Mutual Recognition Procedure

Type II variation
Final Variation Assessment Report

ConcertaXL
Methylphenidate

UK/H/0544/001/II/056

Marketing Authorisation Holder: Janssen-Cilag

Date: 26/4/11

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	
Names of the assessors	**Nonclinical:** **Name(s):** Tel: Email: **Clinical:** **Name(s): SC Morgan** Tel: #44 203 080 6027 Email: Susan.morgan@mhra.gsi.gov.uk

Variation Procedure Start Date	5/5/10
Date of Final Variation Assessment Report (day 90)	26/4/11
Day 120	26/5/11
Deadline for Comments by CMS	16/5/11

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), for the continuation of treatment in ***adults with ADHD***, for the following proposed changes:

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

However, should the MAH accept the RMS's proposals for revised wording for sections 4.2, 4.8 and 5.1 as proposed in this report, a positive outcome would be recommended.

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: The more conservative reanalysis of Studies 3002, 02-159 and 3013 only demonstrates efficacy over placebo for study 3002 (5 week duration), the results of study 02-159 (7 week) are now borderline and study 3013 (13 week) is now clearly a failed study. 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 and long-term cardiovascular effects in the adult population and the abuse potential of crushed Concerta tablets.

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.

Conclusion The efficacy for the proposed indication has not been clearly demonstrated and the MAH have removed this and have instead included the data in sections 4.2, 4.4, 4.8 and 5.1. The currently proposed SmPC changes are not acceptable for the following reasons:

- Sections 4.2 and 4.4 The posology is not acceptable as it encourages off label use due to:

- no mention of a trial of therapy withdrawal
- unnecessary repetition of wording permitting continued treatment in to adulthood (applies to Sections 4.2 and 4.4)

- Section 4.8 A single ADR table should be accompanied by the appropriate footnotes for the adult data.
- Section 5.1 The wording describing the adult data should be amended to reflect the more conservative analysis.

II.1 Scope of the variation

The MAH had applied for a new indication of ADHD in adults who were first diagnosed in childhood but whose symptoms have persisted into adulthood. This has now been amended to the changes described above with no change to Section 4.1.

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III. 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.

IV. ASSESSMENT OF RESPONSE TO RSI

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).**

Addressed in sections 2.3-2.7. Points 2.4-2.7 are considered addressed by the further analysis and withdrawal of the indication. Point 2.3 is considered partially resolved. There are two outstanding efficacy issues relating to the proposed SmPC wording which could be addressed through different wording to Sections 4.2 and 5.1 of the SmPC as detailed in the Conclusion to this report. **Point partially resolved.**

- **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.**

Not addressed as MAH are no longer applying for previously proposed indication. **Point resolved through removal of proposed indication.**

- **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.**

Not addressed as MAH are no longer applying for previously proposed indication. **Point resolved through removal of proposed indication.**

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).

Addressed in sections 2.8-2.12 and 2.25. These are partially addressed see 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.

The applicant has clarified how the missing data was handled in the trials, and has provided a more conservative analysis as requested. Although the applicant was asked to use Dunnett's test to control for multiple doses, the applicant has instead chosen to use the Sidak test. This is acceptable.

The applicant has also clarified how many patients had missing data per arm as requested. For study 3002, statistical significance of all doses compared to placebo has been maintained, but with a much weaker statistical evidence of efficacy, and with much smaller point estimates. For example, taking the 72 mg dose, the initial (incorrect) analysis had a point estimate for efficacy of 59.6%, with placebo having a 27.4% rate, the difference being 32.2%.

When missing data is imputed as failure which is appropriately conservative, the point estimates are now 26.0 and 50.0 respectively, the difference being 24%. It is clear that the magnitude of the efficacy is being driven by the method used to handle the missing data and additionally that the use of LOCF is not appropriately conservative and could bias in favour of active treatment.

For Study 02-159, the requested analysis yields a p-value of 0.055 at the 2-week time-point, marginally failing to reach statistical significance. In the strictest interpretation this could be seen as a failed trial.

For Study 3013 the 13-week time point data is mixed. The initial treatment differences between active and placebo were 10.2% and 18.7% for the 54 mg and 72 mg doses respectively (with only the 72 mg dose being significant, p=0.0098). When using the more appropriate missing as failure analysis, these point estimates become 11.6% and 13.8% respectively, with neither attaining anything near to significance (p=0.274 and p=0.198 respectively). This is clearly a failed trial.

The totality of the data is therefore weak, with one successful, one borderline failure and one clearly failed trial. One key difference is of course that the efficacy measurements were taken at different time points. It

is also of note that the point estimates are always positive and broadly favours Concerta, although they are not as impressive as the initial analysis suggested. The proposed wording in section 5.1 of the SmPC states that "Generally, efficacy of CONCERTA XL was demonstrated in a dose range of 18 to 72 mg/day." The MAH has withdrawn the proposed indication but still wish to add a claim in Section 5.1 which has not been clearly substantiated. The only study that has shown robust efficacy is the 5 week study with the longer term 7 and 13 week failing to consistently demonstrate this. Although numerically the point estimates were all positive this is not assessed as robust enough data to support the claim made in section 5.1. The following wording is considered to reflect the data more appropriately:

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. *Some short-term efficacy has been demonstrated for CONCERTA XL in a dosage the range of 18 to 72mg/day but this has not been consistently shown beyond 5 weeks.*
Point partially addressed.

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.

The applicant has provided the requested analysis. It is noted that a larger proportion of patients who dropped out on active were considered 'responders' in the initial analysis, which helps to clarify the results seen in Question 3 and discussed there.
The point is considered resolved as the MAH has withdrawn the proposed indication.

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.

The applicant has provided the requested analyses. It is of note that in general the response rate is higher in Concerta than in placebo. It is also of note that although the numbers are small there seems to be a better maintenance of response (proportion of patients who initially respond who remain responders at the final visit) in the placebo group. Although interesting, it is not considered that this data is conclusive due to the numbers involved.
The point is considered resolved as the MAH has withdrawn the proposed indication.

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.

The applicant has provided the requested analyses that provide the reassurance that any efficacy is not driven by a *post hoc* inclusion in the statistical model. Although a missing as failure rather than an LOCF model would have been preferred, it is unlikely that further re-analyses would change the interpretation.
The point is resolved.

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.

The applicant has again presented the requested analysis, with a clear visual differentiation of the patient population into early and late diagnosis, and an appropriate age classification of <7, 7-18 and >18.

Balance across all arms of the trials was achieved and there is no evidence that there is an interaction. Accordingly no discussion of this effect (as there is no evidence that there is one) is required.
Point Resolved

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.

The MAH have responded by considering:

- The level of response that poses a risk in adults
- Presentation of Clinical Data relating to vital signs increases.

8.1 Level of response that poses a risk in adults

GU et al High BP and CV MR among US adults: III National Helath and Nutrition Examination Survey
NHANES III study (1988-1994) in adults compared CV mortality sik between hypertensives, prehypertensives to normotensives. Individuals with a mean systolic BP120 mm Hg and a mean diastolic BP80 mm Hg were classified as having normal BP. Individuals with a mean systolic BP between 120 and 139 mm Hg or a mean diastolic BP between 80 and 89 mm Hg were classified as having prehypertension. Individuals with a mean systolic BP > 140 mm Hg or a mean diastolic BP > 90 mmHg were classified as having hypertension. Compared with normotension, the relative risks of CVD mortality were 1.23 (95% confidence interval [95% CI] 0.85–1.79,) for prehypertension, 1.64 (95% CI 1.11–2.41) for hypertension,1.74 (95% CI 1.28–2.49,) for uncontrolled hypertension, and 1.15 (95% CI 0.79–1.80) for controlled hypertension..

Menotti The role of a baseline casual blood pressure measurement and of blood pressure changes in middle age in prediction of cardiovascular and all-cause mortality occurring late in life: a cross-cultural comparison among the European cohorts of the Seven Countries Study
The effect of a 20mmHG increase in systolic BP could be detected on CV MR in subsequent decades with increases of 10mmHG having an impact on all deaths:

The relative risk for 20 mmHg of SBP (and its 95% confidence intervals) in predicting CVD deaths was 1.65 (1.54–1.77) for the first 10-year block; 1.33 (1.24–1.42) for the second block; and 1.22 (1.13–1.31) for the last 10-year block. The corresponding levels of ALL deaths were 1.41 (1.34–1.49), 1.26 (1.19–1.32) and 1.11 (1.05–1.17). Changes in SBP during 10 years (˜-SBP) added predictive power to baseline measurements in a direct and significant way, with a relative risk for a change of 10 mmHg of 1.14(1.10–1.17) for CVD deaths and 1.11 (1.09–1.13) for ALL deaths.

Tverdal 2008 Heart rate and mortality from cardiovascular causes: a 12 year follow-up study of 379 843 men and women aged 40–45 years

A prospective study of participants in cardiovascular surveys that were carried out in 1985–1999 and covered men and women aged 40–45 years in all counties except the capital, Oslo. In total, 180 353 men and 199 490 women aged 40–45 years without cardiovascular history or diabetes accrued 4 775 683 years of follow-up. There was a positive and graded association between heart rate and mortality from all causes, as well as between heart rate and deaths from cardiovascular disease (CVD), ischaemic heart disease, and stroke. However, these associations were greatly reduced when we adjusted for the main risk factors of disease. The hazard ratios for any death were reduced from 3.14 to 1.82 for men (95% CI, 1.62–2.04) and from 2.14 to 1.37 for women (95% CI, 1.19–1.59), when we compared 95 b.p.m. with 65 b.p.m. The corresponding figures for CVD were a reduction from 4.79 to 1.51 for men (95% CI, 1.21–1.87) and

from 2.68 to 0.78 for women (95% CI, 0.53 1.15). The authors conclude that a raise in pulse rate is likely to be a marker rather than an independent risk factor for cardiovascular disease.

Assessor' comments However there are others that consider raised pulse rate as a marker for increased sympathetic activity which is known to cause harm e.g Palatini in a review article refers to the association with increases risk of insulin resistance (Palatini P Heart rate as a cardiovascular risk factor: do women differ from men? Ann Med 2001;33:213-221).

Subjects with sustained elevated blood pressure defined as subjects with SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg for at least 3 consecutive postbaseline visits are provided for the pooled Studies 3002 DB and 3013 , Study 02-159 and the pooled open-label studies . The studies are presented in this fashion since the former had postural readings and the latter just sitting observations. The percentage of subjects in each treatment group experienced sustained elevated blood pressure was numerically higher for methylphenidate in both analyses: pooled Studies 3002 DB and 3013 (6.1% placebo, 7.8% MPH) and Study 02-159 (0.0% placebo, 1.1% MPH). For the pooled open-label studies, 4.7% of the subjects experienced sustained elevated blood pressure. For sustained elevated pulse over 100 there were no cases in pooled Studies 3002 DB and 3013, for Study 02-159 (0% placebo, 1.1% MPH). In the OL studies 0.4% (n=975) had a sustained increase in pulse >100bpm.

Table 25. Studies 3002 DB and 3013: Number (%) of Subjects With Increase Greater Than5mmHg at Any Postbaseline Blood Pressure Measurement
(CONCERTA EU SCS - MHRA RFI: Double-Blind Safety Analysis Set)

	-- Placebo --	ALL CONCERTA
SYSTOLIC BLOOD PRESSURE (mmHg) SUPINE		
Measurements, n (%)		
N	192	477
Increase > 5 mmHg	99 (51.6)	282 (59.1)
DIASTOLIC BLOOD PRESSURE (mmHg) SUPINE		
Measurements, n (%)		
N	192	477
Increase > 5 mmHg	87 (45.3)	257 (53.9)

Note: Supine findings are from the double-blind portion of Studies 3002 and 3013.
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Table 26. Study 02-159: Number (%) of Subjects With Increase Greater Than 5 mmHg at Any Postbaseline Blood Pressure Measurement
(Study 02-159: Safety Analysis Set)

	-- Placebo --	ALL CONCERTA
SYSTOLIC BLOOD PRESSURE (mmHg) SITTING AVG		
Measurements, n (%)		
N	115	102
Increase > 5 mmHg	56 (48.7)	64 (62.7)
DIASTOLIC BLOOD PRESSURE (mmHg) SITTING AVG		
Measurements, n (%)		
N	115	102
Increase > 5 mmHg	50 (43.5)	57 (55.9)

Note: Sitting findings are from the double-blind portion of Study 02-159.

Table 28. Studies 3002 DB and 3013: Number (%) of Subjects With Increase Greater Than 10 mmHg at Any Postbaseline Blood Pressure Measurement
(CONCERTA EU SCS - MHRA RFI: Double-Blind Safety Analysis Set)

	-- Placebo --	ALL CONCERTA
SYSTOLIC BLOOD PRESSURE (mmHg) SUPINE		
Measurements, n (%)		
N	192	477
Increase > 10 mmHg	64 (33.3)	192 (40.3)
DIASTOLIC BLOOD PRESSURE (mmHg) SUPINE		
Measurements, n (%)		
N	192	477
Increase > 10 mmHg	44 (22.9)	115 (24.1)

Note: Supine findings are from the double-blind portion of Studies 3002 and 3013.
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Table 29. Study 02-159: Number (%) of Subjects With Increase Greater Than 10 mmHg at Any Postbaseline Blood Pressure Measurement
(Study 02-159: Safety Analysis Set)

	-- Placebo --	ALL CONCERTA
SYSTOLIC BLOOD PRESSURE (mmHg) SITTING AVG		
Measurements, n (%)		
N	116	110
Increase > 10 mmHg	33 (28)	31 (28)
DIASTOLIC BLOOD PRESSURE (mmHg) SITTING AVG		
Measurements, n (%)		
N	116	110
Increase > 10 mmHg	20 (17)	27 (25)

Note: Sitting findings are from the double-blind portion of Study 02-159.
Source: Summary of Clinical Safety, Appendix App5.1.4.

Table 34. Studies 3002 DB and 3013: Number (%) of Subjects Presenting at Least One Treatment-Emergent Postbaseline Potentially Clinically Important Blood Pressure Measurement in Subjects With Medical History of Hypertension (CONCERTA EU SCS - MHRA RFI: Double-Blind Safety Analysis Set)

	-- Placebo--	ALL CONCERTA
SYSTOLIC BLOOD PRESSURE (mmHg) SUPINE		
Measurements, n (%)		
N	14	30
At Least One PCI Measurement	10 (71.4)	18 (60.0)
Above PCI Range	10 (71.4)	18 (60.0)
DIASTOLIC BLOOD PRESSURE (mmHg) SUPINE		
Measurements, n (%)		
N	14	30
At Least One PCI Measurement	10 (71.4)	15 (50.0)
Above PCI Range	10 (71.4)	15 (50.0)

Note: Supine findings are from the double-blind portion of Studies 3002 and 3013. Only subjects with a medical history of hypertension or a pre-treatment hypertension-related adverse event are included. Does not include study 02-159 as these measurements were sitting.

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Table 35. Study 02-159: Number (%) of Subjects Presenting at Least One Treatment-Emergent Postbaseline Potentially Clinically Important Blood Pressure Measurement in Subjects With Medical History of Hypertension (Study 02-159: Safety Analysis Set)

	-- Placebo--	ALL CONCERTA
SYSTOLIC BLOOD PRESSURE (mmHg) SITTING AVG		
Measurements, n (%)		
N	12	5
At Least One PCI Measurement	3 (25.0)	0
Above PCI Range	3 (25.0)	

No subjects had a diastolic blood pressure measurement above the potentially clinically important range in either the CONCERTA or placebo treatment groups.

Note: Sitting findings are from the double-blind portion of Study 02-159. Only subjects with a medical history of hypertension or a pre-treatment hypertension-related adverse event are included.

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Potentially clinically important (PCI) rises (defined as >140/90) did not show a signal but the denominators are very small. This is not surprising considering the entry criteria and age of population studied.

Assessor's comments

Data from longitudinal studies in the medical literature appear to show that rises in 10mmHG are associated with increase of all cause mortality. Increases in pulse rate were also associated with an increase in MR but largely disappeared when controlled by disease process in one analysis by Tverdal. This is not reassuring since this may be the mechanism through which diseases such as DM cause an increased an increased cardiovascular disease risk.

From the MPH data there is a signal in terms of an increase in those experiencing a raised BP >5mmHG or 10mmHg systolic. Interestingly in those with a diagnosis of hypertension these patients experienced less variability in their BP measurements than those on placebo, implying that treatment prevents transient rises in BP. It would have been more helpful to interpret the significance of the signal of transient rises in BP on MPH by a further analysis comparing those with a consistently raised systolic/diastolic pressure of 5mmHg/10mg Hg over baseline rather than just single measurements. The MAH also presented data from RCT and OL studies on numbers of subjects have at least 1 reading of >130 or >85 including subgroup analyses with those with baseline hypertension and prehypertension. The numbers were very small and as stated previously it is difficult to interpret the significance of isolate readings. There is a signal from the RCTs that there are more elevations in systolic and diastolic BP in subjects on MPH compared to placebo but this is based on any reading post-baseline rather than consistent elevation.

Form the previously submitted data there is a signal that sustained elevations of BP SBP $\geq$ 140 mmHg and/or DBP $\geq$ 90 mmHg occur more frequently with subjects on MPH: pooled Studies 3002 DB and 3013 (6.1% placebo, 7.8% MPH) and Study 02-159 (0.0% placebo, 1.1% MPH). For the pooled open-label studies, 4.7% of the subjects experienced sustained elevated blood pressure. For sustained elevated pulse over 100 there were no cases in pooled Studies 3002 DB and 3013, for Study 02-159 (0% placebo, 1.1% MPH). In the OL studies 0.4% (n=975) had a sustained increase in pulse >100bpm.

Monitoring is already in section 4.4 of the SmPC and continued monitoring will part of the PSURs. **Point resolved.**

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.**

Suicidality

There was no validated instrument used in the studies to assess suicidal ideation. There are 3 cases of suicidal ideation reported (1 subject in Study 3013 and 2 in OL Study 12-304) one of which was associated with a suicide attempt. The narratives have been provided. On case was associated with depression treated with venlafaxine and deemed possibly related to study medication. The individual had a history of a previous suicide attempt. The second case (Subject A10056, a 29-year-old woman, in Study 3013) had a history of MDD but had been asymptomatic for a year. Anxiety, irritability and panic attacks were reported on starting the medication. These increased in severity when the study medication was increased, suicidal ideation was noted on 15th April which culminated in a hospital admission with an overdose 5 days later. The study medication had not been stopped despite the increased in symptoms with an increase in dose and suicidal ideation being noted at the last visit. This is a cause of concern regarding this subject's management within the study. The MAH will be asked to clarify the management of this case. The third case had been on MPH for over 1 year and on a stable dose for more than 6 months. The depression and suicidal ideation were in relation to recurrence of her breast cancer.

Output DAE19D13: Number and Percent of Subjects With an Adverse Event of Special Interest: Aggression
by Seriousness, Severity, Outcome and Treatment Group - Double-Blind and Overall CONCERTA Analysis Sets.

Identified Risk: Aggression*	DOUBLE-BLIND (PLACEBO N=309)	DOUBLE-BLIND (CONCERTA N=596)	OVERALL CONCERTA (N=1369)
Frequency**			
N (%)	17 (5.5)	71 (11.9)	202 (14.8)
Odds Ratio		2.3	
95% confidence interval***		1.3 to 4.3	
Seriousness/outcomes****			
Resulted in Death	0	0	0
Was Serious	0	0	0
Discontinued Treatment	0	13	30
Resolved/Recovered/Recovered From AE	16	65	169
Recovered With Residual Effects	0	0	0
Continuing/Not Yet Recovered	1	6	33
Severity****			
Mild	10	31	91
Moderate	5	30	92
Severe	2	10	19

* MedDRA preferred terms searched for this risk are provided in Annex 4
** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Aggression; The subject is counted only once regardless of the number of events or the number of occurrences.
*** The 2-sided exact 95% CI in odds ratio is of Concerta to the comparator.
**** Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event and if more than one least resolved), and Severity (most severe).

Output DAE19D13: Number and Percent of Subjects With an Adverse Event of Special Interest: Aggression
by Seriousness, Severity, Outcome and Treatment Group - Double-Blind and Overall CONCERTA Analysis Sets.

Identified Risk: Aggression*	DOUBLE-BLIND (PLACEBO N=309)	DOUBLE-BLIND (CONCERTA N=596)	OVERALL CONCERTA (N=1369)
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N (%)	17 (5.5)	71 (11.9)	202 (14.8)
Odds Ratio		2.3	
95% confidence interval***		1.3 to 4.3	
Seriousness/outcomes****			
Resulted in Death	0	0	0
Was Serious	0	0	0
Discontinued Treatment	0	13	30
Resolved/Recovered/Recovered From AE	16	65	169
Recovered With Residual Effects	0	0	0
Continuing/Not Yet Recovered	1	6	33
Severity****			
Mild	10	31	91
Moderate	5	30	92
Severe	2	10	19

* MedDRA preferred terms searched for this risk are provided in Annex 4
** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Aggression; The subject is counted only once regardless of the number of events or the number of occurrences.
*** The 2-sided exact 95% CI in odds ratio is of Concerta to the comparator.
**** Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event and if more than one least resolved), and Severity (most severe).

Assessor's comments

Psychiatric adverse events: subjects demonstrating suicidal ideation (2) or behaviour (1 attempted suicide) were few (n=3 0.2.%). The MAH have not made an attempt to analyse any cases of potential self-harm. **Aggression.** There is a clear signal around aggression with an OR 2.3 no CI included (MPH 11.9% and Placebo 5.5%). Additional medication was seldom used to control the aggression (6/273 occasions). Over 10% of aggressive episodes were considered as serious in the DB studies. During the double-blind

studies, 13 of the 596 subjects receiving MPH (2.2%) were withdrawn for aggression-related adverse events (vs.0% receiving placebo)
This is already has an SmPC warning. These should be monitored in future PSURs.

The MAH will be asked further details on the handling of Subject A10056, a 29-year-old woman, in Study 3013.

Point resolved.

10. Further discussion on the implications of weight loss in adults.
The MAH presented data according to BMI categories of Underweight, Normal, Overweight and Obese weight loss occurred in these groups (MPH vs placebo) 1 (7.7%) vs 0%, 17 (7.1%) vs 0 (0%), 33 (16.2%) vs 3 (2.9%) and 21 (19.1%) vs 5 (6.5%) respectively lost at least 7% of their BMI. In the Open Label studies 1.7% had to have their medication adjusted due to weight loss. There is a lack of detail over when the majority of the weight loss occurred and the trajectory of the change.

Assessor's comments
As expected those on methylphenidate lost more weight than on placebo with 0.7% requiring withdrawal from the study. The majority of the subjects losing weight were in the overweight or obese groups but this is a cause of concern fro those in the underweight and lower ends of the normal weight groups. Only 3 subjects switched status from normal weight to underweight though. There should be wording in section 4.4 requiring weight to be monitored in patients who have stopped growing in they have a low BMI.
Point not resolved.

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).

The MAH state that although the crushed Concerta AUC was equivalent to Ritalin the Cmax and AUC 0-2 hrs was less for the crushed Concerta, thus reducing the abuse potential. No figures were quoted in the response document to support these statements but these were supplied in the original application. They also comment on the fashion that MPH induces dopamine release is less likely to induce abuse as it is slow tonic firing not fast, phasic firing. It is assessed that although the figures adjusted for dose are slightly lower for crushed Concerta than Ritalin the difference is relatively small and that crushing Concerta increases the rate of absorption as measured by AUC0-2 and Cmax in comparison to intact Concerta. The abuse potential for crushed Concerta is likely to be similar to the IR formulation of MPH. This point is considered resolved with the removal of the proposed indication. **Point resolved.**

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.

The MAH refer to the work done for the Article 31 referral 27/5/09. **Point resolved.**

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.

The MAH have not addressed this as they are no longer applying for an indication. The SmPC has instructions to monitor these in all patients receiving Concerta. **Point resolved.**

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.

The MAH have not addressed this as they are no longer applying for an indication. **Point resolved.**

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.

The MAH have not addressed this as they are no longer applying for an indication. This needs to be stated for the proposed continuance of therapy, see proposed wording for section 4.2 below. **Point not resolved.**

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.

The MAH have not addressed this as they are no longer applying for an indication. **Point not resolved.**

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

The MAH have not addressed this as they are no longer applying for an indication. These will be presented in future PSURs. Monitoring weight at those at risk has been dealt with above. **Point resolved.**

RMP Concerns

The MAH have not addressed the majority of these points as they are no longer applying for an indication or they are being addressed through the PSUR work sharing procedure UK/H/PSUR/0068/002. All points are considered resolved as far as this assessment is concerned. **Points resolved.**

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. A similar request was received under the PSUR work sharing and a response is currently being assessed.

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.

Three case of serious unresolved adverse events were presented. Two were psychiatric related which will be captured in future PSURs and the third was a recurrence of breast cancer which is unlikely to be related to study medication. This should be addressed through future PSURs. **Point resolved.**

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 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 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, comorbidities, 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

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)

Assessor's comments
The robustness of the diagnosis, the weak external validity of the studies has been addressed by the MAH amending their proposed wording for the SmPC. They are no longer claiming an adult indication but one of continued treatment in some cases as follows:

The missing has been handled as treatment failure no which reduces the size of the efficacy. Seen. Please see response 3.

The safety concerns have been addressed above.

DAY 85 COMMENTS FROM SWEDEN
Although we think there is an unmet need for an approved psychostimulant drug for treatment of adult ADHD 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.

Assessor's comments
The further analyses demonstrate only borderline efficacy and further long-term data has not been forthcoming, thus a new indication cannot be supported on this data. The MAH have dropped their

proposed new claim for section 4.1 but have proposed an amended wording for section 4.2. This is assessed as not approvable but alternative wording by the RMS is proposed. Please see conclusion below.

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 Methylphenidate 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.
Assessor's 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 Methylphenidate hydrochloride. It is well known that Methylphenidate 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 Methylphenidate only will result in a higher log Pow.

Assessor's comments
As a new indication is no longer being proposed and thus no significant increase in usage, an environmental assessment is no longer required.

COMMENTS FROM ITALY, BELGIUM, DENMARK, IRELAND AND SPAIN

Support PVAR.

Assessor's comments

Please see the full response assessment and conclusion.

DAY 55 COMMENTS FROM NETHERLANDS

"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."

Assessor's comments
The MAH are no longer applying for a new indication. The further analyses do not support this. The new proposed wording for section 4.2 is not assessed as adequately supported and different wording is proposed. Please see the conclusion below.

Day 85 Comments From France

Comment:
"Module IV/Preclinical part
The 4.6 section as proposed by the applicant is considered appropriate and addition of animal data regarding transfer in the milk is not considered necessary due to occurrence of clinical data (Spigset O, Brede WR, Zahlsen K. Excretion of methylphenidate in breast milk. Am J Psychiatry. 2007 Feb;164(2):348 and Hackett LP, Kristensen JH, Hale TW, Paterson R, Ilett KF. Methylphenidate and breast-feeding. Ann Pharmacother. 2006 Oct;40(10):1890-1). The PIL as proposed by the applicant is also considered adequate.
The other concern #11 in relation to the creation of a pregnancy registry as proposed by the UK is considered questionable: indeed, spina bifida signal appear to be only raised by non clinical data (Teo et al Birth Defect Research (part B) 68(2):162-171, 2003 / Beckman et al, Birth Defect Research (part B) 83(5):489-501, 2008). Spina bifida with malrotated hindlimbs has been observed in 2 foetuses (in two separate litters among 18) at one dose level (200 mg/kg/day, AUC=776 ng.h/ml d-methylphenidate and 263 ng.h/ml l-methylphenidate) only in the rabbit. Such effect was not observed at 300 mg/kg/day nor at 200 mg/kg/day in the study performed by Teo et al (corresponding to a lower plasmatic exposure that could explain the lack of malformative effect). Only squeletal variations at maternotoxic levels were observed in the rat at higher exposure levels (until 3678 ng.h/ml d-methylphenidate and 904 ng.h/ml l-methylphenidate in AUC). To our opinion, this is already reflected in the 4.6 section with a non recommendation of use during pregnancy and a registry is not generally requested in this case.
Module 5/Clinical part
Efficacy
- We agree with the RMS that the short term efficacy seems demonstrated in the studied population; however an analysis at the final visit considering missing patients as failures should be provided for the three pivotal studies.
- **The MAH presented for Study 02-159 an analysis by patients age but did not provide an analysis by age of ADHD diagnosis. This latter analysis was presented only for studies 3002 and 3013.**

The MAH should provide a meta-analysis (studies 02-159, 3002 and 3013) for:
- the interaction between treatment effect and patients age; and
- the interaction between treatment effect and age of ADHD diagnosis.
- Because of the chronic course of ADHD, a demonstration of long term efficacy and safety has to be established. The results of the withdrawal study 3004 cannot be interpreted taking into account the small number of patients. The Company should propose a study aiming to further substantiate the long term benefit risk balance in adults.

- Study 3002 showed for all 3 doses an improvement in functioning supported by CGI but not Q-LES-Q and GAE. Sheehan Disability Scale (SDS) showed significant improvement for 18 and 72 mg but not for 36 mg.
In study 02-159, there was at 72 mg significant improvements in CGI, ADHD Impact Module for Adults (except symptoms on daily life) but not for SDS ; the 54 mg dose did not show positive results on CGI, SDS and AIM-A for living, communication and daily life).
Further discussion on the effect of Concerta on patient functioning, that is the ultimate goal of treatment should be provided as the results seem inconsistent.
However, from a clinical point of view, it should be discussed in depth whether the restriction of the indication to only those < 20% patients who were diagnosed in childhood may be excessive since it could unduly deprive the other 80% patients with symptoms during childhood of the drug benefit.
- Safety
The high frequency of psychiatric adverse events, in the overall population studied, is of concern. In France, in study 3013, additional exclusion criteria were planned (marked anxiety and tension, severe depression, psychotic symptoms, or suicidal tendencies).
- RMP assessment
Routine pharmacovigilance is not sufficient to monitor Drug Abuse and Drug dependence. The MAH should put in place proactive pharmacovigilance measures."

-

Assessor's comments The MAH have removed their proposed indication addressing the above points since the further analyses do not robustly support the previously proposed indication. Please see above.

Overall Conclusion

Efficacy
The more conservative analyses of the data submitted in this response demonstrate for study 3002, statistical significance of all doses compared to placebo has been maintained, but with a much weaker statistical evidence of efficacy, and with much smaller point estimates. For example, taking the 72 mg dose, the initial (incorrect) analysis had a point estimate for efficacy of 59.6%, with placebo having a 27.4% rate, the difference being 32.2%. When missing data is imputed as failure which is appropriately conservative, the point estimates are now 26.0 and 50.0 respectively, the difference being 24%. It is clear that the magnitude of the efficacy is being driven by the method used to handle the missing data and additionally that the use of LOCF is not appropriately conservative and could bias in favour of active treatment.

For Study 02-159, the requested analysis yields a p-value of 0.055 at the 2-week time-point, marginally failing to reach statistical significance. In the strictest interpretation this could be seen as a failed trial.

For Study 3013 the 13-week time point data is mixed. The initial treatment differences between active and placebo were 10.2% and 18.7% for the 54 mg and 72 mg doses respectively (with only the 72 mg dose being significant, p=0.0098). When using the more appropriate missing as failure analysis, these point estimates become 11.6% and 13.8% respectively, with neither attaining anything near to significance (p=0.274 and p=0.198 respectively). This is clearly a failed trial.

The totality of the data is therefore weak, with one successful, one borderline failure and one clearly failed trial. One key difference is of course that the efficacy measurements were taken at different time points. It is also of note that the point estimates are always positive and broadly favours Concerta, although they are not as impressive as the initial analysis suggested. The MAH has withdrawn the proposed indication but still wish to add a claim in Section 5.1 which has not been clearly substantiated. The only study that has shown robust efficacy is the 5 week study with the longer term 7 and 13 week failing to consistently demonstrate this. Although numerically the point estimates were all positive this is not assessed as robust enough data to support the claim made in section 5.1 (see below).

Safety

Cardiovascular concerns Data from longitudinal studies appears to show that raises in 10mmHg increases the risk of all cause mortality. Increases in pulse rate were also associated with an increase in MR but largely disappeared when controlled by disease process. This is not reassuring since this may be the mechanism through which DM. There is a signal in terms of an increase in those experiencing a raised BP >5mmHG or 10mmHg systolic. Interestingly in those with a diagnosis of hypertension these patients experienced less variability in their BP measurements than those on placebo, implying that treatment prevents transient rises in BP. The MAH also presented data from RCT and OL studies on numbers of subjects have at least 1 reading of >130 or >85. There is a signal from the RCTs.

Psychiatric adverse events: subjects demonstrating suicidal ideation (2) or behaviour (1 attempted suicide) were few (n=3 0.2.%). The MAH have not made an attempt to analyse any cases of potential self-harm. **Aggression.** There is a clear signal around aggression with an OR 2.3 no CI included (CONCERTA 11.9% and Placebo 5.5%). This is already has an SmPC warning.

Weight loss There is a clear signal for weight loss, whilst this may not be over concern in those who are overweight or obese it is a concern at low BMIs.

The reanalysis of the data which treats missing subjects as failures has produced short-term efficacy results that have borderline significance. When this is taken in the context that this was a retrospective subgroup analysis of the data and with the lack of long-term efficacy the previously proposed indication is not approvable. The MAH have recognised this and proposed new wording for the SmPC:

In adolescents whose symptoms persist into adulthood and who have shown clear benefit from treatment, it may be appropriate to continue treatment into adulthood. However, start of treatment with CONCERTA XL in adults is not appropriate.~~Methylphenidate is not licensed for use in adults in ADHD. Safety and efficacy have not been established in this age group.~~

The following wording is viewed as more appropriate:

Adults

If treatment withdrawal has not been successful when an adolescent has reached 18 years of age continued treatment into adulthood may be necessary. The need for further treatment of these adults should be reviewed regularly and undertaken not less frequently than 2 years.

Safety and efficacy have not been established for the initiation of treatment in adults or the routine continuation of treatment beyond the age of 18 years of age.

The other references to continued treatment in sections 4.2 and 4.4 are not required and should be removed.

A separate table for adults in Section 4.8 is not acceptable. Where an AE is more common/less common an asterisk and relevant footnote can be made. AE only occurring in adults can be added making this clear by use of asterisks and footnote.

Section 5.1

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 in 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 shown.

The totality of the data is therefore weak, with one successful, one borderline failure and one clearly failed trial. One key difference is of course that the efficacy measurements were taken at different time points. It is also of note that the point estimates are always positive and broadly favours Concerta, although they are not as impressive as the initial analysis suggested. The MAH has withdrawn the proposed indication but still wish to add a claim in Section 5.1 which has not been clearly substantiated. The only study that has shown robust efficacy is the 5 week study with the longer term 7 and 13 week failing to consistently demonstrate this. Although numerically the point estimates were all positive this is not assessed as robust enough data to support the claim made in section 5.1 (see below).

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. *Some short-term efficacy has been demonstrated for CONCERTA XL in a dosage the range of 18 to 72mg/day but this has not been consistently shown beyond 5 weeks.*

The PIL: the proposed change to the section ‘what this medicine is for’ is acceptable. The AEs should be amalgamated with the main section as per the SmPC.

The Variation is considered approvable provided the SmPC and PIL are amended as indicated above.

Assessor Name SC Morgan FRCP
Date 24/4/11

ANNEX I
PATIENT INFORMATION LEAFLET

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 between the ages of 6 and 18.
- 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 adults. When treatment has started already at a younger age, it might be appropriate to continue taking CONCERTA XL when you become an adult. Your doctor will advise you about this.~~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 children or young people's behaviour problems. Although there is no cure for ADHD, it can be managed using treatment programmes.

About ADHD

Children and young 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 children and young people struggle to do these things. However, with ADHD they can cause problems with everyday life. Children and young people with ADHD may have difficulty learning and doing homework. They find it hard to behave well at home, at school or in other places.
ADHD does not affect the intelligence of a child or young 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 yours or your child's mental health history, and check if any of your family have 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 for epilepsy
- medicines used to reduce or increase blood pressure
- 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 is 54 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
  - 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
- sudden death
- suicidal attempt
- fits (seizures, convulsions epilepsy)
- skin peeling or purplish red patches
- inflammation or blocked arteries in the brain
- 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

- 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 back
- unexplained fainting, chest pain, shortness of breath (these can be signs of heart problems)
- paralysis or problems with movement and vision, difficulties in speech (these can be signs of problems with the blood vessels in your brain)

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, feeling tired
- 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
- stomach pain, diarrhoea, feeling sick, stomach discomfort and being sick.

Uncommon (affects less than 1 in 100 people)
- constipation
- chest discomfort
- blood in the urine
- shaking or trembling
- 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 or confused
- trouble seeing or double vision
- 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)

- muscle cramps
- small red marks on the skin
- abnormal liver function including liver failure and coma
- changes in test results – including liver and blood tests
- 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
- dilated pupils
- very high fever
- slow, fast or extra heart beats
- a major fit ('grand mal convulsions')
- believing things that are not true
- severe stomach pain, often with feeling and being sick

Effects on growth

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
- dry mouth
- 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 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 contain 18 mg of methylphenidate hydrochloride.
- CONCERTA XL contain 36 mg of methylphenidate hydrochloride.
- CONCERTA XL contain 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 15cp, 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 6cp, macrogol 400.
- **Printing Ink:** black iron oxide (E172), hypromellose 6cp, 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}.