214 (14)	132 (8)	86 (5)

* For Trial C2000045, only subjects who remained in the trial beyond 21 days and who consequently could have been exposed to trial drug for a period up to 12 months were included in the analysis.

---------- Mild
---------- Moderate
———————— Severe
\- Persisting
\+ Resolved
X Drug Withdrawn

(Continued)

Table 18.9: Important Potential Risk: Hostility (Continued)

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).
Nature of the Risk	Hostility is a common comorbid symptom in patients with ADHD. A prospective 3-year follow-up of children and adolescents (mean age 11.7 [SD 1.0] years) in the MTA study found that those in the study had significantly higher rates of delinquency compared with those in a local normative comparison group (27.1% vs. 7.4%; p=0.000) (Molina 2007). More days of pharmacological treatment were associated with more serious delinquency. The authors noted that because these findings were based on observed associations in the data, the findings do not rule out the possibility that behaviour would have been worse without pharmacological treatment.
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.

(Continued)

Table 18.9: Important Potential Risk: Hostility (Continued)

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).
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). Molina BSG (2007), Flory K, Hinshaw SP, et al. Delinquent behavior and emerging substance use in the MTA at 36 months: prevalence, course, and treatment effects. J Am Acad Child Adolesc Psychiatry 2007:46(8):1028-1040.

Table 18.10: Important Potential Risk: Suicidality

Potential Risk: Suicidality*	**All Randomised, Blinded Trials Population (N=321) N (%)**	**All Clinical Trials Population (N=2718) N (%)**
Frequency**		
Concerta	0	7 (0.3)
vs		
Placebo (N=318)	0	
Odds Ratio		
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	5
Discontinued Treatment	0	2
Resolved/Recovered/Recovered From AE	0	2
Recovered With Residual Effects	0	3
Continuing/Not Yet Recovered	0	1
Severity****		
Mild	0	1
Moderate	0	2
Severe	0	4

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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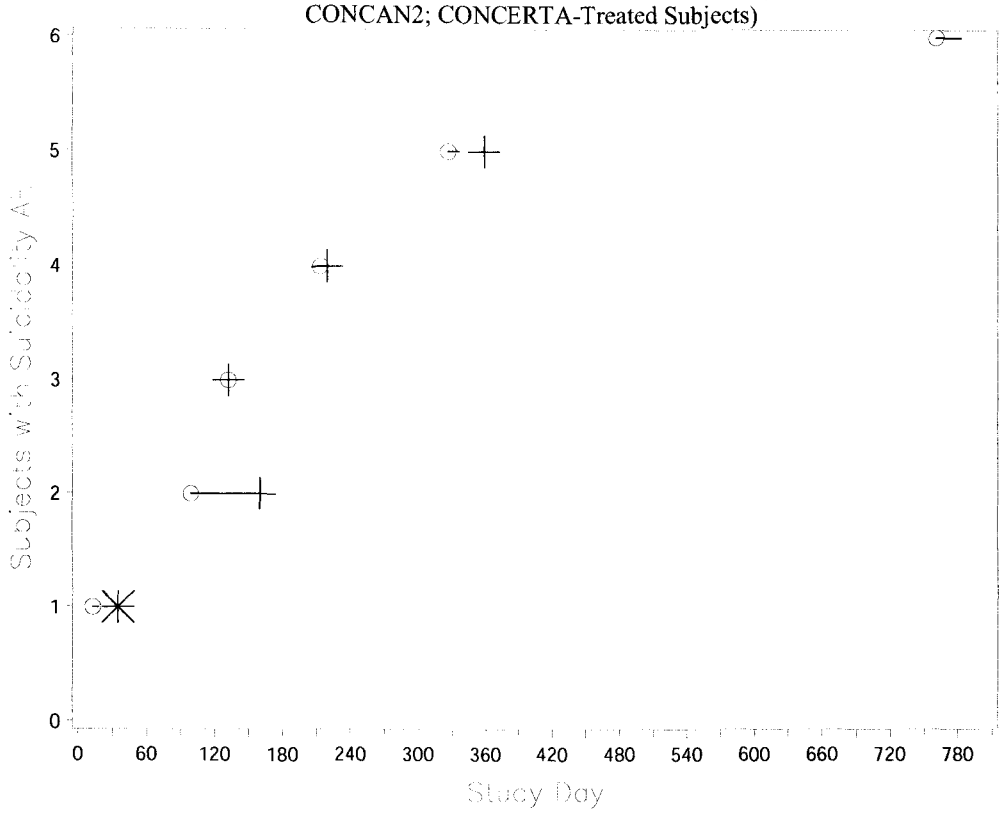
On the basis of the review of aggregate safety data from clinical trials of CONCERTA, a causal relationship was not established for any of the adverse events that may be relevant for this important potential risk.

(Continued)

Table 18.10: Important Potential Risk: Suicidality (Continued)

Onset and Duration of Suicidality: Open-Label Trials of at Least 3 Months (C98012, C99018, C2000045, CONCAN2; CONCERTA-Treated Subjects)



Day	0	30	60	90	120	150	180	210	240	270	300	330	360
N (%)	1583 (100)	1484 (94)	1386 (88)	1308 (83)	1255 (79)	1232 (78)	1152 (73)	1070 (68)	1034 (65)	809 (51)	396 (25)	345 (22)	296 (19)

Day	390	420	450	480	510	540	570	600	630	660	690	720	750	780	810
N	274 (17)	269 (17)	265 (17)	261 (16)	256 (16)	252 (16)	244 (15)	242 (15)	214 (14)	132 (8)	86 (5)	60 (4)	37 (2)	17 (1)	10 (1)

* For Trial C2000045, only subjects who remained in the trial beyond 21 days and who consequently could have been exposed to trial drug for a period up to 12 months were included in the analysis.

---------- Mild
---------- Moderate
———— Severe
\- Persisting
\+ Resolved
X Drug Withdrawn

(Continued)

Table 18.10: Important Potential Risk: Suicidality (Continued)

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[a]	**Nonserious**[b]	**Serious**[b]
Completed suicide	0	14
Intentional self-injury	1	6
Suicide attempt	0	52
Suicidal ideation	1	56
Self-injurious ideation	0	1

[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 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.

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. Patients with ADHD have a higher risk than other patients 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).

The rate of suicidal ideation or behaviour in adults with ADHD has not been described in the published literature. Epidemiologic studies estimate that between 1.1% and 4.3% of the general population attempt suicide at some time in their life. The estimated lifetime prevalence rates of suicidal ideation, plans, and attempts in the National Comorbidity Survey, a nationally representative survey of persons aged 15 to 54 years in the US, were 13.5%, 3.9%, and 4.6%, respectively (Kessler, 1999).

(Continued)

Table 18.10: Important Potential Risk: Suicidality (Continued)

Background Incidence / Prevalence (Continued)	A recent retrospective study in the UK that assessed the association between an increase in the risk of sudden death and the use of stimulants or atomoxetine for the treatment of ADHD reported an increased risk of suicide; suicide was not a primary outcome measure for this study (McCarthy 2009). Children, adolescents, and young adults aged 2 to 21 years with a prescription for methylphenidate, dexamphetamine, or atomoxetine were identified using the UK General Practice Research Database between 1 January 1993 to 30 June 2006. Patients were followed from the date of first prescription to the first of the following events: death, transfer, age >21 years, or the end of the study. Seven deaths were reported from this cohort of 18,637 patient-years. The standardised mortality ratio (SMR) for suicide for patients aged 11 to 14 years was 161.91 (95% CI: 19.6, 584.88) and for patients aged 15 to 21 years was 1.84 (95% CI: 0.05, 10.25). It should be noted that for the group aged 15 to 21 years, there was 1 case of suicide and the 95% CI did not show a statistically significant difference in the rates of suicide for these adolescents and young adults with ADHD compared with the general population. (Patients were categorised into 2 age groups, due to the difference in the definition of suicide used for children and adults.)
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.
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.

(Continued)

Table 18.10: Important Potential Risk: Suicidality (Continued)

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	Enhanced pharmacovigilance through the use of a questionnaire (follow up for suicidality) has been implemented; Table 25 provides details regarding this pharmacovigilance activity. Annex IV of the May 2009 EC Decision states that 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; Table 25 provides details regarding this pharmacovigilance activity. 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 sub-heading): "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 and Suicidal attempt (including completed suicide) are listed as ADRs in Section 4.8 of the EU SmPC. (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.) The frequencies of uncommon and very rare assigned to Suicidal ideation and Suicidal attempt, respectively, are based on clinical trial data in paediatric patients and postmarketing spontaneous reports in both paediatric and adult patients.

(Continued)

Table 18.10: 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. Kessler RC (1999), Borges G, Walters EE. Prevalence of and risk factors for lifetime suicide attempts in the National Comorbidity Survey. Arch Gen Psychiatry 1999;56:617-626. Klein D (2006). The flawed basis for FDA post-marketing safety decisions: The example of anti-depressants and children. Neuropsychopharmacol 2006;31:689-699. McCarthy S (2009), Cranswick N, Potts L, Taylor E, Wong ICK. Mortality associated with attention-deficit hyperactivity disorder (ADHD) drug treatment: A retrospective cohort study of children, adolescents and young adults using the General Practice Research Database. Drug Saf 2009;32(11):1089-1096. 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 18.11: Important Potential Risk: Tics, Tourette's Syndrome, Dystonias

Potential Risk: Tics/Tourettes's Syndrome/Dystonias*	**All Randomised, Blinded Trials Population (N=321) N (%)**	**All Clinical Trials Population (N=2718) N (%)**
Frequency**		
Concerta	1 (0.3)	92 (3.4)
vs	Vs	
Placebo (N=318)	5 (1.6)	
Odds Ratio	0.2	
95% confidence interval***	0.0 to 1.8	
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	24
Resolved/Recovered/Recovered From AE	1	45
Recovered With Residual Effects	0	2
Continuing/Not Yet Recovered	0	42
Severity****		
Mild	1	49
Moderate	0	38
Severe	0	5

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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

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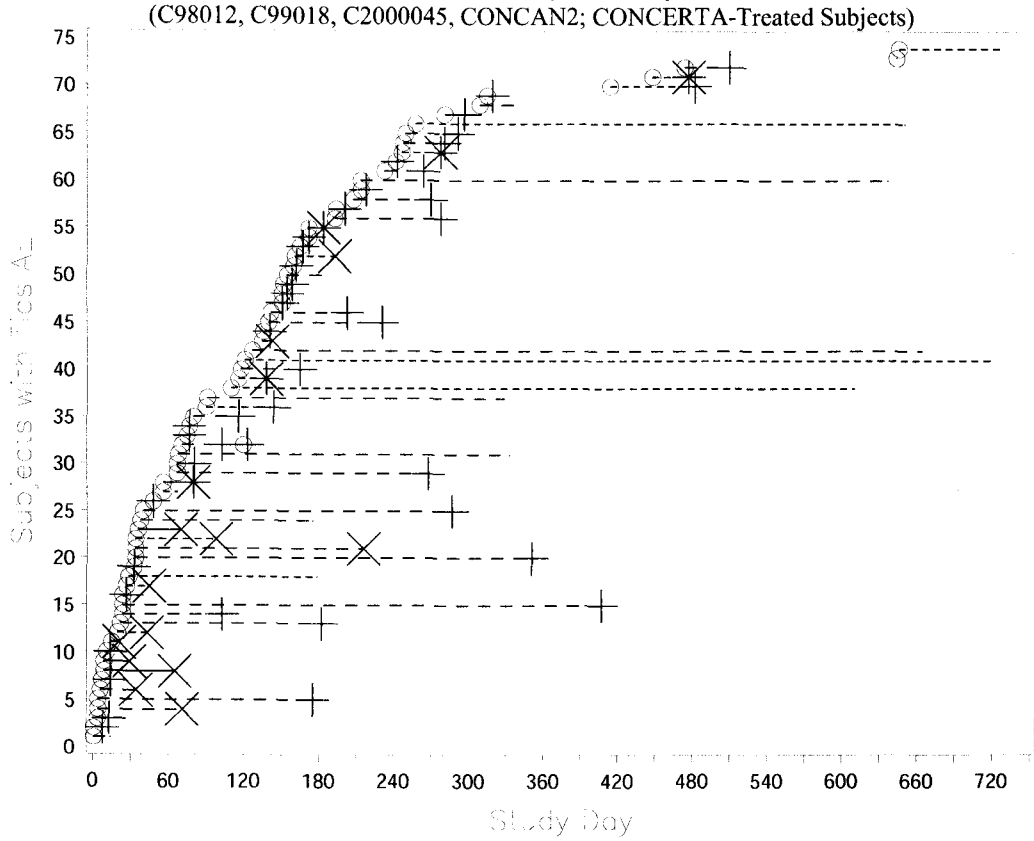
Table 18.11: Important Potential Risk: Tics, Tourette's Syndrome, Dystonias (Continued)

Onset and Duration of Tics, Tourette's Syndrome, Dystonias: Open-Label Trials of at Least 3 Months (C98012, C99018, C2000045, CONCAN2; CONCERTA-Treated Subjects)



Day	0	30	60	90	120	150	180	210	240	270	300	330	360
N (%)	1583 (100)	1484 (94)	1386 (88)	1308 (83)	1255 (79)	1232 (78)	1152 (73)	1070 (68)	1034 (65)	809 (51)	396 (25)	345 (22)	296 (19)

Day	390	420	450	480	510	540	570	600	630	660	690	720	750
N	274 (17)	269 (17)	265 (17)	261 (16)	256 (16)	252 (16)	244 (15)	242 (15)	214 (14)	132 (8)	86 (5)	60 (4)	37 (2)

* For Trial C2000045, only subjects who remained in the trial beyond 21 days and who consequently could have been exposed to trial drug for a period up to 12 months were included in the analysis.

Mild
Moderate
Severe
\- Persisting
\+ Resolved
X Drug Withdrawn

(Continued)

Table 18.11: Important Potential Risk: Tics, Tourette's Syndrome, Dystonias (Continued)

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[a]	**Nonserious**[b]	**Serious**[b]
Tic	4	11
Tourette's disorder	135	56
Dystonia	3	7

[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: 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.)

Nature of the Risk	Tics are a fairly common comorbidity in the ADHD population, especially children with ADHD. 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 patients 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 to 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

(Continued)

Table 18.11: Important Potential Risk: Tics, Tourette's Syndrome, Dystonias (Continued)

Background Incidence/Prevalence (Continued)	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). In a study of adults (ages 19 to 59 years), a significantly greater proportion of the 312 adults with ADHD (12%) had a tic disorder (Tourette's syndrome or non-Tourette's syndrome) than of the 252 adults without ADHD (4%) (Spencer 2001).
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 IR 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 trial, 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 indicate 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 18.11: 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 (i.e., 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", based on clinical trial data in paediatric patients, and "Worsening of pre-existing tics of Tourette's syndrome" are listed as ADRs in SmPC Section 4.8. ("Worsening of pre-existing tics of 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.) Tics was assigned a frequency of common and Worsening of pre-existing tics of Tourette's syndrome was assigned a frequency of uncommon based on clinical trial data in paediatric patients and postmarketing spontaneous reports in both paediatric and adult patients.

(Continued)

Table 18.11: 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. Spencer TJ (2001), Biederman J, Faraone S, et al. Impact of tic disorders on ADHD outcome across the life cycle: findings from a large group of adults with and without ADHD. Am J Psychiatry 2001;158(4):611-617. Van Harten PN (1999), Hoek HW, Kahn RS. Acute dystonia induced by drug treatment. BMJ 1999;319(7210):623-626.

Table 18.12: Important Potential Risk: Effect on Final Height

Potential Risk: Effect on Final Height*	All Randomized, Blinded Trials Population (N=321) N (%)	All Clinical Trials Population (N=2718) N (%)
Frequency**		
Concerta	0	0
vs		
Placebo (N=318)	0	
Odds Ratio		
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	0
Resolved/Recovered/Recovered From AE	0	0
Recovered With Residual Effects	0	0
Continuing/Not Yet Recovered	0	0
Severity****		
Mild	0	0
Moderate	0	0
Severe	0	0

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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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 conclusions drawn from long-term safety exposure specifically, as can be done in long-term controlled clinical trials.)

Nature of 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 children and adolescents 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 have emerged to implicate ADHD itself as having a role (Spencer 1996, 1998).

(Continued)

Table 18.12: Important Potential Risk: Effect on Final Height (Continued)

Nature of Risk (Continued)	Data from a 10-year prospective study of height and weight in children with ADHD (approximately 22 years of age at follow up) found no evidence that ADHD was associated with differential trajectories of height over time or differences at follow up in any growth outcome, as well as no evidence that stimulant treatment was associated with differences in growth (Biederman 2010).
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. At entry to the MTA study, the height and weight of stimulant-naive children at baseline was greater than expected based on population norms. At the 36-month assessment, the stimulant-naive control group that did not receive medication was taller and heavier than population norms (z height: 0.541; z weight: 0.765), while the 2 medicated groups that received about 1,000 days of treatment over 3 years of the MTA follow-up were slightly above or below expected relative size based on norms (newly medicated: z height 0.073 and z weight 0.293; consistently medicated: z height -0.120 and z weight 0.156). The study observed that those children and adolescents left untreated had a greater growth rate over the 36-month period compared to that of the classmate control group or the expectation based on population norms. Subjects who received treatment showed stimulant-related decreases in growth rates for up to 3 years without evidence of growth rebound after discontinuation of stimulant medication within the 3-year period (Swanson 2007). 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.

(Continued)

Table 18.12: Important Potential Risk: Effect on Final Height (Continued)

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) indicate that there is unlikely to be any affect on final height, but long-term research is still being conducted. 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.
Regulatory Action Taken	Annex IV of the May 2009 EC Decision states that MTA study should be evaluated to inform this potential risk; Table 25 provides details regarding this pharmacovigilance activity. 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 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."
Evidence Source	Biederman J (2010), Spencer TJ, Monuteaux MC, Faraone SV. A naturalistic 10-year prospective study of height and weight in children with attention-deficit hyperactivity disorder grown up: sex and treatment effects. J Pediatr 2010;157:635-640. 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.

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Table 18.12: Important Potential Risk: Effect on Final Height (Continued)

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 18.13: Important Potential Risk: Sexual Maturation (Delayed)

Potential Risk: Sexual Maturation (Delayed)*	All Randomized, Blinded Trials Population (N=321) N (%)	All Clinical Trials Population (N=2718) N (%)
Frequency**		
Concerta	0	0
vs		
Placebo (N=318)	0	
Odds Ratio		
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	0
Resolved/Recovered/Recovered From AE	0	0
Recovered With Residual Effects	0	0
Continuing/Not Yet Recovered	0	0
Severity****		
Mild	0	0
Moderate	0	0
Severe	0	0

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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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 18.13: 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)

Preferred Terms[a]	Number of Events	
	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 18.13: 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 hypogonadotropic 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 states that the data from the MTA study and an investigator-initiated study (IIS, a 2-year smoking prevention study in adolescents) should be evaluated to inform the potential risk of delayed sexual maturation; Table 25 provides details regarding this pharmacovigilance activity. No further regulatory action taken.

(Continued)

Table 18.13: 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 18.14: Important Potential Risks: Carcinogenicity

Potential Risk: Carcinogenicity*	**All Randomised, Blinded Trials Population (N=321) N (%)**	**All Clinical Trials Population (N=2718) N (%)**
Frequency**		
Concerta	0	7 (0.3)
vs		
Placebo (N=318)	0	
Odds Ratio		
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	0
Resolved/Recovered/Recovered From AE	0	3
Recovered With Residual Effects	0	0
Continuing/Not Yet Recovered	0	4
Severity****		
Mild	0	6
Moderate	0	1
Severe	0	0

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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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 18.14: 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

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

[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. 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 18.14: 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). Among all ages, there were an estimated 2,996,800 incident cancer cases diagnosed in Europe in 2004. The most common was lung cancer (381,500 cases), followed by colorectal cancer (376,400 cases), and breast cancer (129,900 cases). The cumulative risk for all sites except non-melanoma skin cancer is estimated to be 30.1% in men and 21.7% in women (Boyle 2005).
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 trials. 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 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.

(Continued)

Table 18.14: Important Potential Risk: Carcinogenicity (Continued)

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). Boyle P (2005), Ferlay J. Cancer incidence and mortality in Europe, 2004. Annals Oncology 2005;16:481-488. 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 18.15: Important Potential Risk: Off-Label Use

Potential Risk: Off-Label Use*	**All Randomized, Blinded Trials Population (N=321) N (%)**	**All Clinical Trials Population (N=2718) N (%)**
Frequency**		
Concerta	0	0
vs		
Placebo (N=318)	0	
Odds Ratio		
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	0
Resolved/Recovered/Recovered From AE	0	0
Recovered With Residual Effects	0	0
Continuing/Not Yet Recovered	0	0
Severity****		
Mild	0	0
Moderate	0	0
Severe	0	0

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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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 18.15: 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. Three placebo-controlled trials (1 trial included an open-label extension) and 3 open-label trials (1 trial included a randomised withdrawal phase) in adults with ADHD have been completed. One additional trial (C-99-018) in the paediatric submission included adult subjects up to, and including, the age of 65 years.

Table 18.15: 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	Annex IV of the May 2009 EC Decision includes a drug utilisation study; Table 25 provides details regarding this pharmacovigilance activity. 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 18.15: 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.

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Table 18.15: 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 18.15: 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 18.16: Important Potential Risk: Diversion

Potential Risk: Diversion*	**All Randomized, Blinded Trials Population (N=321) N (%)**	**All Clinical Trials Population (N=2718) N (%)**
Frequency**		
Concerta	0	0
vs		
Placebo (N=318)	0	
Odds Ratio		
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	0
Resolved/Recovered/Recovered From AE	0	0
Recovered With Residual Effects	0	0
Continuing/Not Yet Recovered	0	0
Severity****		
Mild	0	0
Moderate	0	0
Severe	0	0

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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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: Diversion (Continued)

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 US in the preceding 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 (McCabe 2004). In 2007, 3.8% of 12th grade students, 2.8% of 10th grade students, and 2.1% of 8th grade students in the US reported non-medical use of methylphenidate in the previous year (Johnston 2007). 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 (Johnston 2007). Darredeau et al (2007) examined patterns of medication compliance, diversion, and misuse in a sample of 66 adults in Canada (53% male, mean age 27 years [SD 9.4]) currently prescribed methylphenidate recruited through advertisements in a local Montreal newspaper, on college and university based Internet sites/bulletin boards, and a local adult ADHD support group. A total of 44% of the subjects admitted to diverting methylphenidate, primarily by giving it away, and 29% admitted to using methylphenidate inappropriately. Subjects completed an 18-item ADHD symptom checklist based on DSM-IV diagnostic criteria as part of the study; mean (SD) scores were 27.5 (7.9) and 26.2 (10.5) for those categorised as misusers and non–misusers, respectively.

(Continued)

Table 18.16: Important Potential Risk: Diversion (Continued)

Risk Groups or Risk Factors (Continued)	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.
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.

(Continued)

Table 18.16: Important Potential Risk: Diversion (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). Darredeau C (2007), Barrett SP, Jardin B, Pihl RO. Patterns and predictors of medication compliance, diversion, and misuse in adult prescribed methylphenidate users. Hum Psychopharmacol 2007;22(8):529-536. 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 18.17: Important Potential Risk: Withdrawal Syndrome

Potential Risk: Withdrawal Syndrome*	**All Randomised, Blinded Trials Population (N=321) N (%)**	**All Clinical Trials Population (N=2718) N (%)**
Frequency**		
Concerta	0	2 (0.1)
vs		
Placebo (N=318)	0	
Odds Ratio		
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	0
Resolved/Recovered/Recovered From AE	0	1
Recovered With Residual Effects	0	0
Continuing/Not Yet Recovered	0	1
Severity****		
Mild	0	0
Moderate	0	2
Severe	0	0

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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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 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.

(Continued)

Table 18.17: Important Potential Risk: Withdrawal Syndrome (Continued)

Background Incidence / Prevalence	Unknown
Risk Groups or Risk Factors	Unknown
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	The CONCERTA EU SmPC (Annex 2) contains precautionary text under the withdrawal sub-heading (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 18.18: Important Potential Risk: Drug Abuse and Drug Dependence

Potential Risk: Drug Abuse and Drug Dependence*	**All Randomised, Blinded Trials Population (N=321) N (%)**	**All Clinical Trials Population (N=2718) N (%)**
Frequency**		
Concerta	0	3 (0.1)
vs		
Placebo (N=318)	0	
Odds Ratio		
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	0
Resolved/Recovered/Recovered From AE	0	3
Recovered With Residual Effects	0	0
Continuing/Not Yet Recovered	0	0
Severity****		
Mild	0	0
Moderate	0	2
Severe	0	1

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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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 18.18: Important Potential Risk: Drug Abuse and Drug Dependence (Continued)

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

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

[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 SMQ: Drug abuse, dependence and withdrawal.

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

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%).

(Continued)

Table 18.18: Important Potential Risk: Drug Abuse and Drug Dependence (Continued)

Background Incidence / Prevalence (Continued)	Children and adolescents within the MTA study were reported to have significantly higher rates of substance use at 36 months of follow up compared to a local normative comparison group (17.4% vs. 7.8%, respectively). Children and adolescents randomised to intensive behaviour therapy reported less 24-month substance use than other MTA participants; however, no other effects of initial treatment assignment were observed. The authors conclude that the association between medication treatment and substance use need to be re-evaluated at older ages (Molina 2007). 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 2003a). Adults with ADHD are believed to be at greater risk of licit and illicit drug use than those without ADHD (Darredeau 2007). ADHD is over-represented in adults seeking treatment for cocaine and other drug dependence. In a study of 281 cocaine abusers seeking treatment, 12% (n=34) met the definition of childhood ADHD. Of the entire sample, 10% had adult ADHD (Levin 1998).
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. A prospective 3-year follow-up of children and adolescents (mean age 11.7 [SD 1.0] years) in the MTA study found that children and adolescents in the MTA study had significantly higher rates of substance use (17.4% vs. 7.8%; p=0.001) (Molina 2007). Pharmacological treatment was not associated with substance use in this study.
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).

(Continued)

Table 18.18: Important Potential Risk: Drug Abuse and Drug Dependence (Continued)

Potential Mechanisms (Continued)	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 to 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 to 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.
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."

(Continued)

Table 18.18: Important Potential Risk: Drug Abuse and Drug Dependence (Continued)

Regulatory Action Taken (Continued)	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. ("Cases of abuse and dependence . . ." was not identified as an ADR 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.)
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). Darredeau C (2007), Barrett SP, Jardin B, Pihl RO. Patterns and predictors of medication compliance, diversion, and misuse in adult prescribed methylphenidate users. Hum Psychopharmacol 2007;22(8):529-536. 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. 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.

(Continued)

Table 18.18: Important Potential Risk: Drug Abuse and Drug Dependence (Continued)

Evidence Source (Continued)	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. Molina BSG (2007), Flory K, Hinshaw SP, et al. Delinquent behavior and emerging substance use in the MTA at 36 months: prevalence, course, and treatment effects. J Am Acad Child Adolesc Psychiatry 2007:46(8):1028-1040. 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 (2003a), 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 18.19: Important Potential Risk: Lymphocytic Leukemia

Potential Risk: Lymphocytic Leukemia*	**All Randomized, Blinded Trials Population (N=321) N (%)**	**All Clinical Trials Population (N=2718) N (%)**
Frequency**		
Concerta	0	0
vs		
Placebo (N=318)	0	
Odds Ratio		
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	0
Resolved/Recovered/Recovered From AE	0	0
Recovered With Residual Effects	0	0
Continuing/Not Yet Recovered	0	0
Severity****		
Mild	0	0
Moderate	0	0
Severe	0	0

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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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 18.19: 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 18.19: 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 18.19: Important Potential Risk: Lymphocytic Leukaemia (Continued)

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

Potential Risk: Neonatal Cardio-Respiratory Toxicity (Neonatal/Foetal Tachycardia, Respiratory Distress/Apnoea)*	All Randomized, Blinded Trials Population (N=321) N (%)	All Clinical Trials Population (N=2718) N (%)
Frequency**		
Concerta	0	0
vs		
Placebo (N=318)	0	
Odds Ratio		
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	0
Resolved/Recovered/Recovered From AE	0	0
Recovered With Residual Effects	0	0
Continuing/Not Yet Recovered	0	0
Severity****		
Mild	0	0
Moderate	0	0
Severe	0	0

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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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: 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 18.20: 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 18.20: 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 cardiorespiratory 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 18.21: Important Potential Risk: Neonatal Effects on Growth

Potential Risk: Neonatal Effects on Growth)*	All Randomized, Blinded Trials Population (N=321) N (%)	All Clinical Trials Population (N=2718) N (%)
Frequency**		
Concerta	0	0
vs		
Placebo (N=318)	0	
Odds Ratio		
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	0
Resolved/Recovered/Recovered From AE	0	0
Recovered With Residual Effects	0	0
Continuing/Not Yet Recovered	0	0
Severity****		
Mild	0	0
Moderate	0	0
Severe	0	0

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension; The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA to the comparator.

**** 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 if more than one least resolved), and Severity (most severe).

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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 Effects on Growth (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). 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 that 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 18.21: Important Potential Risk: Neonatal Effects on Growth (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 PPA. 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 PPA (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 trials in adults (EU MAA 21-121\Mod5.3.3.1\Trial C-99-002 and Study C-99-025) and children (EU MAA 21 121\ Mod5.3.3.2\Trial 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)** On 20 August 2010, the Food and Drug Administration requested that the current United States Package Insert for CONCERTA be updated to remove the drug interactions statement regarding methylphenidate and clonidine in Section 7.4. The Food and Drug Administration cited lack of evidence in the adverse events reporting system (AERS) database and in controlled clinical trial data to support an association for the potential drug interaction. The Company conducted a review of retrieved SCEPTRE cases and available literature and found no evidence that could identify an interaction between methylphenidate and clonidine resulting in particular serious adverse events (GMS Report 2010). Key factors supporting this conclusion include the lack of sufficiently documented and non-confounded postmarketing cases in addition to evidence in the literature that the combination is safe and common in the treatment of ADHD. Evidence suggesting a pharmacokinetic drug interaction between methylphenidate and clonidine is very limited, and no human studies have conclusively demonstrated such an interaction. The Company Core Data Sheet for CONCERTA has been revised to remove the drug interaction statement regarding methylphenidate and clonidine. At the time of preparation of this RMP update, the Company is in the process of submitting a Clinical Overview to support a similar modification to the SmPC.
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.

(Continued)

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

Interacting substance	**Centrally acting alpha-2 agonists (eg, clonidine) (Continued)**
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).
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.

(Continued)

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

Interacting substance	**Dopaminergic drugs (Continued)**
Discussion (Continued)	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.
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.

(Continued)

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

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 1994), 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 is limited. However, community samples of adolescents report prevalence estimates between 1.5% and 6% (Cuffe 2001). Published estimates of the prevalence of ADHD in adults vary, likely due to methodological and diagnostic differences between studies. In a prospective study of more than 11,000 individuals from 10 countries including the Americas and Europe, the prevalence of ADHD among adults was estimated to be 3.4% (Fayyad 2007).

Selected country-specific prevalence of ADHD in children and adolescents 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 in childhood, ADHD is a risk factor for subsequent conduct and substance abuse problems, which may increase the risk of mortality (Barkley 1996, Wilens 2007).

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.

In a study using data from the National Comorbidity Survey Replication (NCS-R), adult persistence of ADHD, defined as the conditional prevalence of clinician-assessed ADHD in adults among the 8.1% of NCS-R respondents classified as having had ADHD in childhood, was estimated to be 36.3% in the total sample. Persistence does not differ significantly by respondent sex, age, or race-ethnicity (Kessler 2005).

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 ratio of males to females with ADHD in children is usually noted as 3:1 or greater, probably due to the greater incidence of hyperactivity in males. As the hyperactivity recedes in adolescence, the ADHD ratio in adults is 1:1, with the same number of males as females being diagnosed (Greydanus 2007).

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 US 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).

Data from the NCS-R, using multiple imputation methods based on a combination of directly interviewed respondents from the clinical reappraisal sample and multiple imputed cases in the remainder of the sample, found that clinician-assessed adult ADHD was significantly higher among men (odds ratio, 1.6) than women, and among non-Hispanic whites than non-Hispanic blacks (odds ratio, 0.3), Hispanics (odds ratio, 0.3), or other race/ethnicity (odds ratio, 0.6) (Kessler, 2006).

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). The prevalence of autism among adults with ADHD has not been described in the published literature.
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). In a study of ADHD symptoms among adults with RLS or insomnia, and controls without RLS or insomnia, more RLS patients (26%) than insomnia patients (6%) or controls (5%) had ADHD symptoms using age-adjusted total DSM-IV ADHD scores (P <.01). The mean Brown ADD scale score was greater in RLS patients (37±28) than in patients with insomnia (24±18) or controls (21±18) (P <.01). The RLS symptom severity (0-40 scale) was greater in RLS patients with ADHD symptoms (26±9) than in those without ADHD (21±10) (P <.04) (Wagner 2004).
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). Adults with ADHD have been found to have similarly high current and lifetime comorbidity with as equally severe psychiatric symptoms (Roy-Byrne 1997). Studies have found the prevalence of bipolar disorder in adult patients with ADHD to range from 5.1% to 47.1% and the prevalence of depression to range from 36% in females to 27% in males (Wingo 2007, Fishman 2007).
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. Among adults, the lifetime prevalence of severe depression was 36% in females and 27% in males with ADHD (128 subjects) compared with 4% to 6% among 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). Overall, ADHD and oppositional defiant disorder/conduct disorder have been found to co-occur in 30% to 50% of cases in both epidemiologic and clinical samples (Biederman 1991). The prevalence of antisocial and mood disorders each approach 30% among male and female adults with ADHD (Biederman 2004).
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). The co-occurrence of obsessive-compulsive disorder and ADHD has not been described among adult populations in the published literature.
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). The prevalence of anxiety disorders among male and female adults with ADHD approaches 50% (Biederman 2004).
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 128 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. In a study of adults (ages 19 to 59 years) with ADHD, a significantly greater proportion of the 312 adults with ADHD (12%) had a tic disorder (Tourette's syndrome or non-Tourette's syndrome) than of the 252 adults without ADHD (4%) (Spencer 2001).
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). The co-occurrence of Tourette's syndrome (distinct from other tic disorders) and ADHD among adult populations has not been described in the current published literature.
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 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). The co-occurrence of injury and ADHD among adults has not been described in the published literature.
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%. One study showed that more than one-fourth of the world's adult population (totalling nearly 1 billion) had hypertension in 2000, and that this proportion is projected to increase to 29% (1.56 billion) by 2025 (Kearney 2005). There have been no published reports showing an increased prevalence of hypertension for patients 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 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 ED 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%). A community-based study reported the prevalence of paroxysmal supraventricular tachycardia per 1,000 persons as follows (males vs. females, and both sexes, respectively): less than 65 years, 0.95 versus 2.37, 1.65; 65 years or over, 9.69 versus 3.65, 6.16; and all ages, 1.94 versus 2.56, 2.25. If the results could be extrapolated to the entire US population, there would be approximately 570,000 persons with paroxysmal supraventricular tachycardia in the US (Orejarena 1998).
Mortality of condition	Unknown
Identified risk	**Raynaud's Phenomenon**
Incidence of condition	Unknown
Prevalence of condition	There are no data on Raynaud's phenomenon 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 Raynaud's phenomenon. A cross-sectional study in England was conducted to determine the prevalence of Raynaud's phenomenon 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. A total of 720 children (80%) agreed to participate in the study and completed the questionnaire on the occurrence of Raynaud's phenomenon. Responses from 4 children (2 boys, 2 girls)

(Continued)

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

Identified risk	**Raynaud's Phenomenon (Continued)**
Prevalence of condition (Continued)	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 Raynaud's phenomenon. 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 Raynaud's phenomenon. 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). Recent studies aiming to determine Raynaud's phenomenon prevalence showed variable data depending on the diagnostic criteria, the survey technique (sampling design and interview and examination procedures) and the characteristics of the studied population in various geographical regions. Thus, the prevalence of Raynaud's phenomenon estimated in different studies fluctuates between 4% and 20%. Among women the frequency of Raynaud's phenomenon varies between 4% and 15% to 20%. There is also variance in the prevalence of Raynaud's phenomenon in men, although it is found with lower frequency among men compared with women (Voulgari 2000).
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). The rate of hallucinations among adults with ADHD has not been described in the published literature.
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). A prospective 8-year follow up of adolescents (mean age 16.8 [SD 1.0] years) initially enrolled as children in the MTA study found too few reports of psychosis and mania (and hypomania) for reliable statistical analysis; prevalence (≥1 of these conditions) was 2.0% for those receiving medication management, 0.9% for those receiving behavioural therapy, and 2.9% for those receiving combined management (Molina 2009).

(Continued)

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

Identified risk	**Psychosis/Mania (Continued)**
Prevalence of condition (Continued)	The rate of psychosis/mania among adults with ADHD has not been described in the published literature.
Mortality of condition	Not applicable
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). No incidence rates could be identified for symptoms of anorexia as opposed to anorexia nervosa.
Prevalence of condition	In a study of 335 adult patients (126 women and 209 men) with ADHD, 85% of women with ADHD reported a history of anorexia. Rates among men did not differ from the non-ADHD control group (Cumyn 2009).
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 height and weight of stimulant-naive subjects at baseline was greater than expected based on population norms. At the 36-month assessment, the stimulant-naive control group of children and adolescents that did not receive medication was taller and heavier than population norms (z height: 0.541; z weight: 0.765), while the 2 medicated groups that received about 1,000 days of treatment over 3 years of the MTA follow-up were slightly above or below expected relative size based on norms (newly medicated: z height 0.073 and z weight 0.293; consistently medicated: z height -0.120 and z weight 0.156). 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. Subjects who received treatment showed stimulant-related decreases in growth rates for up to 3 years without evidence of growth rebound (Swanson 2007).
Mortality of condition	Not applicable
Identified 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 UK, 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

(Continued)

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

Identified risk	**Aggression (Continued)**
Prevalence of condition (Continued)	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, in children with ADHD relative to the general population of children. At baseline in the MTA study, 14.7% of children with ADHD suffered from conduct disorder. At the 14-month follow up, the prevalence decreased to 7.2% with no significant differences observed between treatment groups (Hechtman 2005). Similarly, at the 6-year follow up no significant differences were observed for mean scores of aggression and conduct based on DSM-IV symptoms of conduct disorder between treated or untreated groups (Molina 2009). Rates of aggression among adults with ADHD have not been described in the published literature.
Mortality of condition	Not Applicable
Identified risk	**Depression**
Incidence of condition	As depression is typically chronic in nature with an unclear onset, it is difficult to accurately quantify incidence. Therefore, there are few published incidence rates.
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 (Jensen 2001). At the 14-month follow up of the MTA study, there were no statistically significant differences of mood disorders among treatment groups (Hechtman 2005). At the 6-year follow up of adolescents (mean age 14.9 [SD 1.0] years) in the MTA study, the incidences of DISC-IV diagnoses of anxiety or depression were lower in those who received behavioural therapy (4.3%) versus those who received medical management (19.1%) and combined management (16.4%) (Molina 2009). 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

(Continued)

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

Identified risk	**Depression (Continued)**
Prevalence of condition (Continued)	evidence of a familial link between the 2 mental disorders in an article reviewing family studies, which also suggested shared familial risk factors (Faraone 1997a). 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). Among adults, the lifetime prevalence of severe depression was 36% in females and 27% in males with ADHD (128 subjects) compared with 4% to 6% among males and females without ADHD (Fishman 2007). These estimates were without regard to treatment status.
Mortality of condition	Unknown

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	The global prevalence of migraine is 324.1 million (WHO 2008). Epidemiologic surveys indicate the prevalence of migraine in the US, the UK, Canada, Belgium, and Sweden is approximately 12%, whereas rates are much lower in Asian countries (Wong 1995). According to data from the American Migraine Prevalence and Prevention study, the 1-year prevalence of migraine was reported as follows in females versus males, by age: ages 12 to 17 years, 6.4% versus 4.0%; ages 18 to 29 years, 17.3% versus 5%; ages 30 to 39 years, 24.4% versus 7.4%; ages 40 to 49 years, 22.2% versus 6.5%; ages 50 to 59 years, 16.0% versus 5.0%; and ages 60 and older, 5.0% versus 1.6% (Lipton 2007). A cross-sectional study of 1,856 children aged 5 to 11 years reported an overall prevalence of migraine of 3.76% and a prevalence of ADHD of 6.1%. The prevalence of ADHD was not statistically different by headache category. However, the prevalence of hyperactivity-impulsivity symptoms was 23.7% in children with migraine compared to 8.1% in children without headache. The authors conclude that migraine is not comorbid to ADHD; however, it may be comorbid to hyperactive-impulsive behaviours (Arruda 2010).
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

(Continued)

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

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. The incidence of atrial fibrillation and flutter in the general population ranges from 20.58 per 100,000 persons per year among males 15 to 44 years of age to 1077.39 per 100,000 persons per year for males ≥85 years of age. In females, corresponding rates are 6.64 per 100,000 persons per year and 1203.7 per 100,000 persons per year, respectively. The incidence of out-of-hospital treated ventricular fibrillation is estimated to be 7.7 per 100,000 persons per year (95% CI: 4.7-11.9) (AHA 2009). The rate of cardiac arrhythmia among children and adults with ADHD has not been described in the published literature.
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%). The worldwide prevalence of atrial fibrillation ranges from 1.6% to 2%. The prevalence in the UK is approximately 1.5%, and in the US is 2.5%. In persons over the age of 65 years with cardiovascular disease, prevalence approaches 10% (Brignole 2000).
Mortality of condition	There were 37,633 deaths directly attributable to cardiac arrhythmias in the US in 2006. The underlying cause of death was atrial fibrillation in 11,555 cases, tachycardia in 586, paroxysmal supraventricular tachycardia in 118, and ventricular fibrillation in 1,076 (AHA 2009). The presence of atrial fibrillation is associated with a 10% to 15% increase in all-cause mortality in men and a 20 to 25% increase in women (Rich 2009).

(Continued)

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

Potential risk	**Sudden death**
Incidence 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). 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 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	**Ischaemic cardiac events**
Incidence of condition	Rates of ischaemic cardiac events in persons with ADHD who are not undergoing treatment have not been described in the published literature. In adults, the annual incidence of hospital admission for acute cardiac ischaemia in Europe is 1,900 per million population (Widimsky 2010), and in the US an estimated 935,000 new and recurrent events are estimated to occur annually (Lloyd-Jones 2010).
Prevalence of condition	The prevalence of myocardial infarction in adults is estimated to be approximately 4% (CDC 2005). Cardiac ischaemic events in adolescents are rare. Approximately 0.25% of paediatric emergency department visits are due to chest pain, and less than 5% of chest pain episodes are linked to a cardiac etiology. A small number of case reports describing myocardial ischaemia without predisposing risk factors in adolescents have been reported sporadically (Cava 2004). The incidence of sudden death varies largely as a function of coronary artery disease prevalence. In the adult population, the incidence of sudden death is 0.1% to 0.2% per year. The global incidence is underestimated because many sudden deaths are not witnessed. Although cardiac causes are the leading cause of sudden death, especially coronary artery disease, the exact incidences of the other causes, particularly causes of non-cardiac origin are not well estimated because sudden death cases are not systematically autopsied (de la Grandmaison 2002). The association between stimulant use and sudden death in children and adolescents aged 7 to 19 years was assessed using a case-control study in the US (Gould 2009). A total of 564 cases of sudden death and a matched group of 564 cases of motor vehicle traffic fatalities (children or adolescents were passengers) were identified using mortality data from state vital statistics records between 1985 to 1996. The primary exposure measure was the presence of amphetamine, dextroamphetamine, methamphetamine, or methylphenidate. A significant association of stimulant use with sudden death was observed based on exact conditional logistic regression (odds ratio, 7.4; 95% CI: 1.4, 74.9).

(Continued)

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

Potential risk	**Ischaemic cardiac events (Continued)**
Prevalence of condition (Continued)	Another recent retrospective study did not find an association between an increase in the risk of sudden death and the use of stimulants or atomoxetine (McCarthy 2009). Children, adolescents, and young adults aged 2 to 21 years with a prescription for methylphenidate, dexamphetamine, or atomoxetine were identified using the UK General Practice Research Database between 1January 1993 to 30 June 2006. Patients were followed from the date of first prescription to the first of the following events: death, transfer, age >21 years, or the end of the study. Seven deaths were reported from this cohort of 18,637 patient-years. For the 6 patients for whom the cause of death was known, none were considered to be sudden death.
Mortality of condition	Approximately 15% of myocardial infarctions that occur in a given year are fatal. In both developed and developing countries, 40% to 75% of all heart attack victims die before reaching the hospital (AHA 2009). Young patients have a more favorable prognosis than older patients. The in-patient mortality rate among patients under the age of 45 years is about 1% to 6%, compared with 8% to 22% in older patients (Choudhury 1999).
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 ischaemic 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 ischaemic 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. 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

(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)	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.

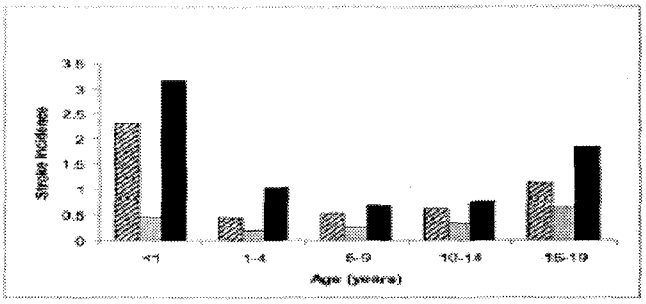

Figure. Annual stroke incidence (stroke admissions per 100,000 person-years) in California children from 1991 through 2000 by age and stroke subtype. Hatched columns = intracerebral hemorrhage; gray columns = subarachnoid hemorrhage; black columns = ischemic stroke.

There have been no published reports showing an increased risk of stroke in children or adolescents diagnosed with ADHD.
Estimated incidence of stroke (per 100,000) for men versus women in selected European countries is provided in Table 18.8, Background Incidence /Prevalence.

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: ischaemic 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 ischaemic 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 ischaemic stroke mortality, the ratio of black to white death rates was 1.7 in 1979 and 1.4 in 1998 (Fullerton 2002). Across all age groups, an estimated 16 million first-ever strokes and 5.7 million stroke deaths occurred in 2005. In the absence of additional population-wide interventions, these numbers are expected to rise to 18 million first-ever strokes and 6.5 million deaths in 2015, and to 23 million first-ever strokes and 7.8 million deaths by 2030. Although the age-specific death rates are projected to decline slightly between 2005 and 2030, population aging worldwide will result in an overall increase in rates of death from stroke for all ages combined from 89 per 100,000 in 2005 to 98 per 100,000 in 2030 (Strong 2007).

(Continued)

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

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
Potential risk	**Suicidality**
Incidence of condition	In the US, 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). 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. A recent retrospective study in the UK in patients (aged 2 to 21 years) who were prescribed stimulants or atomoxetine for the treatment of ADHD noted an increased risk of suicide; suicide was not a primary outcome of this study (McCarthy 2009). Patients were identified using the UK General Practice Research Database between 1 January 1993 and 30 June 2006. Patients were followed from the date of first prescription to the first of the following events: death, transfer, age >21 years, or the end of the study. Seven deaths were reported from this cohort of 18,637 patient-years. The SMR for suicide for patients aged 11 to 14 years was 161.91 (95% CI: 19.6, 584.88) and for patients aged 15 to 21 years was 1.84 (95% CI: 0.05, 10.25). It should be noted that for the group aged 15 to 21 years, there was 1 case of suicide and the 95% CI did not show a statistically significant difference in the rates of suicide for these adolescents and young adults with ADHD compared with the general population. (Patients were categorised into 2 age groups, due to the difference in the definition of suicide used for children and adults.) The rate of suicidal ideation and behaviour among adults with ADHD has not been described in the published literature. Epidemiologic studies estimate that between 1.1% and 4.3% of the general population attempt suicide at some time in their life. The estimated lifetime prevalence rates of suicidal ideation, plans, and attempts in the National Comorbidity Survey, a nationally representative survey of persons aged 15 to 54 years in the US, were 13.5%, 3.9%, and 4.6%, respectively (Kessler, 1999).

(Continued)

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

Potential risk	**Suicidality (Continued)**
Prevalence of condition	Unknown
Mortality of condition	The global burden of suicide is one million deaths per year, corresponding to an annual mortality of 14.5 deaths per 100,000 people (Hawton 2009). According to data from the annual Vital Statistics reports of the US, the annual suicide rates per 100,0000 persons by age group were reported as follows: for ages 15 to 24 years, 9.9; ages 25 to 44 years, 14.0; ages 45 to 64 years, 14.9; and 65 years or older, 15.6 (McKeown 2006).
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 (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. 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). In a study of adults (ages 19 to 59 years), significantly more of the 312 adults with ADHD (12%) had a tic disorder (Tourette's syndrome or non-Tourette's syndrome) than of the 252 adults without ADHD (4%) (Spencer 2001).
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

(Continued)

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

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
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 100,596 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). Among all ages, there were an estimated 2,996,800 incident cancer cases diagnosed in Europe in 2004. The most common was lung cancer (381,500 cases), followed by colorectal cancer (376,400 cases), and breast cancer (129,900 cases). The cumulative risk for all sites except non-melanoma skin cancer is estimated to be 30.1% in men and 21.7% in women (Boyle 2005).
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).

(Continued)

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

Potential risk	**Carcinogenicity (Continued)**
Prevalence of condition (Continued)	The most frequently diagnosed cancers in adults in the EU include lung cancer (13.2%), colorectal cancer (13%), and breast cancer (12.8%) (Boyle 2005).
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). An estimated 1,711,000 cancer deaths occurred among all ages in Europe in 2004. Lung cancer is the leading cause of cancer death (341,800, 20% of all deaths), followed by colorectal cancer (203,700, 11.9%), stomach cancer (137,900, 8.1%) and breast cancer (129,900, 7.6%) (Boyle 2005).
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 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. In 2001, the unadjusted prevalence of illicit methylphenidate use in the US 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 in the US reported nonmedical use of methylphenidate in the previous year. Darredeau et al (2007) examined patterns of medication compliance, diversion, and misuse in a sample of 66 adults in Canada (53% male, mean age 27 years [SD 9.4]) currently prescribed methylphenidate recruited through advertisements in a local Montreal newspaper, on college and university based Internet sites/bulletin boards, and a local adult ADHD support group. A total of 44% of the subjects admitted to diverting methylphenidate, primarily by giving it away, and 29% admitted to using methylphenidate inappropriately. Subjects completed an 18-item ADHD symptom checklist based on DSM-IV diagnostic criteria as part of the study; mean (SD) scores were 27.5 (7.9) and 26.2 (10.5) for those categorised as misusers and non-misusers, respectively.

(Continued)

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

Potential risk	**Diversion [of Methylphenidate] (Continued)**
Mortality of condition	According to poison control data, Toxic Exposure Surveillance System (TESS), there were over 4,900 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
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).
Prevalence of condition	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%). Children and adolescents within the MTA study were reported to have significantly higher rates of substance use at 36 months of follow up compared to a local normative comparison group (17.4% vs 7.8%, respectively). Those randomised to intensive behaviour therapy reported less 24-month substance use than other children and adolescents in the MTA study; however, no other effects of initial treatment assignment were observed. The authors conclude that the association between medication treatment and substance use need to be re-evaluated at older ages (Molina 2007). Adults with ADHD are believed to be at greater risk of licit and illicit drug use than adults without ADHD (Darredeau 2007). ADHD is over-represented in adults seeking treatment for cocaine and other drug dependence. In a study of 281 cocaine abusers seeking treatment, 12% (n=34) met the definition of ADHD in childhood. Of the entire sample, 10% had ADHD in adulthood (Levin 1998).
Mortality of condition	Unknown

(Continued)

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

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).
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**
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 IR formulations.

1.10. Summary - Ongoing Safety Concerns

Important identified and potential risks for which there are specific additional pharmacovigilance and/or additional risk minimisation activities (ongoing or proposed) are indicated by a star (*) 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* Aggression* Depression*
Important potential risks	Migraine Repetitive behaviours QT prolongation Cyanosis Arrhythmias* Sudden death* Ischaemic cardiac events* Cerebrovascular disorders* Hostility* 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
Important missing information[a]	Long-term cardiovascular effects* Long-term cerebrovascular effects* Long-term psychiatric effects*

* Important identified and potential risks for which there are specific additional pharmacovigilance and/or additional risk minimisation activities (ongoing or proposed)

[a] Long-term safety was identified as important missing information in the Rapporteur's (MHRA) Assessment Report dated 3 Dec 2008; long-term cardiovascular, cerebrovascular, and psychiatric effects were specified in the Assessment Report dated 23 Sep 2010.

The planned actions for each of the above ongoing safety concerns are described in Table 25 (additional pharmacovigilance actions) and Table 28 (additional risk minimisation action/educational tool).

2. PHARMACOVIGILANCE PLAN

2.1. Routine Pharmacovigilance Practices

2.1.1. Objectives

The objective of the routine pharmacovigilance program conducted by the Global Medical Safety (GMS) group 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 GMS 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 GMS Physician and other functional groups within GMS, 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]
Aggression Depression	• 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).
Important Potential Risks	
Migraine Repetitive behaviours QT prolongation Cyanosis Hostility Tics/Tourette's syndrome/Dystonias Carcinogenicity Withdrawal syndrome Diversion Drug abuse and Drug Dependence Lymphocytic leukaemia Neonatal cardio-respiratory toxicity(neonatal/foetal tachycardia, respiratory distress/apnoea) Neonatal effects on growth	• 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).
Arrhythmias Ischaemic cardiac events	• Routine pharmacovigilance • Follow up on FDA pharmacoepidemiologic study (ongoing)[a]
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] • Meta-analysis of the risk of suicidality[a]

(Continued)

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

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]
Off-label use	• Routine pharmacovigilance • IMS prescription data drug utilisation survey (DUS) (ongoing)[a]
Important missing information	
Long-term safety (cardiovascular, cerebrovascular, and psychiatric effects)[b]	• Routine pharmacovigilance was described in Section 2.1. • Monitor external research and data collected as part of internal pharmacovigilance activities for relevant safety information including psychiatric effects

[a] See Section 2.3 for further information.
[b] Long-term safety was identified as important missing information in the Rapporteur's (MHRA) Assessment Report dated 3 Dec 2008; long-term cardiovascular, cerebrovascular, and psychiatric effects were specified in the Assessment Report dated 23 Sep 2010.

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**
Actions proposed	Enhanced pharmacovigilance through the use of a questionnaire (follow up for sudden death, cerebrovascular disorders, suicidality) 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, Arrhythmias, Sudden death, Ischaemic cardiac events, Cerebrovascular Disorders**
Action proposed	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 2-24 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, within 6 months of the publication of the data, and will update the Core RMP, and where appropriate the Core SmPC/PIL, to reflect the findings. Study results are expected in the first quarter of 2011.
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	Annex IV of May 2009 EC decision 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 continue to screen for new publications on additional MTA study results and will update the RMP, if relevant for identified/potential risks or indicating new previously unrecognized risks, and where appropriate the SmPC/PIL to reflect the findings. 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 and 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	Annex IV of the May 2009 EC decision 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."

(Continued)

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

Safety Concerns	**Decreased Rate of Growth, Sexual Maturation (Delayed) (Continued)**
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 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 tool) for severe risks with a significant impact on patient safety
Milestones for evaluation and reporting including justification for choice of milestones	This IIS study is ongoing; results to be provided upon completion
Titles of protocols	Not applicable
Safety Concern	**Suicidality**
Action proposed	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."
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	The feasibility report was submitted to MHRA on 31 July 2009. Future milesones include: Commencement of meta-analysis activities: 31 Oct 2010 Completion of data collection: 31 Jan 2011 Completion of independent review of blinded subject narratives: 30 Apr 2011 Completion of meta-analysis: 30 Jun 2011 Submission of final report: 30Sep 2011
Titles of protocols	Not applicable

(Continued)

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

Safety Concerns	**Off-Label Use**
Action proposed	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 5 years.
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 plan to submit a report presenting data from the drug utilisation study for 2009 with PSUR work-share procedure UK/H/PSUR/0068/002 no later than 9 December 2010.
Titles of protocols	Not applicable
Safety Concern	**Long-Term Safety (Cardiovascular, Cerebrovascular, and Psychiatric Effects)**
Action proposed	Monitor external research and data collected as part of internal pharmacovigilance activities for relevant safety information including psychiatric effects
Objective of proposed action	Evaluate adverse cardiovascular, cerebrovascular, and 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	To provide information as it becomes available
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 third 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

* 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.

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" added in parenthesis by the Company)

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.

The second version of the RMP addressed 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 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.)

This RMP update (Version 3) addresses the requests from the P-RMS's (MHRA) Assessment Report dated 23 September 2010 that included the following requests:

- Ischaemic cardiac events was designated a new potential risk (not previously included in the CONCERTA RMP)
- Aggression and depression were designated as identified risks (formerly potential risks)

- Missing information regarding long-term safety related to the key risks of cardiovascular, cerebrovascular, and psychiatric effects was added (Section 1.3.1).

Per the Assessment Report, data on duration of exposure and long-term safety for select risks were added to the tables in Section 1.5. Updates were provided for ongoing pharmacovigilance activities including those specifically mentioned in the Assessment Report (ie, MTA study, meta-analysis of methylphenidate and suicidality, and long-term safety). The Assessment Report clarified that for the potential risk of carcinogenicity, routine (not additional) pharmacovigilance is required. The potential risk of Neonatal effects on growth (via lactation) was revised by deletion of "(via lactation)" for consistency with the name of this risk in the Assessment Report. (The pharmacoviligance activities for diversion remained unchanged; however, they are classified as routine pharmacovigilance.) Requests were also received for revisions to the planned educational tool. In addition, redundancy was removed from the RMP.

The paediatric risk tables (statistical data section) were updated. The search terms utilized to identify particular events were expanded for consistency with the search terms employed for postmarking data (the terms are provided in Annex 5). The updated CONCERTA integrated paediatric database was employed; the updates to the database since the last version of the RMP are as follows: a more recent Medical Dictionary for Regulatory Activities (MedDRA) version was implemented, minor changes to the data resulting from a few corrections to the assignment of treatment emergence were executed, and the data from 136 adult subjects enrolled in Trial C-99-018-00 were removed. (Children, adolescents, and adults with ADHD were enrolled in this open-label trial.) Also, the format of the paediatric risk tables was updated to more closely resemble the current template used by the Company for the preparation of RMPs.

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
Commencement of meta-analysis activities		31 Oct 2010	
Completion of data collection		31 Jan 2011	
Completion of independent review of blinded subject narratives		30 Apr 2011	
Completion of meta-analysis		30 Jun 2011	
Submission of final report		30Sep 2011	
Drug utilisation analysis based on IMS prescription data	2009 Data	9 Dec 2010	Ongoing
Monitor external research and data collected as part of internal pharmacovigilance activities for relevant safety information including psychiatric effects To provide information as it becomes available			Ongoing

[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 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 every 6 months (Sec 4.4, SmPC) Interaction wording between methylphenidate and vasopressor agents, antihypertensive drugs, and non-selective, irreversible MAO-inhibitors (Sec 4.5, SmPC) (hypertension only) Precaution that paediatric patients using methylphenidate may experience changes in diastolic and systolic blood pressure of over 10 mmHg relative to controls (Sec 4.4, SmPC) Hypertension and Tachycardia are listed as ADRs
Raynaud's phenomenon *(Identified risk)*	Yes	Raynaud's phenomenon and Peripheral coldness are listed as ADRs
Hallucinations (auditory, skin sensation, visual disturbance) Psychosis/Mania *(Identified risks)*	[a]	Pre-treatment screening for psychiatric disorders and ongoing monitoring at each adjustment of dose and at least every 6 months 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 is advised at each adjustment of dose and then at least every 6 months. There is additional precautionary language concerning monitoring of psychosis, mania, and delusions with long-term use (more than 12 months) of methylphenidate (Sec 4.4, SmPC) Hallucination, Mania, and Psychotic disorders are listed as ADRs

(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/appetite is required (Sec 4.2 SmPC, Ongoing monitoring; Sec 4.4 SmPC, Long-term use) and patients not gaining weight as expected are advised to have treatment interrupted (Sec 4.4, SmPC) Anorexia and Decreased appetite are listed as ADRs
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 the long-term use of methylphenidate in children" 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
Aggression *(Identified risks)* Hostility Tics/Tourette's syndrome/ Dystonias *(Potential risks)*	[a]	Warning to monitor development or worsening of aggression or hostility, and motor or verbal tics/Tourette's syndrome is advised at each adjustment of dose and then at least every 6 months. There is additional precautionary language concerning monitoring of aggressive or hostile behaviour, and motor or vocal tics with long-term use (more than 12 months) of methylphenidate (Sec 4.4, SmPC). Aggression, Anger, Tics, and "Worsening of pre-existing tics of Tourette's syndrome" are listed as ADRs
Depression *(Identified risk)*	[a]	Contraindicates use in patients with a diagnosis or history of severe depression (Sec 4.3, SmPC) Warning under 'Forms of bipolar disorder' to screen for comorbid depressive symptoms 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 and Transient depressed mood are listed as ADRs
Migraine *(Potential risk)*	Yes	Migraine is listed as an ADR

(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
Repetitive behaviours *(Potential risk)*	Yes	Repetitive behaviours is listed as an ADR
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 patients with palpitations and arrhythmia. 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, Extrasystoles, and Ventricular Extrasystoles are listed as ADRs
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
Ischaemic cardiac events *(Potential risk)*	[a]	Contraindicates use in patients with pre-existing cardiovascular disorders including arterial occlusive disease, angina, and myocardial infarction (Sec 4.3, SmPC) Precautionary language "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" (Sec 4.4, SmPC) Angina pectoris and Myocardial infarction are listed as ADRs

(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
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 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 (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
Suicidality *(Potential risks)*	[a]	Contraindicates use in patients with a diagnosis or history of suicidal tendencies (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 family history of suicide prior to initiating treatment in patients with comorbid bipolar disorder (Sec 4.4, SmPC) Suicidal ideation and "Suicidal attempt (including completed suicide)" are listed as ADRs
Effect on final height *(Potential risk)*	Yes	Pre-treatment screening 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) 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

(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
Off-label use *(Potential risk)*	[a]	States that safety and efficacy of CONCERTA in children under 6 years of age and in the elderly has not been established and should not be used in these populations (Sec 4.2, SmPC) States that "Methylphenidate is not licensed for use in adults in ADHD. Safety and efficacy have not been established in this age group" (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 warnings regarding abuse are given (Sec 4.4, SmPC) "Cases of abuse and dependence have been described, more often with immediate-release formulations" is listed as an ADR
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 cardiorespiratory toxicity, specifically foetal tachycardia and respiratory distress have been reported in spontaneous case reports"
Neonatal effects on growth *(Potential risk)*	Yes	The core EU SmPC was amended to include the following (lactation, Sec 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"

(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
Long-term safety (cardiovascular, cerebrovascular, and psychiatric effects) [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 in SmPC Sections 4.2 and 4.4 for cardiovascular status, ... development of de novo or worsening of pre-existing psychiatric disorders. Psychiatric disorders to monitor for 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

[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] Long-term safety was identified as important missing information in the Rapporteur's (MHRA) Assessment Report dated 3 Dec 2008; long-term cardiovascular, cerebrovascular, and psychiatric effects were specified in the RMP Assessment Report dated 23 Sep 2010.

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

Educational materials are in development as part of the Article 31 referral commitments, to help physicians use methylphenidate in children and adolescents according to the guidance given in the EU harmonised prescribing information. 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.

The Company in coordination with 4 of the other largest MAHs 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 Health Authorities requests regarding this educational tool are being addressed by the MAHs 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 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 may be mentioned during company specific medical educational events on ADHD (symposia etc.) and on materials. The Web site will be accessible to all medical professionals. 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	Pharmacovigilance Activities (Routine and Additional)[a]	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) (HTN) 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]
Anorexia *(Identified risk)*	Routine pharmacovigilance	Labelling: SmPC: Posology/Admin (Sec 4.2) 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]
Aggression *(Identified risk)* 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]
Depression *(Identified risk)*	Routine pharmacovigilance	Labelling: SmPC: Contraindication (Sec 4.3) SmPC: Warning (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	Pharmacovigilance Activities (Routine and Additional)[a]	Risk Minimisation Activities (Routine and Additional)[b]
Arrhythmias Ischaemic cardiac events *(Potential risks)*	Routine pharmacovigilance Follow-up on FDA pharmacoepidemiologic study (ongoing)	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]
Suicidality *(Potential risk)*	Routine pharmacovigilance Enhanced pharmacovigilance (ongoing) 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	Labelling: SmPC: Preclinical safety data (Sec 5.3)

(Continued)

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

Safety Concern	Pharmacovigilance Activities (Routine and Additional)[a]	Risk Minimisation Activities (Routine and Additional)[b]
Off-label use Diversion *(Potential risks)*	Routine pharmacovigilance IMS prescription data drug utilisation survey (DUS)	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) SmPC: Warning (Sec 4.8) 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 *(Potential risk)*	Routine pharmacovigilance	Labelling: SmPC: Warning (Sec 4.6)
Long-term safety (cardiovascular, cerebrovascular, and psychiatric effects) safety[d]	Routine pharmacovigilance Monitor external research and data collected as part of internal pharmacovigilance activities for relevant safety information including psychiatric effects	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] Long-term safety was identified as important missing information in the Rapporteur's (MHRA) Assessment Report dated 3 Dec 2008; long-term cardiovascular, cerebrovascular, and psychiatric effects were specified in the RMP Assessment Report dated 23 Sep 2010.

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