Mutual Recognition Procedure

Type II variation
Preliminary Variation Assessment Report

ConcertaXL
Methylphenidate

UK/H/0544/001/II/056

Marketing Authorisation Holder: Janssen-Cilag

Date: 14/7/10

ADMINISTRATIVE INFORMATION

Name of the medicinal product(s) in the RMS	Concerta XL
INN (or common name) of the active substance(s)	Methylphenidate
Pharmaco-therapeutic group (ATC code)	N06BA
Pharmaceutical form(s) and strength(s)	Prolonged Release Tablets 18mg, 27mg, 36mg, 54mg

Reference Number for the Mutual Recognition Procedure	UK/H/0544/001/II/056
Member States concerned	AT DE EL SE IE NL FR FI ES LU IS BE PT NO

In the Reference Member State:

Marketing authorisation holder's name and address	JANSSEN-CILAG LIMITED 50-100 Holmers Farmway High Wycombe Bucks HP12 4EG
Date of first authorisation	19/2/02
Marketing authorisation number	PL 00242/0373

RMS contact person	**Name: E Davidson** Tel: Email: elizabeth.davidson@mhra.gsi.gov.uk
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Variation Procedure Start Date	5/5/10
Date of Preliminary Variation Assessment Report	14/7/10
Day 90 (excluding clock-off time)	29/7/10
Deadline for Comments by CMS	3/8/10

Nature of change requested	New indication: ADHD in adults whose ADHD diagnosis was established before the age of 18 years and whose symptoms persist into adulthood

I. RECOMMENDATION

Based on the review of the data on safety and efficacy the RMS considers that the variation application UK/H/0544/001/II/056 for Concerta (Methylphenidate MR), in the treatment of ***adult ADHD***, for the following proposed changes:

CONCERTA XL is indicated as part of a comprehensive treatment programme for Attention Deficit Hyperactivity Disorder (ADHD). ***It may be used when remedial measures alone prove insufficient*** in children aged 6 years of age and over ***as well as in adults whose ADHD diagnosis was established before the age of 18 years and whose symptoms persist into adulthood.***

is not approvable since potential serious risks to public health (see section V.1) have been identified which preclude a recommendation for such variation and recommend that the variation to the terms of the Marketing Authorisation should be refused.

II. EXECUTIVE SUMMARY

Introduction: This is a Type II Complex variation undergoing a Mutual Recognition Procedure with the UK as Reference Member State (RMS). The MAH are seeking a new indication of use in adults with Attention Deficit Disorder (ADHD).

Current indication: Methylphenidate has recently been through a harmonisation procedure for its current indication of the treatment of ADHD as part of a comprehensive treatment programme in children aged 6 years or older.

Evidence submitted:

- Environmental Impact Assessment
- Preclinical Studies
- Pharmacokinetic (3) and Abuse Potential Studies (3)
- 2 European fixed dose placebo controlled studies (Studies 3002 and 3013)
- 1 US flexible dosing study (Study 02-159)
- 1 withdrawal study (Study 3004)
- Open label safety studies
- Literature review

Efficacy: Studies 3002 and 02-159 demonstrate efficacy over placebo and study 3013 demonstrated efficacy for the higher dose (72mg) of methylphenidate (MPH) but not the lower dose (54mg). There is a concern over the handling of missing data. The withdrawal study failed to demonstrate longer term efficacy as the benefit over placebo was small and the numbers completing the study were small. The optimum duration of treatment is not clear.

Safety: Concerns are raised over the extent of psychiatric adverse events in the adult population. The proportion of subjects with a sustained increase in heart rate and BP has not presented.

RMP assessment: Many concerns are raised over the psychiatric adverse events, effect of sustained increases in heart rate and blood pressure and clinically significant weight loss. The greater exposure of women with child bearing potential has not been addressed particularly in view of the possible spina bifida signal. There is a need for contraceptive advice and a pregnancy registry.

Conclusion The efficacy for the proposed indication has not been clearly demonstrated. The currently proposed indication would result in inappropriate usage as it is not consistent with DSM IV diagnostic criteria.

II.1 Scope of the variation

The MAH are applying for a new indication of ADHD in adults who were first diagnosed in childhood but whose symptoms have persisted into adulthood.

III. SCIENTIFIC DISCUSSION

Background

The MAH are seeking a new indication of use in adults with Attention Deficit Disorder (ADHD). The MAH estimates a prevalence of adult ADHD of 3.7% based on a prospective study in 1100 individuals by Fayyad 2009 (Clinical Overview). In a European guideline (Taylor et al 2004) the prevalence of childhood ADHD was thought to be between 3-5% and should 30-60% continue into adulthood, this estimate may be too high.

The concept of adult ADHD is generally accepted but the robustness of the diagnosis generates much more concern. One of the key diagnostic symptoms of hyperactivity is not so apparent in adults and they tend to present more with the problems associated with inattention. For a diagnosis of ADHD in children symptoms should have been present from a young age, often less than 2 years. Thus establishing the age of onset retrospectively is another challenge to the diagnosis of individuals that first present in adulthood. There is a CHMP Guideline on the Clinical Investigation of Medicinal Products for the Treatment of ADHD EMEA/CHMP/EWP/431734/2008. Atomoxetine is the only active substance with an indication for adult ADHD, although evidence based guidelines such as British Association for Psychopharmacology and NICE, do support the use of methylphenidate in adult ADHD.

The MAH have sought Scientific Advice on several occasions. The problems surrounding the diagnostic robustness of the studied populations has led the MAH to apply for an indication of ADHD in adults who were first diagnosed in childhood but whose symptoms have persisted into adulthood. The study programme consisted of a mixed adult ADHD population and thus the data that have been presented consist of a retrospective subgroup analysis. This variation assessment report considers the robustness of this approach.

III.1 Quality aspects

N/A

Environmental Impact

The MAH has conducted a satisfactory Environmental Risk Assessment. The results indicate that the increase in production of methylphenidate to supply the new patient population is unlikely to pose a risk to the environment.

III.2 Non clinical aspects

No new studies have been undertaken for this indication but a series of non-clinical studies were conducted for the Japanese Regulatory Authorities. In addition there is one study that is conducted in lactating rats which is deemed relevant to the application. Generally it is assessed that the human data is

now available and takes precedence over the animal data but for the study in lactation only 1 human case in mentioned in Section 4.6 and it is proposed that the following sentence is added:

> ***In rats, methylphenidate-associated radioactivity was found in the milk at concentrations up to around 1.5 times that in the plasma.***

In addition the wording to Section 5.3 should be clarified as follows:

> **Pregnancy-embryonic/foetal development**
> Methylphenidate is not considered to be teratogenic in rats and rabbits. Fetal toxicity ***in the form of total litter loss*** was noted in rats at maternally toxic doses

III.3 Clinical aspects

III.3.1 Clinical pharmacology

Table 1: Table of Clinical Studies Summarized in Module 2.7.2

Study	Study Design / Subject Population	Objectives	Treatments/dosing	Location of Report
02-160	Open-label, fixed-sequence, single- and multiple dose pharmacokinetics and safety study / 27 (20 M/7 F) Healthy adults	To assess single- and multiple-dose PK and safety of high doses of CONCERTA	CONCERTA 54 mg, 72 mg, 108 mg, 144 mg / oral dosing once daily for 4 days	Mod5.3.3.1\02-160 Healthy Subject PK & Initial Tolerability Study Reports
12-004	Open-label, single-dose, randomized, crossover pharmacokinetic study / 19 (14 M/5 F) Healthy adults	To determine the PK of methylphenidate from whole and crushed CONCERTA Tablets and crushed RITALIN tablets	CONCERTA 18 mg (whole and crushed), RITALIN 20 mg (crushed)/oral single dose	Mod5.3.3.1\12-004 Healthy Subject PK and Initial Tolerability Study Reports
12-302	Double-blind, randomized, placebo-controlled, crossover study / 18 (16 M/2 F) Healthy adults with a recent history of substance abuse	To assess the abuse potential of CONCERTA as compared to RITALIN and placebo	RITALIN 60 mg; placebo; CONCERTA 108 mg/oral single dose	Mod5.3.4.1\12-302 Healthy Subject PD and PK/PD Study Reports
12-005	Double blind, placebo-controlled, randomized, crossover study / 49 (37 M/12 F) Healthy adults with a history of recreational stimulant use	To evaluate the abuse potential of CONCERTA as compared to RITALIN and placebo; and to assess the PK-PD relationships (PK-PD) of methylphenidate when dosed as CONCERTA and RITALIN	RITALIN 60 mg; placebo; CONCERTA 108 mg/oral single dose	Mod5.3.4.1\12-005 Healthy Subject PD and PK/PD Study Reports
12-007	Double-blind, placebo-controlled, randomized, crossover study with a qualifying and a treatment phase / 55 (42 M/ 13 F) Healthy normal adults with a history of light (occasional) stimulant drug use	To assess abuse potential of CONCERTA as compared to RITALIN and placebo at comparable doses.	RITALIN 50 and 90 mg; placebo; CONCERTA 54 and 108 mg/oral single dose	Mod5.3.4.1\12-007 Healthy Subject PD and PK/PD Study Reports
12-001	Open-label, multiple-dose, parallel design, pharmacokinetic study / 26 (19 M/7 F) Healthy adolescents with ADHD	To assess the multiple-dose PK of CONCERTA.	CONCERTA 18 mg, 27 mg, 36 mg, 54 mg, 72 mg,/oral dosing once daily for 6 days	Mod5.3.3.2\12-001 Patient PK Study Reports

Study 02-160 (pK healthy adults)

This was an open-label, fixed sequence, four period crossover single and multiple dose pharmacokinetics and safety/tolerability study in healthy male and female adult subjects. In each period, subjects received single oral daily doses of CONCERTA for four days, with sequential dose escalation for each period. The doses evaluated in the study were 54, 72, 108 and 144 mg given as combinations of CONCERTA 36 and 54 mg tablets. On Days 1 and 4 of each period blood samples were collected over 24 hours for characterizing the

pharmacokinetics of Total methylphenidate (nonchiral assay for d- and l- isomers combined) and its major metabolite, α-phenyl piperidine acetic acid (PPAA, also abbreviated as PPA in some reports) (nonchiral assay for d- and l- isomer combined), which has little or no pharmacologic activity. Dosing in study periods was separated by a three-day washout period. Plasma was isolated from the blood samples and analyzed for MPH and PPAA using validated LC/MS/MS methods.

Twenty-seven subjects participated in the study; seven subjects in the weight range of 55 to 73 kg; ten subjects in the weight range of 74 to 91 kg and ten subjects in the weight range of 92 to 109 kg, such that all subjects received methylphenidate doses in the 1 to 2 mg/kg range in some period. Pharmacokinetic data were available and analyzed from 25 subjects who completed blood sampling in all four treatment periods. Two subjects withdrew due to AEs. Due to the short half-life of about 3.5 hours, there is minimal accumulation of methylphenidate upon multiple dosing. Hence, PK parameters obtained from Day 4 represent steady-state.

The mean age of the subjects was 29 years (range 20-50).

methylphenidate obtained from noncompartmental analysis for Days 1 and 4.

Table 2: Mean (SD) Plasma Pharmacokinetic Parameters for Total Methylphenidate for Subjects Who Completed Blood Sampling in All Four Treatments (N = 25)

Dose (mg)	C_{max} (ng/mL)	T_{max}[a] (h)	AUC_{inf} (ng.h/mL)	CL/F (L/h/kg)	$T_{½}$ (h)	Exposure Ratio[b] (AUC_{tau}/AUC_{inf})*
DAY 1						
54	12.0	6	130	5.28	3.58	1.08[c]
	(3.54)	(1-10)	(32.4)	(1.48)	(0.63)	1.02, 1.14
72	17.1	6	196	4.80	3.57	0.96
	(5.80)	(5-10)	(65.7)	(1.50)	(0.62)	0.93, 1.00
108	26.3	6	293[c]	4.73[c]	3.59[c]	1.07[c]
	(6.38)	(5-12)	(76.5)	(1.32)	(0.54)	0.97, 1.04
144	35.8	6	381[d]	4.80[d]	3.65[d]	1.08[d]
	(9.72)	(1-12)	(105)	(1.27)	(0.60)	1.02, 1.14
DAY 4						
Dose (mg)	$C_{max,ss}$ (ng/mL)	$T_{max,ss}$[a] (h)	AUC_{tau} (ng.h/mL)	CL_{ss}/F (L/h/kg)	$T_{½}$ (h)	$C_{min,ss}$ (ng/mL)
54	12.5	6	139[c]	4.81[c]	3.60	0.496
	(2.84)	(1-10)	(33.6)	(1.19)	(0.84)	(0.305)
72	16.1	6	185	4.94	3.63	0.807
	(4.60)	(5-8)	(49.0)	(1.27)	(0.49)	(0.428)
108	26.0	6	291	4.70	3.60	1.23
	(6.99)	(5-10)	(71.1)	(1.19)	(0.56)	(0.607)
144	36.9	6	419	4.55	3.42	1.73
	(11.3)	(1-8)	(137)	(1.77)	(0.50)	(0.894)

[a] Median and range are listed
[b] Mean and 95% confidence interval are listed
[c] N = 24
[d] N = 23
* AUC_{tau} – area under the curve over a dosing interval at steady-state; AUC_{inf} – area under the curve after first dose extrapolated to infinity

Table 3: Mean (SD) Plasma Pharmacokinetic Parameters for Total PPAA for Subjects Who Completed Blood Sampling in All Four Treatments (N = 25)

Dose (mg)	C_{max} (ng/mL)	T_{max}[a] (h)	AUC_{inf} (ng.h/mL)	$T_{½}$ (h)	Exposure Ratio[b] (AUC_{tau}/AUC_{inf})*
			DAY 1		
54	477	8	8068	8.04	1.00[c]
	(108)	(5-10)	(1405)	(1.29)	0.96, 1.04
72	609	10	10713	8.01	1.01
	(95.8)	(5-10)	(1634)	(1.29)	0.99, 1.04
108	937	10	16766[d]	8.09[d]	1.00[d]
	(144)	(5-12)	(2399)	(1.17)	0.96, 1.04
144	1220	8	21429[d]	8.16[d]	1.05[d]
	(212)	(5-12)	(3071)	(1.32)	1.00, 1.10
			DAY 4		
Dose (mg)	C_{max} (ng/mL)	T_{max}[a] (h)	AUC_{tau} (ng.h/mL)	$T_{½}$ (h)	$C_{min,ss}$ (ng/mL)
54	536	8	7941[e]	8.23[e]	120
	(84.7)	(5-12)	(1172)	(2.04)	(45.1)
72	706	8	10788	8.22[e]	167
	(106)	(5-12)	(1446)	(1.03)	(45.3)
108	1061	8	16465	8.45[e]	271
	(165)	(5-12)	(2497)	(1.21)	(81.2)
144	1430	8	22288	9.06[e]	379
	(216)	(1-12)	(3092)	(2.79)	(99.8)

[a] Median and range are listed
[b] Mean and 95% confidence interval are listed
[c] N = 24
[d] N = 22
[e] N = 23
* AUC_{tau} – area under the curve over dosing interval at steady-state; AUC_{inf} – area under the curve after first dose extrapolated to infinity

Safety

Table 10-5. **Mean Systolic Blood Pressure (mm Hg) by Day of Treatment and Time after Treatment with OROS Methylphenidate HCl**

	54 mg (Period 1)	72 mg (Period 2)	108 mg (Period 3)	144 mg (Period 4)	p-Value[a]
Screening	130.3				
Check-in[b]	129.1	121.6	116.0	122.4	<0.001
Before treatment[c]	120.1	116.1	109.9	114.5	<0.001
Day 1	n = 27	n = 27	n = 27	n = 26[e]	
4 hours after dosing	119.4	119.0	120.4	122.5	0.626
8 hours after dosing	121.3	122.8	124.9	127.9	0.136
12 hours after dosing	127.0	126.1	127.8	127.5	0.842
Day 2	n = 27	n = 27	n = 27	n = 26	
4 hours after dosing	120.8	123.1	124.5	129.5	0.044
8 hours after dosing	126.8	127.1	127.3	126.2	0.965
12 hours after dosing	127.0	131.2	128.1	131.7	0.017
Day 3	n = 27	n = 27	n = 27	n = 25	
4 hours after dosing	123.2	127.0	124.6	119.7	0.016
8 hours after dosing	122.2	123.6	125.4	127.7	0.286
12 hours after dosing	134.0	129.1	126.7	129.6	0.077
Day 4	n = 27	n = 27	n = 26	n = 25	
4 hours after dosing	118.1	121.0	122.6	124.5	0.108
8 hours after dosing	127.1	122.7	125.4	123.3	0.074
12 hours after dosing	127.3	130.4	126.2	128.7	0.224
End of Study				n = 27	
After Day 4, Period 4[d]				124.3	

a: Repeated measures ANOVA for differences among treatments
b: Subjects were required to check-in on the day before each treatment period. This usually occurred during the late afternoon or early evening.
c: The measurement before treatment was generally performed about 30 to 45 minutes before drug was administered (at 8:00 AM). This value refers to the measurement performed before the first dose of each study period.
d: This measurement was obtained on the day following the last day of Period 4.
e: Subject 22 took 108 mg instead of 144 mg on Day 1 Period 4 and discontinued after that point. Subject 12 did not take doses for Period 4, Days 3 and 4.

Table 10-6. Mean Diastolic Blood Pressure (mm Hg) by Day of Treatment and Time after Treatment with OROS Methylphenidate HCl

	54 mg (Period 1)	72 mg (Period 2)	108 mg (Period 3)	144 mg (Period 4)	p-Value[a]
Screening	70.5				
Check-in[b]	76.4	72.6	70.3	73.5	0.005
Before treatment[c]	73.5	71.7	68.2	71.2	0.006
Day 1	n = 27	n = 27	n = 27	n = 26[e]	
4 hours after dosing	73.2	72.4	71.6	76.4	0.003
8 hours after dosing	73.4	74.5	74.7	77.0	0.235
12 hours after dosing	75.5	75.0	76.7	77.6	0.359
Day 2	n = 27	n = 27	n = 27	n = 26	
4 hours after dosing	71.8	75.3	76.3	76.5	0.014
8 hours after dosing	74.0	76.4	76.5	77.7	0.090
12 hours after dosing	76.4	81.3	77.3	80.0	<0.001
Day 3	n = 27	n = 27	n = 27	n = 25	
4 hours after dosing	73.6	75.9	76.0	73.9	0.094
8 hours after dosing	75.1	76.3	77.4	77.9	0.483
12 hours after dosing	82.1	77.3	78.3	80.0	0.001
Day 4	n = 27	n = 27	n = 26	n = 25	
4 hours after dosing	72.7	72.7	75.3	76.0	0.147
8 hours after dosing	76.6	76.1	78.0	77.5	0.501
12 hours after dosing	77.7	79.4	77.4	78.3	0.348
End of Study				n = 27	
After Day 4, Period 4[d]				76.0	

a: Repeated measures ANOVA for differences among treatments
b: Subjects were required to check-in on the day before each treatment period. This usually occurred during the late afternoon or early evening.
c: The measurement before treatment was generally performed about 30 to 45 minutes before drug was administered (at 8:00 AM). This value refers to the measurement performed before the first dose of each study period.
d: This measurement was obtained on the day following the last day of Period 4.
e: Subject 22 took 108 mg instead of 144 mg on Day 1 Period 4 and discontinued after that point. Subject 12 did not take doses for Period 4, Days 3 and 4.

Table 10-7. **Mean Heart Rate (beat/min) by Day of Treatment and Time after Treatment with OROS® Methylphenidate HCl**

	54 mg (Period 1)	72 mg (Period 2)	108 mg (Period 3)	144 mg (Period 4)	p-Value[a]
Screening	70.2				
Check-in[b]	77.3	79.6	80.6	79.3	0.611
Before treatment[c]	76.1	70.1	67.7	74.1	<0.001
Day 1	n = 27	n = 27	n = 27	n = 26[e]	
4 hours after dosing	70.8	73.1	78.7	82.1	0.004
8 hours after dosing	83.7	85.3	90.3	93.9	0.017
12 hours after dosing	83.9	87.0	94.3	99.0	<0.001
Day 2	n = 27	n = 27	n = 27	n = 26	
4 hours after dosing	77.8	86.5	87.7	94.1	<0.001
8 hours after dosing	85.0	90.3	89.3	96.5	0.005
12 hours after dosing	87.2	94.3	91.9	98.2	0.007
Day 3	n = 27	n = 27	n = 27	n = 25	
4 hours after dosing	82.0	87.7	90.7	90.1	0.002
8 hours after dosing	83.5	85.6	89.1	93.7	0.046
12 hours after dosing	92.2	94.9	95.8	99.2	0.136
Day 4	n = 27	n = 27	n = 26	n = 25	
4 hours after dosing	76.8	77.5	79.7	89.6	<0.001
8 hours after dosing	83.5	86.9	90.3	96.1	0.002
12 hours after dosing	88.7	92.7	95.0	98.6	0.008
End of Study				n = 27	
After Day 4, Period 4[d]				85.0	

a: Repeated measures ANOVA for differences among treatments
b: Subjects were required to check-in on the day before each treatment period. This usually occurred during the late afternoon or early evening.
c: The measurement before treatment was generally performed about 30 to 45 minutes before drug was administered (at 8:00 AM). This value refers to the measurement performed before the first dose of each study period.
d: This measurement was obtained on the day following the last day of Period 4.
e: Subject 22 took 108 mg instead of 144 mg on Day 1 Period 4 and discontinued after that point. Subject 12 did not take doses for Period 4, Days 3 and 4.

The subjects all wore Holter monitors for the

Table 10-11. Findings in Subjects with Abnormal Holter Monitor Result during Dosing with OROS Methylphenidate HCl

Period	Subject No.	Finding	Investigator Comment
1	014	Frequent SVT	Possible drug effect
2	011	Vagally Mediated Sinus Slowing with Wenckebach	Unlikely drug effect
	014	SVT-Probable Atrial Tachycardia Junctional Rhythm	Possible drug effect Unlikely drug effect
	027	Transient Junctional Rhythm	Unlikely drug effect
3	009	Frequent Wenckebach	Unlikely drug effect
	011	Frequent Wenckebach	Unlikely drug effect
4	007	1 Episode of Mobitz I Block	Unlikely drug effect
	011	Several episodes of Simultaneous Sinus Slowing and Mobitz I AV Block Frequent Mobitz I Block	Unlikely drug effect Unlikely drug effect
	012	VT-NS	Possible drug effect
	014	Frequent Short Runs of SVT	Possible drug effect
	023	Transient Junctional or Ectopic Atrial Rhythm (HR was 68 beats per minute)	Possible drug effect
	027	Transient Junctional Rhythm Junctional Rhythm; Atrial Tachycardia with Block	Unlikely drug effect Possible drug effect

Abbreviations: SVT = supraventricular tachycardia, VT-NS = Ventricular tachycardia, nonsustained, AV = atrioventricular

The MAH concluded:

• CONCERTA produced linear and dose-proportional pharmacokinetics of total MPH and its major metabolite, PPAA, for CONCERTA doses of 54 to 144 mg/day
• The pharmacokinetics of both MPH and PPAA were similar for both genders
• The pharmacokinetics of both MPH and PPAA were similar after single and multiple dosing
• There was minimal accumulation of MPH after multiple dosing

Assessor's comments
The pK study demonstrates linear kinetics for MPH and PPAA. The individual patient pK results have not been presented and will be asked for. Bioequivalence limits were met in mg equivalent comparison by day 4 for the 72mg dose when compared to 54mg dose. HR was measured continuously. Subjects received doses of Concerta in ascending strength. HR and BP did not return to baseline levels in between dosing periods, thus increases observed in HR and BP with higher doses may be less than if subjects had been monitored in a MPH naïve state. The baseline HR and BP for each treatment period and at study end should be presented for each subject. In addition, individual subject data for BP increases greater than 5mm Hg should be presented for each study period.
There were 4 subjects who had ST changes during Tx. These were not described and could have been ST elevation or non-specific. In addition there were dysrhythmias observed in 3 subjects. Further scrutiny of these cases is warranted.

Study 12-004 Concerta Crushed

This open-label study was done in 18 healthy volunteers (M/F 13/5). One individual dropped out for personal reasons and was replaced and Subject 17 had an aberrant result much higher than the 2 either side. This was thought to be a sample labelling error. The results were not included.

Figure 3: Mean (SD) Plasma Concentration Time Profile of *d*-Methylphenidate (N=17) Following Single Doses of Crushed and Intact CONCERTA and Crushed RITALIN (IR MPH) (Inset shows: early concentration time profile up to 4.5 h)

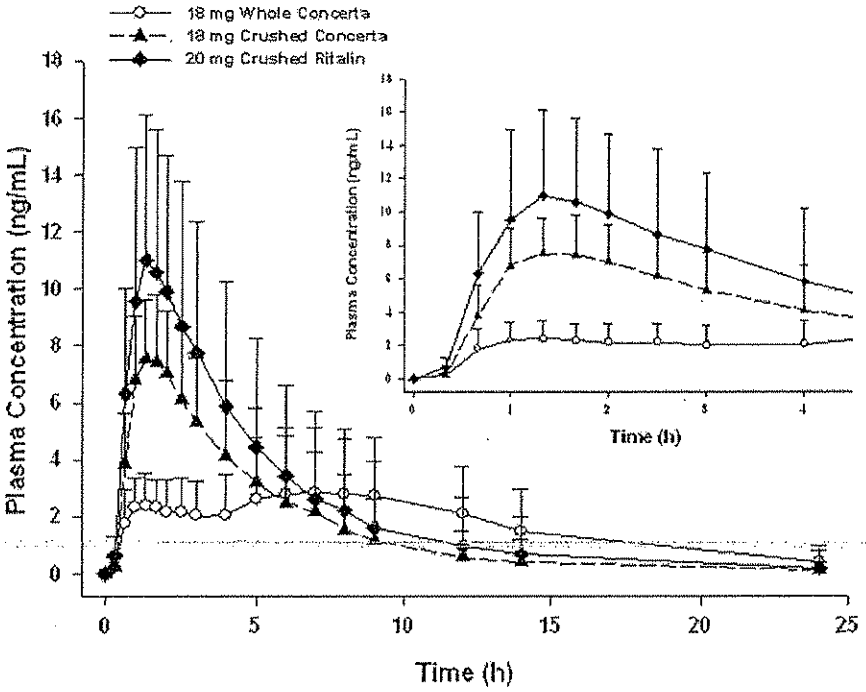


Table 5: Mean (SD) Pharmacokinetic Parameters for *d*-Methylphenidate Following Single Doses of Crushed and Intact CONCERTA and Crushed RITALIN (IR MPH) (N=17)*

	18 mg Whole CONCERTA (Treatment A)	18 mg Crushed CONCERTA (Treatment B)	20 mg Crushed IR MPH (Treatment C)
C_{max} (ng/mL)	3.55 (2.25)	8.17 (2.59)	11.6 (5.01)
T_{max}[a] (h)	6.00 (0.66 - 12.00)	1.33 (0.66 - 2.50)	1.33 (1.00 - 3.00)
AUC_{0-2h} (ng.h/mL)	3.39 (1.56)	9.79 (2.76)	14.4 (6.76)
AUC_t[#] (ng.h/mL)	39.7 (31.0)	37.1 (24.3)	54.5 (48.5)
AUC_{inf} (ng.h/mL)	42.8 (36.2)[$]	38.2 (26.0)[$]	55.1 (51.5)[$]

* N=18 subjects completed the study, however, data from one subject who had a strange PK profile was not included in the PK summary below due to reasons summarized in the report, hence data from N=17 is reported for the primary endpoints of C_{max}, T_{max}, AUC_{0-2h} and AUC_t.

[a] Median (range)

[#] t = 24h

[$] N=18 for CONCERTA treatment arms and N=19 for RITALIN (IR MPH)

Table 9-4. Summary of Post hoc Statistical Analysis for Relative Bioavailability of D-Threo-Methylphenidate Following Single Doses of 18 mg Crushed CONCERTA Tablet Crushed Relative to 20 mg Crushed RITALIN Tablet to Healthy Adults (N = 18)

Pharmacokinetic Parameter	Ratio[a] (%)	90% Confidence Intervals	p value
CMAX/Dose (ng/mL/mg)	81.46	(74.75, 88.78)	0.0008
CMAX (ng/mL)	72.68	(66.68, 79.22)	< 0.0001
AUC_{0-2h}/Dose (ng.h/mL/mg)	80.13	(71.10, 90.31)	0.0054
AUC_{0-2h} (ng.h/mL)	71.49	(63.41, 80.61)	0.0002
AUCMEDIAN/Dose (ng.h/mL/mg)	79.29	(66.33, 94.78)	0.0376

A: Ratio between adjusted geometric means (Test/Reference).

Assessor's comments
Concerta does not appear to have a pK profile when crushed that increases its abuse potential compared to Ritalin when crushed. Crushed Concerta is assessed as not demonstrating a less safe profile compared to Crushed Ritalin in this regard. The Cmax of crushed Concerta would appear of a similar order of magnitude to that obtained from IR. The pK data of crushed Concerta would suggest that the abuse potential of Concerta is similar to MPH IR; however the studies exploring the potential of abuse were done using intact Concerta and thus may under-estimate this. The data on MPH IR is available from these studies so it is possible to gauge the likely effect.

Study 12-302 (Individuals with recent Hx of Substance Abuse)

This was a double-blind, randomized, placebo-controlled, three-period crossover study to assess the pharmacokinetic and pharmacodynamic effects related to abuse potential of single oral doses of placebo, 60 mg immediate release methylphenidate (RITALIN) and 108 mg OROS methylphenidate (CONCERTA) in adults with a diagnosis of substance abuse, based on Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM) IV criteria. Eighteen subjects participated in the study. Over a 24-hour period from dosing, subjects completed Drug Rating Questionnaire. Subject (DRQS), study staff completed Drug Rating Questionnaire. Observer (DRQO), and blood samples were collected for estimation of methylphenidate plasma concentrations (both d- and l- isomer were measured, but PK analysis was performed only for the active d- isomer). In addition, on the final treatment day (at the end of period 3), after last sample collection, subjects completed a Treatment Enjoyment Assessment Questionnaire (TEAQ), where they were asked to provide information on which drug treatment (placebo, RITALIN, CONCERTA), if any, they would prefer to take again. They had a choice of indicating if none of the treatment options from the study were preferred.
This study was designed to assess abuse liability of single doses of CONCERTA versus RITALIN and placebo, with the primary endpoint being time to maximum change from baseline Liking score (question 2 of the DRQS, □gDo you like the drug effect you are feeling now?□h), the working hypothesis being that the maximum effect for both drugs will be

observed when maximum plasma concentrations are reached, hence, CONCERTA would have a longer time to maximum change from baseline for Liking. To examine the primary hypothesis, the statistical analyses used an ANOVA, with step-down pairwise comparisons between RITALIN and placebo, as a measure of assay sensitivity, and if p . 0.05, the RITALIN versus CONCERTA. As per protocol, CONCERTA was not compared with placebo.

Figure 4: Mean (SD) Plasma Concentration Time Profile for *d*-Methylphenidate Following Single Doses of CONCERTA (OROS MPH) and RITALIN (IR MPH)

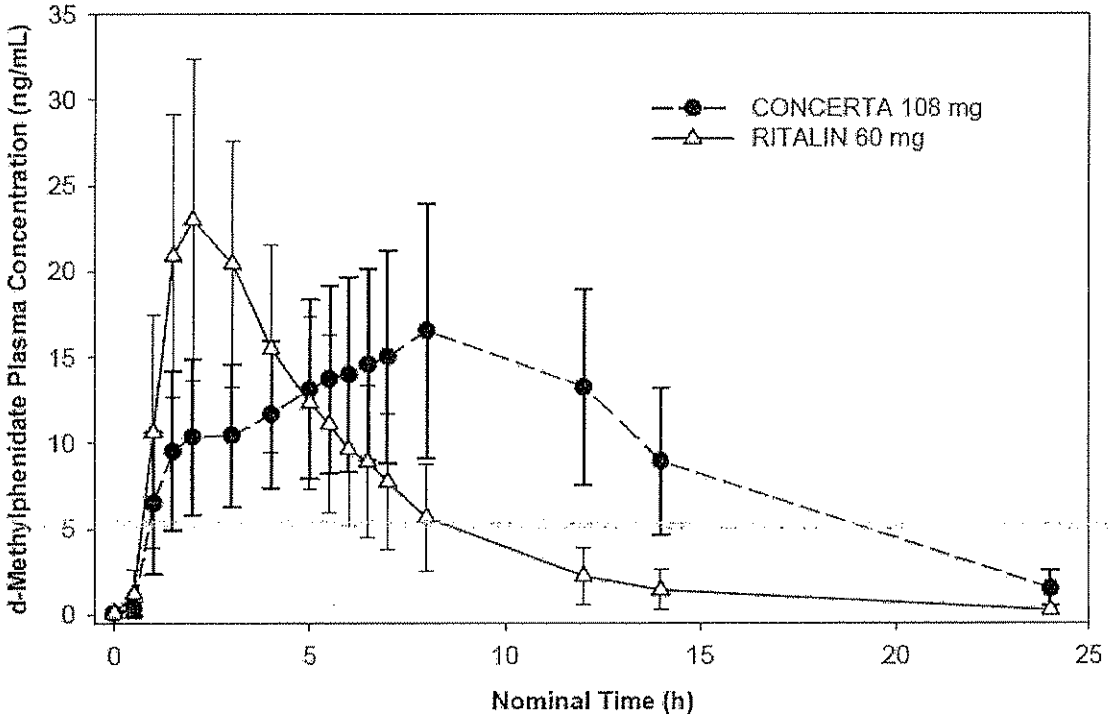
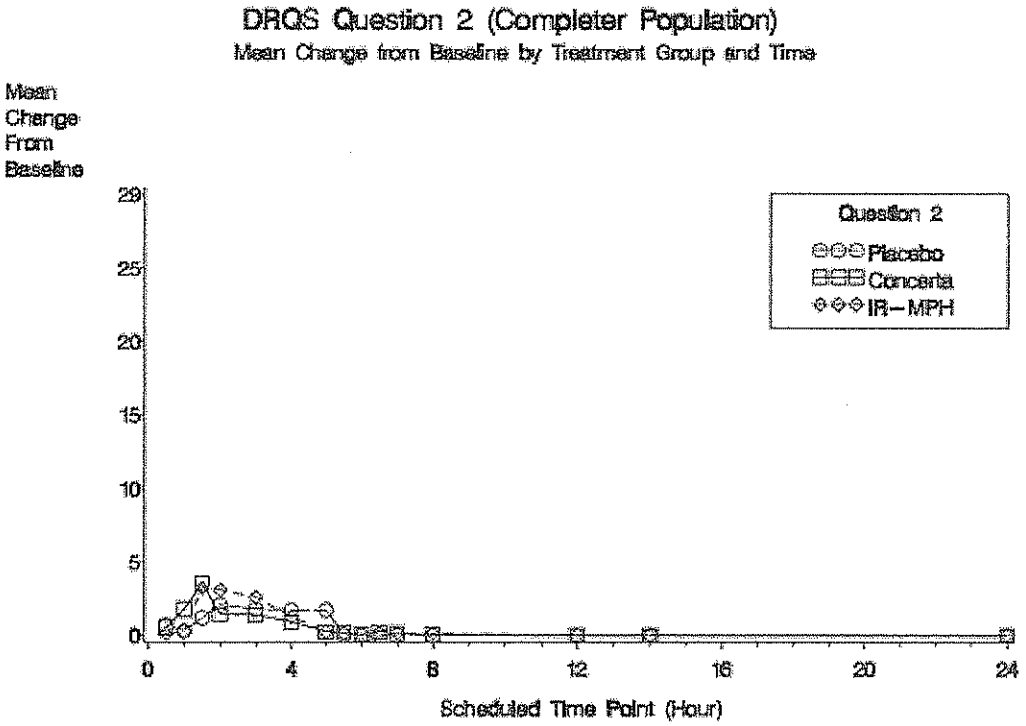


Table 6: Summary of Mean (SD) *d*-Methylphenidate Pharmacokinetic Parameters Following Single Doses of CONCERTA and Immediate-Release Methylphenidate (IR MPH)

Parameter	CONCERTA (OROS MPH) (N= 17)*	IR MPH (N= 17)*
C_{max} (ng/mL)	17.1 (7.11)	24.5 (9.46)
T_{max} (h)	7.56 (2.46)	2.09 (0.566)
AUC_{inf} (ng.h/mL)	220 (95.0)	128 (57.6)
$T_{1/2}$ (h)	3.71 (0.504)	3.62 (0.419)
C_{max} / AUC_{inf}	0.078 (0.009)	0.196 (0.032)

* One subject withdrew from the study after receiving IR MPH treatment, hence, data from N=17 subjects who completed all periods are included in this summary.

Figure 9-2. DRQS Mean Change from Baseline Over Time – Question 2 (0 – 29 Scale)



Assessor's comments

Table 9: Treatment Enjoyment Assessment Questionnaire (TEAQ) (Completer Population)

Preferred Treatment	N of Subjects	Observed (N=17)	Expected (N=17)	p-Value[a]
CONCERTA	1	5.88%	25%	0.181
IR MPH	7	41.2%	25%	
Placebo	2	11.8%	25%	
None	7	41.2%	25%	

[a] p-Value based on Continuity Corrected Chi Square test assuming equal preference among all four choices.

Assessor's comments

There was a very low rating on Item 2 of the DRQS for enjoyment whether with Concerta, MPH-IR or placebo. No concern is raised from this study but it is unlikely that anyone would take Concerta in this fashion should they wish to abuse it. Assessment of a meaningful liking effect was not possible in this population.

Study 12-005 (Recreational Drug Users)

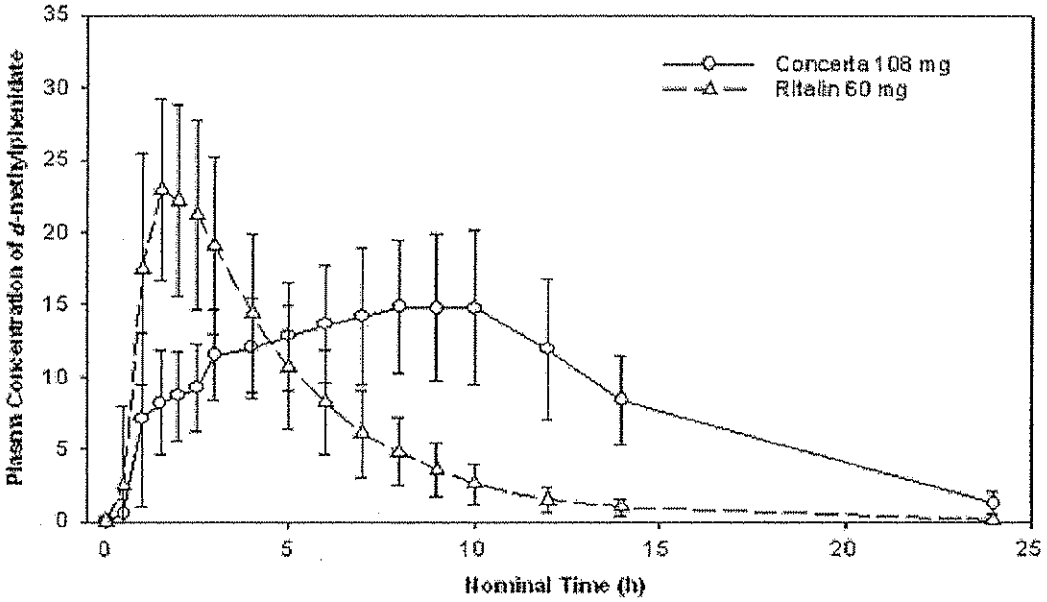
In this single-dose, double-blind, randomized, three-way crossover study in healthy subjects with a history of recreational stimulant use, forty-nine healthy adults, ages 18 to 48 were enrolled. The history of recreational stimulant use was defined as at least ten occasions of use in the previous five years and at least one occasion of use in the previous year. The relevant

stimulant drugs were: cocaine, mixed amphetamine salts, methamphetamine, methylenedioxy-methamphetamine (ecstasy; MDMA), methylphenidate (RITALIN). Subjects were excluded if they were considered substance-dependent per DSM-IV criteria. They received single doses of CONCERTA 108 mg, RITALIN 60 mg, and placebo in a randomized fashion, followed by pharmacokinetic sampling, pharmacodynamic assessments related to drug abuse, and safety assessments over a 24-hour period from dosing. Pharmacodynamic effects related to drug abuse were assessed using Cole/Addiction Research Center Inventory (ARCI), Drug Rating Questionnaire (Subject) - Visual Analog Scales (DRQS-VAS), and Subjective Drug Value Procedure (SDVP). The primary endpoint was maximum value (Emax) of Liking as scored by a subject's response to question 2 ("Do you like the drug effect you are feeling now?") on the DRQS-VAS. Additional parameters used for evaluations included TEmax (time to maximum effect), AUE (area under the response curve) and partial AUEs.

Previous Drug Use

Of subjects in the Randomized population, the primary substances used in the past were cocaine (43 subjects [87.8%]), methylenedioxy-methamphetamine (38 subjects [77.6%]), and methamphetamine (12 subjects [24.5%]). Similarly, in the Completed population, 34 (85.0%) of subjects had used cocaine and methylenedioxy- methamphetamine, and 11 (27.5%) subjects had used methamphetamine. Only three subjects (6.1%) in the Randomized population and two subjects (5.0%) in the Completed population had ever used methylphenidate.

Figure 6: Mean (SD) Plasma Concentration Time Profile of *d*-Methylphenidate Following Single Doses of CONCERTA (108 mg) and Immediate-Release Methylphenidate (RITALIN) (60 mg)



Cross-reference: Mod5.3.4.1\12-007\Figure9-1

Table 11: Key Positive Effects Measures for Placebo, CONCERTA and RITALIN (IR MPH)

Positive Effects Measure	Placebo	CONCERTA 108 mg N=40	IR MPH 60 mg N=40
VAS Liking			
E_{max}, Geometric mean (%CV)	13.7 (1326)*	46.8 (133)	56.6 (125)
$AUE_{0\text{-}MTEmax}$[a], Geometric mean (%CV)	13.5 (3222)*	32.6 (724)	68.1 (233)
1-hour score, Mean (SD)	31.0 (29.8)*	43.8 (32.6)	55.3 (29.0)
2-hour score, Mean (SD)	35.6 (31.0)*	42.8 (27.8)	54.4 (27.4)
Cole/ARCI – Stimulation Euphoria			
1-hour score, Mean (SD)	4.9 (6.63)*	10.2 (10.4)[$]	14.2 (11.9)
2-hour score, Mean (SD)	5.4 (7.22)*	9.4 (8.06)[$]	15.5 (11.6)
Cole/ARCI - Abuse Potential			
1-hour score, Mean (SD)	2.0 (2.97)*	4.6 (4.41)	5.4 (3.93)
2-hour score, Mean (SD)	2.2 (2.97)*	3.7 (4.00)	4.0 (4.91)
ARCI Amphetamine			
1-hour score, Mean (SD)	4.9 (4.90)*	8.8 (7.05)[$]	10.9 (7.62)
2-hour score, Mean (SD)	5.2 (5.07)*	8.9 (5.94)[$]	11.8 (7.34)
ARCI Morphine Benzedrine group[#]			
2-hour score, Mean (SD)	6.1 (7.98)*	10.7 (9.20)[$]	16.7 (12.4)
Subjective Drug Value Procedure			
Subjective drug value ($)[b], Mean (SD)	6.39 (15.5)	6.49 (13.3)	7.85 (14.4)

[a] Calculated with reference to median time to peak effect (TE_{max}) for IR MPH
[b] Canadian dollars (At the time of the study, the exchange value of the local, Canadian dollar was approximately $0.80 to 0.83 in U.S. dollars)
[*] Significant difference between placebo and IR MPH ($p<0.05$)
[$] Significant difference between CONCERTA and IR MPH ($p<0.05$)
[#] Not assessed at 1 hour

The ARCI short form [17] consists of 77 questions extracted from the much larger (550 question) ARCI. The short form contains the following five subscales that are important to the evaluation of abuse potential:

- Morphine-Benzedrine Group scale (the MBG or .euphoria. scale);
- Amphetamine (A) scale;
- Benzedrine Group scale (the BG or .stimulant. scale);
- Lysergic Acid Diethylamide scale (the LSD or .dysphoria. scale);
- Pentobarbital-Chlorpromazine-Alcohol Group scale (the PCAG or .sedation. scale).

A different subset of the original ARCI was later developed [18], using a new factor analysis of responses to some of the 550 questions. This newer form includes seven scales, Sedation.Motor, Sedation.Mental, Unpleasantness.Physical, Unpleasantness.Mental, Stimulation.Motor, Stimulation.Euphoria, and Abuse Liability. The questions in the two stimulation scales do not overlap with each other but do overlap with the Cole/ARCI Abuse Liability and ARCI Amphetamine scales.

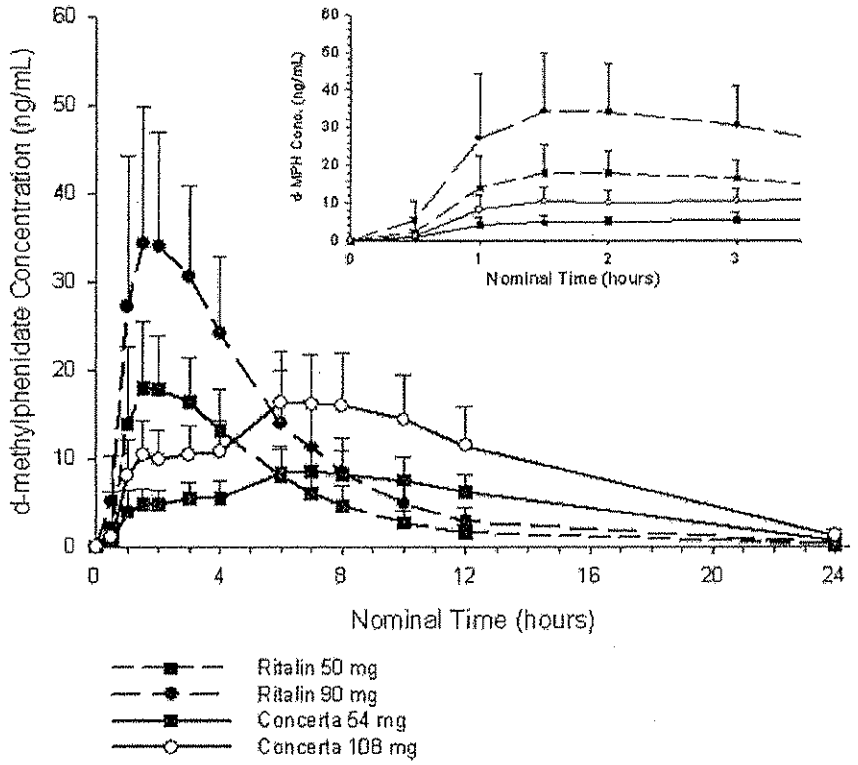
Assessor's comments

The primary endpoint was the comparison of Emax between IR MPH and Concerta. This was based on DRQS-VAS Item 2 'Liking' (0-100 scale). This failed to reach significance. The results clearly suggest that even when Concerta is not crushed (a more likely scenario of abuse) that this imparts a pleasant effect in this population of recreational drug users. If the 72mg Concerta was crushed it would be likely to give Cmax levels around that seen for MPH IR 60mg and thus similar enjoyment rating.

Study 12-007 Abuse Potential in Light (occasional) Drug Users

This was a double-blind, placebo-controlled, randomized, five-way crossover study in 49 healthy subjects with a history of occasional recreational stimulant use. Qualified subjects received single doses of placebo, 54 and 108 mg OROS methylphenidate (CONCERTA), and 50 and 90 mg immediate release methylphenidate (RITALIN). For each treatment, pharmacokinetics, pharmacodynamics and safety were assessed for 24 hours. Pharmacodynamic (subjective) data were collected through standard questionnaires (Addiction Research Center Inventory (ARCI) and visual analog scales (VAS) for positive, stimulant, negative and other effects. The VAS Liking and ARCI/MBG scales were predefined as primary dependent variables. IR and OROS MPH produced expected plasma concentration time profiles of d-methylphenidate. IR MPH (50 and 90 mg) produced statistically significant differences ($p<0.05$) from placebo for primary and secondary subjective measures. For most measures, 108 mg OROS MPH produced statistically significant differences ($p<0.05$) from placebo, while most differences for the 54 mg dose versus placebo were not statistically different. The consistent rank order for magnitude of positive, negative, and stimulant effects was (highest to lowest): IR 90 mg > IR 50 mg > OROS 108 mg > OROS 54 mg > placebo. Most measures showed significant differences ($p<0.05$) between comparable doses of IR and OROS MPH. The linear correlation of concentration with effect (PK-PD) was modest for IR and poor for OROS MPH. In conclusion, for comparable total dose levels, IR MPH had greater subjective effects than OROS MPH, supporting the hypothesis that a formulation can modulate abuse potential by controlling the rate and extent of drug delivery.

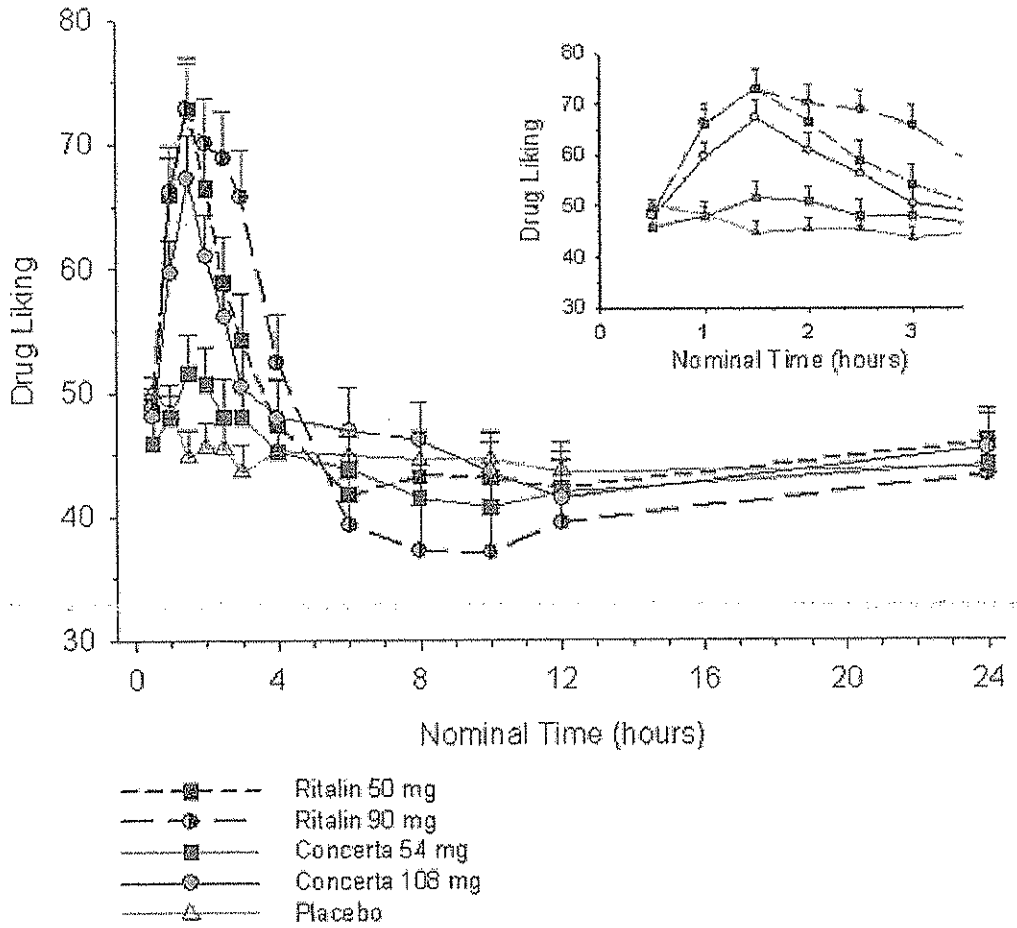
Figure 10: Mean (SD) Plasma Concentration Time Profile of *d*-Methylphenidate Following Single Doses of RITALIN 50 and 90 mg, and CONCERTA 54 and 108 mg



Cross-reference: Mod5.3.4.1\12-007\Figure9-1

Drug Liking Score (0=Max Dislike, 50=Neutral, 100=Max Like)

Figure 9-2. Mean (SD) Time Course of DRQS-VAS Drug Liking Scores



MBG Score ranges from 0-51 points.

Figure 9-3. Mean (SD) Time Course of ARCI Morphine Benzedrine Group (MB
Scores

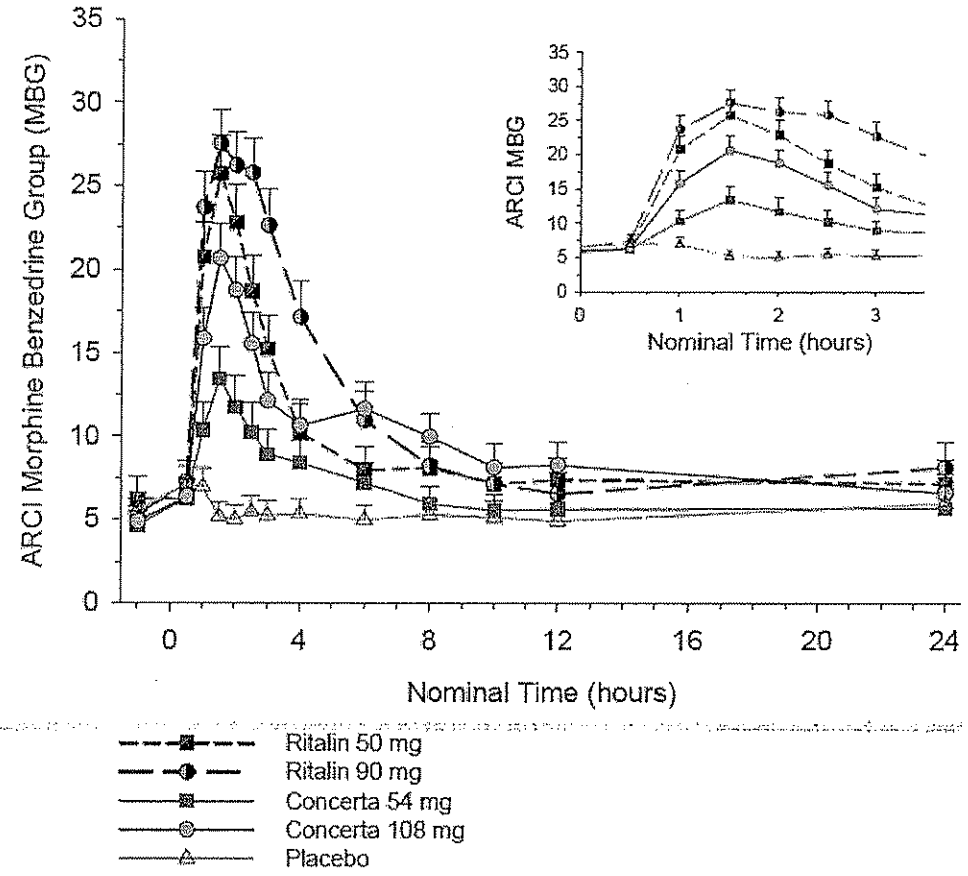


Table 14: Summary of Mean Primary Dependent Variables by Treatment (Positive Effects) Following Single Doses of CONCERTA, RITALIN (IR MPH) and Placebo

Subjective Measure		Placebo	CONCERTA 54 mg	CONCERTA 108 mg	IR MPH 50 mg	IR MPH 90 mg
DRQS-VAS Drug Liking ('at this moment')	AUE_{0-1h}	24.5	23.4[a]	26.9	28.6*	28.8*
	AUE_{0-2h}	70.4	74.0[a]	90.7*	98.2*	99.5*
	AUE_{0-3h}	116	123[a]	147*[b]	158*	168*
	E_{max}	51.7	60.0*[a]	73.8*[b]	78.1*	84.7*
Overall Drug Liking	12 h	40.4	43.0[a]	48.7	53.4*	50.6*
	24 h	38.2	42.1[a]	44.3	53.0*	48.0*
	E_{max}	42.7	46.3[a]	53.3*	58.2*	56.6*
ARCI MBG	AUE_{0-1h}	6.7	6.9[a]	8.4*[b]	9.9*	10.9*
	AUE_{0-2h}	12.2	19.1*[a]	27.3*[b]	33.6*	37.2*
	AUE_{0-3h}	17.5	29.4*[a]	42.8*[b]	52.5*	62.3*
	E_{max}	9.4	17.4*[a]	24.0*[b]	28.8*	33.8*

[a] Significant difference between CONCERTA 54 mg and IR MPH 50 mg ($p<0.05$)
[b] Significant difference between CONCERTA 108 mg and IR MPH 90 mg ($p<0.05$)
* Significantly different from placebo ($p<0.05$)
Statistical significance for VAS Drug Liking, Overall Drug Liking assessed using ANOVA; ARCI MBG assessed using ANCOVA

Assessor's comments
Although the Assessor agrees with the following MAH conclusion:
Overall, a consistent rank order was observed for all subjective measures of abuse as follows:

IR MPH 90 mg > IR MPH 50 mg > CONCERTA 108 mg > CONCERTA 54 mg > placebo

It would appear more likely that if abused the drug would be crushed. Even uncrushed in this naïve population the DRQS Drug Liking Score is higher than in the previously studied populations. Some addiction potential has been demonstrated and also pleasurable effects which raises the question of how much the action seen in the RCTs is due to the euphoric effects of the Concerta.

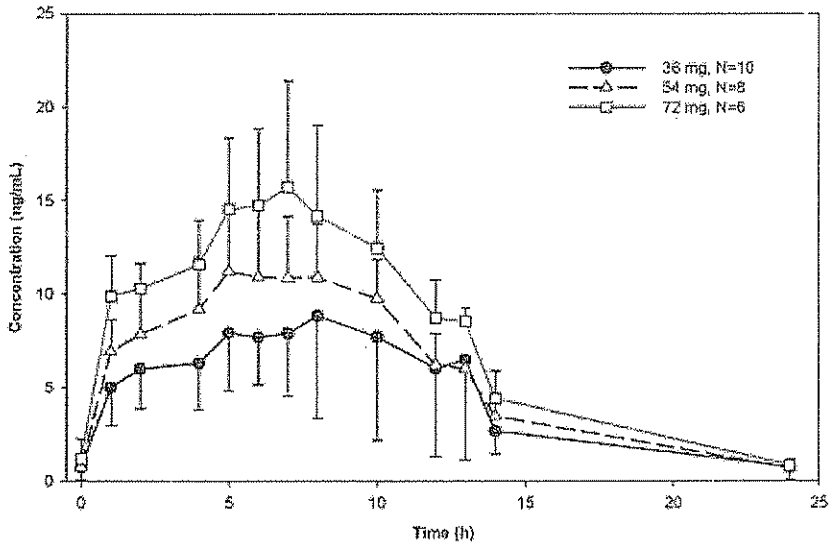
Conclusion on Abuse Potential
Concerta consumption in light and recreational drug users appears to confer a positive effect on the 'Liking' element of the DRQS. This appears to be related to Cmax. If the tablets are crushed then the effects are likely to be heightened. The effect of augmentation of the effects of other drugs of misuse is not known and it is known that diversion is a significant problem (see RMP assessment).

Study 12-001

This was an open-label, multiple dose, 5-dose parallel pharmacokinetic study. Healthy male and female subjects, ages 13 through 17 years, who were already taking CONCERTA® for the treatment of ADHD were enrolled. Subjects were instructed to take single oral daily doses of CONCERTA at the same time each day for five days while at home. On Day 6, subjects reported to the study center and received a final dose of study medication. The CONCERTA

doses evaluated in the study were 18-, 27-, 36-, 54- and 72-mg. On Day 6, blood samples were collected over 24 hours for characterizing the pharmacokinetics of d- and l-methylphenidate and the major metabolite, d- and l-ritalinic acid (PPA), using validated assays.

Figure 14: Mean (SD) Plasma Concentration Time Profile of *d*-Methylphenidate on Day 6 Following Once Daily CONCERTA Dosing



Note: Data from 18- and 27-mg dose groups are not displayed, only 1 subject was dosed at each of these levels.
Cross-reference: Mod5.3.3.2\12-001

Table 20: Mean (SD) Plasma Pharmacokinetic Parameters for Total, *d*- and *l*-Methylphenidate

Dose (mg)	N	C_{max} (ng/mL)	T_{max} (h)	AUC_{tau} (ng.h/mL)	CL_{ss}/F (L/h)	$T_{½}$ (h)	Vz/F (L)	Exposure Ratio[c]
				d-MPH				
36	10	9.5 (5.2)	7.2 (1.6)	110 (53.0)	189 (68.6)	4.60 (2.88)	1221 (682)	0.0475
54	8	12.2 (3.3)	6.8 (1.7)	137 (34.6)	208 (54.4)	3.62 (0.45)	1059 (154)	0.0335
72	6	17.6 (4.6)	7.0 (1.8)	182 (34.6)	203 (37.8)	3.55 (0.50)	1037 (210)	0.0328
				l-MPH				
36	10	0.417 (0.47)	6.5 (2.3)	2.51 (3.12)	18179 (16087	5.93 (5.23)[a]	148427 (202304)[a]	0.0010
54	8	0.681 (1.50)	5.8 (1.0)	3.30 (6.34)	35153 (33954)	1.83[b] (NR)	3777[b] (NR)	0.0010
72	6	0.457 (0.52)	5.7 (0.5)	3.45 (5.16)	30368 (24044)	4.73[b] (NR)	17697[b] (NR)	0.0007
				Total MPH				
36	10	9.9 (5.5)	7.0 (2.1)	112 (55.9)	372 (137)	4.29 (2.03)	2257 (1033)	0.0229
54	8	12.8 (3.4)	6.8 (1.7)	141 (34.3)	406 (108)	3.58 (0.46)	2040 (296)	0.0177
72	6	17.8 (4.5)	7.0 (1.8)	186 (33.9)	399 (73.9)	3.54 (0.49)	2025 (391)	0.0175

[a] n=2; [b] n=1
[c] Parent to metabolite ratio (MPH AUC_{tau}/PPA AUC_{tau})
Data from 18- and 27-mg dose groups are not displayed, only 1 subject was dosed at each of these levels.
Cross-reference: Mod5.3.3.2\12-001

Assessor's comments

The study in adolescents is only relevant to the application in terms of providing a review of the pk data across ages from children to adults and is not considered further.

CLINICAL EFFICACY

Main Studies

Table 1: Double-Blind Controlled Phase 3 Studies of CONCERTA in Adults With ADHD

Protocol No.	No. Sites Enrolling Subjects Region (Country)	Study Design	Daily Dose and Study Duration	Subjects In Efficacy Analyses (M/F)[a]
Placebo-Controlled Studies				
42603ATT3002 (3002)	57 sites Europe: (Great Britain, Germany, Sweden, Denmark, Norway, Finland, Czech Republic, Greece, France, The Netherlands, Spain, Portugal, Switzerland)	Randomized, 5-week double-blind, placebo-controlled, parallel group phase using 3 fixed doses of CONCERTA (18, 36 and 72[b] mg) followed by an open-label extension period of 7-week duration with flexible dosing (18 to 90 mg/day)	Placebo CONCERTA 18 mg 36 mg 72 mg	95 (59/36) 99 (56/43) 101 (46/55) 99 (53/46)
02-159	27 sites United States	Randomized, 7-week double-blind, placebo-controlled, parallel group, dose-titration study of CONCERTA (36 – 108 mg/day)	Placebo CONCERTA (final mean dose = 68 mg/day)	116 (64/52) 110 (63/47)
42603ATT3013 (3013)	42 sites Europe: (Belgium, Denmark, Finland, France, Germany, Great Britain, The Netherlands, Norway, Spain, Sweden, Switzerland)	Randomized, 13-week, double-blind, placebo-controlled, parallel group, dose response study of 2 fixed doses of CONCERTA (54 or 72 mg/day)[c]	Placebo CONCERTA 54 mg 72 mg	97 (52/45) 90 (44/46) 92 (50/42)
Maintenance of Effect – Randomized Withdrawal Study Phase				
42603ATT3004 (3004)[d,e]	14 sites Europe: (Germany, The Netherlands, Spain, Portugal, Switzerland)	Randomized, 4-week, double-blind, placebo-controlled withdrawal phase following at least 52 weeks of open-label treatment; CONCERTA given at dose achieved at end of open-label treatment.	Placebo CONCERTA (mean dose during withdrawal phase = 43 mg/day)	22 (7/15) 23 (11/12)

[a] A total of 899 adult subjects with ADHD were evaluated in the 3 placebo-controlled studies and 45 adult subjects with ADHD were evaluated in the randomized withdrawal phase of Study 3004.

[b] Subjects assigned to CONCERTA 72 mg group were titrated from a starting dose of 36 mg/day for 4 days, to 54 mg/day for 3 days (end of Week 1), after which the assigned final dosage of 72 mg/day was administered for 4 weeks.

[c] Subjects assigned to CONCERTA were titrated from starting dose of 36 mg/day for 1 week to assigned target dose of 54 or 72 mg/day beginning on Day 8.

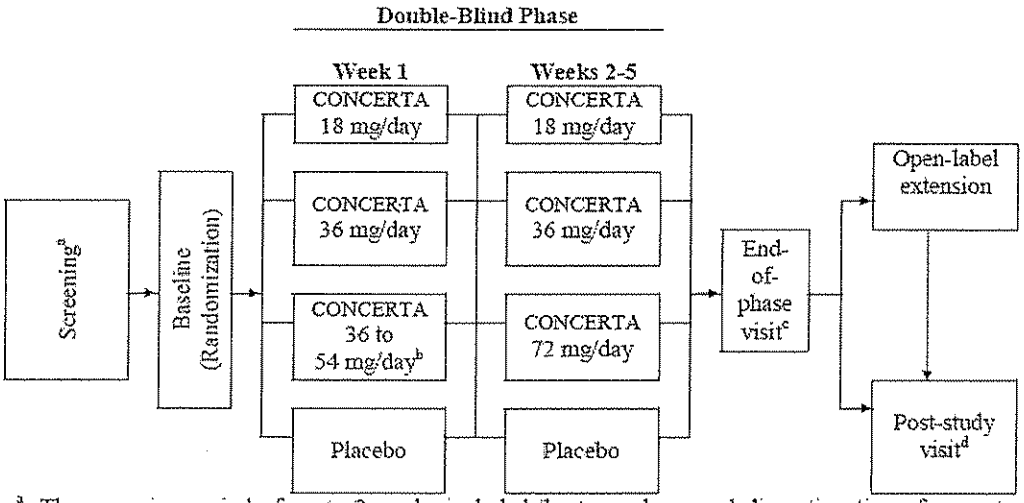
[d] Subjects had been treated in Study 3002 prior to enrollment in Study 3004.

[e] Subjects received up to 108 weeks of open-label treatment with CONCERTA prior to randomized withdrawal phase.

Cross-reference: Mod5.3.5.1/3002, Mod5.3.5.1/02-159, Mod5.3.5.1/3004, Mod5.3.5.1/3013.

Methods - Study designs

Figure 1: Design of Study 3002



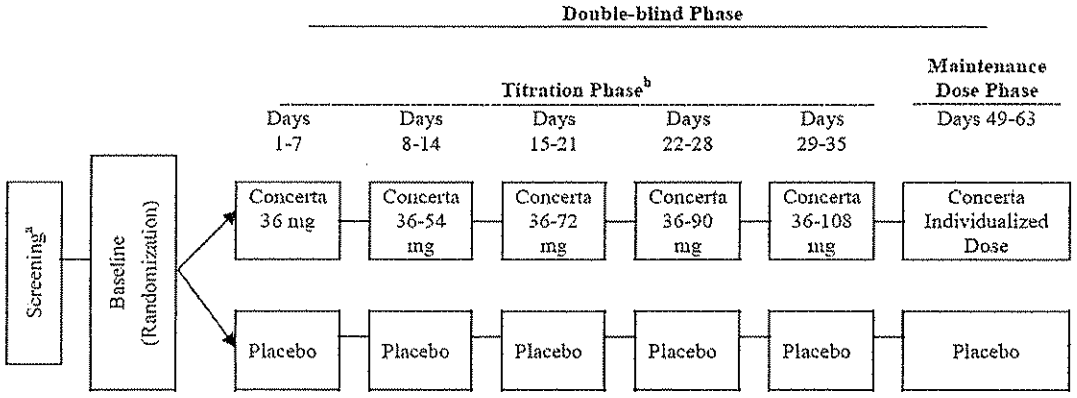
[a] The screening period of up to 2 weeks included the taper down and discontinuation of current disallowed treatment (except if fluoxetine or monoamine oxidase inhibitors needed to be tapered off, then a screening period of 4 weeks was allowed).

[b] Subjects assigned to 72 mg CONCERTA were titrated from a starting dose of 36 mg/day for 4 days, to 54 mg/day for 3 days (end of Week 1), after which the assigned final dosage of 72 mg/day was administered for 4 weeks.

[c] All subjects, including those who withdrew prematurely from the double-blind phase, had end-of-phase procedures performed.

[d] For those subjects not continuing in the open-label extension, the post-study visit was scheduled 1 week after the final dose of study drug in the double-blind phase. For those subjects who continued in the open-label extension, the post-study visit was scheduled 1 week after the final dose of study drug in the open-label extension.

Figure 2: Design of Study 02-159



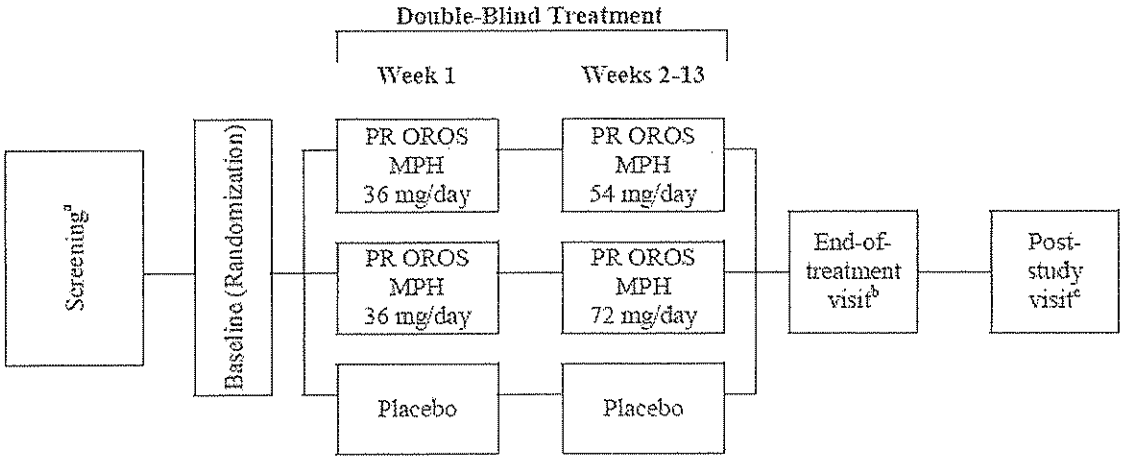
[a] Subjects who were being treated for ADHD at screening had to washout from all ADHD medication for 7 to 14 days. Subjects on atomoxetine hydrochloride returned for baseline visit within a 10 to 14 day window.

[b] Doses were titrated until the individualized dose was achieved. All visits were required, even if a subject had achieved an individualized dose.

All subjects will initiate treatment with 36 mg and continue with incremental increases of 18mg of CONCERTA every seven days (+/- 2 days) until an individualized dose is achieved. The individualized dose is the dose when: AISRS decreases by 30 percent and a Clinical Global Impression-Improvement (CGI-I) rating of 1 or 2 is achieved, or titration to the maximum dose of 108 mg has been achieved. Dose reduction by 18 mg/day for safety reasons was permitted only once during the double-blind phase, and a subsequent dose increase was not allowed. A dose reduction was required for resting heart rate > 100 bpm, systolic blood pressure > 140 mmHg, or diastolic blood

pressure > 90 mmHg (average of triplicate measurements), and for adverse events at the discretion of the investigator.

Figure 3: Design of Study 3013



[a] The screening period of up to 2 weeks included the tapering and discontinuation of current forbidden treatment (except if fluoxetine or monoamine oxidase (MAO) inhibitors needed to be tapered, in which case a screening period of 4 weeks was allowed).
[b] If a subject was withdrawn early, every attempt had to be made to complete the end-of-treatment procedures.
[c] The post-study visit was scheduled 1 week after the final dose of study drug.

Population

ADHD was diagnosed using DSM-IV by qualified mental health professionals experienced in ADHD diagnosis and trained in the use of structured interviews to confirm the diagnosis. Specified axis I disorders and elderly (> 65 years of age) were excluded. Subjects were required to demonstrate a chronic course of ADHD symptomatology from childhood to adulthood, with some symptoms present before the age of 7 years. Description of the chronicity of ADHD symptoms could be subject- or informant-based; if available, documentation of previous diagnosis or onset of symptoms in childhood was obtained from medical and/or psychiatric records, school records, and family member reports. In Studies 3002 and 3013, the Connors' Adult ADHD Diagnostic Interview for DSM-IV (CAADID) was used to confirm the diagnosis while in Study 02-159, the Adult ADHD Clinical Diagnostic Scale (ACDS), version 1.2 was employed.

Statistical Assessor's Comment:
The patient population enrolled does not reflect the population for which the applicant is seeking an indication. In Study 3002 approximately 20% of patients enrolled had a diagnosis of ADHD before the age of 18. It is unlikely that statistically significant results in this sub-population will be obtained (shown later) as the trial is not powered to detect this difference. If no differences between the sub-groups based on age of diagnosis are found, it is a matter of clinical judgement whether an overall positive study is sufficiently supportive of the narrower indication.

Exclusion criteria (see Appendix III)

These were very extensive and excluded any significant psychiatric or physical co-morbidity drug or alcohol abuse.

Endpoints (see Appendix IV)

Randomisation was centrally implemented by computer and stratified by treatment centre. There were very few patients randomised per centre.

Statistical Methods

ANCOVA was used to analyse the primary endpoints of CAARS (or AIRSS) score, with treatment, country and baseline primary efficacy variable (although see below). Due to the small number of patients per treatment centre, centres were grouped by country and this was then included as a covariate. LOCF was the primary method for handling missing data, with BOCF used in study 059 for patients with no post-baseline measurements. Sensitivity analyses using MMRM and using the per-protocol populations were provided.

Statistical Assessor's Comment

The use of ANCOVA is acceptable for this endpoint. The decision to include country instead of the pre-specified covariate of investigator is understandable and supported. However there is concern that arbitrary *post hoc* covariates have been introduced into the final model in some of the trials, which was not specified in the SAP, and is not acceptable.. It is unclear why gender has been included in the model in Study 3002, and age has been included in study 3013, and the applicant should repeat the analysis to provide reassurance that the *post hoc* inclusion of the covariate does not affect the interpretation of the results.

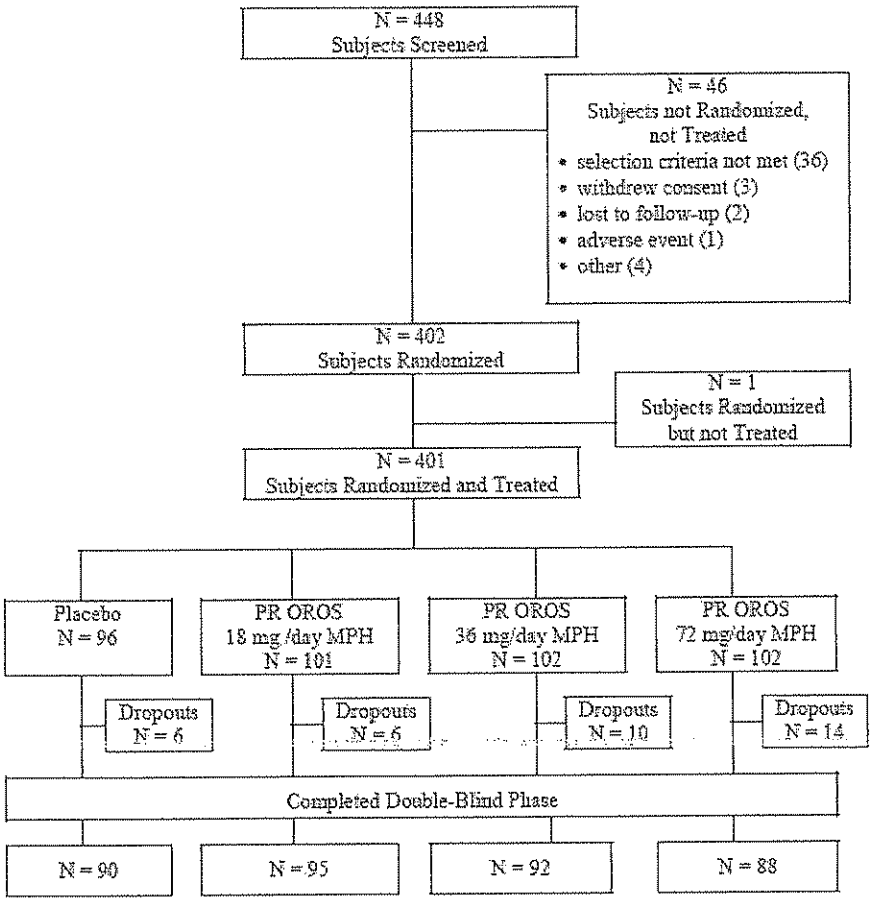
It is unclear whether LOCF is a suitably conservative analysis to handle the missing data. Although the results of the per-protocol analysis and the MMRMM sensitivity analysis have an even more extreme significance, this does not rule out the possibility that neither the per-protocol nor the LOCF method are conservative. The responder analysis may be the most appropriately conservative method to assess the missing data. In Study 3002, the additional *post hoc* definition of a CAARS decrease of 50% indicating response, as well as the pre-specified change of 30% is supported. However what is not clear from the data is how patients who dropped out of the trial have been handled in the responder analysis. The applicant state that "a treatment responder was defined as a subject with a 30% or greater reduction from baseline in CAARS total score at double-blind end point." They go on to define the "the primary end point in the double-blind treatment phase was the change in the sum of the inattention and hyperactivity/impulsivity subscale scores of the investigator-rated CAARS from baseline to the last post-randomization assessment in the double-blind treatment period." One interpretation of this is that all data is considered as LOCF, and therefore even if a patient drops out of the study, they may have been considered a responder if they had a 30% change when they dropped out. This is not an appropriately conservative analysis and the applicant should clarify if this is method used. If so, the applicant should repeat the responder analysis including all patients who dropped out as failures. They should provide the point estimates per treatment group, as well as confidence intervals for the differences between the 3 active dose groups and placebo, and the associated Dunnet adjusted p-values. The same applies for the additional *post hoc* definition of responder of a 50% decrease in CAARS.

Results

Disposition

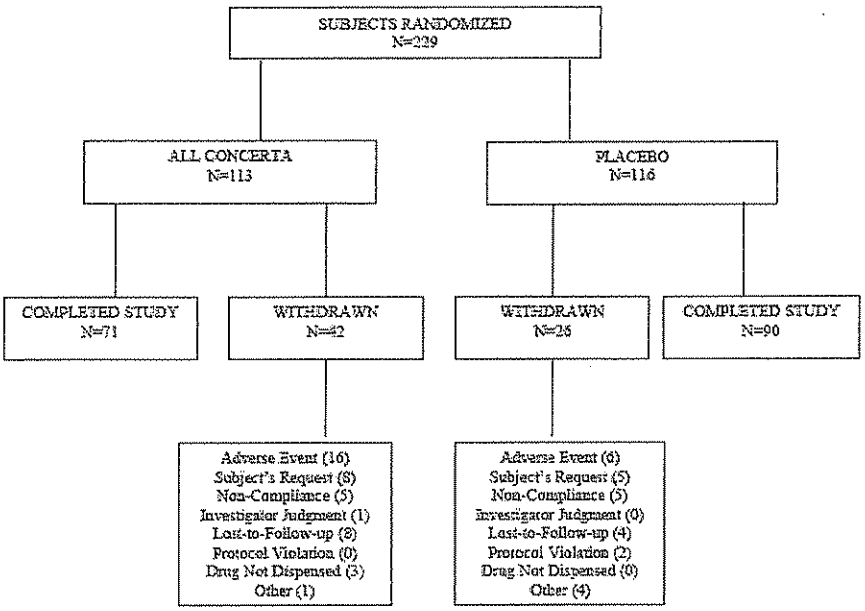
Study 3002

Figure 2: Subject Disposition in the Double-Blind Phase



Study 02-159

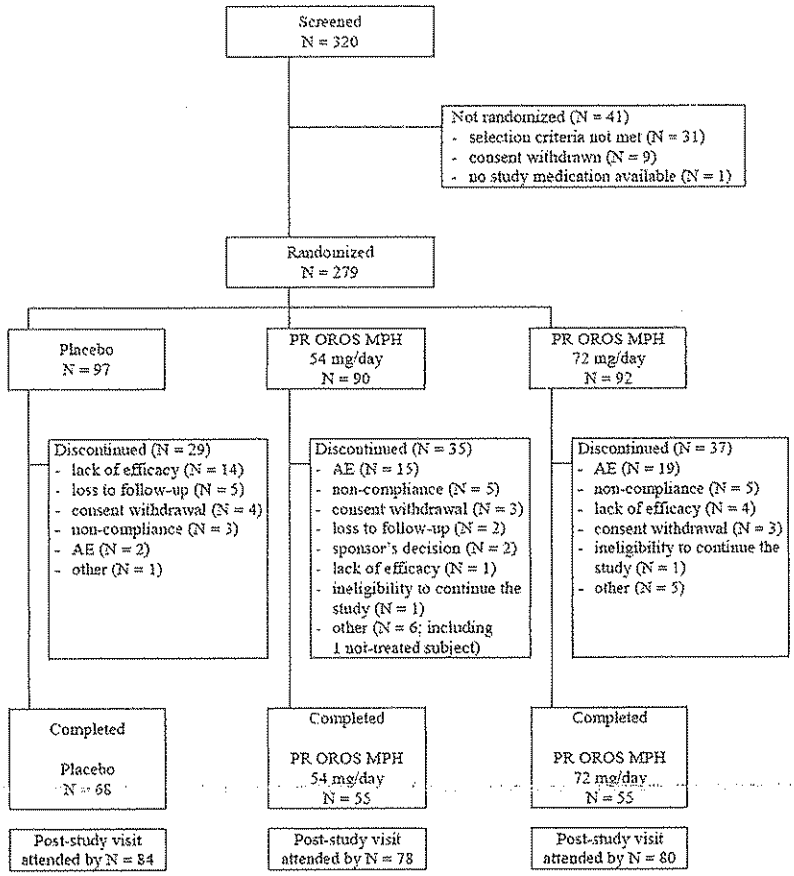
Figure 8-1: Disposition of Subjects



Subjects Completing the Study, N=161

Study 3013

Figure 2: Subject Disposition
(Study 42603ATT3013; All Screened Subjects)



N = number of subjects with data
Source: Attachment 2.2, Attachment 2.3, Attachment 2.5.1 and Attachment 2.6

Statistical Assessor's Comment:

Across all studies, the withdrawal rate for Concerta were higher for that of placebo ,and there is no evidence that the withdrawals happen earlier rather than later (or vice versa) (graphs not shown). There is a clear imbalance between the arms, which leads to the possibility that the primary analysis method (and also the MMRM sensitivity analyses) may not be suitably conservative. In study 3013, there is an incredibly high dropout rate, with 30% of patients not completing in the placebo group, and 40% in the active group. The implications of this are discussed further in the results section.

Demographics

Study 3002

[illegible]3002: LAMDA: FINAL ANALYSIS

DISPLAY GEN.1: INVESTIGATORS: TABULATION

POPULATION: ALL SUBJECTS / DOUBLE BLIND
TABULATION BY COUNTRY

COUNTRY	MDR 18mg OD		MDR 36mg OD		MDR 72mg OD		Placebo		OVERALL	
	N	%	N	%	N	%	N	%	N	%
CZECH REPUBLIC	3	3.0	3	2.9	5	4.9	4	4.2	15	3.7
DENMARK	8	7.9	10	9.8	8	7.8	7	7.3	33	8.2
FINLAND	7	6.9	7	6.9	8	7.8	8	8.3	30	7.5
FRANCE	5	5.0	5	4.9	4	3.9	4	4.2	18	4.5
GERMANY	31	30.7	28	27.5	31	30.4	29	30.2	119	29.7
GREAT BRITAIN	4	4.0	2	2.0	3	2.9	2	2.1	11	2.7
GREECE	2	2.0	3	2.9	2	2.0	1	1.0	8	2.0
NETHERLANDS	7	6.9	8	7.8	8	7.8	7	7.3	30	7.5
NORWAY	6	5.9	7	6.9	6	5.9	7	7.3	26	6.5
PORTUGAL	4	4.0	4	3.9	5	4.9	5	5.2	18	4.5
SPAIN	7	6.9	7	6.9	7	6.9	7	7.3	28	7.0
SWEDEN	10	9.9	11	10.8	10	9.8	9	9.4	40	10.0
SWITZERLAND	7	6.9	7	6.9	5	4.9	6	6.3	25	6.2
** TOTAL **	101	100.0	102	100.0	102	100.0	96	100.0	401	100.0

Study 02-159 – US only

Study 3013

[illegible]3013: LAMDA II: FINAL ANALYSIS

DISPLAY GEN.1: INVESTIGATORS: TABULATION

ANALYSIS SET: INTENT TO TREAT
TABULATION BY COUNTRY

COUNTRY	PLACEBO		54 MG/DAY		72 MG/DAY		OVERALL	
	N	%	N	%	N	%	N	%
BELGIUM	5	5.2	3	3.3	4	4.3	12	4.3
DENMARK	4	4.1	3	3.3	5	5.4	12	4.3
FINLAND	9	9.3	9	10.0	10	10.9	28	10.0
FRANCE	10	10.3	6	6.7	6	6.5	22	7.9
GERMANY	22	22.7	23	25.6	20	21.7	65	23.3
GREAT BRITAIN	4	4.1	3	3.3	3	3.3	10	3.6
NETHERLANDS	5	5.2	4	4.4	6	6.5	15	5.4
NORWAY	8	8.2	9	10.0	9	9.8	26	9.3
SPAIN	12	12.4	14	15.6	12	13.0	38	13.6
SWEDEN	17	17.5	15	16.7	16	17.4	48	17.2
SWITZERLAND	1	1.0	1	1.1	1	1.1	3	1.1
** TOTAL **	97	100.0	90	100.0	92	100.0	279	100.0

Key Demographic Characteristics

Table 10: Key Demographic and Baseline ADHD Characteristics
(Studies 3002, 02-159 and 3013; Intent-to-Treat Population)

	Study 3002				Study 02-159		Study 3013		
		CONCERTA						CONCERTA	
	Placebo (N=93)	18 mg (N=99)	36 mg (N=101)	72 mg (N=99)	Placebo (N=116)	CONCERTA (N=110)	Placebo (N=97)	54 mg (N=90)	72 mg (N=92)
Age, yrs									
Mean	34.6	34.5	33.9	33.7	38.2	39.9	35.5	35.8	35.8
Range	18-57	18-60	18-60	18-63	19-64	18-65	18-57	18-64	18-60
Sex, n (%)									
Male	59 (62.1)	56 (56.6)	46 (45.5)	53 (53.9)	64 (55.2)	63 (57.3)	52 (53.6)	44 (48.9)	50 (54.3)
Race, n (%)									
Caucasian	93 (97.9)	98 (99.0)	98 (97.0)	96 (97.0)	99 (85.3)	96 (87.3)	93 (95.9)	85 (94.4)	89 (96.7)
ADHD Subtype, n (%)									
Combined type	67 (70.5)	62 (62.6)	75 (74.3)	74 (74.7)	94 (81.0)	87 (79.1)	73 (75.3)	60 (66.7)	62 (67.4)
Inattentive type	23 (24.2)	32 (32.3)	19 (18.8)	22 (22.2)	21 (18.1)	22 (20.0)	23 (23.7)	27 (30.0)	28 (30.4)
Hyperactive/ Impulsive type	2 (2.1)	4 (4.0)	7 (6.9)	3 (3.0)	1 (0.9)	1 (0.9)	1 (1.0)	3 (3.3)	2 (2.2)
NOS	3 (3.2)	1 (1.0)	0	0	0	0	0	0	0
Age at ADHD Diagnosis, yr[a]									
N	94	98	101	99	53[a]	55[a]	96	90	91
Mean	31.6	30.8	29.1	28.9	27.1	31.1	31.9	30.8	32.4
Range	4 - 57	4 – 60	0 - 59	2 - 63	5 - 59	4 - 63	3 – 57	3 – 63	3 – 60
Prior Use of ADHD Drugs, n(%)[a,b]									
N	96	101	102	102	116	113	97	90	92
Yes	11 (11.5)	8 (7.9)	6 (5.9)	10 (9.8)	42 (36.2)	39 (34.5)	10 (10.3)[c]	11 (12.2)[c]	3 (3.3)[c]
Co-morbid mood/anxiety disorder, n (%)[a]									
N	96	101	102	102	116	113	97	90	92
Yes	10 (10.4)	10 (9.9)	11 (10.8)	17 (16.7)	15 (12.9)[d]	6 (5.3)[d]	12 (12.4)	13 (14.4)	9 (9.8)

NOS = not otherwise specified.
[a] Based on all randomized subject population.
[b] Defined as within the past 3 months prior to enrollment for Study 3002 and 3013; defined as within 30 days of the screening visit and prior to the first dose of double-blind study medication for Study 02-159.
[c] Defined as prior use of MPH for Study 3013.
[d] Combined number of subjects with anxiety and depression.

Psychiatric Co-morbidity

Study 3002 There were very low levels of co-morbidities apart from anxiety: alcohol (currently active 0.7%: history 13.5%), Mood and Anxiety (currently active 12.0%: history 29.9%), Personality Disorder (currently active 1.0 %) with 91% of the study population was methylphenidate naïve.

Study 02-159 Approximately 35% had taken some form of medication for their ADHD before randomisation which was stopped 30 days prior to randomisation.

Study 3013 Similar pattern to Study 3002: 8.6% stopped methylphenidate prior to randomisation.

Concomitant Therapy

Concomitant therapy with antidepressants was permitted but the dose had to be stable for the last 3 months. MAOIs were not permitted.

Study 3002 There were 10% subjects comedicated with psychoanaleptics and 5% with psycholeptics.

Study 02-159 There were low levels of co-medication with benzodiazepine or related drugs (1.8%), SSRIs up to 9% but high levels of anilide use(up to 20%).

Study 3013 There were 16.8% subjects comedicated with psychoanaleptics and 8.6% with psycholeptics.

Compliance

In Study 02-159 compliance was 73% in the CONCERTA group and 85% in the placebo group being at least 90% compliant (percentage of days that the full dose was taken). There were less stringent

definitions of compliance based on total tablet count and thus >90% of subjects were deemed to be compliant in studies 3002 and 3013.

Exposure

Table 11: Dose Received by Treatment Group
(Study 02-159; Intent-to-Treat Population)

	Dose (mg)	CONCERTA (N=110)	Placebo (N=116)
Maximum dose, n (%)	36	32 (29.1)	11 (9.5)
	54	18 (16.4)	19 (16.4)
	72	15 (13.6)	12 (10.3)
	90	16 (14.5)	6 (5.2)
	108	29 (26.4)	68 (58.6)
Mean Maximum Dose (mg) (SD)		70.7 (28.72)	87.7 (26.70)
Final dose, n (%)	36	36 (32.7)	15 (12.9)
	54	16 (14.5)	16 (13.8)
	72	19 (17.3)	11 (9.5)
	90	16 (14.5)	6 (5.2)
	108	23 (20.9)	68 (58.6)
Mean Final Dose (mg) (SD)		67.7 (27.90)	86.9 (27.81)

Cross-reference: Mod5.3.5.1/02-159/Table 10-2.

Primary Endpoint

ITT population defined as those who had taken 1 dose of medication and 1 post-baseline assessment.

Statistical Assessor's Comment

The definition of ITT that is most appropriate is patients who have received study medication. The decision to exclude patients who did not have a post-baseline measurement is not supported. However there are so few of these patients across the trials, that it is unlikely in the extreme that their inclusion would change the interpretation of the results to any meaningful degree

Study 3002

Table 12: CAARS ADHD Symptoms Total Score: Actual Values and Change From Baseline to Double-Blind End Point -- LOCF
(Study 3002: Intent-to-Treat Population)

		CONCERTA		
	Placebo (N=95)	18 mg (N=99)	36 mg (N=101)	72 mg (N=99)
Baseline				
Mean (SD)	37.2 (7.09)	35.6 (6.91)	37.3 (6.88)	36.6 (6.58)
Range	24, 51	24, 53	25, 51	24, 52
Double-Blind End Point				
Mean (SD)	29.6 (10.60)	25.0 (10.43)	25.8 (10.88)	22.9 (10.95)
Range	4, 50	4, 51	4, 52	1, 50
Change From Baseline to Double-Blind End Point				
Mean (SD)	-7.6 (9.93)	-10.6 (10.34)	-11.5 (9.97)	-13.7 (11.11)
Range	-45, 8	-35, 16	-37, 8	-40, 8
p-value (vs. Placebo)[a]		0.0146	0.0131	<0.0001
Difference of LS means		-3.99	-4.03	-6.59
95% CI		(-7.35, -0.64)	(-7.38, -0.69)	(-9.93, -3.25)

A negative change from baseline indicates an improvement.

[a] Based on ANCOVA model with factors for treatment, gender, and country and baseline value as a covariate. Dunnett's procedure was used to adjust for comparisons between each CONCERTA dose group and placebo.

Study 02-159

Table 13: AISRS Total Score: Actual Values and Change From Baseline to Double-Blind End Point -- LOCF
(Study 02-159: Intent-to-Treat Population)

	Placebo (N=116)	CONCERTA (N=110)
Baseline		
Mean (SD)	38.1 (7.31)	38.6 (6.85)
Range	24, 54	24,54
Double-Blind End Point		
Mean (SD)	31.3 (12.38)	27.6 (13 17)
Range	3, 54	0, 52
Change From Baseline to Double-Blind End Point		
Mean (SD)	-6.8 (11.45)	-10.9 (11.75)
Range	-38, 12	-48, 13
p-value (vs. Placebo)[a]		0.012
Difference of LS means		-3.8
95% CI		(-6.80, -0.86)

A negative change from baseline indicates an improvement.

[a] Based on ANCOVA model with factors for treatment and site and baseline value as a covariate. A step-wise procedure was used to control the overall Type I error rate.

Study 3013

Table 14: CAARS ADHD Symptoms Total Score: Actual Scores and Change From Baseline to Double-Blind End Point (Study 3013: Intent-to-Treat Population)

		CONCERTA	
	Placebo (N = 97)	54 mg (N = 90)	72 mg (N = 92)
Baseline[a]			
Mean (SD)	36.5 (6.05)	35.6 (6.75)	37.3 (6.35)
Range	24 - 51	25 – 54	23 - 50
End point			
Mean (SD)	26.1 (10.59)	23.0 (11.07)	21.6 (10.21)
Range	0 - 52	2 – 52	2 - 44
Change from Baseline to End point			
Mean (SD)	-10.4 (11.03)	-12.5 (10.38)	-15.7 (10.80)
Range	-43 - 7	-37 – 11	-39 - 10
p-value (vs. Placebo)[b]		0.1356	0.0024
Difference in LS means[b]	-	-2.69	-4.89

[a] In case of missing values, the baseline value was imputed with the screening value.
[b] Based on ANCOVA model with factors for treatment, gender, and country, and age and baseline value as a covariate. Comparisons of each dose group with placebo adjusted for multiplicity using Dunnett's procedure.

The CAARS demonstrated numerical improvement above placebo for both subsections inattention and hyperactivity/impulsivity.

Responder Rates The definition of responder is less rigorous in Study 3002 and Study 3013 with only a requirement to demonstrate a 30% improvement on the CAARS and no reference to CGI.

Study 3002

Table 26: Response rate: Percentage of Subjects With a 30% or Greater Reduction From Baseline in CAARS Total Score at Double-Blind End Point (Study 42603ATT3002: *Intent to Treat / Double-Blind*)

		PR OROS MPH		
Timepoint	Placebo (N=95)	18 mg (N=99)	36 mg (N=101)	72 mg (N=99)
Double-Blind End Point				
Responders: n (%)	26 (27.4)	50 (50.5)	49 (48.5)	59 (59.6)
Non-responders: n (%)	69 (72.6)	49 (49.5)	52 (51.5)	40 (40.4)
p-value[a] (comparison versus placebo)		0.0020	0.0074	<0.0001

[a] CMH general association test controlling for country, comparing each dose group with placebo using a Sidak multiplicity correction
N = number of subjects with data; n = number of responders

Study 02-159

Table 19: Number (%) of Responders by Visit Based on the AISRS Total Score and the CGI - Improvement Scale
(Study 02-159; Intent-to-Treat Population)

Visit[a]	CONCERTA	Placebo	Odds Ratio[b]	95% CI	p-value[c]
Titration Visit 1, n/N (%)	20/103 (19.4)	6/115 (5.2)	3.60	(1.42, 9.14)	0.002
Titration Visit 2, n/N (%)	23/98 (23.5)	13/108 (12.0)	2.18	(1.03, 4.65)	0.037
Titration Visit 3, n/N (%)	30/91 (33.0)	19/103 (18.4)	2.13	(1.08, 4.21)	0.028
Titration Visit 4, n/N (%)	35/85 (41.2)	21/97 (21.6)	2.75	(1.38, 5.50)	0.003
Titration Visit 5, n/N (%)	40/81 (49.4)	22/93 (23.7)	3.31	(1.68, 6.55)	<0.001
Two Week Efficacy Visit, n/N (%)	33/74 (44.6)	22/90 (24.4)	2.78	(1.36, 5.65)	0.003
Final Visit (LOCF), n/N (%)	38/103 (36.9)	24/115 (20.9)	2.16	(1.18, 3.95)	0.009

[a]: All subjects initiated treatment with 36 mg of study medication and continued with incremental increases of 18 mg every 7 days until an individualized dose. The mean final dose of CONCERTA was 67.7 mg.
[b] The odds ratio of achieving response for All CONCERTA versus placebo, adjusted for pooled study site.
[c]: p-value from Cochran-Mantel-Haenszel row means score. A responder is a subject who had at least 30% improvement in the AISRS score and had a CGI-Improvement score of 1 or 2 (Very Much Improved or Much Improved). Nominal p-value with no adjustment for multiple testing.
Cross-reference: Mod5.3.5.1/02-159/Table 9-11.

The applicant has also provided a table for the dose at which patients first responded, although this is a post hoc analysis:

Table 9-20: Number (%) of Responders by Dose Based on the AISRS Total Score and the CGI - Improvement Scale
(Study 02-159; Intent-to-treat Population)

	CONCERTA		Placebo	
Dose Level (mg/day)	No. Subjects Evaluated at This Dose	First Responded at This Dose n (%)	No. Subjects Evaluated at This Dose	First Responded at This Dose n (%)
36	103	21 (20.4)	115	9 (7.8)
54	78	11 (14.1)	103	11 (10.7)
72	59	12 (20.3)	85	6 (7.1)
90	44	8 (18.2)	71	1 (1.4)
108	29	5 (17.2)	67	3 (4.5)

The applicant has presented a sensitivity analysis using MMRM on the change from baseline data. In particular, this results in the baseline data not being included in the model. The treatment effect was significant in this model, and the applicant notes that the treatment by time interaction was not.

Statistical Assessor's Comment:

It is unclear from the data presented what precisely is happening. Patients are not up-titrated if they respond, and in total 57 patients responded at any time on Concerta, although there were only 38 responders at the end of the trial. If the applicant considers missing data to be non-responders, this may explain a lot of this apparent discrepancy. The other alternative is that patients are responding throughout the trial but then fail at the final visit. This would raise questions about the longer term efficacy, especially in light of the results of the randomised withdrawal trial. The applicant should clarify the reasons why there is a difference between the total number of responders at the end of the double-blind period, and the total of all responders in the *post hoc* analysis.

The numerator should only be considered in the table above since LOCF has been used at final visit. The data require further scrutiny treating all dropouts as non-responders to gain a more realistic view on the degree of efficacy.

The usual method of interpreting the MMRM analysis is to consider the treatment by time interaction test. However, because the applicant has presented a change from baseline analysis, which excludes baseline, it

is the treatment effect which is the most important in assessing the efficacy of the product. The interaction test would show whether the improvement from baseline increases as the trial continues, whereas the treatment effect shows whether there is any difference between the 2 treatments. Therefore the sensitivity analysis does not provide evidence against efficacy, although it is still arguable that neither method provides a suitably conservative analysis.
The dosing regimen used in the trial does not support the proposed dosing regimen in the SmPC, with much higher doses being permitted in this trial. However efficacy does seem to be demonstrated at the lower dose groups, as shown in the *post hoc* analysis above.

Study 3013

DISPLAY EFF.28: RESPONDER RATE: DESCRIPTIVE STATISTICS

ANALYSIS SET: INTENT TO TREAT
A) TABULATION OF RESPONSE AT DOUBLE-BLIND ENDPOINT

	RESPONSE?					
	NO		YES		TOTAL	
	N	%	N	%	N	%
PLACEBO	53	54.6	44	45.4	97	100.0
54 MG/DAY	40	44.4	50	55.6	90	100.0
72 MG/DAY	33	35.9	59	64.1	92	100.0
ALL MPH	73	40.1	109	59.9	182	100.0

		PR OROS MPH		
	Placebo (N = 97) n (%)	54 mg/day (N = 90) n (%)	72 mg/day (N = 92) n (%)	Total (N = 279) n (%)
Completed	68 (70.1)	55 (61.1)	55 (59.8)	178 (63.8)
Discontinued	29 (29.9)	35 (38.9)	37 (40.2)	101 (36.2)
Adverse event	2 (2.1)	15 (16.7)	19 (20.7)	36 (12.9)
Lack of efficacy	14 (14.4)	1 (1.1)	4 (4.3)	19 (6.8)
Non-compliance	3 (3.1)	5 (5.6)	5 (5.4)	13 (4.7)
Consent withdrawal	4 (4.1)	3 (3.3)	3 (3.3)	10 (3.6)
Loss to follow-up	5 (5.2)	2 (2.2)	0	7 (2.5)
Sponsor's decision	0	2 (2.2)	0	2 (0.7)
Ineligibility to continue the study	0	1 (1.1)	1 (1.1)	2 (0.7)
Other	1 (1.0)	6 (6.7)	5 (5.4)	12 (4.3)

Statistical Assessor's Comment:

The most appropriate method for handling missing data is to consider those that drop out as treatment failures. As noted earlier there is an incredibly high dropout rate in this study, with 30% of patients not completing in the placebo group, and 40% in the active group. It is clear from the data presented that in this trial the applicant has not treated missing as failure, as more patients appear to have responded than actually finished the trial in the 72 mg/day group. Whilst it is accepted that this study is longer in duration than the other efficacy studies and thus it may be reasonable to expect a higher dropout, there is so much missing data that the robustness of the results could be called into question. Furthermore, it adds weight to the concern that carrying forward a good value using LOCF when a patient drops out for a safety-related AE is not a suitably conservative analysis.

CGI-I results

Table 21: CGI-I: Summary Statistics at Double-Blind End Point
(Studies 3002. 02-159, and 3013; Intent-to-Treat Population)

		CONCERTA				
CGI-I Rating	Placebo	18 mg	36 mg	54 mg	72 mg	All Concerta
Study 3002						
N	93	97	100		98	295
Mean (SD) score at LOCF end point	3.4 (0.92)	2.8 (0.90)	3.0 (1.04)		2.7 (1.08)	2.8 (1.02)
p-value (vs. Placebo)[a]		0.0004	0.0108		<0.0001	<0.0001
CGI-I Scores, n (%)						
Much or very much improved	17 (18.3)	37 (38.2)	36 (36.0)		47 (47.9)	120 (40.7)
Minimally improved	30 (32.3)	35 (36.1)	29 (29.0)		26 (26.5)	90 (30.5)
No change	41 (44.1)	24 (24.7)	30 (30.0)		21 (21.4)	75 (25.4)
Minimally - Much worse[b]	5 (5.4)	1 (1.0)	5 (5.0)		4 (4.1)	10 (3.4)
Study 02-159						
N	115					103[c]
LS Mean (SE) score at LOCF end point[d]	3.43 (0.11)					3.02 (0.11)
p-value (vs. Placebo)[e]						0.008
CGI-I Scores, n (%)						
Much or very much improved	25 (21.8)					39 (37.9)
Minimally improved	17 (14.8)					23 (22.3)
No change	68 (59.1)					34 (33.0)
Minimally - Much worse[b]	5 (4.3)					7 (6.8)

Continued

Table 21: CGI-I: Summary Statistics at Double-Blind End Point, Continued
(Studies 3002, 02-159, and 3013; Intent-to-Treat Population)

		CONCERTA				
CGI-I Rating	Placebo	18 mg	36 mg	54 mg	72 mg	All Concerta
Study 3013						
N	93			84	92	176
Mean (SD) score at end point	3.0 (1.17)			2.7 (1.17)	2.5 (1.18)	2.6 (1.15)
p-value (vs. Placebo)[a]				0.0518	0.0018	0.0034
CGI-I Scores, n (%)						
Much or very much improved	31 (33.4)			42 (50.0)	56 (60.9)	98 (55.7)
Minimally improved	26 (28.0)			14 (16.7)	15 (16.3)	29 (16.5)
No change	30 (32.3)			25 (29.8)	17 (18.5)	42 (23.9)
Minimally - Much worse[b]	6 (6.5)			3 (3.6)	4 (4.4)	7 (4.0)

A lower mean CGI-I score indicates greater improvement relative to baseline.
Shaded area indicates treatment group was not represented in that study.

[a] Based on ANOVA model on ranks controlling for country and gender. Comparison between each CONCERTA dose group and placebo adjusted using Dunnett's procedure for Study 3002; comparisons unadjusted for mulitiplicity in Study 3013.

[b] No subject in any treatment group had a CGI-I rating of very much worse at double-blind end point.

[c] Mean final dose of 68 mg/day.

[d] Data represent LS mean (± SE).

[e] Based on ANOVA model with factors for treatment and site. A step-wise procedure was used to control the Type I error rate.

Overview of Primary and Secondary Endpoints

Table 3: Overview of Efficacy Results
(Study 3002; Intent-to-Treat Population)

Efficacy Variable	Placebo	CONCERTA 18 mg	CONCERTA 36 mg	CONCERTA 72 mg
Primary Efficacy Variable				
CAARS ADHD symptoms total Score, n	95	99	101	99
Mean change (SD)[a]	-7.6 (9.93)	-10.6 (10.34)*	-11.5 (9.97)*	-13.7 (11.11)*
Secondary Efficacy Variables				
CAARS Inattention Subscale, n	95	99	101	99
Mean change (SD)[a]	-3.7 (5.23)	-5.9 (5.76)*	-6.5 (5.92)*	-7.6 (6.29)*
CAARS Hyperactivity/Impulsivity Subscale, n	95	99	101	99
Mean change (SD)[a]	-3.9 (5.46)	-4.7 (5.54)	-4.9 (5.04)	-6.0 (6.18)*
CAARS-S:S Total Score, n	91	93	95	92
Mean change (SD)[a]	-5.8 (11.26)	-10.4 (12.90)*	-11.3 (12.42)*	-14.4 (15.52)*
CGI-S, n	93	97	100	98
Median change (range)[a]	0.0 (-3, 1)	-1.0 (-4, 1)*	-1.0 (-4, 1)*	-1.0 (-4, 1)*
CGI-I, n	93	97	100	98
Mean value (SD)[c]	3.4 (0.92)	2.8 (0.9)*	3.0 (1.06)*	2.7 (1.08)*
SDS Total Score, n	74	76	79	75
Mean change (SD)[a]	-2.2 (3.90)	-4.8 (6.25)*	-4.1 (5.62)	-5.1 (6.96)*
Q-LES-Q-SF Total Score, n	78	82	86	78
Mean change (SD)[b]	5.0 (14.17)	5.6 (12.30)	4.7 (15.68)	6.7 (18.97)
GAE, n	93	97	100	98
Median value (range)[d]	0.0 (0, 3)	1.0 (0, 3)	1.0 (0, 3)	1.0 (0, 3)

[a] Negative change from baseline value indicates improvement relative to baseline value.
[b] Positive value or change from baseline value indicates improvement relative to baseline value.
[c] CGI-I scale ranged from 1 (very much improved) to 7 (very much worsened).
[d] GAE was rated using 4-point scale (0 = poor to 3 = excellent).
* Denotes a statistically significant (p-value<0.05) difference relative to placebo, adjusted for comparisons between each CONCERTA dose group and placebo using Dunnett's procedure.

Cross-reference: Mod5.3.5.1/3002/Section 5.2 and Section 5.3.

Table 4: Overview of Efficacy Results
(Study 02-159, Intent-to-Treat Population)

Variable[a]	CONCERTA	Placebo	p-value[b]
AISRS Total Score (primary variable), n	110	116	
Mean change (SD)	-10.9 (11.75)	-6.8 (11.45)	0.012
CGI-I, n:	103	115	
LS Mean (SE)[b]	3.0 ± 0.11	3.4 ± 0.11	0.008
CAARS-S:S Total Score:, n	102	115	
Mean change (SD)	-13.3 (15.81)	-8.8 (13.19)	0.029
Treatment Responder Rate[c]:			
% (n/N)	36.9 (38/103)	20.9 (24/115)	0.009
SDS Work Subscale Score, n	90	99	
Mean change (SD)	-1.4 (2.79)	-1.0 (2.44)	0.397
CGI-S, n	103	115	
Mean change (SD)	-1.0 (1.22)	-0.5 (1.00)	0.009[d]
AIM-A: Work/Home/School Domain, n	94	107	
Mean change (SD)	17.4 (26.68)	9.6 (22.53)	0.016[d]

[a] Lower values indicate greater improvement for AISRS Total score, CGI-I, CAARS-S:S Total score, SDS - Work subscale score, and CGI-S. Higher values indicate greater effectiveness for AIM-A Work/Home/School Domain score.

[b] Data represented as LS mean (± standard error).

[c] Treatment responder defined as subjects with 30% improvement in AISRS total score and a CGI-Improvement rating of much or very much improved.

[d] Nominal p-values. Formal testing was not performed due to multiple-testing hierarchy.

Note: The number of subjects reported for each variable is not the same because the baseline value was carried forward to final visit only for the AISRS total score for subjects with missing post-baseline assessments.

Table 5: Overview of Efficacy Results
(Study 3013: Intent-to-Treat Population)

Efficacy Variable	Placebo	CONCERTA 54 mg	CONCERTA 72 mg
Primary Efficacy Variable			
CAARS ADHD symptoms total Score, n	97	90	92
Mean change at end point (SD)[a]	-10.4 (11.03)	-12.5 (10.38)	-15.7 (10.80)*
Secondary Efficacy Variables			
CAARS Inattention Subscale, n	97	90	92
Mean change at end point (SD)[a]	-5.5 (6.35)	-7.0 (6.14)*	-8.9 (6.37)*
CAARS Hyperactivity/Impulsivity Subscale, n	97	90	92
Mean change at end point (SD)[a]	-4.9 (5.84)	-5.6 (5.19)	-6.8 (5.67)*
CAARS-S:S Total Score, n	94	85	90
Mean change at end point (SD)[a]	-8.5 (11.64)	-12.8 (13.42)*	-12.6 (13.84)*
CGI-S, n	97	90	92
Mean change at end point (SD)[a]	-0.9 (1.35)	-1.0 (1.19)	-1.4 (1.31)*
CGI-I, n	93	84	92
Mean value at end point (SD)[b,c]	3.0 (1.17)	2.7 (1.17)	2.5 (1.13)*
SDS Total Score, n	88	77	83
Mean change at end point (SD)[a]	-3.6 (5.33)	-4.4 (6.35)	-4.6 (6.58)
AIM-A: Work, Home, & School – Performance and Daily Functioning, n	97	88	92
Mean change at end point (SD)[b]	10.3 (18.95)	16.4 (22.95)*	19.8 (22.47)*
AIM-A: Living with ADHD, n	97	88	92
Mean change at end point (SD)[b]	2.0 (11.91)	4.3 (13.24)	5.9 (12.11)*
AIM-A: Impact of Symptoms on Daily Life, Daily Interference Scale, n	96	88	90
Mean change at end point (SD)[b]	12.7 (19.37)	17.5 (22.57)*	17.6 (21.63)*
AIM-A: General Well-Being, n	97	88	92
Mean change at end point (SD)[b]	4.7 (14.95)	9.5 (16.69)*	8.7 (16.48)
AIM-A: Relationships/Communication, n	97	88	92
Mean change at end point (SD)[b]	5.7 (20.96)	9.5 (18.88)	13.5 (21.17)*
AIM-A: Impact of Symptoms on Daily Life, Bother/Concern, n	97	88	92
Mean change at end point (SD)[b]	13.4 (19.53)	16.8 (21.28)	16.6 (24.62)

[a] Negative change from baseline indicates improvement relative to baseline value.
[b] Positive value or change from baseline indicates improvement relative to baseline value.
[c] CGI-I scale ranged from 1 (very much improved) to 7 (very much worsened).
* Denotes a statistically significant (p-value<0.05) difference relative to placebo, adjusted for comparisons between each CONCERTA dose group and placebo; Dunnett's procedure was used for the primary efficacy variable.

Subgroup Analysis in special populations

Table 25: Subgroup Analyses of CAARS ADHD Symptoms Total Score: Difference (Versus Placebo) in LS Mean Change From Baseline at Double-Blind End Point (Studies 3002 and 3013; Intent-to-Treat Population)

Subgroup/ Treatment Group	Study 3002 Diff in LS Mean Change (N)[a] Subgroup 1	Subgroup 2	Subgroup 3	Study 3013 Diff in LS Mean Change (N)[b] Subgroup 1	Subgroup 2	Subgroup 3
Age at ADHD Diagnosis	<18 yrs	≥18 yrs	N/A	<18 yrs	≥18 yrs	N/A
CONCERTA 18 mg	-5.7 (16)	-4.4 (82)				
CONCERTA 36 mg	-6.8 (21)	-3.8 (80)				
CONCERTA 54 mg				-2.2 (18)	-4.2 (72)	
CONCERTA 72 mg	-6.6 (17)	-6.6 (82)		-12.9 (11)	-5.0 (80)	
ADHD Subtype	Combined	Inattention	Hyperactive/ Impulsivity	Combined	Inattention	Hyperactive/ Impulsivity
CONCERTA 18 mg	-4.3 (62)	-2.7 (32)	NE			
CONCERTA 36 mg	-4.6 (75)	-1.6 (19)	NE			
CONCERTA 54 mg				-2.2 (60)	-5.7 (27)	NE
CONCERTA 72 mg	-6.4 (74)	-4.1 (22)	NE	-4.2 (62)	-8.0 (28)	NE
Age at Study Entry	18-24 yrs	24-35 yrs	36-49 yrs	18-24 yrs	24-35 yrs	36-49 yrs
CONCERTA 18 mg	-5.6 (21)	-5.5 (31)	-3.6 (37)			
CONCERTA 36 mg	-3.8 (28)	-4.0 (27)	-6.5 (40)			
CONCERTA 54 mg				-2.2 (18)	-0.6 (32)	-5.1 (28)
CONCERTA 72 mg	-5.6 (22)	-5.4 (35)	-9.3 (36)	-1.3 (13)	-2.6 (35)	-9.2 (34)
Age in Study Entry	50-65 yrs			50-65 yrs		
CONCERTA 18 mg	-2.0 (10)					
CONCERTA 36 mg	3.6 (6)					
CONCERTA 54 mg				-7.4 (12)		
CONCERTA 72 mg	-5.7 (6)			-7.6 (10)		
Gender	Male	Female	N/A	Male	Female	N/A
CONCERTA 18 mg	-4.2 (56)	-3.7 (43)				
CONCERTA 36 mg	-3.9 (46)	-4.6 (55)				
CONCERTA 54 mg				-3.4 (44)	-2.4 (46)	
CONCERTA 72 mg	-5.8 (53)	-7.0 (46)		-5.6 (50)	-4.1 (42)	
BMI at Study Entry (kg/m^2)	< 25 (normal)	25-<30 (overweight)	≥ 30 (obese)	< 25 (normal)	25-<30 (overweight)	≥ 30 (obese)
CONCERTA 18 mg	-3.5 (49)	-3.6 (30)	-3.7 (18)			
CONCERTA 36 mg	-2.2 (55)	-5.2 (31)	-6.6 (15)			
CONCERTA 54 mg				-1.5 (40)	-4.3 (35)	-1.4 (15)
CONCERTA 72 mg	-5.2 (48)	-6.9 (37)	-9.6 (14)	-3.2 (40)	-6.1 (34)	-2.8 (17)
Current Psychiatric Comorbidity	Yes	No	N/A	Yes	No	N/A
CONCERTA 18 mg	-4.0 (14)	-4.1 (85)				
CONCERTA 36 mg	-5.3 (18)	-4.1 (83)				
CONCERTA 54 mg				-0.3 (20)	-3.8 (70)	
CONCERTA 72 mg	-4.6 (18)	-6.8 (81)		-6.2 (18)	-4.5 (74)	
History/Current Psychiat. Comorbid.	Yes	No	N/A	Yes	No	N/A
CONCERTA 18 mg	-2.6 (46)	-4.9 (53)				
CONCERTA 36 mg	-1.9 (55)	-5.9 (46)				
CONCERTA 54 mg				-1.9 (49)	-3.5 (41)	
CONCERTA 72 mg	-4.3 (49)	-8.3 (50)		-4.5 (48)	-5.1 (44)	

Footnotes on next page.

Continued.

Table 25: Subgroup Analyses of CAARS ADHD Symptoms Total Score: Difference (Versus Placebo) in LS Mean Change From Baseline at Double-Blind End Point (Studies 3002 and 3013; Intent-to-Treat Population) (Continued)

Subgroup/ Treatment Group	Study 3002 Diff in LS Mean Change (N)[a] Subgroup 1	Subgroup 2	Subgroup 3	Study 3013 Diff in LS Mean Change (N)[b] Subgroup 1	Subgroup 2	Subgroup 3
Prior MPH Exposure	**Naive**	**Non-naive**	**N/A**	**Naive**	**Non-naive**	**N/A**
CONCERTA 18 mg	-3.7 (91)	-3.5 (8)				
CONCERTA 36 mg	-4.0 (95)	-1.7 (6)				
CONCERTA 54 mg				-2.5 (79)	-4.9 (11)	
CONCERTA 72 mg	-6.2 (90)	-5.6 (9)		-5.3 (89)	1.8 (3)	

NE = LS mean difference could not be estimated because of too few subjects.

[a] The difference in LS means is based on an ANCOVA model, with treatment, country, and gender as factors and baseline score as a covariate.

[b] The difference in LS means is based on an ANCOVA model with treatment, country, and gender as factors, and age and baseline score as a covariate.

Light shaded areas indicate treatment group not represented in that study.

The applicant has also presented an analysis by age for Study 02-159

Subgroup	All CONCERTA LSMean ± SEM (N)	Placebo LSMean ± SEM (N)	p-Value[a]
Male	-12.1 ± 1.56 (63)	-6.6 ± 1.46 (64)	0.009
Female	-9.9 ± 1.95 (47)	-6.7 ± 1.80 (52)	0.231
Age 18 to 35	-9.2 ± 2.01 (42)	-7.5 ± 1.85 (47)	0.510
Age 36 to 49	-11.3 ± 1.07 (40)	-7.0 ± 1.79 (48)	0.089
Age 50 to 65	-11.6 ± 2.93 (28)	-3.4 ± 3.45 (21)	0.092

Statistical Assessor's Comment

The analysis by age in study 02-159 suggests that there is a much stronger effect in older patients compared to younger patients. The response to active increases as age increases, and the response to placebo decreases. If there is a correlation between age in study and age of diagnosis, this could have important implications for the proposed wording. In particular it would suggest weaker efficacy in the indicated population and the applicant should investigate this further.

Dose Response

Table 29: Placebo-Adjusted Mean Differences in Key Efficacy Variables (Study 3002; Intent-to-Treat Population)

Efficacy Variable Change at End Point[a]	LS Mean Difference vs. Placebo CONCERTA 18 mg	CONCERTA 36 mg	CONCERTA 72 mg
CAARS ADHD Symptoms Total score	-4.00	-4.03	-6.59
CAARS Inattention subscale	-2.80	-3.06	-4.16
CAARS Hyperactivity/Impulsivity subscale	-1.15	-0.97	-2.41
CAARS-S:S Total score	-6.08	-6.11	-9.23
SDS Total score	-2.77	-2.11	-3.02

[a] Based on ANCOVA on change from baseline at end point with treatment, country and gender as factors and baseline score as covariate.

Table 30: Placebo-Adjusted Mean Differences in Key Efficacy Variables (Study 3013; Intent-to-Treat Population)

Efficacy Variable Change at End Point	LS Mean Difference vs. Placebo CONCERTA 54 mg	CONCERTA 72 mg
CAARS ADHD Symptoms Total score	-2.69[a,b]	-4.89[a,b]
CAARS Inattention subscale	-1.90[a,b]	-3.21[a,b]
CAARS Hyperactivity/Impulsivity subscale	-0.80[a,b]	-1.73[a,b]
CAARS-S:S Total score	-4.25[a,b]	-4.43[a,b]
AIM-A Work, Home, School – Performance and Daily Functioning score	8.00[a,c,d]	9.76[a,c,d]
CGI-S score	13.53[b,c,d]	37.61[b,c,d]

[a] Based on ANCOVA on change from baseline at end point with treatment, country and gender as factors, and age and baseline score as covariate.
[b] A negative LS means difference indicates greater improvement in CONCERTA group compared to placebo group.
[c] Difference in LS means ranks based on ANCOVA on ranks, comparing each CONCERTA group with placebo.
[d] A positive LS means difference indicates greater improvement in the CONCERTA group compared to placebo group.

Assessor's comments

Although formal statistical testing with Johkheere-Terpestra trend test was negative for study 3002, there is a consistent numerical dose response in the main items seen in both studies. This is perhaps surprising as all doses clearly separate from placebo and there are clear numerical differences. There is heterogeneity in the subscales, possibly due to a lack of power.

Literature of short-term efficacy

Results from the 3 non-Sponsor initiated placebo-controlled studies of CONCERTA, involving a total of 211 adults with ADHD diagnosed using DSM-IV, reported larger symptomatic improvement with CONCERTA compared with placebo.

- In a 6-week study, adults with ADHD were randomly assigned to double-blind treatment with CONCERTA (n=67) or placebo (n=74) (Biederman 2006a). Dosing for both drugs was individualized and was initiated at 36 mg/day and titrated to optimal response based on efficacy and safety, up to a maximum dose of 1.3 mg/kg/day. The mean dose of study drug at Week 6 was 80.9 mg/day for CONCERTA. Treatment with CONCERTA was associated with a statistically significantly larger reduction from baseline in the AISRS total score compared with placebo beginning at Week 3 that was sustained through Week 6. At end point, 66% of subjects in the CONCERTA p21decrease in AISRS total score and a CGI-I rating of much or very much improved.
- A randomized, double-blind cross-over study compared flexible-dosing with CONCERTA or placebo for 4 weeks among 47 adults with ADHD (Reimherr 2007). Approximately 40% of subjects had ADHD with significant emotional and oppositional symptoms. Treatment was initiated at a dose of 18 mg/day and was titrated to optimal response at 9-mg increments every 2-3 days to a maximum dose of 90 mg/day. At a mean dose of 64.0 mg/day, CONCERTA was superior to placebo for all clinical efficacy measures. Statistically significantly larger decreases from baseline to end point were seen with CONCERTA compared with placebo for the total ADHD-RS score (41% vs 14% decrease in score, respectively) and total Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS) (42% vs 13% decrease in score, respectively).

- In a randomized, double-blind study of 23 mother-child dyads, both diagnosed with ADHD, treatment with CONCERTA was shown to be associated with significant improvements in ADHD symptoms as well as in objective measures of parenting (Chronis-Tuscano 2008). In this study, all mothers participated in a 5-week double-blind titration phase; during this phase, dosing was started with placebo and adjusted upwards on a weekly basis to CONCERTA doses of 36, 54, 72, and 90 mg/day until subjects achieved an optimal response based on prespecified criteria. At the conclusion of the titration phase, subjects were randomly assigned to 2 weeks of treatment with placebo or their optimal dose of CONCERTA. At the end of the titration phase, statistically significant improvements from baseline (i.e., treatment during Week 1 of titration phase) relative to placebo were seen with CONCERTA (mean dose of 83.7 mg/day) for ADHD Hyperactivity/Impulsivity and Inattention subscale scores and for the CGI-S ratings compared with placebo. Mean scores on ADHD Inattention and Hyperactivity/Impulsivity subscales and CGI-S at the end of the randomized treatment phase of the study suggested that there were fewer symptoms among the 9 subjects who continued on CONCERTA relative to the 11 subjects who were switched to placebo. Measures of maternal involvement, poor monitoring/supervision, and inconsistent discipline at the end of the randomized treatment phase also showed positive treatment effect for CONCERTA.

Assessor's comments

The choice of end points appears appropriate in accordance with the CHMP Guideline on the Treatment of ADHD. CAARS was used in the studies submitted for atomoxetine which gained a similar indication and . The validation of the AISRS is supported by a paper by Spencer et al.

The primary endpoint was significantly positive for all the ITT analyses except for the 54mg dose in Study 3013. It should be noted that in this study the placebo response was greater. The magnitude of the response from baseline was -12.5 which is what would be expected if extrapolating from Study 3002 which showed changes from baseline of -11.5 for the 36mg dose and -13.7 for the 72mg dose. In addition 2 pre-specified sensitivity analyses (PP and Modified ITT were statistically significant). However, the robustness of these analyses is called in to question for the following reasons. In the LOCF analysis subjects were included as responders even when they had withdrawn due to an AE. The withdrawal rates in both placebo (30%) and active (40%) groups were high. The withdrawal rates and adherence were related to dose (non-compliance with study medication intake 8%, 22% and 25% for placebo and CONCERTA 54 mg and 72 mg groups, respectively).

Study 3002 was positive for the primary outcome for all 3 doses 18mg, 36mg and 72mg on ITT LOCF analysis. This result was supported by most ((CAARS inattention subscale, CAARS-S:S, CGI-S, CGI-I) but not all (Q-LES-Q and GAE) secondary endpoints. The CAARS hyperactivity subscale was only positive for 72mg but the lower doses showed a positive trend. SDS showed significant improvement in Studies 3002 for the 18mg and 72mg doses but not the 36mg dose (numerical improvement).

Study 02-159 was positive for the primary endpoint AISRS and supported by CGI-I, CAARS-S:S, Treatment Responder Rate, CGI-S and AIM-A but not the SDS Work Subscale.

Study 3013 was positive for the 72mg dose but not the 54mg dose for the primary endpoint (Total CAARS). The 72mg dose was supported by statistically significant improvements in the CAARS subscales, CGI-S, CGI-I, AIM-A [Performance, Living, Daily Life, Communication but not Symptoms on Daily Life or SDS. The secondary endpoints for the 54mg dose were mixed although all (including the primary endpoint) demonstrated positive trends.

As presented the studies appear positive for short-term efficacy in the studied population but further analyses of the results is required treating all withdrawals as treatment failures before a firm conclusion can be drawn.

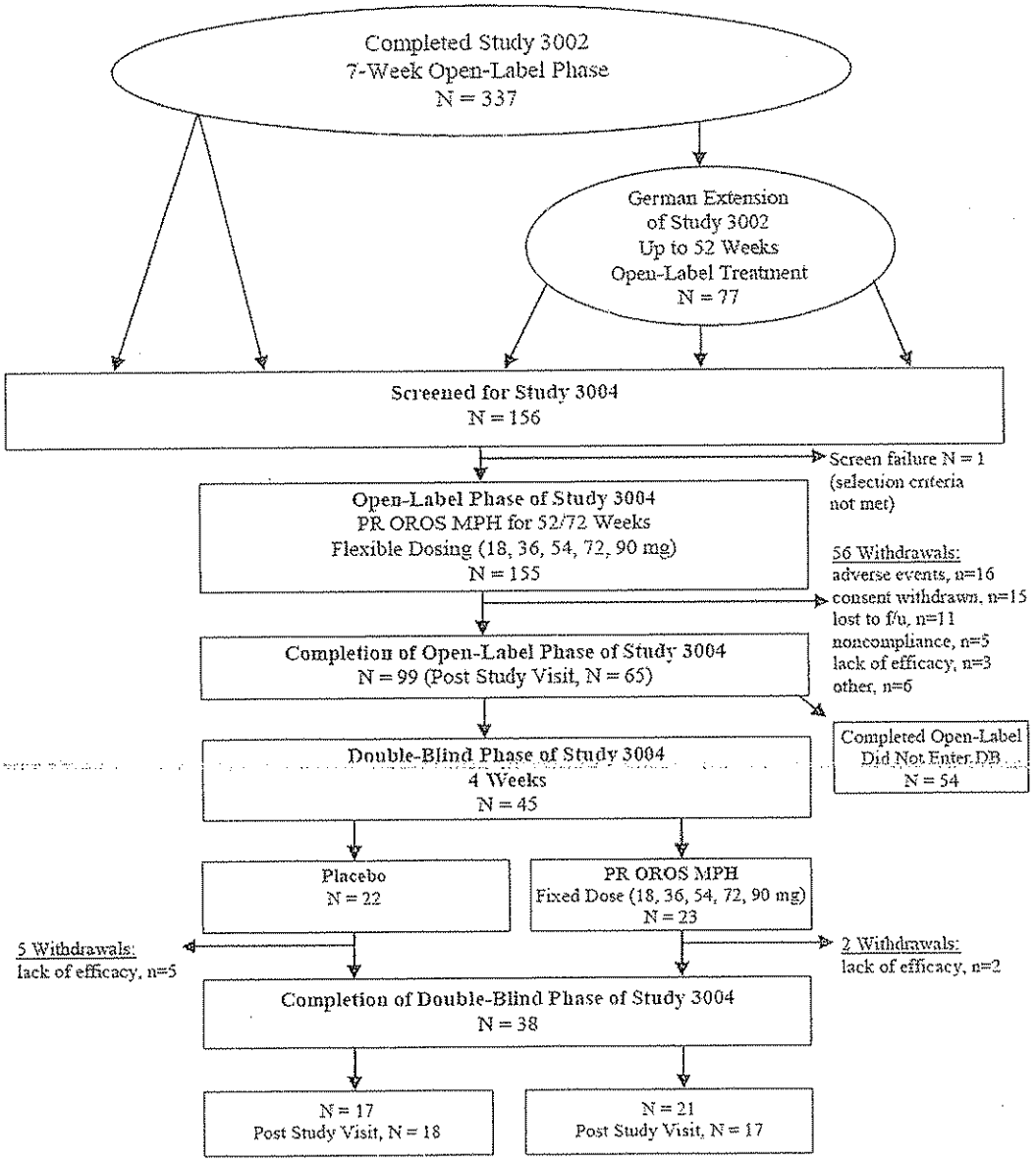
The subgroup analysis of primary interest is the one examining whether original diagnosis occurred before or after 18 years, since the indication sought is the in the former population. Less than 20% of the study group met this criterion. In Study 3002, treatment effect for those diagnosed <18 years compared to those diagnosed as adults was numerically greater for the 18mg and 36mg dose and identical for the 72mg dose. In Study 3013 treatment effect was greater in the <18 year population. This provides some reassurance that the data from patients diagnosed after the age of 18 may support the proposed indication, but it is of note that no statistical significance was observed in this subgroup, and there are still concerns regarding Study 02-259 where the opposite trend was observed.

There were heterogeneous results according to ADHD subtype between studies 3002 and 3013. No consistent effect in relation to age at recruitment or gender was seen.

BMI was positively correlated with effect size in Study 3002 but not Study 3013. Current Psychiatric morbidity and a history of Psychiatric Morbidity appeared to reduce the effect size (excluding the 72mg dose in Study 3013. No obvious pattern of differences was seen in whether the adult was MPH naïve or not.

Maintenance of effect

Figure 9: Subject Disposition
(Study 3004: All Subjects/ Open-Label and Double-Blind Populations)



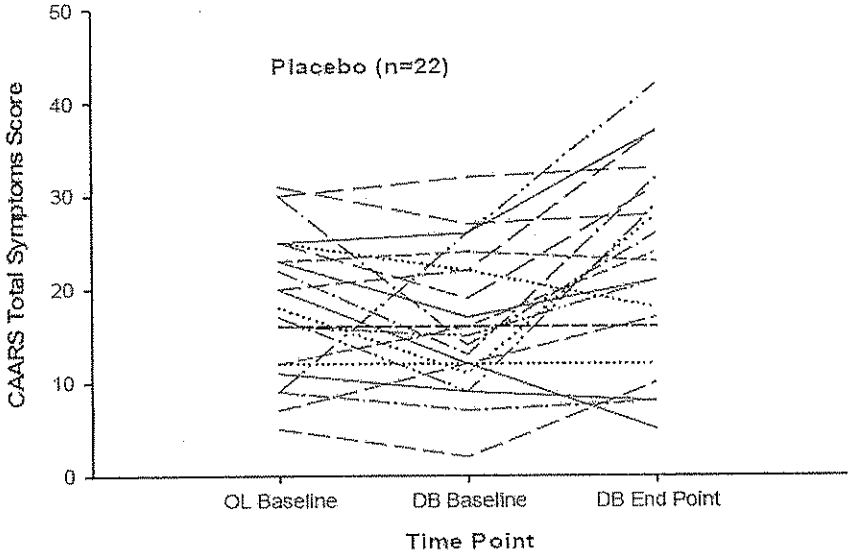
Cross-reference: Mod5.3.5.1/3004/Figure 1

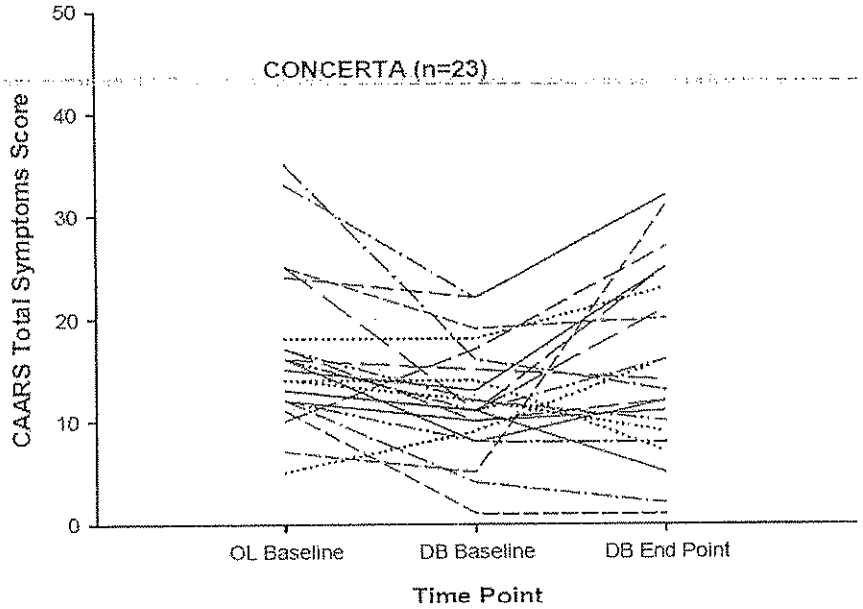
Results are shown below:

	Placebo (N=22)	PR OROS MPH (N=23)
Visit 7, baseline		
Mean (SD)	16.5 (7.49)	12.1 (5.34)
Median	15.5	11.0
Range	2 - 32	1 - 22
Endpoint		
Mean (SD)	23.0 (10.41)	16.2 (9.42)
Median	23.5	14.0
Range	5 - 42	1 - 32
Change from Baseline to Endpoint		
Mean (SD)	6.5 (7.82)	4.0 (7.61)
Median	5.5	2.0
Range	-7 - 20	-7 - 26
LS Means (p-value)[a]	2.89 (0.2586)	

[a] ANCOVA

Figure 10: Multiple Line Plot of Individual Subjects: CAARS ADHD Symptoms Total Score (Study 3004; Intent-to-Treat/Double Blind Population)





Maintenance of effect from published studies

Rösler M (2009), Fischer R, Ammer R, et al. A randomized, placebo-controlled, 24-week, study of low-dose extended-release methylphenidate in adults with attention-deficit/ hyperactivity disorder. Eur Arch Psychiatry Clin Neurosci 2009;259:120-9.

In one study, 359 adults with ADHD were randomly assigned to double-blind treatment with extended-release (ER) MPH (formulation consisting of 50% immediate release [IR] MPH and MPH ER) or placebo for 24 weeks. Treatment was initiated at a dose of 10 mg/day and titrated to optimal response up to 60 mg/day. The mean daily doses at Week 24 were 41.2 mg in the MPH ER group and 40.8 mg in the placebo group. Statistically significantly larger mean improvements from baseline to end point were seen

in the MPH ER group compared with the placebo group on the mean WRAADDS score as well as on the CAARS ADHD symptoms total score. The response rate at end point was also significantly higher for the MPH ER group (61%) than for the placebo group (42%); response was defined as a 30% or greater reduction in WRAADDS score.

In the second study, subjects who demonstrated a clinical response during an initial 6-week double-blind, placebo-controlled trial of MPH IR and placebo were enrolled in a double-blind maintenance study and continued on their same medication for an additional 6 months to assess stability of response. There was little change in the mean severity of ADHD symptoms from Week 0 to Week 24 of the maintenance phase for the MPH IR (n=59) or placebo (n=6) groups. However, a significantly higher percentage of subjects who continued on placebo (43%) compared with those maintained on MPH IR (15%) exhibited worsening of ADHD symptoms, defined as the loss of at least 25% of improvement on ADHD symptom rating scale.

Assessors' comments

No maintenance of effect has been demonstrated from the failed withdrawal Study 3004, which was probably under powered but the difference between placebo and Concerta is modest which may also explain the results. There is some evidence of maintenance of effect from the paper by Rosler. The second paper is available as a short extract only and cannot be assessed. In addition the robustness of the results from Study 3013 is also in question.

EFFICACY CONCLUSION

There are 3 randomised, double-blind studies, 2 in Europe and 1 in the US. The European studies both used fixed doses. The MAH are not applying to use the higher doses studied (90mg and 108mg) although they are proposing to increase the current approved dosage range to 72mg for the proposed adult population. There appears to be a dose related efficacy (and safety) effect. The population recruited to the studies was stated to be diagnosed in line with DSM IV criteria. However, the details around the characteristics of the populations and how they were deemed to be suitable for study entry are not included. This will require further scrutiny. There is an apparent contradiction when it is then stated that only a subgroup have had their ADHD diagnosed <18 years of age. This population formed less than 20% of the overall study population. There is a major concern over the robustness of diagnosis of ADHD in the population recruited to the studies. In addition there are extensive exclusion criteria that result in the recruitment of a population with little psychiatric or physical co-morbidity. Subgroup analysis reveals that Current Psychiatric morbidity or a History of Psychiatric Morbidity appeared to reduce the effect size (excluding the 72mg dose in Study 3013). This weakens the external validity of the studies.

The primary endpoint was significantly positive for all the ITT analyses except for the 54mg dose in Study 3013. It should be noted that in this study the placebo response was greater. The magnitude of the response from baseline was -12.5 which is what would be expected if extrapolating from Study 3002 which showed changes from baseline of -11.5 for the 36mg dose and -13.7 for the 72mg dose. In addition 2 pre-specified sensitivity analyses (PP and Modified ITT were statistically significant). However, the robustness of these analyses is called in to question for the following reasons. In the LOCF analysis subjects were included as responders even when they had withdrawn due to an AE. The withdrawal rates in both placebo (30%) and active (40%) groups were high. The withdrawal rates and adherence were related to dose (non-compliance with study medication intake 8%, 22% and 25% for placebo and CONCERTA 54 mg and 72 mg groups, respectively).

Study 3002 was positive for the primary outcome for all 3 doses 18mg, 36mg and 72mg on ITT LOCF analysis. This result was supported by most ((CAARS inattention subscale, CAARS-S:S, CGI-S, CGI-I) but not all (Q-LES-Q and GAE) secondary endpoints. The CAARS hyperactivity subscale was only

positive for 72mg but the lower doses showed a positive trend. SDS showed significant improvement in Studies 3002 for the 18mg and 72mg doses but not the 36mg dose (numerical improvement).

Study 02-159 was positive for the primary endpoint AISRS and supported by CGI-I, CAARS-S:S, Treatment Responder Rate, CGI-S and AIM-A but not the SDS Work Subscale.

Study 3013 was positive for the 72mg dose but not the 54mg dose for the primary endpoint (Total CAARS). The 72mg dose was supported by statistically significant improvements in the CAARS subscales, CGI-S, CGI-I, AIM-A [Performance, Living, Daily Life, Communication but not Symptoms on Daily Life or SDS. The secondary endpoints for the 54mg dose were mixed although all (including the primary endpoint) demonstrated positive trends.

As presented the studies appear positive for short-term efficacy in the studied population but further analyses of the results is required treating all withdrawals as treatment failures before a firm conclusion can be drawn.

There is some evidence of efficacy is available up to 13 weeks but the long-term withdrawal study lacked sufficient power. There is some long-term efficacy from a published paper by Rossler 2009 but there is insufficient detail in the published paper to fully understand the population being studied.

Overall the evidence to support the proposed indication wording is considered weak.

Other Concerns

It is unclear how the applicant has defined whether a patient is a responder when the data is missing. For each of the 3 pivotal short term efficacy studies, the applicant should clarify how this has been done. For each trial, if this analysis has not already presented, an analysis including missing data as failures should be presented, including point estimates, p-values and confidence intervals, adjusted using Dunnett's procedure for controlling the Type I error.

For all studies the applicant should provide details on how many patients who did drop out were considered responders. In particular, if this is much higher on treatment compared to placebo, a full discussion of why LOCF and MMRM are appropriately conservative methods for handling missing data should be provided.

For Study 0159 the applicant should clarify how many patients initially responded (and at what dose) but were not considered to be responders by the end of the study.

For Study 3002, the applicant should provide the results of the analysis for the primary endpoint without gender in the model. For study 3013, age should be removed from the model.

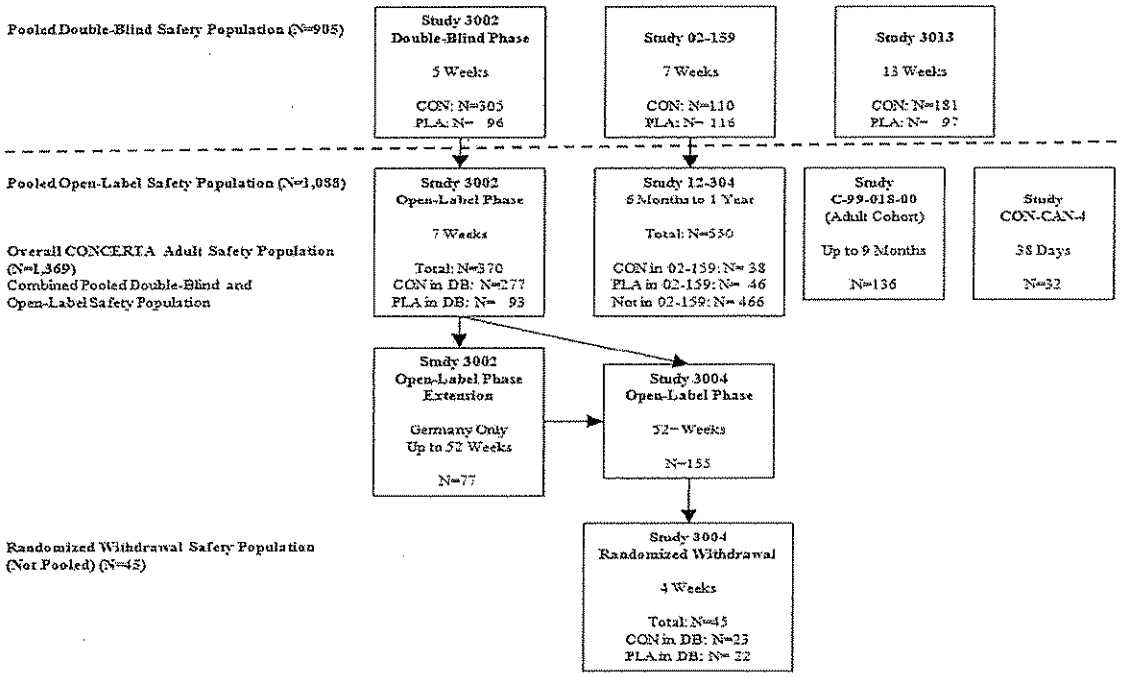
The applicant should investigate whether there is an interaction in any of the studies between age of diagnosis and age at enrolment in the study. If there is, the applicant should discuss further the apparent decrease in efficacy seen in younger patients in study 0159.

CLINICAL SAFETY

• Double-Blind Safety Analysis Set: Subjects from the double-blind portion of Study 3002 (3002 DB) and Studies 02-159 and 3013. • Open-Label Safety Analysis Set: Subjects from the open-label portion of Study 3002 (3002 OL), the open-label portion of Study 3004 (3004 OL), and Studies 12-304, C-99-018-00, and CON-CAN-4.
• Overall CONCERTA Analysis Set: All subjects receiving CONCERTA from Studies 3002 DB, 02-159, 3013, 3002 OL, 3004 OL, 12-304, C-99-018-00, and

CON-CAN-4. This population was only used to summarize overall demographics and exposure.

Figure 1: Phase 3 Double-Blind and Open-Label Studies Using CONCERTA in Adults With ADHD



Patient exposure

Table 5: Summary of Dose Received for CONCERTA Subjects - Double-Blind Safety Analysis Set
(CONCERTA EU SCS: Double-Blind Safety Analysis Set)

	---- ALL CONCERTA ---- (N=595)
Maximum dose, n (%)	
N	595
18 mg	101 (17.0)
36 mg	134 (22.5)
54 mg	106 (17.8)
72 mg	209 (35.1)
90 mg	16 (2.7)
108 mg	29 (4.9)
Maximum dose (days on drug)	
N	595
Mean (SD)	53.76 (24.180)
Median	54.00
Range	(18.0;108.0)
Length of time on maximum dose	
N	595
Mean (SD)	41.05 (26.757)
Median	35.00
Range	(1.0;106.0)
Final dose, n (%)	
N	595
18 mg	101 (17.0)
36 mg	138 (23.2)
54 mg	104 (17.5)
72 mg	213 (35.8)
90 mg	16 (2.7)
108 mg	23 (3.9)

Note: The lowest dose will be used in the analysis if a tie occurs.

Table 6: Duration of Exposure by Treatment Group - Open-Label Safety Analysis Set
(CONCERTA EU SCS: Open-Label Safety Analysis Set)

	--- ALL CONCERTA -- (N=1088)
Duration (days)	
N	1088
Category, n (%)	
1 - 30	142 (13.1)
31 - 60	274 (25.2)
61 - 90	45 (4.1)
91 - 180	130 (11.9)
181 - 270	189 (17.4)
271 - 360	137 (12.6)
> 360	171 (15.7)
Mean (SD)	197.82 (199.713)
Median	165.00
Range	(1.0;943.0)
Total Exposure (subject years)	589.3
At least 6 months, n (%)	
N	1088
Yes	497 (45.7)
No	591 (54.3)
At least 1 year, n (%)	
N	1088
Yes	171 (15.7)
No	917 (84.3)

Note: Subjects were allowed to change CONCERTA dose as needed clinically and may be counted in more than one dose group.
Note: 6 months is defined as 181 days.
Note: 1 year is defined as 361 days.
Note: Person Years of Exposure is the cumulative duration of exposure (days) for all subjects divided by 365.24.
rex02_tsub40b.rtf generated by rex02.sas.

Table 12: Concomitant Medications Taken by ≥ 3% of Subjects in One or More Treatment Groups by Treatment Group - Double-Blind Safety Analysis Set
(CONCERTA EU SCS: Double-Blind Safety Analysis Set)

Medication Name	PLACEBO (N=309) n (%)	ALL CONCERTA (N=596) n (%)	Total (N=905) n (%)
Total no. subjects WITH ANY CONCOMITANT MEDICATION	208 (67.3)	394 (66.1)	602 (66.5)
Acetylsalicylic acid	10 (3.2)	23 (3.9)	33 (3.6)
Ibuprofen	41 (13.3)	82 (13.8)	123 (13.6)
Loratadine	14 (4.5)	10 (1.7)	24 (2.7)
Multivitamins	19 (6.1)	19 (3.2)	38 (4.2)
Paracetamol	44 (14.2)	81 (13.6)	125 (13.8)

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Includes all medications taken after the first dose of study medication.
rcm01_tsub32a.rtf generated by rcm01.sas.

Adverse events

Serious adverse events and deaths

Table 13: Summary of All Adverse Events by Treatment Group - Double-Blind Safety Analysis Set
(CONCERTA EU SCS: Double-Blind Safety Analysis Set)

Evaluation	PLACEBO (N=309) n (%)	ALL CONCERTA (N=596) n (%)
Subjects with Adverse Events	213 (68.9)	491 (82.4)
Subjects with Serious Adverse Events	2 (0.6)	9 (1.5)
Subjects who discontinued due to Adverse Events	8 (2.6)	63 (10.6)
Deaths	0	0

Note: Percentages calculated with the number of subjects in each group as denominator.
rae01_tae01a.rtf generated by rae01.sas.

Table 14: Summary of All Adverse Events - Open-Label Safety Analysis Set
(CONCERTA EU SCS: Open-Label Safety Analysis Set)

Evaluation	ALL CONCERTA (N=1088) n (%)
Subjects with Adverse Events	891 (81.9)
Subjects with Serious Adverse Events	26 (2.4)
Subjects who discontinued due to Adverse Events	147 (13.5)
Deaths	0

Note: Percentages calculated with the number of subjects in each group as denominator.
rae01_tae01b.rtf generated by rae01.sas.

There were no deaths.

Table 17: Number and Percent of Subjects With Serious Adverse Events by MedDRA System Organ Class, Preferred Term and Treatment Group - Double-Blind Safety Analysis Set
(CONCERTA EU SCS: Double-Blind Safety Analysis Set)

Body System Or Organ Class Dictionary-Derived Term	PLACEBO (N=309) n (%)	ALL CONCERTA (N=596) n (%)
Total no. subjects WITH ADVERSE EVENTS	2 (0.6)	9 (1.5)
Gastrointestinal disorders	0	1 (0.2)
Abdominal pain	0	1 (0.2)
Nausea	0	1 (0.2)
Infections and infestations	1 (0.3)	0
Cholecystitis infective	1 (0.3)	0
Injury, poisoning and procedural complications	1 (0.3)	1 (0.2)
Concussion	0	1 (0.2)
Joint injury	1 (0.3)	0
Musculoskeletal and connective tissue disorders	0	1 (0.2)
Interveriebral disc protrusion	0	1 (0.2)
Nervous system disorders	0	2 (0.3)
Cerebrovascular accident	0	1 (0.2)
Migraine	0	1 (0.2)
Psychiatric disorders	0	3 (0.5)
Anxiety disorder	0	1 (0.2)
Depression	0	1 (0.2)
Suicidal ideation	0	1 (0.2)
Suicide attempt	0	1 (0.2)
Reproductive system and breast disorders	0	1 (0.2)
Ovarian cyst ruptured	0	1 (0.2)

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
rae03_tae08a.rtf generated by rae03.sas.

Withdrawal Adverse Events

Study 3002

Table 38: Adverse Events Emerging During Double-Blind With Action Taken Permanently Stopped Trial Medication, Reported by ≥2 Subjects in the Overall Group

(Study 42603ATT3002: *All Subjects / Double-Blind*)

Body System Preferred Term n (%)	Placebo (N=96)	PR OROS MPH 18 mg (N=101)	36 mg (N=102)	72 mg (N=102)	Overall (N=401)
Any AE in this category	1 (1.0)	1 (1.0)	4[b] (3.9)	8 (7.8)	14 (3.5)
Nervous System Disorders	0	0	1 (1.0)	4 (3.9)	5 (1.2)
Insomnia	0	0	0	2 (2.0)	2 (0.5)
Tremor	0	0	0	2 (2.0)	2 (0.5)
Psychiatric Disorders	0	0	4 (3.9)	7 (6.9)	11 (2.7)
Anxiety	0	0	1 (1.0)	3 (2.9)	4 (1.0)
Irritability	0	0	1 (1.0)	2 (2.0)	3 (0.7)
Nervousness	0	0	1 (1.0)	2 (2.0)	3 (0.7)
Restlessness	0	0	0	2 (2.0)	2 (0.5)
Vascular Disorders	1 (1.0)	0	0	1 (1.0)	2 (0.5)
Hypertension	1[a] (1.0)	0	0	1 (1.0)	2 (0.5)

[a] subject A11047 discontinued trial medication in the open-label phase because of an adverse event that emerged during the double-blind phase.

[b] subject 10871 discontinued trial medication in the open-label phase because of an adverse event that emerged during the double-blind phase.

Source: Attachment 47

Study 02-159

Dose	Withdrawal (%)	Dose Reduction (n)
36mg (n=110)	4 (3.6%)	0
54mg (n=78)	7 (9.0%)	3 (3.8%)
72mg (n=60)	2 (3.3%)	3 (5%)
90mg (n=45)	1 (2.4%)	6 (13.3%)
108mg (n=29)	2 (6.7%)	5 (17.2%)
Placebo (n=116)	6 (5.2%)	5 (4.3%)

Study 3013

prematurely.

Table 8: Study Completion/Withdrawal Information
(Study 42603ATT3013: Intent-to-Treat)

	Placebo (N = 97) n (%)	PR OROS MPH 54 mg/day (N = 90) n (%)	PR OROS MPH 72 mg/day (N = 92) n (%)	Total (N = 279) n (%)
Completed	68 (70.1)	55 (61.1)	55 (59.8)	178 (63.8)
Discontinued	29 (29.9)	35 (38.9)	37 (40.2)	101 (36.2)
Adverse event	2 (2.1)	15 (16.7)	19 (20.7)	36 (12.9)
Lack of efficacy	14 (14.4)	1 (1.1)	4 (4.3)	19 (6.8)
Non-compliance	3 (3.1)	5 (5.6)	5 (5.4)	13 (4.7)
Consent withdrawal	4 (4.1)	3 (3.3)	3 (3.3)	10 (3.6)
Loss to follow-up	5 (5.2)	2 (2.2)	0	7 (2.5)
Sponsor's decision	0	2 (2.2)	0	2 (0.7)
Ineligibility to continue the study	0	1 (1.1)	1 (1.1)	2 (0.7)
Other	1 (1.0)	6 (6.7)	5 (5.4)	12 (4.3)

N = number of subjects with data; n = number of subjects with observation
Source: Attachment 2.6

Assessor's Comments There is evidence of a greater risk of DAEs at higher doses of MPH particularly at the upper end of the doses studied.

Common Adverse Events

Table 15: Number and Percent of Subjects With Adverse Events Where CONCERTA ≥ 1% and > Placebo by MedDRA System Organ Class, Preferred Term and Treatment Group - Double-Blind Safety Analysis Set
(CONCERTA EU SCS: Double-Blind Safety Analysis Set)

Body System Or Organ Class Dictionary-Derived Term	PLACEBO (N=309) n (%)	ALL CONCERTA (N=596) n (%)
Total no. subjects WITH ADVERSE EVENTS	213 (68.9)	491 (82.4)
Cardiac disorders	4 (1.3)	63 (10.6)
Palpitations	2 (0.6)	27 (4.5)
Tachycardia	0	36 (6.0)
Ear and labyrinth disorders	5 (1.6)	23 (3.9)
Vertigo	1 (0.3)	12 (2.0)
Eye disorders	8 (2.6)	34 (5.7)
Accommodation disorder	0	8 (1.3)
Vision blurred	3 (1.0)	8 (1.3)
Gastrointestinal disorders	65 (21.0)	206 (34.6)
Constipation	2 (0.6)	9 (1.5)
Dry mouth	11 (3.6)	90 (15.1)
Dyspepsia	6 (1.9)	12 (2.0)
Nausea	15 (4.9)	85 (14.3)
Vomiting	2 (0.6)	11 (1.8)
General disorders and administration site conditions	37 (12.0)	99 (16.6)
Asthenia	0	7 (1.2)
Fatigue	13 (4.2)	28 (4.7)
Irritability	9 (2.9)	31 (5.2)
Thirst	2 (0.6)	11 (1.8)
Infections and infestations	50 (16.2)	99 (16.6)
Sinusitis	3 (1.0)	8 (1.3)
Upper respiratory tract infection	3 (1.0)	10 (1.7)
Investigations	30 (9.7)	102 (17.1)
Alanine aminotransferase increased	0	6 (1.0)
Blood pressure increased	6 (1.9)	15 (2.5)
Heart rate increased	6 (1.9)	18 (3.0)

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

(continued)

Table 15: Number and Percent of Subjects With Adverse Events Where CONCERTA ≥ 1% and > Placebo by MedDRA System Organ Class, Preferred Term and Treatment Group - Double-Blind Safety Analysis Set (Continued)
(CONCERTA EU SCS: Double-Blind Safety Analysis Set)

Body System Or Organ Class Dictionary-Derived Term	PLACEBO (N=309) n (%)	ALL CONCERTA (N=596) n (%)
Investigations (continued)		
Weight decreased	11 (3.6)	52 (8.7)
Metabolism and nutrition disorders	30 (9.7)	180 (30.2)
Anorexia	4 (1.3)	25 (4.2)
Decreased appetite	19 (6.1)	148 (24.8)
Musculoskeletal and connective tissue disorders	33 (10.7)	61 (10.2)
Muscle spasms	1 (0.3)	6 (1.0)
Muscle tightness	0	8 (1.3)
Nervous system disorders	90 (29.1)	225 (37.8)
Dizziness	17 (5.5)	44 (7.4)
Headache	58 (18.8)	144 (24.2)
Paresthesia	0	7 (1.2)
Tension headache	1 (0.3)	6 (1.0)
Tremor	2 (0.6)	20 (3.4)
Psychiatric disorders	62 (20.1)	236 (39.6)
Affect lability	2 (0.6)	8 (1.3)
Aggression	2 (0.6)	7 (1.2)
Agitation	2 (0.6)	19 (3.2)
Anxiety	9 (2.9)	50 (8.4)
Bruxism	2 (0.6)	9 (1.5)
Confusional state	1 (0.3)	6 (1.0)
Depressed mood	8 (2.6)	26 (4.4)
Depression	2 (0.6)	9 (1.5)
Initial insomnia	8 (2.6)	34 (5.7)
Insomnia	24 (7.8)	79 (13.3)
Libido decreased	2 (0.6)	8 (1.3)
Nervousness	2 (0.6)	14 (2.3)
Panic attack	1 (0.3)	8 (1.3)
Restlessness	0	24 (4.0)
Tension	1 (0.3)	8 (1.3)

See footnotes on the first page of the table.

(continued)

Table 15: Number and Percent of Subjects With Adverse Events Where CONCERTA ≥ 1% and > Placebo by MedDRA System Organ Class, Preferred Term and Treatment Group - Double-Blind Safety Analysis Set (Continued)
(CONCERTA EU SCS: Double-Blind Safety Analysis Set)

Body System Or Organ Class Dictionary-Derived Term	PLACEBO (N=309) n (%)	ALL CONCERTA (N=596) n (%)
Reproductive system and breast disorders	7 (2.3)	17 (2.9)
Erectile dysfunction	1 (0.3)	6 (1.0)
Respiratory, thoracic and mediastinal disorders	14 (4.5)	35 (5.9)
Cough	3 (1.0)	7 (1.2)
Dyspnoea	2 (0.6)	7 (1.2)
Oropharyngeal pain	4 (1.3)	9 (1.5)
Skin and subcutaneous tissue disorders	12 (3.9)	49 (8.2)
Hyperhidrosis	4 (1.3)	34 (5.7)
Vascular disorders	13 (4.2)	32 (5.4)
Hot flush	2 (0.6)	8 (1.3)
Hypertension	5 (1.6)	13 (2.2)

See footnotes on the first page of the table.
rae03_rae06a.rtf generated by rae03.sas.

Assessor's comments

The wide range of psychiatric adverse events is considered a cause for concern. Cardiovascular adverse events are very common but the number of individuals with recorded increases in heart rate and blood pressure are much lower from the AE data, this may relate to the study population and the protocol on treatment reduction and withdrawal.

Adverse events of Special Interest

Table 19: Number and Percent of Subjects With At Least One Adverse Event Within Any Adverse Event Category of Special Interest By Treatment Group - Double-Blind and Overall
CONCERTA Safety Analysis Set
(CONCERTA EU SCS: All Treated Subjects Analysis Set)

Adverse Event Category Of Special Interest	PLACEBO (N=309) n (%)	DB CONCERTA (N=596) n (%)	TOTAL CONCERTA (N=1369) n (%)
Total no. subjects WITH ADVERSE EVENTS	87 (28.2)	307 (51.5)	815 (59.5)
Hypertension	12 (3.9)	32 (5.4)	136 (9.9)
Tachycardia	0	36 (6.0)	81 (5.9)
Raynaud's phenomenon	2 (0.6)	3 (0.5)	6 (0.4)
Psychosis/mania	3 (1.0)	17 (2.9)	45 (3.3)
Anorexia	23 (7.4)	174 (29.2)	394 (28.8)
Migraine	6 (1.9)	7 (1.2)	25 (1.8)
Repetitive behaviours	0	1 (0.2)	1 (0.1)
QT prolongation	1 (0.3)	0	4 (0.3)
Arrhythmias	11 (3.6)	80 (13.4)	240 (17.5)
Cerebrovascular disorders	0	1 (0.2)	1 (0.1)
Aggression	17 (5.5)	71 (11.9)	202 (14.8)
Hostility	0	3 (0.5)	11 (0.8)
Depression	32 (10.4)	100 (16.8)	270 (19.7)
Suicidality	0	1 (0.2)	3 (0.2)
Tics/tourette's syndrome/dystonias	4 (1.3)	25 (4.2)	72 (5.3)
Carcinogenicity	0	0	5 (0.4)
Withdrawal syndrome	0	1 (0.2)	1 (0.1)

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
rae12_tae26.rtf generated by rae12.sas.

Hypertension and Tachycardia There were more cases of hypertension and tachycardia reported on Concerta than placebo. Those who had BPs above 120/80 at baseline largely had BP reduction noted during the studies suggesting a 'white coat' effect. The analysis in those without hypertension at baseline (<140/80) was as follows:

Subjects must have had at least 2 post-baseline study visits; the development of hypertension was defined as either a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg at 2 or more post-baseline study visits.

Study 3002 CONCERTA 72 mg (8.9%), 36 mg (5.1%) 18mg (2.6%) placebo (6.8%)
In Study 02-159, CONCERTA compared with placebo (4% vs. 2%)
Study 3013 CONCERTA (72 mg, 18.9%; 54 mg, 14.5%) placebo (7.4%)

In 1.9% (n=26) in the Overall CONCERTA Safety Analysis Set the event resulted in the discontinuation of CONCERTA therapy. In 2/3 of cases the hypertension was said to have resolved.

Raynaud's

There was no signal.

Psychosis/mania

In all Concerta the incidence of psychosis/mania was 3.3%. In the double-blind studies, the likelihood of experiencing an adverse event coded to psychosis/mania adverse event category of special interest was higher on CONCERTA than on placebo (2.9% vs. 1.0%, odds ratio: 3.0). Events leading to

discontinuation included Thinking abnormal (severe), Delusions of reference (severe), and Abnormal behavior (severe), and all of these events resolved following discontinuation.

Anorexia (and Weight)

For Studies 3002 and 3013, potentially clinically important decreases from baseline in body weight (≥7% of body weight) were observed for a higher percentage of CONCERTA versus placebo subjects (8.3% vs. 0.3%). There is some evidence that the rate of weight loss reduces after 6 months treatment.

Migraine

In the double-blind studies, the likelihood of experiencing an adverse event within the migraine adverse event category of special interest was not higher on CONCERTA (1.2%) than on placebo (1.9%) (odds ratio: 0.6). For one of these subjects, the event was serious, a computerized tomography (CT) scan revealed a slight expansion of the frontal horn of the right lateral ventricle with a probable lacunar infarct in the nucleus caudate. A specialist in neuroradiology judged the findings as an old lesion.

Repetitive behaviours

There was only 1 case, which consisted of repetitive lip biting. This resolved after 40 days without treatment discontinuation.

QT Prolongation

There were 4 cases in the Overall CONCERTA Safety Analysis Set, 0 in the double-blind and 1 in the placebo group. No case required treatment withdrawal.

Arrhythmias

Adverse events within the arrhythmias adverse event category of special interest were reported for 17.5% of adult subjects treated with CONCERTA across all clinical studies. Most of these adverse events were related to increased heart rate, with the most common arrhythmia-related adverse events in the Overall CONCERTA Safety Analysis Set being Tachycardia (n=80, 5.8%), Palpitations (n=79, 5.8%), and Heart rate increased (n=78, 5.7%). There were no reports of Ventricular fibrillation, Ventricular tachycardia, or Atrial fibrillation in any adult subject receiving CONCERTA. Arrhythmia-related adverse events led to discontinuation of CONCERTA therapy in 32 of the 1369 (2.3%) adults in the Overall CONCERTA Safety Analysis Set. In the Double-Blind Safety Analysis Set, the risk of experiencing an adverse event within the arrhythmias adverse event category of special interest was higher on CONCERTA (13.4%) than on placebo (3.6%) (odds ratio: 4.2)

CVD

Single case of cerebral infarction secondary to dissection in right posterior inferior cerebellar artery.

Aggression

For the Double-Blind Safety Analysis Set, 13 of the 596 subjects receiving CONCERTA (2.2%) were withdrawn for aggression-related adverse events (vs. none receiving placebo).

Hostility

In the Double-Blind Safety Analysis Set, 3 subjects receiving CONCERTA (0.5%) and no subject receiving placebo had an adverse events within the hostility adverse event category of special interest.

Depression

Approximately 20% of adult subjects in the Overall CONCERTA Safety Analysis Set reported an adverse events within the depression adverse event category of special interest (19.7%). In the Double-Blind Safety Analysis Set, the likelihood of experiencing an adverse events within the depression adverse event category of special interest was higher on CONCERTA (16.8%) than on placebo (10.4%) (odds ratio: 1.8 [CI 1.1-2.8]) .

In the Overall CONCERTA Safety Analysis Set, adverse events within the suicidality adverse event category of special interest were reported for 3 subjects (0.2%). These events consisted of a single report of a suicide attempt accompanied by suicidal ideation and 2 reports of suicidal ideation without an accompanying suicide attempt

Tic/Tourettes/dystonias
In the double-blind studies, the likelihood of an adverse event within the tics/Tourette's syndrome/dystonias adverse event category of special interest was approximately 3-fold higher on CONCERTA (4.2%) than on placebo (1.3%) (odds ratio: 3.3)

Carcinogenicity
No signal was seen from the adult data.

Withdrawal reactions

No signal was seen from the small withdrawal study.

Assessor's comments

AEs related to Arrthymia were due to sinus tachycardia related events (tachycardia, palpitations or heart rate increase) rather than any evidence of more malign arrythmias. These largely resolved 200/240 but required treatment withdrawal in 32 cases.

Safety in special populations

Table 34: Summary of All Adverse Events by Age at Diagnosis of ADHD and Treatment Group - Double-Blind Safety Analysis Set
(CONCERTA EU SCS: Double-Blind Safety Analysis Set)

	PLACEBO			ALL CONCERTA		
	Total	Age at Diagnosis of ADHD, n (%)		Total	Age at Diagnosis of ADHD, n (%)	
Evaluation	(N=309) n (%)	<18 years (N=39)	≥ 18 years (N=205)	(N=596) n (%)	<18 years (N=93)	≥ 18 years (N=445)
Subjects with Adverse Events	213 (68.9)	28 (71.8)	145 (70.7)	491 (82.4)	71 (76.3)	370 (83.1)
Subjects with Serious Adverse Events	2 (0.6)	1 (2.6)	1 (0.5)	9 (1.5)	1 (1.1)	8 (1.8)
Subjects who discontinued due to Adverse Events	8 (2.6)	2 (5.1)	3 (1.5)	63 (10.6)	8 (8.6)	48 (10.8)
Deaths	0	0	0	0	0	0

Note: Percentages in 'Total' column for each group calculated with the number of subjects in each group as denominator.
Percentages of age at diagnosis of ADHD sub-groups calculated with number of subjects per sub-group as denominator.
Note: Subjects with missing values for age at diagnosis of ADHD are included in the total column.
rae01_ins01g.rtf generated by rae01.sas.

Assessor's comments

There is a signal that individuals diagnosed after the age of 18 years experience more AEs and more serious (including withdrawal) AEs on active treatment. This pattern is not observed in the placebo group. To explore this further it would be of interest to know the age of those individuals diagnosed with ADHD <18 years vs. those diagnosed as adults.

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SAFETY CONCLUSION

The main new safety concern from the study data is around the frequency of psychiatric adverse events and that this is often de novo. Of note is the incidence of anxiety but also rates of depression and aggressive and hostile behaviour are raised. The latter AE, although occurring in a small proportion of individuals, is by its nature a particular cause for concern. There is a small signal of suicidality from the data. It is not clear if this has been analysed by Columbia Criteria with ideation removed as a pre-requisite.

The known cardiovascular AEs are of particular concern in an adult population, potentially on long-term treatment. There is clear evidence from these studies of tachycardia and rises in BP. There is no discussion around what level of BP increase that could pose a risk to the individual and the data on sustained increases in BP have not been presented. The MAH will be asked for these data.

An observation study in the US (Vanderbilt Study) may provide more informative data in the future but currently the data are very limited and the studies do not provide robust information on individuals with cardiovascular co-morbidities.

Clinically important weight loss (>7%) has been demonstrated to be a common AE in an adult population.

RISK MANAGEMENT PLAN ASSESSMENT (APPENDIX II)

In this version of the RMP, the MAH has proposed updates to the Core RMP (required by CHMP following the Article 31 referral for all methylphenidate products) to support a type II variation for a new indication for Concerta in treating adults with ADHD whose diagnosis was established before the age of 18 years and whose symptoms persist into adulthood. Exposure, demographic, and important identified and potential risk data from double-blind and open-label clinical trials in adults with ADHD, and information from literature pertaining to adults with ADHD where applicable, were added to this RMP. I

Generally, there was a lack of adequate information on the epidemiology of ADHD in adults, specifically in the EU but also worldwide.

The Core important identified and potential risks for all methylphenidate products were reviewed for relevance in the adult ADHD population. A number of major risks were identified from the adult clinical trial data, which were either new, or were reported with a higher frequency category than in the paediatric population. Some of these should be categorised as important risks in the safety specification of the RMP for adults, these include: Anxiety/Anxiety disorders, depression, suicide-related events, aggression, agitation, mania/delusions, tics, cardiac arrhythmias, hypertension and clinically important changes in weight. The potential for other clinical significant adverse cardiovascular and cerebrovascular outcomes, as a consequence of effects on heart rate and blood pressure in adults, cannot be excluded and is considered a potential risk. These should be subject to proactive pharmacovigilance and risk minimisation measures.

Further analysis of the adult study data in relation to effects on diastolic and systolic blood pressure and heart rate should be requested, with the aim of characterising as fully as possible, the patterns of change in blood pressure and heart rate over time in patients who at any time point have experienced important changes.

In order to better understand the study population and its relationship to the target indicated adult population (in the RMP safety specification), the MAH should provide details of when the adult trial participants were initially diagnosed with ADHD, the pervasiveness and persistency, and severity of the symptoms over time, and details of prior/existing treatments (both pharmaceutical and non-pharmaceutical). The MAH should determine whether any of these factors have an impact on the safety or efficacy of Concerta in adults.

Important missing information in the Safety Specification should include: maintenance of the short-term effect in adults, long-term efficacy, effectiveness and safety (especially for key risks: cardiovascular risks, cerebrovascular risks and *de novo* or worsening of pre-existing psychiatric disorders including: mood disorders, depression, anxiety, agitation, suicide-related events, psychosis /mania/delusion), safety & efficacy in new or continuing users of methylphenidate.

Because of the adult trial exclusion criteria, there is also important missing information from patients with a range of important cardiovascular, cerebrovascular neurological and psychiatric comorbidities, history

of abuse/misuse/SUD, liver or renal insufficiency, and in some studies, from patients with other past or current non-drug treatments, known non-responders to methylphenidate (or other ADHD drugs), recent users of methylphenidate, patients weighing < 45.4 KG.

Not all adults with ADHD will be eligible for treatment with Concerta, and the actual adult ADHD population who may be eligible for Concerta use is likely to be only a minority of those who were diagnosed with ADHD as children. The potential for off-label use in adults and the risk of diversion remain considerable. Measures proposed in the RMP to characterise the risks of off-label use and diversion and measures proposed to minimise them are considered inadequate and need to be addressed. Additionally, the MAH's proposed wording for sections 4.1, 4.2 and 4.4 of the SPC will allow use in adults who have been diagnosed with ADHD at any age up to 18 years of age, which is not in line with current guidelines which state ADHD should be diagnosed before the age of 7.

As per the utilisation studies for the child and adolescent population that were requested by CHMP during the Article 31 Referral, the MAH should propose methods to obtain data to characterise usage in the adult population over time, and to evaluate off-label use and the risk of diversion, in all member states. Collaboration with specialist treatment centres for Adults with ADHD should be considered in the proposals.

The MAH should submit proposals to further evaluate the risks in adults of suicidality and cerebrovascular disorders and the long-term effects on psychiatric outcomes.

The MAH should provide educational tools similar to those proposed for HCPs in the childhood and adolescence ADHD indication, specifically for adult patients.

The MAH should ensure that the risk minimisation measures adequately address : that specialists in adult ADHD are responsible for correct and appropriate diagnosis, pre-treatment screening, initiation of prescribing and review of the need for ongoing treatment with Concerta in adults ; the initiation of treatment within a comprehensive treatment programme, and only when remedial measures alone have proven insufficient; adherence to the required pre-treatment screening and ongoing monitoring; the lack of evidence on long-term safety, effectiveness and maintenance of short-term effects of Concerta in the adult population; need for regular evaluation of the need for continuing treatment; evaluation of the maintenance of effect in adults.

The MAH should consider whether the current Core SPC guidance and frequencies for neurological, psychiatric, weight and appetite monitoring are also appropriate for adults or whether they need to be modified.

Product information

PL and labelling are harmonised for this product.

Summary of Product Characteristics

Section 4.1

CONCERTA XL is indicated as part of a comprehensive treatment programme for Attention Deficit Hyperactivity Disorder (ADHD). ***It may be used when remedial measures alone prove insufficient*** in children aged 6 years of age and over ***as well as in adults whose ADHD diagnosis was established before the age of 18 years and whose symptoms persist into adulthood.***

Treatment must be under the supervision of a specialist in behavioural disorders ***in children or adults.*** Diagnosis should be made according to DSM-IV criteria or the guidelines in ICD-10 and should be based on a complete history and evaluation of the patient. Diagnosis cannot be made solely on the presence of one or more symptom.

The specific aetiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use of medical and specialised psychological, educational, and social resources.

A comprehensive treatment programme typically includes psychological, educational and social measures as well as pharmacotherapy and is aimed at stabilising ***patients*** with a behavioural syndrome characterised by symptoms which may include chronic history of short attention span, distractibility, emotional lability, impulsivity, moderate to severe hyperactivity, minor neurological signs and abnormal EEG. Learning may or may not be impaired.

CONCERTA XL treatment is not indicated in all patients with ADHD and the decision to use the drug must be based on a very thorough assessment of the severity and chronicity of the ***patient's*** symptoms ***with reference to the patient's age at diagnosis.***

Appropriate educational placement is essential, and psychosocial intervention is generally necessary. Where remedial measures alone prove insufficient, the decision to prescribe a stimulant must be based on rigorous assessment of the severity of the ***patient's*** symptoms. The use of methylphenidate should always be used in this way according to the licensed indication and according to prescribing / diagnostic guidelines.

Assessor's Comments

Section 4.1 As detailed in the efficacy conclusion the population proposed is wider than that described in DSM IV and should be tightly defined. Prescribing should be limited to experts in adult ADHD.

The inclusion of the posology for the 72 mg dose will be reviewed once the further analyses on the efficacy data are assessed. There does appear to be a dose response from the data submitted.

The wording regarding warnings for use in women of child-bearing age should be tightened.

The current warning in section 4.4 of the proposed SPC entitled "Anxiety, agitation and tension" is inadequate, as the adult studies show a clear potential for de novo anxiety and agitation in patients treated with Concerta. The warning should be modified to reflect the evidence for the risk of new-onset anxiety, tension and agitation and the MAA should consider making the warning more prominent in this section of the SPC.

There is a lack of data addressing the optimal duration of treatment and this should be clearly stated in the posology and the need for regularly reviewing treatment continuation.

PIL

The proposed wording will need to be reviewed when the SPC has been appropriately amended. Issues around the psychiatric adverse events and possibility of pregnancy will need to be addressed. These may more appropriately be done in a separate adult leaflet.

Educational tools for healthcare professionals (see RMP Assessment Appendix II).

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The applicant has conducted 3 randomised, double-blind studies, 2 in Europe (Studies 3002 and 3013) and 1 in the US (Study 02-159). The European studies both used fixed doses. The MAH are not applying to use the higher doses studied in Study 02-159 (90mg and 108mg) although they are proposing to increase

the current approved dosage range from 54mg to 72mg for the proposed adult population. There appears to be a dose related efficacy (and safety) effect. As presented, the studies are appear positive for short-term efficacy in the population studied but further analyses of the results is required treating missing data more conservatively. The current handling of the missing data is a Major Concern in the demonstration of short-term efficacy.

There is some evidence of efficacy is available up to 13 weeks but the long-term withdrawal study lacked sufficient power. There is some long-term efficacy from a published paper by Rossler 2009 but there is insufficient detail in the published paper to fully understand the population being studied.

The population recruited to the studies was stated to be diagnosed in line with DSM IV criteria. However, the details around the characteristics of the populations and how they were deemed to be suitable for study entry are not included. This will require further scrutiny. There is an apparent contradiction when it is then stated that only a subgroup have had their ADHD diagnosed <18 years of age. This population formed less than 20% of the overall study population. There is a major concern over the robustness of diagnosis of ADHD in the population recruited to the studies. In addition there are extensive exclusion criteria that result in the recruitment of a population with little psychiatric or physical co-morbidity. Subgroup analysis reveals that Current Psychiatric morbidity or a History of Psychiatric Morbidity appeared to reduce the effect size (excluding the 72mg dose in Study 3013). This weakens the external validity of the studies.

Overall the evidence to support the proposed indication wording is considered weak as it is based on a post hoc sub-group analysis in less than 20% of the studied population. Even then it is not clear if this sub-population adequately meets the DSM IV diagnostic criteria, as the MAH have not presented these data. Although, it should be noted that this sub-group analysis is from a group of positive efficacy studies rather than the more commonly seen manoeuvre of attempting to 'save' a negative study. This does lend more weight to the analysis.

There is a significant burden of adverse events from the studies. The psychiatric adverse events, particularly anxiety but also depression, aggression and hostile behaviour causes for concern. The latter AE, although occurring in a small proportion of individuals, is by its nature a cause may pose a clinical risk. There is a small signal of suicidality from the data. It is not clear if this has been analysed by Columbia Criteria with ideation removed as a pre-requisite. The MAH will be asked to address this.

There is clear evidence of the known risk of tachycardia and rise in BP. There is no discussion around what level of BP increase that could pose a risk to the individual and the data on sustained increases in BP have not been presented. The MAH will be asked for these data. Data from the pK Study 02-160 suggest dose dependent increases in HR and BP. The effect did not return to baseline between the dosing periods (3 days off medication). A clear presentation of baseline HR and BP for each treatment period should be presented from the pK study and similarly the individual patient data from the RCTS should be clearly presented for sustained HR and BP increases and whether these returned to normal after medication withdrawal.

An observation study in the US (Vanderbilt Study) may provide more informative data in the future but currently the data are very limited and the studies do not provide robust information on individuals with cardiovascular co-morbidities. The MAH will be asked about data from this study.

Clinically important weight loss (>7%) has been demonstrated to be a common AE in an adult population. Weight in adults should be monitored.

Many issues have arisen from the RMP assessment and these should be addressed. In particular the pD studies assessing the reward effect of Concerta show a clear effect in 'Light Drug Users'. Crushed Concerta delivers methylphenidate at a comparable rate and extent to IR MPH. It is assessed there is a significant abuse and diversion risk with Concerta.

The wording in the SPC and PIL will require revision if the data are reviewed sufficiently robust after further scrutiny. The safety data from the studies should be added even if the indication is not approved.

V REQUEST FOR SUPPLEMENTARY INFORMATION AS PROPOSED BY THE RMS

Questions must be divided into "potential serious risks to public health" and/or "other concerns", which are defined as follow:

"Potential serious risks to public health", preclude a recommendation to the variation to the term of the marketing authorisation. In principle, one 'potential serious risk to public health' may entail more than one question and the use of bullet points or subheadings is encouraged. It is vital that the structure and content of the objection are clear and understandable to the reader. Detailed comments may be necessary along with a reference to guidance documents

Ideally, the objection should include a clarification as to what kind of response/action by the MAH could be considered to solve the problem.

"Other concerns", may affect the proposed conditions to the variation to the terms of the marketing authorisation and product information.

V.1 Potential serious risks to public health

V.1.3 Clinical efficacy

1. Efficacy for the proposed indication has not been clearly demonstrated as follows:

- A robust and clinically relevant estimate of short term efficacy for the indicated population has not been demonstrated. Further analyses are requested (see other efficacy concerns).

- The relevance of the data derived from the population who were diagnosed after the age of 18 to the indicated population is unclear. Clear detail of how the study populations were assessed to have met DSM IV criteria for adult ADHD for the study populations in general and for the subgroup analysis population diagnosed <18 years of age should be provided.

- Long term efficacy. The withdrawal study failed to demonstrate efficacy. The published paper by Rosser lacks the required detail for an efficacy assessment. Data from that study should be submitted if the MAH wishes to use these as the primary supportive evidence.

V.1.4 Clinical safety

The safety of Concerta in the proposed indication has not been adequately described (see safety concerns below).

V.2 Other concerns

V.2.2 Non clinical aspects

The non clinical concerns can be addressed through amending sections 4.6 and 5.3 of the SPC (see below).

V.2.3 Clinical efficacy

2. It is unclear how the applicant has defined whether a patient is a responder when the data is missing. For each of the 3 pivotal short term efficacy studies, the applicant should clarify how this has been done. For each trial, if this analysis has not already presented, an analysis including missing data as failures should be presented, including point estimates, p-values and confidence intervals, adjusted using Dunnett's procedure for controlling the Type I error.

3. For all studies the applicant should provide details on how many patients who did drop out were considered responders. In particular, if this is much higher on treatment compared to placebo, a full discussion of why LOCF and MMRM are appropriately conservative methods for handling missing data should be provided.

4. For Study 0159 the applicant should clarify how many patients initially responded (and at what dose) but were not considered to be responders by the end of the study.

5. For Study 3002, the applicant should provide the results of the analysis for the primary endpoint without gender in the model. For study 3013, age should be removed from the model.

6. The applicant should investigate whether there is an interaction in any of the studies between age of diagnosis and age at enrolment in the study. If there is, the applicant should discuss further the apparent decrease in efficacy seen in younger patients in study 0159.

V.2.4 Clinical safety

7. Cardiovascular safety.
   - Discuss what level of BP and heart rate increase that could pose a risk to adults and present data on sustained increases in BP and heart rate.
   - For all studies increases in BP above 5mmHg and 10mmHg should also be presented as well as clinically significant sustained levels in HR.
   - Any cases where the HR or BP have not returned to baseline values after stopping Concerta should also be presented.
   - Additionally in Study 02-160 HR and BP did not return to baseline levels in between dosing periods, thus increases observed in HR and BP with higher doses may be less than if subjects had been monitored in a MPH naïve state. The baseline HR and BP for each treatment period and at study end should be presented for each subject. In addition, individual subject data for BP increases greater than 5mm Hg should be presented for each study period. There were 4 subjects who had ST changes during Tx. These were not described and could have been ST elevation or non-specific. In addition there were dysrhythmias observed in 3 subjects. Further scrutiny of these cases is warranted.

8. Psychiatric adverse events. Further discussion of the psychiatric adverse events is required with particular focus on:
   - Suicidality. Discuss whether all potential cases were identified in terms of a Columbia style analysis with intention not considered as a criterion for inclusion.
   - Aggression with a description of the individual events and their severity.

9. Further discussion on the implications of weight loss in adults.

10. Further discussion around the risk of abuse in light of the pharmacokinetics seen in study 12-004 Crushed Concerta and the Abuse potential seen in Study 12-007 (Light Drug Users).

11. The proposed indication will result in increased exposure of women of child-bearing potential. Adequate warnings should be in place in the SMC. The MAH should commit to capturing and evaluating relevant data on pregnancy outcomes using a pregnancy registry. In addition further investigation of the signal for spina bifida / neural tube defects from the WHO Collaborating Centre for the Epidemiological Surveillance of Congenital Anomalies (EUROCAT) and any other relevant sources.

V.2.5 Product information

12. The proposed wording for sections 4.1, 4.2 and 4.4 of the SPC will allow off-label use in adults who have been diagnosed with ADHD at any age up to 18 years of age, allowing inappropriate/off-label use in patients incorrectly diagnosed over 7 years of age, or who may have partial symptoms and not full ADHD. To prevent off-label use, the MAH should ensure that the wording of the proposed indication in the SPC is compliant with DSM-IV guidelines on the correct diagnosis of ADHD in childhood (i.e. before the age of 7 years). The MAA should also ensure that the wording of the SPC does not allow use of Concerta to treat partial symptoms (i.e. not full ADHD) in Adults.

13. The optimal treatment duration has not been established. This should be clearly stated in the SPC with the requirement for regular review of the need for continued treatment, which should include regular planned withdrawal of treatment.

14. The current warning in section 4.4 of the proposed SPC entitled "Anxiety, agitation and tension" is inadequate, as the adult studies show a clear potential for de novo anxiety and agitation in patients treated with Concerta. The warning should be modified to reflect the evidence for the risk of new-onset anxiety, tension and agitation and made more prominent.

15. Wording for the appropriate monitoring of AEs in adults should be added for example regarding weight loss and mood.

16. The preclinical data should be addressed by adding to Section 4.6 as only 1 human case is currently described:

    In rats, methylphenidate-associated radioactivity was found in the milk at concentrations up to around 1.5 times that in the plasma.

In addition the wording to Section 5.3 should be clarified as follows:

Pregnancy-embryonic/fetal development
Methylphenidate is not considered to be teratogenic in rats and rabbits. Fetal toxicity ***in the form of total litter loss*** was noted in rats at maternally toxic doses

RMP Concerns

The concerns raised from the RMP assessment should be addressed and in particular the following points answered:

17. The MAH should provide an evaluation of the results of the ongoing FDA / AHRQ / Vanderbilt University pharmacoepidemiological study (risk of cardiovascular disorders, cerebrovascular disorders, sudden death) as soon as the results are available and propose regulatory action in the context of the target Adult population.

18. Currently used educational tools should be modified for an adult population and adapted to ensure the correct adult ADHD population is identified for treatment.

Other RMP Points

The Risk Management Plan for Concerta in Adults should be revised based on the following points:

19. Most of the post-marketing, non-study exposure for Concerta is in patients from 6 – 20 years of age. It is important that the MAH has in place proactive pharmacovigilance measures to capture and analyse good quality post-marketing data specifically on for the adult population.

20. The following risks should be added to the adult RMP as important risks:

21. The risks of anxiety/anxiety disorders, depression, aggression, agitation restlessness, suicide-related events, psychosis, mania/delusions, decreased appetite, clinically important decreased weight, cardiac arrhythmias, tics/worsening of tics or Tourette's syndrome should be added to the Safety Specification as Important **Identified** Risks.

22. In relation to effects on diastolic and systolic blood pressure and heart rate in adults, the MAH should provide, for each time point, summary treatment group (by dose) data (including mean, SD, maximum and minimum) and summary change from baseline data (including mean, SD, maximum and minimum) together with individual patient data on which this is based for heart rate, systolic and/or diastolic blood pressure to describe the temporal relationship throughout the duration of all clinical trials. A table of data showing detailed data for patients where systolic and/or diastolic blood pressure increased ≥5 mmHG and significant changes in changes in heart rate should also be presented. The summary of the number and percentage of patients with an increase of at least 5 mmHg / significant changes in changes in heart rate should be included. Details of patient baseline characteristics (e.g. age, prior medications, prior illnesses, any other characteristics) should also be provided

23. An important aim of this analyses is to characterise as fully as possible, the patterns of change in blood pressure and heart rate over time in patients who at any time point have fallen into the category of concern (i.e. experienced changes of ≥5 mmHG, or important changes in pulse rate). Thus, the full temporal record of cardiovascular outcomes in patients who at any time point have experienced a change in blood pressure of ≥5 mmHG or important changes in heart rate should be provided and included in the overall analysis.

24. The analysis must include a complete description of the hazard function over time for each patient who experienced a change in blood pressure of ≥5 mmHG or changes in pulse rate.

25. Description of the risks per 1,000 patients should be provided.

26. The MAH should describe the evidence for maintenance of effect beyond short-term use and describe what is proposed for section 4 of the SPC and other risk minimisation measures in this regard. The MAH proposes to add to section 5.1 of the SPC, the following statement: "the maintenance of effect of Concerta XL during long-term use in adults with ADHD has not been fully established". No adequate evidence was presented in the RMP that maintenance of effect has been either partially or fully established, and the criteria for these definitions in not known, therefore the MAH should remove "fully" from the proposed text and add this information to relevant parts of section 4 of the SPC, the PIL and educational tools.

27. Not all adults with ADHD will be eligible for treatment with Concerta, and the actual adult ADHD population who may be eligible for Concerta use is likely to be only a minority of those who were diagnosed with ADHD as children. The potential for off-label use is considerable. The MAH should describe their proposals to reduce the risks of off-label use, in adults who are not indicated for Concerta treatment (for example, use for residual symptoms, which may not be responsive to methylphenidate; use in those with poorly or inappropriately diagnosed ADHD at any age up to 18 years; use in adults with a first diagnosis in adulthood; use outside of a comprehensive treatment programme; use before other remedial measures are tried etc).

28. The MAH should confirm whether the adult trials were designed to determine statistically significant differences in safety outcomes between the higher doses of Concerta, i.e. 54 MG -108 MG and above.

29. The MAH should provide a detailed analysis of all study subjects who experienced any important adverse effect (as identified in this report) that did not resolve without residual effects, including a description of the duration of symptoms, severity, seriousness, treatments required, action taken with drug and any other relevant factors, and discuss whether further pharmacovigilance activities or risk minimisation is required for any risks with persistent effects.

30. The MAH should include the following as Important Missing Information in the adult population, and provide study proposals to address the lack of data on these issues:

    a. Long-term safety (especially for key risks: cardiovascular, cerebrovascular, psychiatric risks including: mood disorders, depression, anxiety, agitation, suicide-related events,

psychosis/mania/delusion). This should include proposals to study the risks of cerebrovascular disorders (including stroke) and suicidality in adults.

b. Maintenance of effect (MAH state in proposed SPC section 5.1 that "the maintenance of effect of Concerta XL during long-term use in adults with ADHD has not been fully established".
c. Long-term effectiveness (and efficacy).
d. Efficacy/safety in patients who have/have not used methylphenidate before.

31. The MAH should discuss the impact of the exclusion criteria in the adult studies on the safe and effective use of Concerta in the proposed target adult population, and discuss what risk minimisation measures and further studies are needed.

32. The MAH should add the following to table 18.16 in the list of potential off-label indications: use in adults poorly or incorrectly diagnosed with ADHD, adults with partial symptoms, adults not diagnosed correctly in childhood (i.e. < 7 years of age), use alone (i.e. not within a comprehensive treatment programme that includes other remedial measures), use in adults with no accurate diagnosis of ADHD in childhood/with a first diagnosis in adulthood, or use in adults with unreliable retrospective diagnosis of ADHD in childhood or adolescence. The MAH should propose how these potential risks can be properly characterised and also adequately minimised, including but not limited to SPC and PIL wording.

33. The MAH should provide an analysis of the severity, pervasiveness and persistence of the ADHD symptoms, as well as age at diagnosis, details of diagnosis (including whether diagnosis of ADHD in childhood was done retrospectively or during childhood) and treatment history at baseline in the adult trial population and determine if any of these factors had any impact on the safety or efficacy of Concerta.

34. The MAH must propose adequate methods to measure the risk of diversion in adults in all Member States (including use of national records) and also propose risk minimisation measures including, but not limited to the SPC and PIL, as these alone are likely to have a limited impact, especially on diversion by individual users. The MAH should clarify what is meant by the statement in Table 24 on the risk of Diversion: *"monitoring supply of controlled substances follows National regulations"* and how this relates to their activities to characterise the risk of diversion in all member states

35. The two potential risks of neonatal cardio-respiratory toxicity and effects on neonatal growth should remain in this RMP as important potential risks. The means of exposure of children to these risks is through the mother who will be exposed to methylphenidate, thus these risks should be included as relevant and important in the adult ADHD population, especially as the number of possible female patients of child-bearing age, who are or may become pregnant or breast-feeding and be exposed to Concerta will increase.

36. It will be important to ensure that the risks in neonatal and infant children of adult female patients are adequately minimised thus the MAH should include these in educational tools for HCPs treating adult female patients and for the patients themselves.

37. The MAH should discuss the impact of the lack of data on adults with the Hyperactive-Impulsive subtype of ADHD on the validity of the proposed indication.

38. As per the utilisation studies for the child and adolescent population that were requested by CHMP during the Article 31 Referral, the MAH should propose methods to obtain data to characterise usage in the adult population over time, and to evaluate off-label use and the risk of diversion, in all member states. Collaboration with specialist treatment centres for adults with ADHD should be considered in the proposals. The MAHs should consider alternative methods of completing the drug utilisation studies in the countries without appropriate databases. The methods used will have to be tailored to be suitable each member state and must include ad-hoc designed analyses where needed, to allow data collection in all member states. Measures should include: information on total amount used, patient age, gender, details of indication, details of diagnosis, range, severity, pervasiveness, persistence of symptoms, change in symptoms from childhood to adulthood, age at diagnosis, previous/ongoing treatments (including non-drug treatments), dose, duration of use, treatment continuity, co-morbidities, concomitant medications, data on patterns of use, prescriber speciality. In the Member States that are covered by the IMS database, the MAH could utilise this resource to evaluate off-label use of methylphenidate but should undertake alternative methods for completing the review of usage and off-label use in the Member States that are not currently covered by multi-national (EU-wide) databases such as IMS.

39. The MAH should submit proposals for targeted questionnaires to follow-up reports of changes in hepatic enzymes, bilirubin or any hepatobiliary disorder in adults.

40. The MAH should provide educational tools similar to those proposed for HCPs in the childhood and adolescence ADHD indication, specifically for adult patients.

41. The identified risks (from trials) of anxiety, aggression, agitation, depression, psychosis/mania/delusions in adults are of concern and the MAH should propose proactive measures to minimise these risks.

42. The MAH should ensure that the risk minimisation measures (including but not limited to the SPC, PIL and educational tools for HCPs and patients) adequately address : that specialists in adult ADHD are responsible for correct and appropriate diagnosis, pre-treatment screening, initiation of prescribing and review of the need for ongoing treatment with Concerta in adults ; the initiation of treatment within a comprehensive treatment programme, and only when remedial measures alone have proven insufficient; adherence to the required pre-treatment screening and ongoing monitoring; the lack of evidence on long-term safety, effectiveness and maintenance of short-term effects of Concerta in the adult population; need for regular evaluation of the need for continuing treatment; evaluation of the maintenance of effect in adults.

43. The MAH should review whether it would be appropriate to use the brand name Concerta in the SPC as opposed to methylphenidate, to minimise off-label use of other methylphenidate-containing medicinal products without an adult indication.

44. The MAH should discuss whether the frequencies for reviewing long-term need for Concerta as stated in the current Core SPC for children & adolescents ('at least once-yearly') are appropriate for the adult ADHD population or whether the frequency should be modified.

45. The MAH should consider whether the current Core SPC guidance and frequencies for neurological and psychiatric monitoring in children & adolescents are also appropriate for adults or whether they need to be modified.

46. Given the evidence for anorexia, decreased appetite and clinically important weight loss in adults, the removal from the SPC of the requirement for regular monitoring for changes to weight and appetite, so that it does not apply to adults, is not appropriate. This should be rectified in the SPC, PIL and educational tools,, so that appetite and weight of adult patients is monitored at baseline and then at least every 6 months.

47. The MAH proposal to omit from the SPC, the requirement (including frequencies) for monitoring cardiovascular status (blood pressure and heart rate) in adults is not acceptable. Not acceptable. The current cardiovascular pre-treatment screening and ongoing monitoring requirements should also apply to the adult population and be included in the SPC, PIL and Educational Tools for HCPs and patients, or modified to be more appropriate for the adult population if necessary.

48. The MAH should provide a full review of the data used as a basis for the proposed addition of dyspnoea to the SPC as a side effect in adults. This should include a discussion of whether dyspnoea was a symptom of or associated with any respiratory, cardiovascular or other medical disorder.

49. The MAH should ensure adequate audit of the effectiveness of the risk minimisation tools proposed or requested in the adult population and should provide details of how this will be achieved.

ANNEX I:
PROPOSED CHANGES TO THE SPC, PL ANNOTATED WITH THE RMS'S COMMENTS AFTER EACH SECTION

For highlighted versions see separate attachments.

SUMMARY OF PRODUCT CHARACTERISTICS

Section 4.□ **NAME OF THE MEDICINAL PRODUCT**

CONCERTA XL 18 mg prolonged-release tablets.

Section 4.□ **QUALITATIVE AND QUANTITATIVE COMPOSITION**

One tablet contains 18 mg of methylphenidate hydrochloride.

Excipients: contains 6.49 mg of lactose.

For a full list of excipients, see section 6.1.

SECTION 4.□ **PHARMACEUTICAL FORM**

Prolonged-release Tablet.
Capsule-shaped yellow tablet with "alza 18" printed on one side in black ink.

4. CLINICAL PARTICULARS

Section 4.6 **Therapeutic indications**

Attention-Deficit/Hyperactivity Disorder (ADHD)
CONCERTA XL is indicated as part of a comprehensive treatment programme for Attention Deficit Hyperactivity Disorder (ADHD). It may be used when remedial measures alone prove insufficient in children aged 6 years of age and over as well as in adults whose ADHD diagnosis was established before the age of 18 years and whose symptoms persist into adulthood.

Treatment must be under the supervision of a specialist in behavioural disorders in children or adults. Diagnosis should be made according to DSM-IV criteria or the guidelines in ICD-10 and should be based on a complete history and evaluation of the patient. Diagnosis cannot be made solely on the presence of one or more symptom.

The specific aetiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use of medical and specialised psychological, educational, and social resources.

A comprehensive treatment programme typically includes psychological, educational and social measures as well as pharmacotherapy and is aimed at stabilising patients with a behavioural syndrome characterised by symptoms which may include chronic history of short attention span, distractibility, emotional lability, impulsivity, moderate to severe hyperactivity, minor neurological signs and abnormal EEG. Learning may or may not be impaired.

CONCERTA XL treatment is not indicated in all patients with ADHD and the decision to use the drug must be based on a very thorough assessment of the severity and chronicity of the patient's symptoms with reference to the patient's age at diagnosis.

Appropriate educational placement is essential, and psychosocial intervention is generally necessary. Where remedial measures alone prove insufficient, the decision to prescribe a stimulant must be based on rigorous assessment of the severity of the patient's symptoms. The use of methylphenidate should always be used in this way according to the licensed indication and according to prescribing / diagnostic guidelines.

Section 4.6 **Posology and method of administration**

Treatment must be initiated under the supervision of a specialist in behavioural disorders in children or adults.

CONCERTA XL must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed (see section 4.4).

CONCERTA XL may be administered with or without food (see section 5.2).

CONCERTA XL is taken once daily in the morning.

Pre-treatment screening:
Prior to prescribing, it is necessary to conduct a baseline evaluation of a patient's cardiovascular status including blood pressure and heart rate. A comprehensive history should document concomitant medications, past and present co-morbid medical and psychiatric disorders or symptoms, and family history of sudden cardiac/unexplained death. For children and adolescents, pre-treatment height and weight should be accurately recorded and entered on a growth chart (see sections 4.3 and 4.4)

Ongoing monitoring:
Psychiatric and cardiovascular status should be continuously monitored in all patients. Growth should be monitored in children and adolescents (see also section 4.4).

- Blood pressure and pulse should be monitored, and for children and adolescents recorded on a centile chart, at each adjustment of dose and then at least every 6 months;
- Height, weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart for children and adolescents;
- Development of *de novo* or worsening of pre-existing psychiatric disorders should be monitored at every adjustment of dose and then at least every 6 months and at every visit.

Patients should be monitored for the risk of diversion, misuse and abuse of methylphenidate.

Dose titration
Careful dose titration is necessary at the start of treatment with CONCERTA XL. Dose titration should be started at the lowest possible dose.

Other strengths of this medicinal product and other methylphenidate-containing products may be available.

Dosage may be adjusted in 18 mg increments. In general, dosage adjustment may proceed at approximately weekly intervals.

The maximum daily dosage of CONCERTA XL is 54 mg in children and adolescents and 72 mg in adults whose ADHD diagnosis was established before the age of 18 and whose symptoms persist into adulthood (see section 5.1).

Patients New to Methylphenidate: Clinical experience with CONCERTA XL is limited in children and adolescents new to methylphenidate (see section 5.1). CONCERTA XL may not be indicated in all patients with ADHD syndrome. Lower doses of short-acting methylphenidate formulations may be

considered sufficient to treat patients new to methylphenidate. Careful dose titration by the physician in charge is required in order to avoid unnecessarily high doses of methylphenidate. The recommended starting dose of CONCERTA XL for patients who are not currently taking methylphenidate, or for patients who are on stimulants other than methylphenidate, is 18 mg once daily.

Patients Currently Using Methylphenidate: The recommended dose of CONCERTA XL for patients who are currently taking methylphenidate three times daily at doses of 15 to 45 mg/day is provided in Table 1. Dosing recommendations are based on current dose regimen and clinical judgement.

TABLE 1

III.3.1.1.1.1.1 Recommended Dose Conversion from

Other Methylphenidate Regimens, where available, to CONCERTA XL

III.3.1.1.2 Previous Methylphenidate Daily Dose	III.3.1.1.2.1.1.1 Recommended **CONCERTA XL Dose**
5 mg Methylphenidate three times daily	18 mg once daily
10 mg Methylphenidate three times daily	36 mg once daily
15 mg Methylphenidate three times daily	54 mg once daily

If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

Long-term (more than 12 months) use
The safety and efficacy of long-term use of methylphenidate has not been systematically evaluated in controlled trials. Methylphenidate treatment should not and need not, be indefinite. Methylphenidate treatment is usually discontinued during or after puberty. The physician who elects to use methylphenidate for extended periods (over 12 months) in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that methylphenidate is de-challenged at least once yearly to assess the patient's condition (for children and adolescents, preferable during times of school holidays). Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Dose reduction and discontinuation
Treatment must be stopped if the symptoms do not improve after appropriate dosage adjustment over a one-month period. If paradoxical aggravation of symptoms or other serious adverse events occur, the dosage should be reduced or discontinued.

Adults
CONCERTA XL is not licensed for adult patients whose diagnosis was established after the age of 18.Elderly
Methylphenidate should not be used in the elderly. Safety and efficacy has not been established in this age group.

Children under 6 years of age
Methylphenidate should not be used in children under the age of 6 years. Safety and efficacy in this age group has not been established.

Section 4.6 **Contraindications**

- Known sensitivity to methylphenidate or any of the excipients
- Glaucoma
- Phaeochromocytoma
- During treatment with non-selective, irreversible monoamine oxidase (MAO) inhibitors, or within a minimum of 14 days of discontinuing those drugs, due to the risk of hypertensive crisis (see section 4.5)
- Hyperthyroidism or Thyrotoxicosis
- Diagnosis or history of severe depression, anorexia nervosa/anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder
- Diagnosis or history of severe and episodic (Type I) Bipolar (affective) Disorder (that is not well-controlled)
- Pre-existing cardiovascular disorders including severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies (disorders caused by the dysfunction of ion channels).
- Pre-existing cerebrovascular disorders cerebral aneurysm, vascular abnormalities including vasculitis or stroke

Section 4.6 **Special warnings and precautions for use**

Methylphenidate treatment is not indicated in all patients with ADHD. The use of methylphenidate is part of a comprehensive treatment programme for ADHD and may be used when remedial measures alone prove insufficient in children aged 6 years of age and over as well as in adults whose ADHD diagnosis was established before the age of 18 years and whose symptoms persist into adulthood. The decision to use the drug must be based on a very thorough assessment of the severity and chronicity of the patient's symptoms with reference to the patient's age at diagnosis.

Long-term use (more than 12 months)
The safety and efficacy of long-term use of methylphenidate has not been systematically evaluated in controlled trials. Methylphenidate treatment should not and need not, be indefinite. Methylphenidate treatment is usually discontinued during or after puberty. Patients on long-term therapy (i.e. over 12 months) must have careful ongoing monitoring according to the guidance in sections 4.2 and 4.4 for cardiovascular status, growth for children and adolescents, weight, appetite, development of *de novo* or worsening of pre-existing psychiatric disorders. Psychiatric disorders to monitor for are described below,

and include (but are not limited to) motor or vocal tics, aggressive or hostile behaviour, agitation, anxiety, depression, psychosis, mania, delusions, irritability, lack of spontaneity, withdrawal and excessive perseveration.

The physician who elects to use methylphenidate for extended periods (over 12 months) in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that methylphenidate is de-challenged at least once yearly to assess the patient's condition (for children and adolescents, preferably during times of school holidays). Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Use in the elderly
Methylphenidate should not be used in the elderly. Safety and efficacy has not been established in this age group.

Use in children under 6 years of age
Methylphenidate should not be used in children under the age of 6 years. Safety and efficacy in this age group has not been established.

Cardiovascular status
Patients who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden cardiac or unexplained death or malignant arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further specialist cardiac evaluation if initial findings suggest such history or disease. Patients who develop symptoms such as palpitations, exertional chest pain, unexplained syncope, dyspnoea or other symptoms suggestive of cardiac disease during methylphenidate treatment should undergo a prompt specialist cardiac evaluation.

Analyses of data from clinical trials of methylphenidate in children, adolescents, and adults with ADHD showed that patients using methylphenidate may commonly experience changes in diastolic and systolic blood pressure of over 10 mmHg relative to controls. The short- and long-term clinical consequences of these cardiovascular effects are not known, but the possibility of clinical complications cannot be excluded as a result of the effects observed in the clinical trial data. **Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate.** See section 4.3 for conditions in which methylphenidate treatment in contraindicated.

Cardiovascular status should be carefully monitored. Blood pressure and pulse should be monitored, and for children and adolescents recorded on a centile chart, at each adjustment of dose and then at least every 6 months.

The use of methylphenidate is contraindicated in certain pre-existing cardiovascular disorders **unless specialist cardiac advice has been obtained (see section 4.3).**

Sudden death and pre-existing structural cardiac abnormalities or other serious cardiac disorders
Sudden death has been reported in association with the use of stimulants of the central nervous system at usual doses in children and adults, some of whom had structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone may carry an increased risk of sudden death, stimulant products are not recommended in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant medicine.

Misuse and cardiovascular events
Misuse of stimulants of the central nervous system may be associated with sudden death and other serious cardiovascular adverse events.

Cerebrovascular disorders
See section 4.3 for cerebrovascular conditions in which methylphenidate treatment is contraindicated. Patients with additional risk factors (such as a history of cardiovascular disease, concomitant medications that elevate blood pressure) should be assessed at every visit for neurological signs and symptoms after initiating treatment with methylphenidate.

Cerebral vasculitis appears to be a very rare idiosyncratic reaction to methylphenidate exposure. There is little evidence to suggest that patients at higher risk can be identified and the initial onset of symptoms may be the first indication of an underlying clinical problem. Early diagnosis, based on a high index of suspicion, may allow the prompt withdrawal of methylphenidate and early treatment. The diagnosis should therefore be considered in any patient who develops new neurological symptoms that are consistent with cerebral ischemia during methylphenidate therapy. These symptoms could include severe headache, numbness, weakness, paralysis, and impairment of coordination, vision, speech, language or memory.

Treatment with methylphenidate is not contraindicated in patients with hemiplegic cerebral palsy.

Psychiatric disorders
Co-morbidity of psychiatric disorders in ADHD is common and should be taken into account when prescribing stimulant products. In the case of emergent psychiatric symptoms or exacerbation of pre-existing psychiatric disorders, methylphenidate should not be given unless the benefits outweigh the risks to the patient.

Development or worsening of psychiatric disorders should be monitored at every adjustment of dose, then at least every 6 months, and at every visit; discontinuation of treatment may be appropriate.

Exacerbation of pre-existing psychotic or manic symptoms
In psychotic patients, administration of methylphenidate may exacerbate symptoms of behavioural disturbance and thought disorder.

Emergence of new psychotic or manic symptoms
Treatment-emergent psychotic symptoms (visual/tactile/auditory hallucinations and delusions) or mania in patients without prior history of psychotic illness or mania can be caused by methylphenidate at usual doses. If manic or psychotic symptoms occur, consideration should be given to a possible causal role for methylphenidate, and discontinuation of treatment may be appropriate.

Aggressive or hostile behaviour
The emergence or worsening of aggression or hostility can be caused by treatment with stimulants. Patients treated with methylphenidate should be closely monitored for the emergence or worsening of aggressive behaviour or hostility at treatment initiation, at every dose adjustment and then at least every 6 months and every visit. Physicians should evaluate the need for adjustment of the treatment regimen in patients experiencing behaviour changes.

Suicidal tendency
Patients with emergent suicidal ideation or behaviour during treatment for ADHD should be evaluated immediately by their physician. Consideration should be given to the exacerbation of an underlying psychiatric condition and to a possible causal role of methylphenidate treatment. Treatment of an

underlying psychiatric condition may be necessary and consideration should be given to a possible discontinuation of methylphenidate.

Tics
Methylphenidate is associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported. Family history should be assessed and clinical evaluation for tics or Tourette's syndrome should precede use of methylphenidate. Patients should be regularly monitored for the emergence or worsening of tics during treatment with methylphenidate. **Monitoring should be at every adjustment of dose and then at least every 6 months or every visit.**

Anxiety, agitation or tension
Methylphenidate is associated with the worsening of pre-existing anxiety, agitation or tension. Clinical evaluation for anxiety, agitation or tension should precede use of methylphenidate and patients should be **regularly monitored for the emergence or worsening of these symptoms during treatment, at every adjustment of dose and then at least every 6 months or every visit.**

Forms of bipolar disorder
Particular care should be taken in using methylphenidate to treat ADHD in patients with comorbid bipolar disorder (including untreated Type I Bipolar Disorder or other forms of bipolar disorder) because of concern for possible precipitation of a mixed/manic episode in such patients. Prior to initiating treatment with methylphenidate, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. **Close ongoing monitoring is essential in these patients (see above 'Psychiatric Disorders' and section 4.2). Patients should be monitored for symptoms at every adjustment of dose, then at least every 6 months and at every visit.**

Growth
Moderately reduced weight gain and growth retardation have been reported with the long-term use of methylphenidate in children.

The effects of methylphenidate on final height and final weight are currently unknown and being studied.

Growth should be monitored during methylphenidate treatment in children and adolescents: height, weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart. Children and adolescents who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Seizures
Methylphenidate should be used with caution in patients with epilepsy. Methylphenidate may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and rarely in patients without a history of convulsions and no EEG abnormalities. If seizure frequency increases or new-onset seizures occur, methylphenidate should be discontinued.

Abuse, misuse and diversion
Patients should be carefully monitored for the risk of diversion, misuse and abuse of methylphenidate.

Methylphenidate should be used with caution in patients with known drug or alcohol dependency because of a potential for abuse, misuse or diversion.

Chronic abuse of methylphenidate can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes can occur, especially in response to parenteral abuse.

Patient age, the presence of risk factors for substance use disorder (such as co-morbid oppositional-defiant or conduct disorder and bipolar disorder), previous or current substance abuse should all be taken into account when deciding on a course of treatment for ADHD. Caution is called for in emotionally unstable patients, such as those with a history of drug or alcohol dependence, because such patients may increase the dosage on their own initiative.

For some high-risk substance abuse patients, methylphenidate or other stimulants may not be suitable and non-stimulant treatment should be considered.

Withdrawal
Careful supervision is required during drug withdrawal, since this may unmask depression as well as chronic over-activity. Some patients may require long-term follow up.

Careful supervision is required during withdrawal from abusive use since severe depression may occur.

Fatigue
Methylphenidate should not be used for the prevention or treatment of normal fatigue states.

Excipients: galactose intolerance
This medicinal product contains lactose: patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Choice of methylphenidate formulation
The choice of formulation of methylphenidate-containing product will have to be decided by the treating specialist on an individual basis and depends on the intended duration of effect.

Drug screening
This product contains methylphenidate which may induce a false positive laboratory test for amphetamines, particularly with immunoassay screen test.

Renal or hepatic insufficiency
There is no experience with the use of methylphenidate in patients with renal or hepatic insufficiency.

Haematological effects
The long-term safety of treatment with methylphenidate is not fully known. In the event of □hepatobiliary, thrombocytopenia, anaemia or other alterations, including those indicative of serious renal or hepatic disorders, discontinuation of treatment should be considered.

Potential for gastrointestinal obstruction
Because the CONCERTA XL tablet is nondeformable and does not appreciably change in shape in the gastrointestinal (GI) tract, it should not ordinarily be administered to patients with pre-existing severe GI narrowing (pathologic or iatrogenic) or in patients with □epatobil or significant difficulty in swallowing tablets. There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in nondeformable prolonged-release formulations.

Due to the prolonged-release design of the tablet, CONCERTA XL should only be used in patients who are able to swallow the tablet whole. Patients should be informed that CONCERTA XL must be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

Section 4.6 **Interaction with other medicinal products and other forms of interaction**

Pharmacokinetic interactions
It is not known how methylphenidate may affect plasma concentrations of concomitantly administered drugs. Therefore, caution is recommended at combining methylphenidate with other drugs, especially those with a narrow therapeutic window.

Methylphenidate is not metabolised by cytochrome P450 to a clinically relevant extent. Inducers or inhibitors of cytochrome P450 are not expected to have any relevant impact on methylphenidate pharmacokinetics. Conversely, the d- and l- enantiomers of methylphenidate do not relevantly inhibit cytochrome P450 1A2, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A.

However, there are reports indicating that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (eg, phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). When starting or stopping treatment with methylphenidate, it may be necessary to adjust the dosage of these drugs already being taken and establish drug plasma concentrations (or for coumarin, coagulation times).

Pharmacodynamic interactions
Anti-hypertensive drugs
Methylphenidate may decrease the effectiveness of drugs used to treat hypertension.

Use with drugs that elevate blood pressure
Caution is advised in patients being treated with methylphenidate with any other drug that can also elevate blood pressure (see also sections on cardiovascular and cerebrovascular conditions in Section 4.4).

Because of possible hypertensive crisis, methylphenidate is contraindicated in patients being treated (currently or within the preceding 2 weeks) with non-selective, irreversible MAO-inhibitors (see section 4.3).

Use with alcohol
Alcohol may exacerbate the adverse CNS effect of psychoactive drugs, including methylphenidate. It is therefore advisable for patients to abstain from alcohol during treatment.

Use with halogenated anaesthetics
There is a risk of sudden blood pressure increase during surgery. If surgery is planned, methylphenidate treatment should not be used on the day of surgery.

Use with centrally acting alpha-2 agonists (e.g. clonidine)
Serious adverse events, including sudden death, have been reported in concomitant use with clonidine. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

Use with domapinergic drugs
Caution is recommended when administering methylphenidate with dopaminergic drugs, including antipsychotics. Because a predominant action of methylphenidate is to increase extracelluar dopamine levels, methylphenidate may be associated with □epatobiliary□c interactions when co-administered with direct and indirect dopamine agonists (including DOPA and tricyclic antidepressants) or with dopamine antagonists including antipsychotics.

Section 4.6 **Pregnancy and lactation**

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

Cases of neonatal cardiorespiratory toxicity, specifically foetal tachycardia and respiratory distress have been reported in spontaneous case reports.

Studies in animals have shown evidence of reproductive toxicity at maternally toxic doses (see section 5.3).

Methylphenidate is not recommended for use during pregnancy unless a clinical decision is made that postponing treatment may pose a greater risk to the pregnancy.

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

There is one case report of an infant who experienced an unspecified decrease in weight during the period of exposure but recovered and gained weight after the mother discontinued treatment with methylphenidate. A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from methylphenidate therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Section 4.6 **Effects on ability to drive and use machines**

Methylphenidate can cause dizziness, drowsiness and visual disturbances including difficulties with accommodation, □epatobi and blurred vision. It may have a moderate influence on the ability to drive and use machines. Patients should be warned of these possible effects and advised that if affected, they should avoid potentially hazardous activities such as driving or operating machinery.

4.8 Undesirable effects

The table below shows all adverse drug reactions (ADRs) observed during clinical trials in children and adolescents with ADHD and post-market spontaneous reports in both paediatric and adult patients with CONCERTA XL and those, which have been reported with other methylphenidate hydrochloride formulations. If the ADRs with CONCERTA XL and the methylphenidate formulation frequencies were different, the highest frequency of both databases was used.

Frequency estimate:
- very common (≥ 1/10)
- common (≥ 1/100 to < 1/10)
- uncommon (≥ 1/1000 to <1/100)
- rare (≥ 1/10,000 to <1/1000)
- very rare (<1/10,000)
- not known (cannot be estimated from the available data).

System Organ Class	Adverse Drug Reaction					
	Frequency					
	Very common	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations		Nasopharyngitis				
Blood and lymphatic system disorders					Anaemia, Leucopenia, Thrombocytopenia, Thrombo-cytopenic purpura	Pancytopenia
Immune system disorders			Hypersensitivity reactions such as Angioneurotic oedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias, Pruritus, Rashes, and Eruptions			
Metabolism and nutritional disorders*		Anorexia, Decreased appetite, Moderately reduced weight and height gain during prolonged use in children*				
Psychiatric disorders*	Insomnia, Nervousness	Anorexia, Affect lability, Aggression*, Agitation*, Anxiety*, Depression*, Irritability, Abnormal behaviour	Psychotic disorders*, Auditory, visual and tactile hallucinations*, Anger, Suicidal ideation*, Mood altered, Mood swings, Restlessness, Tearfulness, Tics*, Worsening of pre-existing tics of Tourette's syndrome*, Hypervigilance, Sleep disorder	Mania*, Disorientation, Libido disorder	Suicidal attempt (including completed suicide)*, Transient depressed mood*, Abnormal thinking, Apathy, Repetitive behaviours, Over-focussing	Delusions*, Thought disturbances*, Confusional state, dependence. Cases of abuse and dependence have been described, more often with immediate release formulations
Nervous system	Headache	III.3.1.2 Di	Sedation, Tremor		Convulsions, Choreo-	Cerebrovascular disorders*

System Organ Class	Adverse Drug Reaction					
	Frequency					
	Very common	Common	Uncommon	Rare	Very rare	Not known
disorders		zziness, Dyskinesia, Psychomotorhyperactivity, Somnolence			athetoid movements, Reversible ischaemic neurological deficit, Neuroleptic malignant syndrome (NMS; Reports were poorly documented and in most cases, patients were also receiving other drugs, so the role of methylphenidate is unclear).	(including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), Grand mal convulsions*, Migraine
Eye disorders			Diplopia, Blurred vision	Difficulties in visual		

System Organ Class	Adverse Drug Reaction					
	Frequency					
	Very common	Common	Uncommon	Rare	Very rare	Not known
				accommodation, Mydriasis, Visual disturbance		
Cardiac disorders*		Arrhythmia, Tachycardia, Palpitations	Chest pain	Angina pectoris	Cardiac arrest; Myocardial infarction	Supraventricular tachycardia, Bradycardia, Ventricular □epatobiliary, Extrasystoles
Vascular disorders*		Hypertension			Cerebral arteritis and/or occlusion, Peripheral coldness, Raynaud's phenomenon	
Respiratory, thoracic and □epatobilia disorders		Cough, Pharyngolaryngeal pain	Dyspnoea			
Gastrointestinal disorders		Dry mouth	Constipation			
Hepatobiliary disorders			Hepatic enzyme elevations		Abnormal liver function, including hepatic coma	
Skin and subcutaneous tissue disorders		Alopecia, Pruritis, Rash, Urticaria	Angioneurotic oedema, Bullous conditions, Exfoliative conditions	Hyperhidrosis, Macular rash; Erythema	Erythema multiforme, Exfoliative dermatitis, Fixed drug eruption	
Musculoskeletal, connective tissue and bone disorders		Arthralgia	Myalgia, Muscle twitching		Muscle cramps	
Renal and urinary disorders			Haematuria			
Reproductive system and breast disorders				Gynaecomastia		
General disorders and administration site		Pyrexia, Growth retardation during	Chest pain, Fatigue		Sudden cardiac death*	Chest discomfort, Hyperpyrexia

System Organ Class	Adverse Drug Reaction					
	Frequency					
	Very common	Common	Uncommon	Rare	Very rare	Not known
conditions		prolonged use in children*				
III.3.1.2.1.1.1.1.		Changes in blood pressure and heart rate (usually an increase)*, Weight decreased*	Cardiac murmur*, Hepatic enzyme increased		Blood alkaline phosphatase increased, Blood bilirubin increased, Platelet count decreased, White blood cell count abnormal	

*see Section 4.4

The safety profile of CONCERTA XL in adult subjects with ADHD was generally similar to that seen in children and adolescents with ADHD. The following additional ADRs were identified either as new ADRs or in a higher frequency category than the pediatric population during clinical trials in adult subjects with ADHD. These ADRs may also be relevant in the pediatric population.

System Organ Class	Adverse Drug Reaction				
	Frequency				
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**
Infections and infestations		Upper respiratory tract infection, Sinusitis			
Blood and lymphatic system disorders			Leucopenia	Anaemia	
Metabolism and nutrition disorders*	Decreased appetite				
Psychiatric disorders*	Anxiety*	Initial insomnia, Restlessness, Depressed mood, Libido decreased, Tension*, Bruxism, Panic attack	Confusional state, Mania*, Apathy, Delusion*	Suicide attempt*	
Nervous system disorders		Tremor, Migraine, Paresthesia, Tension	Lethargy	Cerebrovascular accident*	

System Organ Class	Adverse Drug Reaction				
	Frequency				
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**
		headache			
Eye disorders		Blurred vision	Dry eye, Accommodation disorder		
Ear and labyrinth disorders		Vertigo			
Cardiac disorders*				Extrasystoles, Ventricular □epatobiliary	
Vascular disorders*			Hot flush, Peripheral coldness		
Respiratory, thoracic and □epatobilia disorders		Dyspnoea			
Gastrointestinal disorders	Dry mouth, Nausea	Dyspepsia, Constipation			
Skin and subcutaneous tissue disorders		Hyperhidrosis			
Musculoskeletal, connective tissue and bone disorders		Muscle tightness, Myalgia, Muscle spasms			
Reproductive system and breast disorders		Erectile dysfunction			
General disorders and administration site conditions		Irritability, Fatigue, Feeling jittery, Asthenia, Chest discomfort, Thirst			
Investigations		Alanine aminotransferase increased	Blood bilirubin increased		

*see Section 4.4

Section 4.6 **Overdose**

When treating patients with overdose, allowances must be made for the delayed release of methylphenidate from this formulation.

Signs and Symptoms

Acute overdose, mainly due to overstimulation of the central and sympathetic nervous systems, may result in vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma),

euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, □epatobil, and dryness of mucous membranes.

Treatment
There is no specific antidote to methylphenidate overdosage.

Treatment consists of appropriate supportive measures.

The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. If the signs and symptoms are not too severe and the patient is conscious, gastric contents may be evacuated by induction of vomiting or gastric lavage. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. In the presence of severe intoxication, a carefully titrated dose of a benzodiazepine be given before performing gastric lavage.

Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal haemodialysis for overdose of methylphenidate has not been established.

5. PHARMACOLOGICAL PROPERTIES

Section 4.6 **Pharmacodynamic properties**

Pharmacotherapeutic group: psychoanaleptics, psychostimulants and nootropics, centrally acting sympathomimetics: ATC code: N06BA04

Methylphenidate HCl is a mild central nervous system (CNS) stimulant. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Methylphenidate is thought to block the reuptake of noradrenaline and dopamine into the presynaptic neurone and increase the release of these monoamines into the extraneuronal space. Methylphenidate is a racemic mixture comprised of the d- and l-isomers. The d-isomer is more pharmacologically active than the l-isomer.

In the pivotal clinical studies in children with ADHD, CONCERTA XL was assessed in 321 patients already stabilised with immediate release preparations (IR) of methylphenidate and in 95 patients not previously treated with IR preparations of methylphenidate.

Clinical studies in children with ADHD showed that the effects of CONCERTA XL were maintained until 12 hours after dosing when the product was taken once daily in the morning.

Eight hundred ninety-nine (899) adults with ADHD aged 18 to 65 years were evaluated in three double-blind, placebo-controlled studies of 5 to 13 weeks duration. Generally, efficacy of CONCERTA XL was demonstrated at a dose range of 18 to 72 mg/day. The maintenance of effect of CONCERTA XL during long-term use in adults with ADHD has not been fully established.

Section 4.6 **Pharmacokinetic properties**

Absorption
Methylphenidate is readily absorbed. Following oral administration of CONCERTA XL to adults the drug overcoat dissolves, providing an initial maximum drug concentration at about 1 to 2 hours. The

methylphenidate contained in the two internal drug layers is gradually released over the next several hours. Peak plasma concentrations are achieved at about 6 to 8 hours, after which plasma levels of methylphenidate gradually decrease. CONCERTA XL taken once daily minimises the fluctuations between peak and trough concentrations associated with immediate-release methylphenidate three times daily. The extent of absorption of CONCERTA XL once daily is generally comparable to conventional immediate release preparations.

Following the administration of CONCERTA XL 18 mg once daily in 36 adults, the mean pharmacokinetic parameters were: C_{max} 3.7 ± 1.0 (ng/mL), T_{max} 6.8 ± 1.8 (h), AUC_{inf} 41.8 ± 13.9 (ng.h/mL), and $t_{½}$ 3.5 ± 0.4 (h).

No differences in the pharmacokinetics of CONCERTA XL were noted following single and repeated once daily dosing, indicating no significant drug accumulation. The AUC and $t_{1/2}$ following repeated once daily dosing are similar to those following the first dose of CONCERTA XL 18 mg.

Following administration of CONCERTA XL in single doses of 18, 36, and 54 mg/day to healthy adults, C_{max} and $AUC_{(0\text{-}inf)}$ of methylphenidate were proportional to dose. In healthy adults, single and multiple dosing of once daily CONCERTA XL doses from 54 to 144 mg/day resulted in linear and dose proportional increases in C_{max} and AUC_{inf} for methylphenidate (MPH).

Distribution
Plasma methylphenidate concentrations in adults decline biexponentially following oral administration. The half-life of methylphenidate in adults following oral administration of CONCERTA XL was approximately 3.5 h. The rate of protein binding of methylphenidate and of its metabolites is approximately 15%. The apparent volume of distribution of methylphenidate is approximately 13 litres/kg.

Metabolism
In humans, methylphenidate is metabolised primarily by de-esterification to alpha-phenyl-piperidine acetic acid (PPA, approximately 50 fold the level of the unchanged substance) which has little or no pharmacologic activity. In adults the metabolism of CONCERTA XL once daily as evaluated by metabolism to PPA is similar to that of methylphenidate three times daily. The metabolism of single and repeated once daily doses of CONCERTA XL is similar.

Excretion
The elimination half-life of methylphenidate in adults following administration of CONCERTA XL was approximately 3.5 hours. After oral administration, about 90% of the dose is excreted in urine and 1 to 3% in faeces, as metabolites within 48 to 96 hours. Small quantities of unchanged methylphenidate are recovered in urine (less than 1%). The main urinary metabolite is alpha-phenyl-piperidine acetic acid (60-90%).

After oral dosing of radiolabelled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPA, accounting for approximately 80% of the dose.

Food Effects
In patients, there were no differences in either the pharmacokinetics or the □epatobiliary□c performance of CONCERTA XL when administered after a high fat breakfast on an empty stomach.

Special Populations
Gender
In healthy adults, the mean dose-adjusted $AUC_{(0\text{-}inf)}$ values for CONCERTA XL were 36.7 ng.h/mL in men and 37.1 ng.h/mL in women, with no differences noted between the two groups.

Race
In healthy adults receiving CONCERTA XL, dose-adjusted $AUC_{(0\text{-}inf)}$ was consistent across ethnic groups; however, the sample size may have been insufficient to detect ethnic variations in pharmacokinetics.

Paediatric Population
The pharmacokinetics of CONCERTA XL has not been studied in children younger than 6 years of age. In children 7-12 years of age, the pharmacokinetics of CONCERTA XL after 18, 36 and 54 mg were (mean±SD): C_{max} 6.0±1.3, 11.3±2.6, and 15.0±3.8 ng/mL, respectively, T_{max} 9.4±0.02, 8.1±1.1, 9.1±2.5 h, respectively, and $AUC_{0\text{-}11.5}$ 50.4±7.8, 87.7±18.2, 121.5±37.3 ng.h/mL, respectively.

Renal Insufficiency
There is no experience with the use of CONCERTA XL in patients with renal insufficiency. After oral administration of radiolabelled methylphenidate in humans, methylphenidate was extensively metabolised and approximately 80% of the radioactivity was excreted in the urine in the form of PPA. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of CONCERTA XL.

Hepatic Insufficiency
There is no experience with the use of CONCERTA XL in patients with hepatic insufficiency.

Section 4.6 **Preclinical safety data**

Carcinogenicity
In life-time rat and mouse carcinogenicity studies, increased numbers of malignant liver tumours were noted in male mice only. The significance of this finding to humans is unknown.

Pregnancy-embryonal/foetal development
Methylphenidate is not considered to be teratogenic in rats and rabbits. Foetal toxicity (i.e. total litter loss) and maternal toxicity was noted in rats at maternally toxic doses.

6. PHARMACEUTICAL PARTICULARS

Section 4.6 **List of excipients**

Butylhydroxytoluene (E321)

Cellulose acetate 398-10
Hypromellose cp
Phosphoric acid concentrated
Poloxamer 188
Polyethylene oxides 200K and 7000K
Povidone K29-32
Sodium chloride
Stearic acid
Succinic acid
Black iron oxide (E172)
Ferric oxide yellow (E172)

Film Coat:
Ferric oxide yellow (E172)
Hypromellose 15 cp
Lactose monohydrate
Stearic acid

Titanium dioxide (E171)
Triacetin

Clear Coat:
Carnauba wax
Hypromellose 6 cp
Macrogol 400

Printing Ink:
Black iron oxide (E172)
Hypromellose 6 cp
Isopropyl alcohol
Propylene glycol
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

Section 4.6 **Special precautions for storage**

Keep the bottle tightly closed. Do not store above 30°C.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottle with a child-resistant polypropylene closure with one or two desiccants enclosed.

28 or 30 tablets.

Not all pack sizes may be marketed.

Section 4.6 **Special precautions for disposal <and other handling>**

No special requirements.

Section 4.□ **MARKETING AUTHORISATION HOLDER**

<To be completed nationally>

Section 4.□ **MARKETING AUTHORISATION NUMBER(S)**

<To be completed nationally>

Section 4.□ **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: <To be completed nationally>

Date of last renewal: <To be completed nationally>

Section 4.□ **DATE OF REVISION OF THE TEXT**

<To be completed nationally>

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu.

PACKAGE LEAFLET: INFORMATION FOR THE USER

CONCERTA XL 18 mg Prolonged Release Tablets
CONCERTA XL 36 mg Prolonged Release Tablets
CONCERTA XL 54 mg Prolonged Release Tablets
methylphenidate hydrochloride

The name of this medicine is CONCERTA XL, it contains the active substance 'methylphenidate hydrochloride'. The name 'methylphenidate' will also be used in this leaflet.

Read all of this leaflet carefully before you or your child starts taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you or your child. Do not pass it on to others. It may harm them, even if they have the same symptoms.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What CONCERTA XL is and what it is used for

What it is used for
CONCERTA XL is used to treat 'attention deficit hyperactivity disorder' (ADHD).
- it is used in children and young people up to the age of 18 and in adults who were diagnosed with ADHD before they turned 18 and whose symptoms continued into adulthood.
- it is used only after trying treatments which do not involve medicines. Such as counselling and behavioural therapy.

CONCERTA XL is not for use as a treatment for ADHD in children under 6 years of age or in the elderly. It is not known if it is safe or of benefit in these people.

How it works
CONCERTA XL improves the activity of certain parts of the brain which are under-active. The medicine can help improve attention (attention span), concentration and reduce impulsive behaviour.

The medicine is given as part of a treatment programme, which usually includes:
- psychological
- educational and
- social therapy.

It is prescribed only by doctors who have experience in behaviour problems in children or adults. Although there is no cure for ADHD, it can be managed using treatment programmes.

About ADHD
People with ADHD find it:
- hard to sit still and
- hard to concentrate.

It is not their fault that they cannot do these things.

Many people struggle to do these things. However, with ADHD they can cause problems with everyday life. People with ADHD may have difficulty in learning and in doing work. They find it hard to behave well at home, at school or in other places. ADHD does not affect the intelligence of a person.

2. Before you or your child takes methylphenidate

Do not take methylphenidate if you or your child:
- is allergic (hypersensitive) to methylphenidate or any of the other ingredients of CONCERTA XL (listed in Section 6)
- has a thyroid problem
- has increased pressure in the eye (glaucoma)
- has a tumour of the adrenal gland (phaeochromocytoma)
- has an eating problem when you do not feel hungry or want to eat – such as 'anorexia nervosa'
- has very high blood pressure or narrowing of the blood vessels, which can cause pain in the arms and legs
- has ever had heart problems – such as a heart attack, uneven heartbeat, pain and discomfort in the chest, heart failure, heart disease or was born with a heart problem
- has had a problem with the blood vessels in the brain – such as a stroke, swelling and weakening of part of a blood vessel (aneurysm), narrow or blocked blood vessels, or inflammation of the blood vessels (vasculitis)
- is currently taking or has taken within the last 14 days an antidepressant (known as a monoamine oxidase inhibitor) – see Taking other medicines
- has mental health problems such as:
  - a 'psychopathic' or 'borderline personality' problem
  - abnormal thoughts or visions or an illness called 'schizophrenia'
  - signs of a severe mood problem like:
    - feeling like killing yourself
    - severe depression, where you feel very sad, worthless and hopeless
    - mania, where you feel unusually excitable, over-active, and un-inhibited.

Do not take methylphenidate if any of the above apply to you or your child. If you are not sure, talk to your doctor or pharmacist before you or your child takes methylphenidate. This is because methylphenidate can make these problems worse.

Take special care with CONCERTA XL if:
- **if you or your child:**
  - has liver or kidney problems
  - has problems with swallowing or swallowing whole tablets
  - has a narrowing or blockage of the gut or food-pipe
  - has had fits (seizures, convulsions, epilepsy) or any abnormal brain scans (EEGs)
  - has ever abused or been dependent on alcohol, prescription medicines or street drugs
  - is female and has started having periods (see the 'Pregnancy and breast-feeding' section below)
  - has hard-to-control, repeated twitching of any parts of the body or repeats sounds and words
  - has high blood pressure
  - has a heart problem which is not in the 'Do not take' section above

- has a mental health problem which is not in the 'Do not take' section above. Other mental health problems include:
  - mood swings (from being manic to being depressed – called 'bipolar disorder')
  - starting to be aggressive or hostile, or aggression gets worse
  - seeing, hearing or feeling things that are not there (hallucinations)
  - believing things that are not true (delusions)
  - feeling unusually suspicious (paranoia)
  - feeling agitated, anxious or tense
  - feeling depressed or guilty.

Tell your doctor or pharmacist if any of the above apply to you or your child before starting treatment. This is because methylphenidate can make these problems worse. Your doctor will want to monitor how the medicine affects you or your child.

Checks that your doctor will make before you or your child start taking methylphenidate
These checks are to decide if methylphenidate is the correct medicine for you or your child. Your doctor will talk to you about:

- any other medicines you or your child is taking
- whether there is any family history of sudden unexplained death
- any other medical problems (such as heart problems) you or your family may have
- how you or your child is feeling, such as feeling high or low, having strange thoughts or if you or your child has had any of these feelings in the past
- whether there is a family history of 'tics' (hard-to-control, repeated twitching of any parts of the body or repeating sounds and words)
- any mental health or behaviour problems you or your child or other family members have ever had. Your doctor will discuss whether you or your child is at risk of having mood swings (from being manic to being depressed – called 'bipolar disorder'). They will check your or your child's mental health history, and check if any of your family has a history of suicide, bipolar disorder or depression.

It is important that you provide as much information as you can. This will help your doctor decide if methylphenidate is the correct medicine for you or your child. Your doctor may decide that other medical tests are needed before you or your child start taking this medicine.

Taking other medicines
Do not take methylphenidate if you or your child:

- is taking a medicine called a 'monoamine oxidase inhibitor' (MAOI) used for depression, or has taken an MAOI in the last 14 days. Taking an MAOI with methylphenidate may cause a sudden increase in blood pressure.

If you or your child is taking other medicines, methylphenidate may affect how well they work or may cause side effects. If you or your child is taking any of the following medicines, check with your doctor or pharmacist before taking methylphenidate:

- other medicines for depression
- medicines for severe mental health problems
- medicines used to reduce or increase blood pressure
- medicines for epilepsy
- some cough and cold remedies which contain medicines that can affect blood pressure. It is important to check with your pharmacist when you buy any of these products
- medicines that thin the blood to prevent blood clots

If you are in any doubt about whether any medicines you or your child is taking are included in the list

above, ask your doctor or pharmacist for advice before taking methylphenidate.

Please tell your doctor or pharmacist if you or your child is taking or has recently taken any other medicines, including medicines obtained without a prescription.

Having an operation
Tell your doctor if you or your child is going to have an operation. Methylphenidate should not be taken on the day of surgery if a certain type of anaesthetic is used. This is because there is a chance of a sudden rise in blood pressure during the operation.

Drug testing
This medicine may give a positive result when testing for drug use. This includes testing used in sport.

Taking methylphenidate with alcohol
Do not drink alcohol while taking this medicine. Alcohol may make the side effects of this medicine worse. Remember that some foods and medicines contain alcohol.

Pregnancy and breast-feeding
- It is not known if methylphenidate will affect an unborn baby. Tell your doctor or pharmacist before using methylphenidate if you or your daughter:
- is having sex. Your doctor will discuss contraception.
- is pregnant or think might be pregnant. Your doctor will decide whether methylphenidate should be taken.
- is breast-feeding or planning to breast-feed. It is possible that methylphenidate is passed into human breast milk. Therefore, your doctor will decide whether you or your daughter should breast-feed while taking methylphenidate.

Driving or using machines
You or your child may feel dizzy, have problems focussing or have blurred vision when taking methylphenidate. If these happen it may be dangerous to do things such as drive, use machines, ride a bike or horse or climb trees.

Important information about some of the ingredients of CONCERTA XL
This medicine contains lactose (a type of sugar). If you or your child has an intolerance to some sugars, talk to your doctor before taking this medicine.

3. How to take CONCERTA XL

How much to take
You or your child should always take CONCERTA XL exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
- your doctor will usually start treatment with a low dose and increase it gradually as required.
- the maximum daily dose for children and young people up to the age of 18 is 54 mg. The maximum daily dose for adults is 72 mg.
- you or your child should take CONCERTA XL once each day in the morning with a glass of water. The tablet should be swallowed whole and not chewed, broken, or crushed. The tablet may be taken with or without food.

The tablet does not dissolve completely after all of the drug has been released and sometimes the tablet shell may appear in the stools. This is normal.

If you or your child does not feel better after 1 month of treatment
If you or your child does not feel better, tell your doctor. They may decide a different treatment is needed.

Not using CONCERTA XL properly
If CONCERTA XL is not used properly, this may cause abnormal behaviour. It may also mean that you or your child starts to depend on the medicine. Tell your doctor if you or your child has ever abused or been dependent on alcohol, prescription medicines or street drugs.

This medicine is only for you or your child. Do not give this medicine to anyone else, even if their symptoms seem similar.

If you or your child takes more CONCERTA XL than you should
If you or your child takes too much medicine, talk to a doctor or call an ambulance straight away. Tell them how much has been taken.

Signs of overdose may include: being sick, feeling agitated, shaking, increased uncontrolled movements, muscle twitching, fits (may be followed by coma), feeling very happy, being confused, seeing, feeling or hearing things that are not real (hallucinations), sweating, flushing, headache, high fever, changes in heart beat (slow, fast or uneven), high blood pressure, dilated pupils and dry nose and mouth.

If you or your child forgets to take CONCERTA XL
Do not take a double dose to make up for a forgotten dose. If you or your child forgets a dose, wait until it is time for the next dose.

If you or your child stops taking CONCERTA XL
If you or your child suddenly stops taking this medicine, ADHD symptoms may come back or unwanted effects such as depression may appear. Your doctor may want to gradually reduce the amount of medicine taken each day, before stopping it completely. Talk to your doctor before stopping CONCERTA XL.

Things your doctor will do when you or your child is on treatment
Your doctor will do some tests

- before you or your child starts – to make sure that CONCERTA XL is safe and will be of benefit.
- after you or your child starts – they will be done at least every 6 months, but possibly more often. They will also be done when the dose is changed.
- these tests will include:
  - checking appetite
  - measuring height and weight in children and young people
  - measuring blood pressure and heart rate
  - checking problems with mood, state of mind or any other unusual feelings. Or if these have got worse while taking CONCERTA XL.

Long-term treatment
CONCERTA XL does not need to be taken for ever. If you or your child takes CONCERTA XL for more than a year, your doctor should stop treatment for a short time, this may happen during a school holiday. This will show if the medicine is still needed.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, methylphenidate can cause side effects, but not everybody gets them. Although some people get side effects, most people find that methylphenidate helps them. Your doctor will talk to you about these side effects.

Some side effects could be serious. If you or your child has any of the side effects below, see a doctor straight away:

Common (affects less than 1 in 10 people)
- uneven heartbeat (palpitations)
- mood changes or mood swings or changes in personality

Uncommon (affects less than 1 in 100 people)
- thinking about or feeling like killing yourself
- seeing, feeling, or hearing things that are not real, these are signs of psychosis
- uncontrolled speech and body movements (Tourette's)
- signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing

Rare (affects less than 1 in 1,000 people)
- feeling unusually excited, over-active and un-inhibited (mania)

Very rare (affects less than 1 in 10,000 people)
- heart attack
- fits (seizures, convulsions epilepsy)
- skin peeling or purplish red patches
- muscle spasms which you cannot control affecting your eyes, head, neck, body and nervous system due to a temporary lack of blood supply to the brain
- paralysis or problems with movement and vision, difficulties in speech (these can be signs of problems with the blood vessels in your brain)
- decrease in number of blood cells (red cells, white cells and platelets) which can make you more likely to get infections, and make you bleed and bruise more easily
- a sudden increase in body temperature, very high blood pressure and severe convulsions ('Neuroleptic Malignant Syndrome'). It is not certain that this side effect is caused by methylphenidate or other drugs that may be taken in combination with methylphenidate.

Other side effects (how often they happen is not known)
- unwanted thoughts that keep coming bac
- unexplained fainting, chest pain, shortness of breath (these can be signs of heart problems)

If you or your child has any of the side effects above, see a doctor straight away.

Other side effects include the following, if they get serious, please tell your doctor or pharmacist:
Very common (affects more than 1 in 10 people)
- headache
- feeling nervous
- not being able to sleep.

Common (affects less than 1 in 10 people)
- joint pain
- dry mouth

- high temperature (fever)
- unusual hair loss or thinning
- feeling unusually sleepy or drowsy
- loss of appetite or decreased appetite
- itching, rash or raised red itchy rashes (hives)
- cough, sore throat or nose and throat irritation
- high blood pressure, fast heart beat (tachycardia)
- feeling dizzy, movements which you cannot control, being unusually active
- feeling aggressive, agitated, anxious, depressed, irritable and abnormal behaviour
- .

Uncommon (affects less than 1 in 100 people)
- constipation
- chest discomfort
- blood in the urine
- shaking or trembling
- double vision or blurred vision
- muscle pain, muscle twitching
- shortness of breath or chest pain
- increases in liver test results (seen in a blood test)
- anger, feeling restless or tearful, excessive awareness of surroundings, problems sleeping.

Rare (affects less than 1 in 1,000 people)
- changes in sex drive
- feeling disorientated
- dilated pupils, trouble seeing
- swelling of the breasts in men
- excessive sweating, redness of the skin, red raised skin rash

Very rare (affects less than 1 in 10,000 people)
- heart attack
- sudden death
- muscle cramps
- small red marks on the skin
- inflammation or blocked arteries in the brain
- abnormal liver function including liver failure and coma
- changes in test results – including liver and blood tests
- suicidal attempt, abnormal thinking, lack of feeling or emotion, doing things over and over again, being obsessed with one thing
- fingers and toes feeling numb, tingling and changing colour (from white to blue, then red) when cold ('Raynaud's phenomenon').

Other side effects (how often they happen is not known)
- migraine
- very high fever
- slow, fast or extra heart beats
- a major fit ('grand mal convulsions')
- believing things that are not true, confusion
- severe stomach pain, often with feeling and being sick
- problems with the blood vessels of the brain (stroke, cerebral arteritis or cerebral occlusion).

Effects on growth in children and young people
When used for more than a year, methylphenidate may cause reduced growth in some children. This affects less than 1 in 10 children.

- there may be lack of weight gain or height growth.
- your doctor will carefully watch your or your child's height and weight, as well as how well you or your child is eating.
- if you or your child is not growing as expected, then treatment with methylphenidate may be stopped for a short time.

If any of the side effects worry you, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

Side effects reported in clinical trials of CONCERTA XL in adults (i.e., 18 years of age and older)
The following side effects were either not reported as such in studies of children and young people or occurred more often in adult clinical trials. However, these side effects may also be relevant for children and young people:

Very common (affects more than 1 in 10 people)

- decreased appetite
- feeling anxious
- feeling sick

Common (affects less than 1 in 10 people)

- upper respiratory tract infection, sinus infection
- trouble falling asleep, feeling restless, nervous, or tense
- decreased interest in sex
- clenching or grinding your teeth, feeling of panic
- shaking or trembling
- migraine, tension headache
- feeling of tingling, prickling, or numbness of the skin
- blurred vision
- dizziness (vertigo)
- shortness of breath
- upset stomach or indigestion, constipation
- excessive sweating
- muscle tightness, muscle pain, muscle cramps
- thirst
- inability to develop or maintain an erection
- chest discomfort, feeling irritable, tired, or jittery
- increased alanine aminotransferase level in your blood

Uncommon (affects less than 1 in 100 people)

- decreased white blood cells in your blood, increase of a substance called bilirubin in your blood
- feeling confused, abnormally elevated mood, feeling indifferent, believing things that are not true
- feeling tired
- dry eye
- cold fingers and toes

Rare (affects less than 1 in 1,000 people)

- decreased red blood cells in your blood
- suicide attempt
- stroke, chest pain, extra heart beats

5. How to store CONCERTA XL

Keep out of the reach and sight of children.

Do not use CONCERTA XL after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

Do not store above 30°C.

Keep the bottle tightly closed to protect from moisture.

The pack contains one or two pouches. These pouches are used to keep the tablets dry and should not be eaten.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further information

What CONCERTA XL contains

The active substance is methylphenidate hydrochloride

- CONCERTA XL Prolonged Release Tablets contains 18 mg of methylphenidate hydrochloride.
- CONCERTA XL Prolonged Release Tablets contains 36 mg of methylphenidate hydrochloride.
- CONCERTA XL Prolonged Release Tablets contains 54 mg of methylphenidate hydrochloride.

The other ingredients are:

- butylhydroxytoluene (E321), cellulose acetate 398-10, hypromellose 3 cp, phosphoric acid concentrated, poloxamer 188, polyethylene oxides 200K and 7000K, povidone K29-32, sodium chloride, stearic acid, succinic acid, black iron oxide (E172), ferric oxide yellow (E172), and ferric oxide red (E172, 54 mg tablet only).
- **Film coat:** hypromellose 15 cp, lactose monohydrate, titanium dioxide (E171), triacetin, ferric oxide yellow (E172, 18 mg and 54 mg tablets only), ferric oxide red (E172, 54 mg tablet only) and stearic acid (18 mg tablet only).
- **Clear coat:** carnauba wax, hypromellose 6 cp, macrogol 400.
- **Printing Ink:** black iron oxide (E172), hypromellose 6 cp, isopropyl alcohol, propylene glycol and purified water.

What CONCERTA XL looks like and contents of the pack

CONCERTA XL is available in three strengths: 18 mg, 36 mg and 54 mg. Each capsule shaped tablet is individually marked to aid identification:

- 18 mg: Yellow, with 'alza 18' printed on one side in black ink
- 36 mg: White with 'alza 36' printed on one side in black ink.
- 54 mg: Brownish-red with 'alza 54' printed on one side in black ink.

The medicinal product is available in bottles containing 28 or 30 tablets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

[To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:

CONCERTA:	Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Iceland, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden
CONCERTA XL:	Ireland, United Kingdom
CONCERTA LP:	France

This leaflet was last approved in {MM/YYYY}.

Appendix II RMP Assessment

SECTION 4.6 **INTRODUCTION**

Immediate-release (IR) methylphenidate formulations have a duration of effect of around 3-4 hours leading to the development of various formulations and delivery methods of extended/prolonged release methylphenidate products. The development of an extended-release formulation has been achieved by this MAH using OROS technology. Concerta (OROS methylphenidate) is a prolonged-release formulation with a 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.

Previous Risk Management Plans (RMPs) for Concerta were limited to the paediatric population for the currently approved indication, with the exception of the post-marketing data and some of the referenced literature that included an adult population. RMP, Version 2, addressed the important core identified and potential risks for methylphenidate-containing products that were identified in the Rapporteur's previous Assessment Report dated 3 December 2008 that was related to the Article 31 Committee for Medicinal Products for Human Use (CHMP) referral procedure. Also, as part of the Article 31 referral, the additional Core pharmacovigilance and Core risk minimisation activities were specified by the CHMP for the EU marketing authorisation holders (MAHs) of methylphenidate-containing products for ADHD in the European Union (EU) including Novartis, Janssen-Cilag Ltd, Shire, Laboratorios Rubio and Medice.

This version of the Risk Management Plan (RMP, Version 3) principally proposes updates to support a type II variation for a new indication for the use of Concerta in treating adults with attention-deficit/hyperactivity disorder (ADHD) whose diagnosis was established before the age of 18 years and whose symptoms persist into adulthood.

SECTION 4.6 **SAFETY SPECIFICATION**

Non-clinical safety issues

The table below shows safety concerns identified in the Article 31 referral for which the sources of evidence that may impact benefit/risk arise partially from non-clinical data.

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.

Summary of ongoing safety Concerns

The table below summarises the important identified and potential risk identified in the Article 31 Referral, for which there are specific pharmacovigilance activities (ongoing or proposed).

Table 23: Summary of On-Going Safety Concerns

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

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

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 in the Article 31 referral Rappourter/Co-Rapporteur Assessmen report Assessment Report: lymphocyticleukaemia, neonatal cardio-respiratory toxicity (neonatal/foetal tachycardia, respiratory distress/apnoea), and neonatal effects on growth (via lactation). The Company also conducted a review of the risks for Concerta in adults with ADHD and has identified no new safety concerns beyond those presented in Section 1.5.2 of the RMP.

Details of Important Identified and Potential Risks

The MAH has evaluated the identified risks for methylphenidate-containing products and these are outline in **table 24 of the MAH submission** . No additional identified risks are proposed in relation to the new indication.

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 studies and post-marketing surveillance. These identified risks are characterised in Tables 17.1 to 17.7 of the submitted RMP. Post-marketing data is only provided for those terms not identified as ADRs from the Concerta clinical trials database.

Of the potential risks outline in table 23, a causal relationship with Concerta was established for aggression, tics and depression. The potential risks are characterised in Tables 18.1 to 18.22 of the RMP. Post-marketing data is provided for those terms not identified as ADRs from the Concerta clinical trials database.

Assessor's comment

Important risks in the adult population identified from adult study data

The following are important risks in the adult population, mostly identified from adult trial data and should be included as important risks in the Safety specification for adults:

1. *Abuse potential, risk of abuse misuse, diversion (survey suggested diversion in about 44% of adults with ADHD and 29% used MPH inappropriately)*
2. *off-label use*
3. *cardiovascular risks (arrhythmias (OR:4.2), tachycardia [6% vs. 0%], hypertension, clinically important changes in: pulse, diastolic blood pressure [9.8% vs. 3.8%] and systolic blood pressure [7.8% vs. 6.1%])*
4. *potential for serious clinical cardiovascular outcomes*
5. *cerebrovascular risks*
6. *de-novo and worsening of psychiatric risks (including anxiety, panic attack, depression (OR: 1.8))*
7. *psychosis/mania (OR:3.0)*
8. *delusions*
9. *suicide-related events [3 events (0.2%) vs. o events]*
10. *mood disorders*
11. *tics (OR: 3.3)*
12. *dystonias*
13. *restlessness [4% vs. 0%]*
14. *aggression (OR: 2.3)*
15. *agitation*
16. *tension*
17. *irritability*
18. *anorexia (OR: 5.1)*
19. *decreased appetite*
20. *clinically significant decreased weight*
21. *abnormal liver enzymes/bilirubin*

These risks must be subject to adequate risk minimisation including information in the SPC and PIL, but also educational tools for HCPs, and patients.

The following risks should be included as important ***identified*** *risks in the safety specification, based on adult clinical trial data: aggression, agitation, restlessness, anxiety/anxiety disorders, suicide-related events, psychosis, mania/delusions, decreased appetite, decreased weight, cardiac arrhythmias, tics/worsening of tics.*

Important Missing Information

The Rapporteur's previous assessment report identified long-term safety as an area of important missing information. Long-term safety is listed in Table 23: Summary of Ongoing Safety Concerns. Also, routine and additional pharmacovigilance activities are listed for this concern in Part 2 of the RMP.

Assessor's comments

There is inadequate evidence of:

1. *Long-term safety (especially for key risks: cardiovascular, cerebrovascular, psychiatric risks including: mood disorders, depression, anxiety, agitation, suicide-related events, psychosis/mania/delusion)*

2. *Maintenance of effect (MAH state in proposed SPC section5.1 that "the maintenance of effect of Concerta XL during long-term use in adults with ADHD has not been fully established"*
3. *Long-term effectiveness (and efficacy).*
4. *Efficacy/safety in patients who have / have not used methylphenidate before*

There are no proposals to acquire any data on the long-term safety (and effectiveness) of Concerta in the adult population. The MAH should provide proposals to address this lack of data in the adult population

MAH view on Epidemiology of the Indication/Target Population
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).

According to DSM-IV-TR, ADHD is a developmental disorder that requires an onset of symptoms before age 7 years. 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).

The MAH described in Table 21 of the RMP, the important co-morbidities in patients with ADHD, where possible, in adults as well as children & adolescents.

Assessor's comment

The MAH should provide details of when the adult trial participants were diagnosed with ADHD. It is important to know when the initial diagnosis was made, what the pervasiveness and persistent, and severity of the symptoms were, over time, as well as other factors such as the diagnosis and range/severity/pervasiveness/persistence of symptoms at baseline in adulthood, and details of prior/existing treatments (both pharmaceutical and non-pharmaceutical).

- *The MAH should provide details of whether the trial participants were benefiting from methylphenidate or any other drug therapy for ADHD during childhood and adolescence, and whether this had any bearing on the safety or efficacy in adulthood.*

- *The MAH should describe the evidence for maintenance of effect beyond short-term use and describe what is proposed for section 4 of the SPC and other risk minimisation measures in this regard.*

Section 1.7.1.5 of the RMP indicates that "as many as 65% of children with ADHD will have ADHD or some residual symptoms of ADHD as adults". This is not referenced, and is a very vague statement. It highlights concerns regarding the poor characterisation of the target population and the great potential for off-label use in patients who are not indicated for Concerta treatment as adults (for example, use for residual symptoms, which may not be responsive to methylphenidate, use in those with poorly or

inappropriately diagnosed ADHD at any age up to 18 years, use outside of a comprehensive treatment programme etc). The MAH should describe their proposals to reduce these risks.

Section 1.7.1.5 then goes on to describe findings of a study using data from the National Comorbidity Survey Replication, describing the "adults persistence of ADHD" in respondents having had ADHD in childhood as about 36%. This in contrast with the statement above that 65% of children with ADHD will have ADHD or residual symptoms as adults ADHD, again highlighting the poor characterisation of ADHD in adults. Not all Adults with ADHD will be eligible for treatment with Concerta, and the actual adult ADHD population who may be eligible for Concerta use is likely to be only a minority of those who were diagnosed with ADHD as children. The potential for off-label use is considerable.

- *The MAH should describe their proposals to reduce the risk of Concerta use in adults who are not indicated for Concerta therapy.*

In November 2009, PhVWP concluded that none of the important positive findings regarding the risk of carcinogenicity with methylphenidate, such as those resulting from the El-Zein study in 2004, have been independently reproduced to date. Despite a few other unresolved positive or equivocal findings, the majority of the studies conducted to date do not indicate a genotoxic potential for MPH. Based on an evaluation of all relevant data from all sources, including the new study data submitted as a follow-up measure to the Article 31 referral, it was be concluded that there is no strong evidence of a genotoxic or carcinogenic potential for methylphenidate. Carcinogenicity should remain in the Core table of Risks and subject to routine pharmacovigilance in the Pharmacovigilance Plan of the Core RMP for methylphenidate.

Post-marketing exposure

The table below shows the post-marketing (non-study) exposure to Concerta, by age group.

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

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

[a] (000)
EU (G4) = France (launch = May 2004), Germany (launch = January 2003), Spain (launch = April 2004), and UK (launch = March 2002)
Rx = prescription

Assessor's comment

Most of the post-marketing, non-study exposure for Concerta is in patients from 6 – 20 years of age. It is important that the MAH has in place proactive pharmacovigilance measures to capture good quality post-marketing / spontaneous data on the key risks in adults.

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

This RMP updates the 23 November 2009 Concerta Paediatric EU RMP and takes into account changes proposed to support the additional indication for use in adults whose ADHD diagnosis was established before the age of 18 years and whose symptoms persist into adulthood. The following pharmacovigilance and risk minimisation actions are currently in progress 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).

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

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

Product Information – Package Leaflet
The Company (with the other MAHs) has revised and user tested the core Patient Information Leaflet (PIL) text provided in Annex III of the EC decision (Annex 4). As of the preparation of this RMP update, the results of the user testing have been filed with EU Health Authorities for assessment.

Suicidality
The Company (with the other MAHs) has completed its investigation of the feasibility of carrying out a meta-analysis of the risk of suicidality associated with the use of methylphenidate in children and adolescents with ADHD on the basis of data from placebo-controlled studies available to the MAHs. This was submitted to MHRA on 31 July 2009. As of the preparation of this RMP update, the MHRA/CHMP assessment is ongoing.

Long-Term Safety
The Company (with the other MAHs) has submitted a detailed feasibility assessment for a scientifically valid, well designed and suitably powered long-term safety study to examine specific endpoints for adverse cognitive and psychiatric outcomes. As of the preparation of this RMP update, the MHRA/CHMP assessment is ongoing.

Drug Utilisation

The Company (with the other MAHs) will provide all available retrospective drug utilisation data using health-related electronic databases in all Member States where methylphenidate is commercially available, to allow an evaluation of changes in usage over time. An evaluation of methylphenidate usage in 2008 will be submitted for assessment in December 2009.

Educational Tools
The Company (with the other MAHs) will submit fully harmonised risk minimisation tools (physician's guide to prescribing and prescriber's checklist) which will contain all of the important information from the Clinical Particulars section of the core SmPC for assessment. As of the preparation of this RMP update, these materials are being finalised in preparation for submission in December 2009 as part of the PSUR work-sharing procedure.

PSUR Work-Sharing
At the request of the EU Member States, the Company (with the other MAHs) will harmonise the PSUR reporting schedule for methylphenidate-containing products.

Assessor's overall comments:

Anxiety/Anxiety disorders

Adult studies have identified anxiety as a very common risk in adults (the risk is common in children & adolescents from pooled MAH studies and post-marketing data), and is one the most frequent reasons for withdrawal or dose reduction in adult studies. This is a major concern for the benefit/risk in this proposed variation. The risk of anxiety/anxiety disorders should be added to the Safety Specification (table of risks) as an ***Important Identified Risk****.*

Depression and Aggression

Following evaluation of the adult clinical trial data, depression and aggression should be changed from important potential risks to important ***identified*** *risks.*

Analysis of study data on cardiovascular effects

In relation to diastolic and systolic blood pressure and heart rate in adults, the MAH should provide, for each time point, summary treatment group (by dose) data (including mean, SD, maximum and minimum) and summary change from baseline data (including mean, SD, maximum and minimum) together with individual patient data on which this is based for heart rate, systolic and/or diastolic blood pressure to describe the temporal relationship throughout the duration of all clinical trials. A table of data showing detailed data for patients where systolic and/or diastolic blood pressure increased ≥5 mmHG and significant changes in changes in heart rate should also be presented.

The summary of the number and percentage of patients with an increase of at least 5 mmHg / significant changes in changes in heart rate should be included. Details of patient baseline characteristics (e.g. age, prior medications, prior illnesses, any other characteristics) should also be provided.
An important aim of this analyses is to characterise as fully as possible, the patterns of change in blood pressure and heart rate over time in patients who at any time point have fallen into the category of concern (i.e. experienced changes of ≥5 mmHG, or important changes in pulse rate). Thus, the full temporal record of cardiovascular outcomes in patients who at any time point have experienced a change in blood pressure of ≥5 mmHG /important changes in heart rate should be provided and included in the overall analysis.

- *The analysis must include a complete description of the hazard function over time for each patient who experienced a change in blood pressure of ≥5 mmHG or changes in pulse rate.*
- *A description of the risks per 1,000 patients should be provided.*

Dose-dependency of adverse effects

There is evidence to indicate that many of the important neurological, psychiatric and cardiovascular risks in adults treated with Concerta are dose-dependent.

- *The MAH should confirm whether the adult trials were designed to determine statistically significant differences in safety outcomes between the higher doses of Concerta, i.e. 54 MG -108 MG and above.*

Trial subjects with residual adverse effects (important risk of special interest)

In a proportion of trial subjects who experienced adverse effects of special interest, the adverse effect did not resolve without residual effects (including hypertension, tachycardia, psychosis/mania, arrhythmias, aggression, depression, tics).

- *The MAH should provide a detailed analysis of subjects who experienced any important adverse effect (as identified in this report) that did not resolve without residual effects, including a description of the duration of symptoms, severity, seriousness, treatments required, action taken with drug and any other relevant factor, and discuss whether further pharmacovigilance activities or risk minimisation is required for any risks with persistent effects.*

Adverse effects (safety specification of RMP and SPC section 4.8)

Adverse events from adult clinical trials that were newly identified or identified as being associated with a higher reporting frequency than those identified from child/adolescent trials and post-marketing data, which may also be of particular concern for the benefit/risk are:

- *Anxiety*
- *Depressed mood*
- *Panic attack*
- *Delusion*
- *Mania*
- *Cerebrovascular accident*
- *Irritability*
- *Restlessness*
- *Tension*
- *Dyspnoea*
- *Confusional state*
- *Fatigue, Lethargy*
- *Feeling jittery*
- *Decreased appetite*
- *Initial insomnia*
- *Apathy*

Off-label use

The MAH has summarised the important potential risk of off-label use in table 18.16 of the Safety Specification. It is clear from this summary that the prevalence for off-label use, particularly in adults, is poorly understood.

- *The MAH should propose how these potential risks can be properly characterised and also adequately minimised, including but not limited to SPC and PIL wording.*

Diagnosis in the target population (see also proposed SPC wording)

The MAH proposed wording for section 4.1 and 4.2 (and 4.4.) of the Concerta SPC is not in line with diagnostic criteria for ADHD (ICD-10 or DSM-IV). The proposed wording implies that it can be used in

patients whose diagnosis was established before the age of 18. However, diagnostic criteria in ICD-10 states that "onset of disorder should be no later than 7 years" and DSM-IV states that ADHD symptoms that cause impairment should be present before 7 years of age. The proposed wording will allow potentially inappropriate use in adults who have been diagnosed with ADHD at any age up to 18 years of age, or who may have partial symptoms and not full ADHD.

- *The MAH should propose alternative wording that complies with diagnostic guidelines in DSM-IV and ICD-10 and also ensure that the wording does not allow use of Concerta to treat partial symptoms (i.e. not full ADHD) in adults.*
- *The MAH should provide an analysis of the severity, pervasiveness and persistence of the ADHD symptoms, as well as age at diagnosis, details of diagnosis and treatment history at baseline in the adult trial population and determine if any of these factors had any impact on the safety or efficacy of Concerta.*

Diversion

The MAH has cited a small study in adults in Canada, where 44% of subjects admitted to diverting methylphenidate, primarily by giving it away. As the MAH states in table 18.17 regarding the preventability of the risk of diversion, that from a review of public information sources, it appears that there are currently no databases in place at an EU or national Member State level to directly monitor pharmaceutical product diversion in the EU. Methylphenidate is a controlled substance, distribution, prescription, and dispensing is restricted by national laws. However, these restrictions are unlikely to be adequate in preventing diversion by the individuals prescribed Concerta.

The MAH mention that the maintenance of records in some Member States of the supply of methylphenidate to the patients may provide an opportunity for measuring the possibility of product diversion. The extent to which this record keeping is electronic or centrally organised within each Member State is likely to vary. The MAH does not propose any measures to study this issue nor to minimise the risk beyond a statement in the SPC advising that patients should be monitored for the risk of diversion.

The limited evidence on the extent of this risk indicates that it is likely to be important, potentially common and may have a significant public health impact.

- *The MAH must propose methods to measure the risk of diversion in adults in all Member States and also propose risk minimisation measures including, but not limited to SPC and PIL wording, as these alone are likely to have a limited impact, especially on diversion by individual users.*

Use in pregnancy & lactation / neonatal cardio-respiratory toxicity (neonatal/foetal tachycardia; respiratory distress; apnoea) / neonatal effects of growth

The SWP and CHMP reviewed all relevant data on use in pregnancy and lactation during the Article 31(2) referral for all methylphenidate-containing medicinal products. As a result, the contraindication was removed and replaced with information and advice in section 4.6 and 5.3 of the core SPC reflecting the evidence, in line with current guidelines.

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 also states that methylphenidate has been found in breast-milk and mentions a report of decreased weight in an infant, whose mother was exposed to methylphenidate, with a positive dechallenge, and concludes that a risk to the suckling child cannot be excluded. 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 SPC.

Section 4.6 of the SPC also states that "cases of neonatal cardio-respiratory toxicity, specifically foetal tachycardia and respiratory distress have been reported in spontaneous case reports."

It is likely that the number of patients of child-bearing age will increase if Concerta is used in adults, thus it is important to ensure that the information and guidance on safety and use in pregnancy/lactation in the SPC is adhered to.

- *The MAH should include this information in the Educational tools for HCPs and patients.*

The two potential risks of neonatal cardio-respiratory toxicity and effects on neonatal growth were identified from review of post-marketing data during the Article 31 referral, and included in the Core RMP as potential risks. The MAH suggest that these risks are specific to the child population. However the means of exposure of children to these risks is through the mother who will be exposed to methylphenidate, thus these risks should be included as relevant and important in the adult ADHD population, especially as the number of possible female patients of child-bearing age, who are or may become pregnant or are breast-feeding and be exposed to Concerta will increase.

- *The risks of neonatal cardio-respiratory toxicity and effects on neonatal growth should be considered a potential risk for both neonates receiving methylphenidate and women who are pregnant or breast-feeding.*

Evidence in Hyperactive-Impulsive subtype of ADHD

The adult trials contained very few subjects with the Hyperactive-Impulsive subtype of ADHD. Most subjects were categorised as having combined type (about 70%) and the rest had the Inattentive-subtype.

- *The MAH should discuss the impact of this on the validity of the proposed indication.*

SECTION 4.6 PHARMACOVIGILANCE PLAN

Routine pharmacovigilance

The MAH described their methodology for their proposed routine pharmacovigilance practices, including real-time review of single cases, scheduled reviews of aggregate data, aggregate reviews at pre-specified intervals to identify safety signals related to product quality and manufacturing, data mining of regulatory databases (such as FDA AERS,WHO Vigibase), including medically confirmed and unconfirmed reports.

The MAH has provided a summary of their pharmacovigilance action plan for each of the safety concerns and detailed their action plan for each of the specific concerns identified in the Article 31 Referral in **table 25 of their submission.** A summary of their action plan, from Table 24 of the MAH submission, is presented below:

Table 24: Summary of Safety Concerns and Planned Pharmacovigilance Actions

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

(Continued)

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

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

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

Assessor's comment

The MAH has provided details of their proposed routine pharmacovigilance practices, which appear adequate.

Diversion

- *There are no proposals from the MAH to measure or monitor the risk of diversion beyond routine pharmacovigilance. Table 24 of the RMP states that for the risk of diversion, "monitoring supply of controlled substances follows National regulations". The MAH should clarify what this means and how it relates to their activities to characterise the risk of diversion in all Member States.*
- *The MAH must propose methods to measure the risk of diversion in adults in all Member States and also propose risk minimisation measures including, but not limited to, SPC and PIL wording, as these alone are likely to have a limited effect.*

Hepatic disorders

- *The MAH should submit proposals for targeted questionnaires to follow-up of reports of changes in hepatic enzymes, bilirubin or any □epatobiliary disorder in adults.*

Summary of outstanding actions, including milestones (of the Core RMP)

The present list of actions, based on requirements following the Article 31 referral (for the childhood and adolescent ADHD indication), are summarised below.

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

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

[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.

Assessor's comments:

The following points are subject to ongoing assessment in the context of the child/adolescent ADHD Core RMP but the first two may not be relevant to the target adult population.

1) **Feasibility of a proposed meta-analysis of the collaborating MAHs' pooled data on suicidality**
2) **The collaborating MAHs' feasibility statement on studying long-term effects of MPH on psychiatric outcomes/cognition**
3) **Risk of cardiovascular disorders, cerebrovascular disorders, sudden death: follow-up of FDA/AHRQ/Vanderbilt University pharmacoepidemiological study**

- *The MAH should submit proposals to further evaluate the risk of suicidality and the long-term effects of Concerta in adults.*

The results of the ongoing FDA pharmacoepidemiological study may provide useful data on the cardiovascular and cerebrovascular risks in adults exposed to ADHD medications, including methylphenidate.

- *The MAH should provide an evaluation of the results of the ongoing FDA/AHRQ/Vanderbilt University study as soon as the results are available and propose regulatory action in the context of the target adult population.*

Patients excluded from adult trials

There is missing information from patients with a range if important cardiovascular, cerebrovascular neurological and psychiatric co-morbidities, history of abuse/misuse/SUD, liver or renal insufficiency, and in some studies, from patients with other past or current non-drug treatments, known non-responders to methylphenidate (or other ADHD drugs), recent users of methylphenidate, weight below 45.4 KG.

- *The MAH should discuss the impact of these exclusions on the safe and effective use of Concerta in the proposed target adult population and discuss what risk minimisation measures or further studies are required.*

Use in pregnancy & lactation / neonatal cardio-respiratory toxicity (neonatal/fetal tachycardia; respiratory distress; apnoea) / neonatal effects of growth / Signal for Spina bifida / neural tube defect

During the Article 31 Referral the Safety Working Party of CHMP reviewed all data relating to safety in pregnancy and lactation from all MAHs, and noted that there were a few weak cases of spinda bifida/neural tube defect in humans and one rabbit study which showed cases in treated subjects, but not statistically higher than controls. The SWP recommended that more information should be obtained on this signal, and that the WHO Collaborating Centre for the Epidemiological Surveillance of Congenital Anomalies (EUROCAT) may have relevant data.

- *Given the predicted wider exposure of Concerta in the adult population the MAH should commit to capturing and evaluating relevant data on pregnancy outcomes, specifically a pregnancy registry should be considered.*
- *As previously recommended the MAH should also obtain and evaluate data on these issues from the WHO Collaborating Centre for the Epidemiological Surveillance of Congenital Anomalies (EUROCAT) and any other relevant sources.*

Drug utilisation studies

MAHs must provide utilisation data for all Member States where their product is used. The MAHs should consider alternative methods of completing the drug utilisation studies in the countries without appropriate databases. The methods used will have to be tailored to be suitable each member state and must include ad-hoc designed analyses where needed, to allow data collection in all member states. The method for each member state can be decided at a national level to ensure it is suitable for capturing the required data.

Measures should include: information on total amount used, patient age, gender, details of indication, details of diagnosis, range, severity, pervasiveness, persistence of symptoms, change in symptoms from childhood to adulthood, age at diagnosis, previous/ongoing treatments (including non-drug treatments), dose, duration of use, treatment continuity, co-morbidities, concomitant medications, data on patterns of use, prescriber speciality.

- *Collaboration with specialist treatment centres for adults with ADHD should be considered in the proposals.*

- *As per the utilisation studies for the child and adolescent population that were requested by CHMP during the Article 31 Referral, the MAH should propose methods to obtain data to characterise usage in the adult population over time, and to evaluate off-label use and the risk of diversion, in all member states.*

Important missing information on long term: safety (especially for key risks), effectiveness, maintenance of (short-term) effects

- *The MAH has not proposed any proactive pharmacovigilance (studies) to address these issues, which should be rectified.*

SECTION 4.6 **RISK MINIMISATION PLAN**

SPC and additional measures
The MAH believes that the current contraindications, warnings and precautions within the proposed harmonised EU SPC 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 in the Article 31 referral that MAHs of methylphenidate produce a risk minimisation tool (an education tool).

Proposed SPC

The MAH proposed an SPC with revisions to support the Type II variation for use of Concerta in adults. The ADR section in the current Core SPC, Section 4.8, is based on the assessment by the major EU MAHs of methylphenidate-containing products of their individual paediatric clinical databases and/or post-marketing pharmacovigilance information.

The MAH state that incorporation of newly identified ADRs from the adult Concerta clinical database into a single table would require implementation in the SPCs of all methylphenidate containing products, as the current table is part of the core SPC of methylphenidate-containing products for the treatment of ADHD (in children). To maintain transparency of the current core SPC ADR table, the MAH proposes to add a new table with ADRs that were identified on the basis of adverse events reported in clinical studies of Concerta in adults with ADHD and are either not listed in the current ADR table in the SPC or are reported more frequency than in the current ADR table on the basis of adult clinical study data. It is not the intention of the MAH to position the newly identified ADRs as relevant for adults only. An introductory sentence to this additional ADR table is proposed:

"The following additional ADRs were identified either as new ADRs or in a higher frequency category than the paediatric population during clinical trials in adult subjects with ADHD. These ADRs may also be relevant in the paediatric population."

Assessor's comments:

It is recommended that "or in a higher frequency category than the paediatric" is replaced with " or reported more frequently than in the paediatric".

Additional Risk Minimisation measures

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 SPC (based on the child/adolescent ADHD indication).

- 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 holders of methylphenidate (Novartis, Shire, Medice, and Laboratorios Rubio) are working to produce such an educational programme. It has been agreed that it would be appropriate for the MAHs to work with an independent group to produce the

educational tool. In this way, the educational tools will be applicable to all methylphenidate products, rather than company or brand specific.

Table 28 in the MAH submission provides information on the proposed educational tools (specific to the child/adolescent ADHD indication).

The Company will also review the educational materials developed for children and adolescents following approval of wording for an indication for continued treatment of adults with ADHD within the SPC; this review and any applicable educational materials would be independent of the other MAHs of methylphenidate-containing products for the treatment of ADHD due to the revised wording within the Concerta label only.

Risk Minimisation measures / Educational Tools specifically for the Adult ADHD population

The MAH (with other MAHs for methylphenidate products in the EU) will submit fully harmonised risk minimisation tools (physician's guide to prescribing and prescriber's checklist) which will contain all of the important information from the Clinical Particulars section of the core SPC for assessment.

As of the preparation of this RMP update, these materials are being finalised in preparation for submission as part of the PSUR work-sharing procedure.

Assessor's comments:

Risk Minimisation measures / Educational Tools specifically for the adult ADHD population

- *Educational tools (for HCPs) as proposed in the Core RMP for the childhood and adolescence ADHD indication, should be modified to be specific for the adult population, and include issues that are of particular concern in the adult population.*
- *Risk minimisation measures are also important for **patients**, and the MAH should provide educational tools similar to those proposed for HCPs in the childhood and adolescence ADHD indication, specifically for adult patients.*

Anxiety/anxiety disorders, aggression, depression and suicide-related events

- *Adult studies have identified anxiety as a very common risk in adults and is a major concern for the benefit/risk in this proposed variation. The risk of anxiety/anxiety disorders should be added to the Safety Specification (table of risks) as an **Important Identified Risk**. The MAH should propose proactive measures to minimise this risk.*
- *The risk of aggression, depression and suicide-related events should also be added to the Safety Specification (table of risks) as an **Important Identified Risk**.*
- *The current warning in section 4.4 of the proposed SPC entitled "Anxiety, agitation and tension" is inadequate, as the adult studies show a clear potential for de novo anxiety and agitation in patients treated with Concerta. The warning should be modified to reflect the evidence for the risk of new-onset anxiety, tension and agitation and the MAH should consider making the warning more prominent in this section of the SPC.*

Use in pregnancy & lactation/neonatal cardio-respiratory toxicity (neonatal/foetal tachycardia; respiratory distress; apnoea) /neonatal effects of growth

Section 4.6 states that methylphenidate has been found in breast-milk and mentions a report of decreased weight in an infant, whose mother was exposed to methylphenidate, with a positive dechallenge, and concludes that a risk to the suckling child cannot be excluded. 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 SPC. Section 4.6 of the SPC also states that "cases of neonatal cardio-respiratory toxicity, specifically foetal tachycardia and respiratory distress have been reported in spontaneous case reports."

- *It will be important to ensure that the risks in neonatal and infant children of adult female patients are adequately minimised thus the MAH should including these in educational tools for HCPs treating adult female patients and for the patients themselves.*

Specialist initiation and prescribing

The MAH should ensure that the risk minimisation measures (including but not limited to the SPC, PIL and educational tools for HCPs and patients) are adequate in ensuring : that specialists in adult ADHD are responsible for prescribing Concerta in adults; the correct and appropriate diagnosis of Adult ADHD; the initiation of treatment within a comprehensive treatment programme, and only when remedial measures alone have proven insufficient; adherence to the required pre-treatment screening and ongoing monitoring; regular evaluation of the need for continuing treatment and the maintenance of effect in adults.

Important missing information on long term: safety (especially for key risks), effectiveness, maintenance of (short-term) effects &
Evidence of maintenance of effect beyond short-term use

- *The MAH must ensure the SPC (section 4), PIL and educational tools for HCPs, and for carers adequately address the lack of evidence on long-term safety, effectiveness and maintenance of short-term effects of Concerta in the adult population.*

Specialist initiation and prescribing

- *The MAH should give further consideration to what risk minimisation measures (including the SPC and PIL and educational tools) are needed to ensure correct and appropriate diagnosis, pre-treatment screening, initiation of prescribing and review of the need for ongoing treatment by specialists.*

Use of 'Concerta' vs 'methylphenidate' in SPC

- *The MAH should review whether it would be appropriate to use the brand name Concerta in the SPC as opposed to methylphenidate, to minimise off-label use of other methylphenidate-containing medicinal products without an adult indication.*

Determining long-term usefulness

- *The MAH should discuss whether the frequencies for reviewing long-term need for Concerta as stated in the Core SPC ('at least once-yearly') are appropriate for the adult ADHD population or whether the frequency should be modified.*

Pre-treatment screening

- *The MAH should consider whether any further modifications required to the pre-treatment screening advice in the Core SPC, in order to be more appropriate for the Adult ADHD population.*

Ongoing monitoring (in SPC and Educational Tools)
Cardiovascular

- *The MAH are proposing to omit from the SPC, the requirement and frequencies for monitoring cardiovascular status (blood pressure and heart rate) in adults. This is not acceptable. The current cardiovascular monitoring requirements should also apply to the adult population and be included in the Educational Tools for HCPs and patients.*

Effects on weight and appetite

- *Regular monitoring for changes to weight and appetite are currently is required for children & adolescents, but the MAH propose to omit this requirement for adults. Given the evidence for anorexia, decreased appetite and clinically important weight loss in adults, this is not appropriate and*

should be rectified in the SPC, PIL and educational tools,, so that appetite and weight of adult patients is monitored at baseline and then at least every 6 months.

- *The MAH should consider whether the current Core SPC guidance and frequencies for neurological and psychiatric monitoring are also appropriate for adults or whether they need to be modified.*

Maintenance of effect

- *The MAH proposes to add to section 5.1 of the SPC, the following statement: "the maintenance of effect of Concerta XL during long-term use in adults with ADHD has not been fully established". There is no adequate evidence that it has been partially established, therefore the MAH should remove "fully" from the proposed text and add this information to relevant parts of section 4 of the SPC, the PIL and educational tools.*

Possible Adverse effects (Section 4.8 of the proposed SPC)

- *Adverse events from adult clinical trials that were newly identified or identified as being of a higher frequency than those identified form child/adolescent trials and post-marketing data, which may be of particular concern for the benefit/risk (in addition to the important risks identified from child/adolescent trials and all post-marketing data) are:*

Anxiety
Depressed mood
Panic attack
Delusion
Mania
Cerebrovascular accident
Irritability
Restlessness
Tension

Dyspnoea
Confusional state
Fatigue, Lethargy
Feeling jittery
Decreased appetite
Initial insomnia
Apathy

- *The proposed wording in section 4.8 of the SPC is acceptable.*

AUDIT TOOLS

- *MAH needs to ensure adequate audit of the effectiveness of the risk minimisation tools proposed or requested in the adult population and should provide details of how this will be achieved.*

5.0 OVERVIEW

In this version of the RMP, the MAH has proposed updates to the Core RMP (required by CHMP following the Article 31 referral for all methylphenidate products) to support a type II variation for a new indication for Concerta in treating adults with ADHD whose diagnosis was established before the age of 18 years and whose symptoms persist into adulthood. Exposure, demographic, and important identified

and potential risk data from double-blind and open-label clinical trials in adults with ADHD, and information from literature pertaining to adults with ADHD where applicable, were added to this RMP. I

Generally, there was a lack of adequate information on the epidemiology of ADHD in adults, specifically in the EU but also worldwide.

The Core important identified and potential risks for all methylphenidate products were reviewed for relevance in the adult ADHD population. A number of major risks were identified from the adult clinical trial data, which were either new, or were reported with a higher frequency category than in the paediatric population. Some of these should be categorised as important risks in the safety specification of the RMP for adults, these include: Anxiety/Anxiety disorders, depression, suicide-related events, aggression, agitation, mania/delusions, tics, cardiac arrhythmias, hypertension and clinically important changes in weight. The potential for other clinical significant adverse cardiovascular and cerebrovascular outcomes, as a consequence of effects on heart rate and blood pressure in adults, cannot be excluded and is considered a potential risk. These should be subject to proactive pharmacovigilance and risk minimisation measures.

Further analysis of the adult study data in relation to effects on diastolic and systolic blood pressure and heart rate should be requested, with the aim of characterising as fully as possible, the patterns of change in blood pressure and heart rate over time in patients who at any time point have experienced important changes.

In order to better understand the study population and its relationship to the target indicated adult population (in the RMP safety specification), the MAH should provide details of when the adult trial participants were initially diagnosed with ADHD, the pervasiveness and persistency, and severity of the symptoms over time, and details of prior/existing treatments (both pharmaceutical and non-pharmaceutical). The MAH should determine whether any of these factors have an impact on the safety or efficacy of Concerta in adults.

Important missing information in the Safety Specification should include: maintenance of the short-term effect in adults, long-term efficacy, effectiveness and safety (especially for key risks: cardiovascular risks, cerebrovascular risks and *de novo* or worsening of pre-existing psychiatric disorders including: mood disorders, depression, anxiety, agitation, suicide-related events, psychosis /mania/delusion), safety & efficacy in new or continuing users of methylphenidate.

Because of the adult trial exclusion criteria, there is also important missing information from patients with a range of important cardiovascular, cerebrovascular neurological and psychiatric comorbidities, history of abuse/misuse/SUD, liver or renal insufficiency, and in some studies, from patients with other past or current non-drug treatments, known non-responders to methylphenidate (or other ADHD drugs), recent users of methylphenidate, patients weighing < 45.4 KG.

Not all adults with ADHD will be eligible for treatment with Concerta, and the actual adult ADHD population who may be eligible for Concerta use is likely to be only a minority of those who were diagnosed with ADHD as children. The potential for off-label use in adults and the risk of diversion remain considerable. Measures proposed in the RMP to characterise the risks of off-label use and diversion and measures proposed to minimise them are considered inadequate and need to be addressed. Additionally, the MAH's proposed wording for sections 4.1, 4.2 and 4.4 of the SPC will allow use in adults who have been diagnosed with ADHD at any age up to 18 years of age, which is not in line with current guidelines which state ADHD should be diagnosed before the age of 7.

As per the utilisation studies for the child and adolescent population that were requested by CHMP during the Article 31 Referral, the MAH should propose methods to obtain data to characterise usage in the adult population over time, and to evaluate off-label use and the risk of diversion, in all member states.

Collaboration with specialist treatment centres for Adults with ADHD should be considered in the proposals.

The MAH should submit proposals to further evaluate the long-term effects on psychiatric outcomes, the risks of suicidality and of cerebrovascular disorders, in Adults.

The MAH should provide educational tools similar to those proposed for HCPs in the childhood and adolescence ADHD indication, specifically for adult patients.

The MAH should ensure that the risk minimisation measures adequately address : that specialists in adult ADHD are responsible for correct and appropriate diagnosis, pre-treatment screening, initiation of prescribing and review of the need for ongoing treatment with Concerta in adults ; the initiation of treatment within a comprehensive treatment programme, and only when remedial measures alone have proven insufficient; adherence to the required pre-treatment screening and ongoing monitoring; the lack of evidence on long-term safety, effectiveness and maintenance of short-term effects of Concerta in the adult population; need for regular evaluation of the need for continuing treatment; evaluation of the maintenance of effect in adults.

The MAH should consider whether the current Core SPC guidance and frequencies for neurological, psychiatric, weight and appetite monitoring are also appropriate for adults or whether they need to be modified.

Appendix III

Inclusion and Exclusion criteria for Studies 3002, 02-059 and 3013

Population recruitment requirements for Study 3002

throughout the study, and had to have a negative urine pregnancy test at screening.

7. Informed Consent Form signed by the subject.

8. Subject agreed to take only the supplied study drug as treatment for ADHD during the study.

9. Subject agreed not to initiate a new behavioral modification program during the study or if at entry was using a behavioral modification program agreed not to change this program during the study.

10. Subject was able to comply with the study visit schedule and willing and able to complete the protocol-specified assessments.

11. Healthy on the basis of a physical examination, medical history, anamnesis, and the results of blood biochemistry or hematology tests. If the results of the biochemistry or hematology tests were not within the laboratory's normal reference ranges, the subject could be included if the investigator considered the deviations not clinically relevant. This had to be clearly recorded in the subject's source documents and the Trial Manager informed.

3.2.3. Exclusion Criteria

Potential subjects who met any of the following criteria were excluded from participation in the study:

1. Known to be a non-responder to methylphenidate, or subject had a child known to be a non-responder to methylphenidate.

2. Had been treated with any methylphenidate-containing medication within 1 month of screening visit. One month was considered a reasonable time for subjects treated with methylphenidate to return to a disease status baseline.

3. Known allergy or hypersensitivity to methylphenidate, or components of PR OROS methylphenidate.

4. Any clinically unstable psychiatric condition including, but not limited to, the following: acute mood disorder, bipolar disorder, acute obsessive-compulsive disorder (OCD), anti-social personality disorder, borderline personality disorder.

5. Subjects with a family history of schizophrenia or family history of affective psychosis.

6. Autism or Asperger's syndrome.

7. Subjects with presence of motor tics, history of Tourette's syndrome or family history of Tourette's syndrome.

8. A diagnosis of substance use disorder (abuse/dependence) according to DSM-IV criteria within 6 months prior to screening evaluation (nicotine and caffeine dependence were not exclusionary). Episodic abuse in the past was not an exclusion criterion.

9. Current eating disorder (e.g., bulimia, anorexia nervosa) or history of an eating disorder.

10. Known or suspected mental retardation.

11. Hyperthyroidism, myocardial infarction or stroke in the 6 months prior to screening for this study.

12. Subjects with history of seizures, glaucoma or uncontrolled hypertension.

13. Subjects with angina pectoris or cardiac arrhythmias.

14. Pregnant or breast-feeding females.

15. Any co-existing medical condition or use of any concomitant medication that was likely to interfere with safe administration of methylphenidate including any herbal or homeopathic remedies; herbal and over-the-counter weight loss or diet preparations or drugs that contain stimulants.

16. Use of monoamine oxidase inhibitors, except if tapering off, within 4 weeks of the baseline visit.

17. Use of other anti-depressants (unless subject had been on a stable dosage for at least 3 months prior to screening, in which case treatment could be continued so long as dosage remained unchanged for the duration of the study) or mood stabilizers (e.g., anti-epileptics, lithium), except if tapering off, within 2 weeks of the baseline visit (for fluoxetine within 4 weeks). Any medication likely to interfere with safe administration of methylphenidate.

18. Use of clonidine or other alpha-2 adrenergic receptor agonists, antipsychotic medications, theophylline, coumarin anticoagulants, anticonvulsants.

19. Subjects who had clinically significant gastrointestinal problems, including severe narrowing (pathologic or iatrogenic) of the gastrointestinal tract.

20. Subjects who were unable to swallow the study medication with the aid of liquids (participants could not chew, divide, dissolve or crush the study medication).

21. History of severe drug allergy or hypersensitivity.

22. Any serious illnesses, including but not limited to, liver or renal insufficiency, significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurological, psychiatric or metabolic disturbances.

23. Confirmed cancer or malignancy.

24. Participation in an investigational drug trial in the 30 days prior to selection.

25. Employee of the investigator or the institution who had direct involvement in the trial or other trials under the direction of the investigator or their members.

Population recruitment requirements for Study 02-159

7.3 Selection of Study Population
7.3.1 Inclusion Criteria
Subjects were enrolled in the study provided they satisfied the following inclusion criteria:
1. Investigator determined diagnosis of ADHD (any type: Combined, Predominantly Inattentive, or Predominantly Hyperactive-Impulsive) as defined by the DSM-IV criteria. Subjects were required to:
a. Describe a chronic course of ADHD symptomatology from childhood to adulthood, with symptoms present before age seven years and continue to meet full DSM-IV criteria at the time of assessment.
b. Have had the diagnosis confirmed by the ACDS at the Baseline Visit.
c. Have had an AISRS score of 24 or greater as determined by the investigator at the Baseline Visit.
2. 18 to 65 years of age, inclusive, and at least the state-specific legal age of majority at screening.
3. GAF scale score of 41 to 60, inclusive, at the Baseline Visit.
4. Willing and able to read and comprehend all study related documents and to complete all protocol specified assessments.
5. Males or non-pregnant, non-lactating females. All female subjects had to have a negative urine pregnancy test at screening and baseline, with the exception of women who had been post-menopausal for a minimum of 12 months prior to screening and those who had undergone hysterectomy or bilateral oophorectomy. Female subjects had to agree to use an effective and medically acceptable form of birth control for at least one month prior to study entry and to continue use throughout the entire study period and for one month (30 days) after study completion. Medically acceptable, effective methods of contraception that could be used by the subject and/or her partner included abstinence, prescription hormonal contraceptives (oral, patch, vaginal ring, implant or injection), diaphragm with spermicide, intrauterine device, condom with spermicide, surgical sterilization or vasectomy.
6. Sign and date an informed consent form to participate in the study as outlined in Section 3.3.
7. Subjects were required to weigh a minimum of 100 lbs (45.4 kg) at the Screening Visit.
8. Negative urine drug test at the Screening and Baseline Visits when tested for drugs of abuse (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine and opioids), unless the positive result(s) were attributed by the investigator to a concomitant medication taken by the subject (eg, subject provided a current prescription for a benzodiazepine, cannabinoid, or opioid or

subject was receiving stimulant therapy at screening). Subject must have washed-out from stimulant therapy before the Baseline Visit.

7.3.2 Exclusion Criteria

Subjects were excluded from participation in the study if they fulfilled any of the following criteria:

1. Known to be non-responders to methylphenidate or other stimulants for the treatment of ADHD.
2. History of allergy, sensitivity, or contraindication to methylphenidate or components of CONCERTA.
3. Any coexisting medical condition or taking any concomitant medication that was likely to interfere with safe administration of methylphenidate, in the investigator's opinion.
4. Known or suspected structural cardiac abnormality, as assessed by history, physical examination, and/or ECG.
5. A diagnosis of or a family history of Tourette's syndrome (307.23, DSM-IV), or motor or verbal tics.
6. A history of a seizure disorder other than febrile seizures in childhood.
7. Glaucoma.
8. Uncontrolled hyperthyroidism or hypothyroidism.
9. Marked anxiety, tension or agitation or a HAM-A score of 21 or greater at baseline.
10. Moderate severity of depression ratings using HAM-D score of 17 or greater at baseline.
11. Co-morbid psychiatric diagnosis per DSM-IV criteria of bipolar disorder (Type I, II, or not otherwise specified), cyclothymic disorder, schizophrenia, schizoaffective disorder, pervasive developmental disorder or severe obsessive-compulsive disorders, or any other diagnosis that in the judgment of the investigator could have deemed the subject to be inappropriate for the study. Subjects with depressive symptoms were to be screened for risk for bipolar

disorder; with a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.
12. History of drug or alcohol abuse or dependence within the past six months prior to screening for this study.
13. Any current psychotic symptomatology or a history of hospitalization for psychotic disorder in the last five years.
14. Suicidal ideation or behavior in the past year.
15. Recreational cocaine or methamphetamine use in the last three months.
16. Current or history of an eating disorder (eg, bulimia, anorexia nervosa) in the last three years.
17. Known or suspected mental retardation or significant learning disorder.
18. Organic brain syndromes or dementia.
19. Blood pressure measurement of > 140 mmHg systolic or 90 mmHg diastolic or pulse > 100 bpm (average of triplicate measurements) at Screening or Baseline Visits. Subjects on anti-hypertensive medications whose blood pressures were below these limits were eligible to participate.
20. History of myocardial infarction or ischemia, cerebrovascular accident or transient ischemic attack, cardiomyopathy, serious cardiac problems or clinically significant arrhythmia or cardiovascular disease (eg, coronary artery disease).
21. At high risk for cardiovascular disease as assessed by medical and family history, physical examination, and laboratory test results in the opinion of the investigator.
22. ECG abnormalities that were deemed potentially clinically important (PCI) by the

investigator (eg, left bundle branch block, right bundle branch block, QTC > 460 msec, QRS > 120 msec, or PR > 219 msec). Subjects having ECG evidence of ischemia or arrhythmia as reviewed by an independent cardiologist.
23. Potentially clinically important abnormalities on results of any of the following laboratory tests at screening: complete blood count (CBC) including hemoglobin, hematocrit, platelet count, white blood cell count with differential; chemistry profile including sodium, potassium, bicarbonate, chloride, blood urea nitrogen (BUN), creatinine, glucose; and liver function tests (LFTs) including albumin, total protein, gamma-glutamyl-transferase (GGT), total bilirubin, alkaline phosphatase; thyroxine (T4); thyroid stimulating hormone (TSH); lipid profile; ipoprotein (a); and C-reactive protein.
24. Serum creatinine ≥ 2.0 mg/dL.
25. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1.5 x the upper limit of normal
26. Currently taking an antipsychotic medication or monoamine oxidase inhibitor or had taken either in the 30 days before the Screening Visit.
27. Required any of the following medications or anticipated the possibility of needing to take any of the following medications during the course of the study: bupropion, modafinil, clonidine or other alpha-2 adrenergic receptor agonists, tricyclic antidepressants, theophylline, coumarin anticoagulants, anticonvulsants, monoamine oxidase inhibitors, or guanethidine.
28. Currently taking a serotonin norepinephrine reuptake inhibitor (SNRI) or had taken an SNRI in the 30 days prior to the Screening Visit (eg, venlafaxine, duloxetine).
29. Subjects taking a selective serotonin reuptake inhibitor (SSRI) who were not stable on their medication for at least 30 days prior to the Screening Visit (eg, fluoxetine, paroxetine, sertraline, citalopram, escitalopram).
30. Pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic, eg, small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudo-obstruction, or Meckel's diverticulum).
31. Unable to swallow the study medication whole.
32. Another member of their household currently participating in the study.
33. Planned to take any medication as treatment for ADHD in addition to the supplied study drug during the study.
34. Planned to initiate a new cognitive therapy, psychotherapy, or behavioral modification program during the study, or if currently using a behavioral modification program, planned to change this program during the study.
35. Planned to actively do anything to substantially change their weight during the course of the study.
36. Unable to comply with the study visit schedule.
37. Unable to understand or follow the instructions given in the study, in the investigator's opinion.
38. Planned surgery requiring hospitalization or general anesthesia during the time of study participation.
39. Unwilling or unable to read and comprehend all study related documents and to complete all protocol specified assessments.
40. Had taken an investigational medication or product 30 days prior to the Screening Visit.
41. Related to those persons involved directly or indirectly with the conduct of this study (ie, principal investigator, sub-investigators, study coordinators, other study personnel, employees of McNeil, contractors of McNeil, Johnson & Johnson subsidiaries, and the families of each).

In addition to the above restrictions, study subject selection was consistent with all of the warnings, precautions, and contraindications associated with the study medication. The investigator was to be familiar with the content of the approved labeling for CONCERTA.
The investigator was allowed to disqualify any study subject for any sound medical reason. The Study Director or their designee approved any deviations from these entrance criteria prior to randomization. All deviations and rationale were clearly documented in the subject's source documents and in the appropriate section of the CRF.

Population recruitment requirements for Study 3013

3.2. Study Population

3.2.1. Overview

Adult subjects with a diagnosis of ADHD according to the criteria described in the DSM-IV, with some symptoms before age 7 years who continued to meet the DSM-IV criteria at the time of assessment, were enrolled in this study. ADHD was not diagnosed if the symptoms were better accounted for by another psychiatric disorder (e.g., mood disorder, anxiety disorder, psychotic disorder, personality disorder). The Structured Clinical Interview for DSM-IV (SCID) was performed to identify other disorders.

Confirmation of adult diagnosis of ADHD based on Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID) was required.

Subjects with at least mild to moderate symptoms of ADHD (CAARS score of ≥ 24 as determined by investigator at screening visit) were enrolled.

Included subjects had to be at least 18 years of age.

A total of approximately 300 subjects, 100 in each treatment group, were required for the 13-week double-blind treatment period.

3.2.2. Inclusion Criteria

Subjects enrolled in this study were required to meet the following inclusion criteria:

1. Subjects could be male or female.
2. Subjects had to be aged between 18 and 65 years, inclusive.
3. Diagnosis of ADHD according to the DSM-IV[16] and confirmed by the CAADID.
4. Described chronic course of ADHD symptomatology from childhood to adulthood, with some symptoms present before age 7 years and continued to meet DSM-IV criteria at the time of assessment. ADHD was not diagnosed if the symptoms were better accounted for by another psychiatric disorder (e.g., mood disorder [especially bipolar disorder], anxiety disorder, psychotic disorder, personality disorder).
5. CAARS score of ≥ 24 as determined by the investigator at the screening visit.
6. Women had to be postmenopausal since 1 year, surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal ligation, or otherwise be incapable of pregnancy), abstinent (at the discretion of the investigator), or, if sexually active, be practicing an effective method of birth control (e.g., prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method [e.g., condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel], male partner sterilization) before entry and continue to use the same method of contraception throughout the study.

   Note that for German subjects, this inclusion criterion differed slightly: women had to be postmenopausal (no spontaneous menses for at least 2 years), surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal ligation, or otherwise be incapable of pregnancy), abstinent, or, if sexually active, be practicing an effective method of birth control (e.g., prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, male partner sterilization) before entry and continue to use the same method of contraception throughout the study and for 1 week after the completion of the study.
7. ICF signed by the subject.
8. Subject agreed to take only the supplied study drug as treatment for ADHD during the study.

9. Subject agreed not to initiate a new behavioral modification program during the study or if currently using a behavioral modification program, agreed not to change this program during the study.
10. Subject was able to comply with the study visit schedule and willing and able to complete the protocol-specified assessments.
11. Healthy on the basis of a physical examination, medical history and the results of blood biochemistry and hematology tests. If the results of the biochemistry or hematology tests were not within the laboratory's normal reference ranges, the subject could be included if the investigator considered the deviations not clinically relevant. This had to be clearly recorded in the subject's source documents and the Project Manager Medical Affairs was to be informed of the abnormal laboratory values in case of alert values.

3.2.3. Exclusion Criteria

Potential subjects who met any of the following criteria were excluded from participating in the study:

1. were known to be a non-responder to MPH, or had a child known to be a non-responder to MPH;
2. had been treated with any MPH-containing medication within 1 month of the screening visit. One month was considered a reasonable time for patients treated with MPH to return to a disease status baseline;
3. had participated in and withdrew prematurely from the 42603ATT3002 study or 42603ATT3004 study;
4. had a known allergy or hypersensitivity to MPH, or components of PR OROS MPH;
5. had any clinically unstable psychiatric condition including, but not limited to, the following: acute mood disorder, bipolar disorder, acute obsessive-compulsive disorder (OCD), anti-social personality disorder, borderline personality disorder;
6. had a family history of schizophrenia or family history of affective psychosis;
7. had autism or Asperger's syndrome;
8. had motor tics, history of Tourette's syndrome or family history of Tourette's syndrome;
9. were diagnosed with substance use disorder (abuse/dependence) according to DSM-IV criteria within 6 months prior to screening evaluation (nicotine and caffeine dependence were not exclusionary) (episodic abuse in the past was not an exclusion criterion);
10. had a current eating disorder (e.g., bulimia, anorexia nervosa) or history of an eating disorder;
11. had known or suspected mental retardation;
12. had hyperthyroidism, myocardial infarction or stroke in the 6 months prior to screening for this study;

13. had a history of seizures, glaucoma or uncontrolled hypertension; for German subjects, the following definition was added: uncontrolled hypertension[17,18] was defined as systolic blood pressure at screening or baseline ≥ 140 mmHg or diastolic blood pressure at screening or baseline ≥ 90 mmHg;
14. had angina pectoris or cardiac arrhythmias; for German subjects, the following definition was added: cardiac arrhythmias was defined as clinically significant cardiac arrhythmias according to medical judgment or tachycardia (heart rate of > 100 bpm);
15. were pregnant or breast-feeding females;
16. had any co-existing medical condition or were taking any concomitant medication that was likely to interfere with safe administration of MPH including any herbal or homeopathic remedies, herbal and over-the-counter weight loss or diet preparations, or drugs containing stimulants;
17. used MAO inhibitors, except if tapering, within 4 weeks of the baseline visit;
18. used other anti-depressants (unless subject had been on a stable dosage for at least 3 months prior to screening, in which case treatment could continue so long as dosage remained unchanged for the duration of the study), mood stabilizers (e.g., anti-epileptics, lithium), except if tapering, within 2 weeks of the baseline visit (for fluoxetine within 4 weeks), or any medication likely to interfere with safe administration of MPH;
19. used clonidine or other alpha-2 adrenergic receptor agonists, antipsychotic medications, theophylline, coumarin anticoagulants, anticonvulsants;
20. had clinically significant gastrointestinal problems, including severe narrowing (pathologic or iatrogenic) of the gastrointestinal tract;
21. were unable to swallow the study medication whole with the aid of liquids (participants could not chew, divide, dissolve or crush the study medication);
22. had a history of severe drug allergy or hypersensitivity;
23. had any serious illnesses including, but not limited to liver or renal insufficiency, significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurological, psychiatric or metabolic disturbances;
24. had confirmed cancer or malignancy;
25. participated in an investigational drug study in the 30 days prior to selection;
26. were an employee of the investigator or the institution who had direct involvement in the study or other studies under the direction of the investigator or their members.

Additionally, in France, subjects with marked anxiety and tension, severe depression, psychotic symptoms, or suicidal tendencies, were not to be enrolled.

3.3. Removal of Subjects From Therapy or Assessment

A subject was withdrawn from the study if:

- the investigator believed that for safety reasons (e.g., AE) it was in the best interest of the subject to stop treatment;

Appendix IV

Endpoints

The CAARS scale used in the Phase 3 studies was comprised of 18 items, each corresponding to the 18 DSM-IV symptoms for ADHD. Each item is rated by a trained clinician using a 4-point Likert scale of 0 = not at all, never; 1 = just a little, once in a while; 2 = pretty much, often; and 3 = very much, very frequently. Scores of individual items are summarized using 2 subscale scores (hyperactivity/impulsivity subscale; inattention subscale) and a total score (sum of 2 subscale scores; maximum score = 54), with higher scores indicating more symptoms

Scales

Adult ADHD Investigator Symptom Rating Scale (AISRS) (Study 02-159)

The AISRS was the primary efficacy assessment instrument for Study 02-159. It is a scripted version of the ADHD Rating Scale (ADHD-RS). Like the CAARS, the AISRS is comprised of 18 items, each corresponding to the 18 DSM-IV symptoms for ADHD. Items are rated by a trained clinician using a 4-point Likert scale of 0 = none; 1 = mild; 2 = moderate; and 3 = severe. Scores of individual items are summed to yield a total score (maximum value = 54), with higher scores indicating more severe symptoms.

Conners' Adult ADHD Rating Scale- Self Report - Short Form (CAARS-S:S)

(Studies 3002, 02-159, 3013, and 3004 Randomized Withdrawal Phase)

A 26-item self-report scale that evaluates symptoms based on DSM-IV criteria for ADHD. Subjects rate the items using the same 4-point scale described for the CAARS. The CAARS-S:S contains 5 subscales: Inattention/Memory Problems (5 items), Hyperactivity/Restlessness (5 items), Impulsivity/Emotional Lability (5 items), Problems with Self-concept (5 items), and ADHD Index (12 items that best distinguish individuals with ADHD from those without the disorder)(Erhardt 1999). In addition, an Inconsistency Index (8 pairs, 16 items) can be calculated which is useful in detecting an inconsistent response style. The total score is calculated by adding the individual scores from the 26 items, and the range of possible total scores is 0 to 78, with higher scores indicating greater symptoms. The CAARS-S:S was provided to subjects in their local language.

Clinical Global Impression (CGI) Rating Scales (Studies 3002, 02-159, 3013, and 3004 Randomized Withdrawal Phase)

Responses on the CGI-S are made using a 7-point scale, ranging from 1 (not ill) to 7 (extremely severe). The CGI-Improvement (CGI-I) rates how much the subject's illness has improved or worsened relative to the baseline assessment using a 7-point scale (1 = very much improved; 7 = very much worse).

Global Assessment of Effectiveness (GAE) (Studies 3002, 02-159, and 3004 Randomized Withdrawal Phase)

Effectiveness of study treatment using a 4-point scale (0 = poor, 3 = excellent). If possible, the same rater was to complete this scale at each visit for a given subject.

ADHD Impact Module for Adults (AIM-A) (Studies 02-159 and 3013) 14-item subject-rated, disease-specific questionnaire that is comprised of:

- 5 multi-item scales that capture areas impacted by ADHD: Living with ADHD, General Well-being, Daily Performance and Functioning, Relationships/Communication, Impact of Symptoms: Bother/Concern and Interference; scored on scale from 0 to 100, with higher scores indicating better quality of life.
- 4 single items in the Quality of Life section: current quality of life (10-point scale: worst to best), global limitation (5-point scale: a lot to not at all), on the right track (4-point scale: definitely to not at all), and more good days than bad (5-point scale: strongly agree to strongly disagree)
- 5 single items in the Economic Impact: number in past year of motor vehicle infringements, doctor visits for injuries/accidents, doctor visits for ADHD, school/work days missed, and jobs (total number)

Sheehan's Disability Scale (SDS) (Studies 3002, 02-159, 3013, and 3004 Randomized Withdrawal Phase)

It is a subject-rated scale that measures the extent to which the subject's work, social life/leisure activities, and home life/family responsibilities are impaired by his/her symptoms. For each of these 3 areas, subjects

rated the degree of impairment on a 10-point visual analogue scale, with a higher score indicating greater impairment.

Quality of Life Enjoyment and Satisfaction Questionnaire: Short Form (Q-LES-Q-SF)
(Studies 3002, 02-159, and 3004 Randomized Withdrawal Phase) It is a 16-item, self-administered questionnaire concerning physical health, feelings, work, household duties, work and leisure time activities, and social relations across 5 response categories, ranging from very poor to very good, with higher scores indicating greater enjoyment or satisfaction.

Sheehan Disability Scale
The Sheehan Disability Scale is a self-administered scale designed to measure the extent to which subject's work, social life or leisure activities and home life or family responsibilities are impaired by his/her symptoms on a 10-point visual analogue scale.

Global Assessment of Efficacy The GAE was used to assess the effectiveness of the subject's treatment using a 4-point scale (0 = poor to 3 = excellent). The GAE was assessed by a trained clinician. If possible, the same person administered this scale at all visits.

Drug Use Screening Inventory Revised (DUSI-R)

DUSI-R is a 159-item instrument that documents the level of involvement with a variety of drugs and quantifies severity of consequences associated with drug use. The profile identifies and prioritizes intervention needs and provides an informative and facile method of monitoring treatment course and aftercare. The DUSI-R is a self-administered instrument and can be administered either by paper-pencil or computerized self-report. Two profiles are obtained: (1) Absolute Problem Density Profile, and (2) Relative Problem Density Profile.

<ANNEX II
<RMS'S QUESTIONS ON THE ASM (ACTIVE SUBSTANCE MANUFACTURER) RESTRICTED/CLOSED PART OF THE EDMF

Name of Product, Applicant, Procedure Ref. No.:

Active Substance (Drug Substance):

Name of ASM:

Address of ASM:

NOTES:
The structure of the report in this Annex should reflect the relevant parts of Module 3.2.S
Where there is more than one EDMF cited in the dossier, a separate annex is needed for each EDMF
These annexes will not be sent to the MAH but only to the relevant ASM / holder of the EDMF

Safeguarding public health

MS. B Livingston
JANSSEN-CILAG LIMITED
50-100 HOLMERS FARM WAY
HIGH WYCOMBE
BUCKINGHAMSHIRE
HP12 4EG
UNITED KINGDOM

02/08/2010

Dear MS. Livingston,

REQUEST FOR FURTHER INFORMATION

Our Reference:	PL 00242/0373 - 0085
Your Reference:	V6281-4
Product:	Concerta® XL 36mg Prolonged-Release Tablets
Type of Procedure:	Mutual Recognition
Submission Type:	Variation
Submission Category:	Type II
Submission Complexity:	Complex
EU Procedure Number (if applicable):	UK/H/0544/002/II/056
Reason:	To add the treatment of ADHD in adults whose ADHD diagnosis was established before the age of 18 years and whose symptoms persist into adulthood, at doses ranging from 18 mg to 72 mg per day as a new clinical indication. Sections 4.1 (Therapeutic indications), 4.2 (Posology and method of administration), 4.4 (Special warnings and precautions for use), 4.8 (Undesirable effects), 5.1 (Pharmacodynamic properties) and 5.2 (Pharmacokinetic properties) of the SPC have been updated.

With reference to the above submission, further information is needed, as outlined in the following points.

There are major objections and many other points of concern regarding this variation. Please see the list of points below and the comments from the CMS.

The response letter, discussion and all updated dossier documents (in their entirety) should be submitted electronically, quoting the above reference number.

The information should be received within 60 calendar days of the date of this letter, otherwise the application will be refused. An extension to this time limit may be agreed in exceptional circumstances.

Please quote our reference in all future correspondence regarding this submission.

Do not hesitate to contact me if you wish to discuss any issues further.

Yours sincerely,

Dr SC Morgan FRCP
Licensing Division

This letter refers to Collection ID 93231 and covers the following submissions: PL 00242/0400 - 0042,PL 00242/0374 - 0088,PL 00242/0372 - 0088.

Major Objections

1. **Efficacy for the proposed indication has not been clearly demonstrated as follows:**

- **A robust and clinically relevant estimate of short term efficacy for the indicated population has not been demonstrated. Further analyses are requested (see other efficacy concerns).**
- **The relevance of the data derived from the population who were diagnosed after the age of 18 to the indicated population is unclear. Clear detail of how the study populations were assessed to have met DSM IV criteria for adult ADHD for the study populations in general and for the subgroup analysis population diagnosed <18 years of age should be provided.**
- **Long term efficacy. The withdrawal study failed to demonstrate efficacy. The published paper by Rosser lacks the required detail for an efficacy assessment. Data from that study should be submitted if the MAH wishes to use these as the primary supportive evidence.**

2. **The safety of Concerta in the proposed indication has not been adequately described particularly:**

- **Cardiovascular risk**
- **Psychiatric adverse events**
- **Dependence and abuse risks**

(see safety concerns below).

Other Efficacy Concerns

3. It is unclear how the applicant has defined whether a patient is a responder when the data is missing. For each of the 3 pivotal short term efficacy studies, the applicant should clarify how

this has been done. For each trial, if this analysis has not already presented, an analysis including missing data as failures should be presented, including point estimates, p-values and confidence intervals, adjusted using Dunnett's procedure for controlling the Type I error.

4. For all studies the applicant should provide details on how many patients who did drop out were considered responders. In particular, if this is much higher on treatment compared to placebo, a full discussion of why LOCF and MMRM are appropriately conservative methods for handling missing data should be provided.

5. For Study 0159 the applicant should clarify how many patients initially responded (and at what dose) but were not considered to be responders by the end of the study.

6. For Study 3002, the applicant should provide the results of the analysis for the primary endpoint without gender in the model. For study 3013, age should be removed from the model.

7. The applicant should investigate whether there is an interaction in any of the studies between age of diagnosis and age at enrolment in the study. If there is, the applicant should discuss further the apparent decrease in efficacy seen in younger patients in study 0159.

Safety Concerns

8. Cardiovascular safety. Discuss what level of BP and heart rate increase that could pose a risk to adults and present data on sustained increases in BP and heart rate. Increases in BP above 5mmHg and 10mmHg should also be presented as well as clinically significant sustained levels in HR.

9. Psychiatric adverse events. Further discussion of the psychiatric adverse events is required with particular focus on:
   - Suicidality. Discuss whether all potential cases were identified in terms of a Columbia style analysis with intention not considered as a criterion for inclusion.
   - Aggression with a description of the individual events and their severity.

10. Further discussion on the implications of weight loss in adults.

11. Further discussion around the risk of dependence and abuse in light of the pharmacokinetics seen in study 12-004 Crushed Concerta and the Abuse potential seen in Study 12-007 (Light Drug Users).

12. The proposed indication will result in increased exposure of women of child-bearing potential. Adequate warnings should be in place in the SMC. The MAH should commit to capturing and evaluating relevant data on pregnancy outcomes using a pregnancy registry. In addition further investigation of the signal for spina bifida / neural tube defects from the WHO Collaborating Centre for the Epidemiological Surveillance of Congenital Anomalies (EUROCAT) and any other relevant sources.

Product Information

13. Clear guidance in section 4.4 should be added on the monitoring of HR and BP before use and during treatment. The guidance should include instructions on the level of HR or BP increase that should initiate dose reduction or withdrawal.

14. The proposed wording for sections 4.1, 4.2 and 4.4 of the SPC will allow off-label use in adults who have been diagnosed with ADHD at any age up to 18 years of age, allowing inappropriate/off-label use in patients incorrectly diagnosed over 7 years of age, or who may have partial symptoms and not full ADHD. To prevent off-label use, the MAH should ensure that the wording of the proposed indication in the SPC is compliant with DSM-IV guidelines on the correct diagnosis of ADHD in childhood (i.e. before the age of 7 years). The MAA should also ensure that the wording of the SPC does not allow use of Concerta to treat partial symptoms (i.e. not full ADHD) in Adults.

15. The optimal treatment duration has not been established. This should be clearly stated in the SPC with the requirement for regular review of the need for continued treatment, which should include regular planned withdrawal of treatment.

16. The current warning in section 4.4 of the proposed SPC entitled "Anxiety, agitation and tension" is inadequate, as the adult studies show a clear potential for de novo anxiety and agitation in patients treated with Concerta. The warning should be modified to reflect the evidence for the risk of new-onset anxiety, tension and agitation and made more prominent.

17. Wording for the appropriate monitoring of AEs in adults should be added for example regarding weight loss and mood.

RMP Concerns

The concerns raised from the RMP assessment should be addressed and in particular the following points answered:

18. The MAH should provide an evaluation of the results of the ongoing FDA / AHRQ / Vanderbilt University pharmacoepidemiological study (risk of cardiovascular disorders, cerebrovascular disorders, sudden death) as soon as the results are available and propose regulatory action in the context of the target Adult population.

19. Currently used educational tools should be modified for an adult population and adapted to ensure the correct adult ADHD population is identified for treatment.

Other RMP Points

The Risk Management Plan for Concerta in Adults should be revised based on the following points:

20. Most of the post-marketing, non-study exposure for Concerta is in patients from 6 – 20 years of age. It is important that the MAH has in place proactive pharmacovigilance measures to capture and analyse good quality post-marketing data specifically on for the adult population.

21. The risks of anxiety/anxiety disorders, depression, aggression, agitation restlessness, suicide-related events, psychosis, mania/delusions, decreased appetite, clinically important decreased weight, cardiac arrhythmias, tics/worsening of tics or tourrette's syndrome should be added to the Safety Specification as Important **Identified** Risks.

22. The MAH should describe the evidence for maintenance of effect beyond short-term use and describe what is proposed for section 4 of the SPC and other risk minimisation measures in this regard. The MAH proposes to add to section 5.1 of the SPC, the following statement: "the maintenance of effect of Concerta XL during long-term use in adults with ADHD has not been fully established". No adequate evidence was presented in the RMP that maintenance of effect has been either partially or fully established, and the criteria for these definitions in not known, therefore the MAH should remove "fully" from the proposed text and add this information to relevant parts of section 4 of the SPC, the PIL and educational tools.

23. Not all adults with ADHD will be eligible for treatment with Concerta, and the actual adult ADHD population who may be eligible for Concerta use is likely to be only a minority of those who were diagnosed with ADHD as children. The potential for off-label use is considerable. The MAH should describe their proposals to reduce the risks of off-label use, in adults who are

not indicated for Concerta treatment (for example, use for residual symptoms, which may not be responsive to methylphenidate; use in those with poorly or inappropriately diagnosed ADHD at any age up to 18 years; use in adults with a first diagnosis in adulthood; use outside of a comprehensive treatment programme; use before other remedial measures are tried etc).

24. The MAH should confirm whether the adult trials were designed to determine statistically significant differences in safety outcomes between the higher doses of Concerta, i.e. 54 MG - 108 MG and above.

25. The MAH should provide a detailed analysis of the subjects who experienced any important adverse effect (as identified in this report) that did not resolve without residual effects, including a description of the duration of symptoms, severity, seriousness, treatments required, action taken with drug and any other relevant factors, and discuss whether further pharmacovigilance activities or risk minimisation is required for any risks with persistent effects.

26. The MAH should include the following as Important Missing Information in the adult population, and provide proposals to address the lack of data on these issues:
a. Long-term safety (especially for key risks: cardiovascular, cerebrovascular, psychiatric risksincluding: mood disorders, depression, anxiety, agitation, suicide-related events, psychosis/mania/delusion). This should include proposals to study the risks of cerebrovascular disorders (including stroke) and suicidality in adults.
b. Maintenance of effect (MAH state in proposed SPC section5.1 that"the maintenance of effect of Concerta XL during long-term use in adults with ADHD has not been fully established".
c. Long-term effectiveness (and efficacy).
d. Efficacy/safety in patients who have/have not used methylphenidate before.

27. The MAH should discuss the impact of the exclusion criteria in the adult studies on the safe and effective use of Concerta in the proposed target adult population, and discuss what risk minimisation measures and further studies are needed.

28. The MAH should add the following to table 18.16 in the list of potential off-label indications: use in adults poorly or incorrectly diagnosed with ADHD, adults with partial symptoms, adults not diagnosed correctly in childhood (i.e. < 7 years of age), use alone (i.e. not within a comprehensive treatment programme that includes other remedial measures), use in adults with no accurate diagnosis of ADHD in childhood/with a first diagnosis in adulthood, or use in adults with unreliable retrospective diagnosis of ADHD in childhood or adolescence. The MAH should propose how these potential risks can be properly characterised and also adequately minimised, including but not limited to SPC and PIL wording.

29. The MAH should provide an analysis of the severity, pervasiveness and persistence of the ADHD symptoms, as well as age at diagnosis, details of diagnosis and treatment history at baseline in the adult trial population and determine if any of these factors had any impact on the safety or efficacy of Concerta.

30. The MAH must propose adequate methods to measure the risk of diversion in adults in all Member States (including use of national records) and also propose risk minimisation measures including, but not limited to the SPC and PIL, as these alone are likely to have a limited impact, especially on diversion by individual users. The MAH should clarify what is meant by the statement in Table 24 on the risk of Diversion: *"monitoring supply of controlled substances follows National regulations"* and how this relates to their activities to characterise the risk of diversion in all member states

31. The two potential risks of neonatal cardio-respiratory toxicity and effects on neonatal growth should remain in this RMP as important potential risks. The means of exposure of children to these risks is through the mother who will be exposed to methylphenidate, thus these risks should be included as relevant and important in the adult ADHD population, especially as the number of possible female patients of child-bearing age, who are or may become pregnant or breast-feeding and be exposed to Concerta will increase.

32. It will be important to ensure that the risks in neonatal and infant children of adult female patients are adequately minimised thus the MAH should include these in educational tools for HCPs treating adult female patients and for the patients themselves.

33. The MAH should discuss the impact of the lack of data on adults with the Hyperactive-Impulsive subtype of ADHD on the validity of the proposed indication.

34. As per the utilisation studies for the child and adolescent population that were requested by CHMP during the Article 31 Referral, the MAH should propose methods to obtain data to characterise usage in the adult population over time, and to evaluate off-label use and the risk of diversion, in all member states. Collaboration with specialist treatment centres for adults with ADHD should be considered in the proposals. The MAHs should consider alternative methods of completing the drug utilisation studies in the countries without appropriate databases. The methods used will have to be tailored to be suitable each member state and must include ad-hoc designed analyses where needed, to allow data collection in all member states. Measures should include: information on total amount used, patient age, gender, details of indication, details of diagnosis, range, severity, pervasiveness, persistence of symptoms, change in symptoms from childhood to adulthood, age at diagnosis, previous/ongoing treatments (including non-drug treatments), dose, duration of use, treatment continuity, co-

morbidities, concomitant medications, data on patterns of use, prescriber speciality. In the Member States that are covered by the IMS database, the MAH could utilise this resource to evaluate off-label use of methylphenidate but should undertake alternative methods for completing the review of usage and off-label use in the Member States that are not currently covered by multi-national (EU-wide) databases such as IMS.

35. The MAH should submit proposals for targeted questionnaires to follow-up reports of changes in hepatic enzymes, bilirubin or any hepatobiliary disorder in adults.

36. The MAH should provide educational tools similar to those proposed for HCPs in the childhood and adolescence ADHD indication, specifically for adult patients.

37. The identified risks (from trials)of anxiety, aggression, agitation, depression, psychosis/mania/delusions in adults are of concern and the MAH should propose proactive measures to minimise these risks.

38. The MAH should ensure that the risk minimisation measures (including but not limited to the SPC, PIL and educational tools for HCPs and patients) adequately address : that specialists in adult ADHD are responsible for correct and appropriate diagnosis, pre-treatment screening, initiation of prescribing and review of the need for ongoing treatment with Concerta in adults ; the initiation of treatment within a comprehensive treatment programme, and only when remedial measures alone have proven insufficient; adherence to the required pre-treatment screening and ongoing monitoring; the lack of evidence on long-term safety, effectiveness and maintenance of short-term effects of Concerta in the adult population; need for regular evaluation of the need for continuing treatment; evaluation of the maintenance of effect in adults.

39. The MAH should review whether it would be appropriate to use the brand name Concerta in the SPC as opposed to methylphenidate, to minimise off-label use of other methylphenidate-containing medicinal products without an adult indication.

40. The MAH should discuss whether the frequencies for reviewing long-term need for Concerta as stated in the current Core SPC for children & adolescents ('at least once-yearly') are appropriate for the adult ADHD population or whether the frequency should be modified.

41. The MAH should consider whether the current Core SPC guidance and frequencies for neurological and psychiatric monitoring in children & adolescents are also appropriate for adults or whether they need to be modified.

42. Given the evidence for anorexia, decreased appetite and clinically important weight loss in adults, the removal from the SPC of the requirement for regular monitoring for changes to weight and appetite, so that it does not apply to adults, is not appropriate. This should be rectified in the SPC, PIL and educational tools,, so that appetite and weight of adult patients is monitored at baseline and then at least every 6 months.

43. The MAH should ensure adequate audit of the effectiveness of the risk minimisation tools proposed or requested in the adult population and should provide details of how this will be achieved.

CMS Comments

DAY 85 COMMENTS FROM THE NORWEGIAN MEDICINES AGENCY

Product name:	Concerta XL (methylphenidate) Janssen-Cilag
Procedure No.:	UK/H/0544/001-004/II/056
Dosage form and strength:	Prolonged release tablets, 18/27/36/54 mg
Date:	2010-07-20
Our reference:	10/09291

Overall conclusion regarding the medicinal product:

The Norwegian Medicines Agency (NoMA) is of the opinion that there are potentially serious public health concerns related to the use of this product for the extension of the indication (marked in bold below):
"CONCERTA XL is indicated as part of a comprehensive treatment programme for Attention Deficit Hyperactivity Disorder (ADHD)***. It may be used when remedial measures alone prove insufficient*** in children aged 6 years of age and over ***as well as in adults whose ADHD diagnosis was established before the age of 18 years and whose symptoms persist into adulthood***" and is therefore not prepared to approve this extension of the indication at this stage.

POTENTIAL SERIOUS RISK TO PUBLIC HEALTH

2.4 Part IV/Module 5 – Clinical

We fully endorse the conclusions made by the RMS.

Some of the main concerns are:

Efficacy:
There is a major concern over the robustness of diagnosis of ADHD in the population recruited to the studies. The evidence to support the proposed indication wording is considered weak as it is based on a post hoc sub-group analysis in less than 20% of the studied population (ADHD diagnosed < 18 years of age).

In addition there were extensive exclusion criteria that result in the recruitment of a population with little psychiatric or physical co-morbidity. Subgroup analysis reveals that Current Psychiatric Morbidity or a History of Psychiatric Morbidity appeared to reduce the effect size (except for the 72 mg dose in Study 3013). This weakens the external validity of the studies.

There is some evidence available of efficacy up to 13 weeks but the long-term withdrawal study lacked sufficient power. There is some long-term efficacy data from a published paper by Rösler *et al.* 2009 but it is not detailed enough to fully understand the population being studied and hence evaluate the results.

There are concerns regarding the treatment of missing data and the definition of responders.

Safety:
Several adverse events are of concern:

- Psychiatric adverse events (e.g. anxiety, depression, aggression, hostile behaviour and suicidality)
- Cardiovascular adverse events (e.g. tachycardia and rise in blood pressure)
- Weight loss (anorexia)

DAY 85 COMMENTS FROM SWEDEN

Although we think there is an unmet need for an approved psychostimulant drug for treatment of adult ASDHD we agree overall with the RMS assessment and the conclusion that the present application is currently not approvable. We have no additional potential serious risks to public health or other concerns, but would like to give some comments on the potential serious risks to public health.

- With respect to short-term efficacy our interpretation the RMS assessment is that an effect can be considered demonstrated provided that robustness of the primary analysis is shown in adequate responder analyses. We share this view.
- There is no reason to believe that the overall study results should not be valid for the proposed restricted indication.
- We agree that more detailed information from the study by Rösler could provide valuable information for the evaluation of maintenance of effect.

DAY 85 COMMENTS FROM IRELAND

Ireland agrees with the conclusions of the RMS AR.

DAY 85 COMMENTS FROM GERMANY

DE has the following comments regarding the ERA:

Environmental Impact / Environmental risk assessment

Non clinical aspects
This Type II Variation is to apply for an additional therapeutic indication of Methylphenidat for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Due to this new indication a significant increase in extended use and consequently an increased release into the environment may result.
The applicant provided an environmental risk assessment (ERA) according to the EMEA guideline (EMEACHMP/SWP/4447/00) for Concerta in which data were only cited and study reports were not provided. The applicant concluded that the use of Concerta will not pose a risk to the environment.

Assessors comments:

UBA does not agree with the Rapporteur because no study reports were presented. In order to assess the presented Environmental Risk Assessment of Concerta the cited studies reports should be provided.
Furthermore, we would like to stress that the logPow as stated in the ERA was determined with the Methylphenidat hydrochloride. It is well known that Methylphenidat is highly soluble in lipids. Therefore, the presented logPow might underestimate the risk of bioaccumulation. Hence, the applicant is asked to discuss if the n-octanol/water partition constant with undissociated Methylphenidat only will result in a higher log Pow.

DAY 55 COMMENTS FROM ITALY

Product name:	**CONCERTA**
Procedure No.:	UK/H/544/01-03/II/056
Dosage form and strength:	Prolonged Release Tablets 18mg, 27mg, 36mg, 54mg
Date:	29/7/2010

We agree with the conclusion of the RMS, the variation is not approvable.

Concerned Member State Comments on Preliminary Variation Assessment Report

1. This document is sent by:

CMS	The Netherlands
Contact point, project team leader (name) phone email	Hans van Gompel ☎ + 31 70 356 7423 💻 ah.v.gompel@cbg-meb.nl
Assessors, if applicable (name e-mail, phone)	Dr. Liesbeth Rook (PK) Dr. Tamar Wohlfarth (Clinical) Dr. Ineke Crijns (PhVig.)
Date/Day of procedure	30 July 2010 / Day 100 comments

2. This document concerns:

Name of the product in the RMS	Concerta XL
Name of the active substance	Methylphenidate
Applicant	Janssen – Cilag
Procedure number	UK/H/0544/001-004/II/56
Deadline for comments	**29 July 2010**

3. Comments, general

3.1 Assessment of the RMS

We fully endorse the RMS assessment, and have no further comments ☐

We endorse the RMS assessment, but also have additional comments ☒

We do not fully endorse the RMS assessment, and have other comments ☐

3.2 Conclusions on the product

Our conclusion is that the product is

Approvable ☐

Approvable, provided that satisfactory responses are given to the list of questions and/or the SmPC/PL/labelling is changed according to the comments ☐

Non-approvable ☒

3.3. List of Questions/Proposed conditions for marketing authorisation

We have grounds of potential serious risks to public health on the following part of the assessment report not already raised by the RMS

Quality ☐

Non-Clinical ☐

Clinical ☒

SmPC ☐

PL ☐

Labelling ☐

We have additional points for clarification on the following part of the assessment report

Quality ☐

Non-Clinical ☐

Clinical ☐

SmPC ☐

PL ☐

Labelling ☐

Module 1 – Application related comments (including product name) ☐

4. Potential serious risk to public health

We fully support the position of the RMS that the B/R of Concerta in the proposed indication is negative but would argue that given uncertainties and controversies surrounding the diagnosis of ADHD in adults and the fact that most adults in the studies were diagnosed after the age of 18, the nature of study population is unclear and that this is the main problem of this dossier. In addition, long-term efficacy was not demonstrated. The lack of demonstrated efficacy coupled with the safety issues, especially cardiovascular safety (potential long-term effects of increase in BP),abuse potential, and psychiatric/aggression AEs render the B/R negative for the proposed indication.

We therefore especially support the second bullet-point from clinical Potential serious risk to public health (PSRPH) 1, but do not consider this issue can be solved by further clarification.

The concerns regarding safety are supported and are considered to be PSRPHs. Additionally the misuse/abuse potential of methylphenidate is considered a major safety concern: in combination with the concerns regarding the reliability of the diagnosis, adults may try to get diagnosed for ADHD to retrieve methylphenidate in a legalised way.