Mutual Recognition Procedure

Type II variation
Final Variation Assessment Report Including Day 115 Response to Comments

ConcertaXL
Methylphenidate

UK/H/0544/001/II/056

Marketing Authorisation Holder: Janssen-Cilag

Date: 26/5/11

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	

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 to section 4.2:

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 (see section 4.4 and section 5.1).

is approvable.

The CMS are referred to this additional FVAR dealing with the comments received and the amended wording for the SmPC which addresses the comments received.

II. ASSESSMENT OF DAY115 COMMENTS AND RESPONSES

1 Summary

The Day 115 Responses form the CMS from NL, FR, ES, NO and IT all support the conclusion of the FVAR. There were further comments on the precise wording of the SmPC and RMP from NL, NO and FR. It is proposed that these comments are addressed as follows:

Section 4.2

Both NL and FR support the CHMP wording previously used for atomoxetine. FR raises the concern of how the MAH will ensure that a given adult who is prescribed MPH had been treated with the drug during childhood or adolescence and benefited from it. The RMS has similar concerns which were behind the new proposed wording which emphasised the need for a withdrawal before assuming continued benefit of therapy.

The RMS proposes the following to address these issues:

The harmonised wording is used in **section 4.2** as follows:

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 in adults is not appropriate.

A cross-reference is added to the above statement to Section 4.4 and 5.1:

Section 4.4

Use in Adults

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

In addition there are safety points raised by FR and NL which the MAH have addressed (please see following assessment of the DAY 115 Response). Comments have also been addressed from NO.

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. Some short-term efficacy has been demonstrated for CONCERTA XL in a dosage range of 18 to 72 mg/day, but this has not been consistently shown beyond 5 weeks. In one study, in which response was defined as at least a 30% reduction from baseline in CAARS ADHD Symptoms total score at Week 5 (endpoint) and analysed assuming subjects with missing data at their final visit were non-responders, a significantly higher proportion of patients responded to treatment with CONCERTA XL at doses of 18, 36, or 72 mg/day compared to placebo. In the two other studies, when analysed assuming subjects with missing data at their final visit were non-responders, there were numerical advantages for CONCERTA XL compared to placebo but a statistically significant difference in the proportion of patients meeting predefined response criteria was not demonstrated between CONCERTA XL and placebo.

Conclusion

The variation is recommended for approval.

2 Assessment of Day 115 Comments from RMS

2.1 RMS Comment 1 – Executive Summary and Recommendation

Conclusion The efficacy for the proposed indication has not been clearly demonstrated and the Marketing Authorisation Holder (MAH) has removed this and has 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:

o no mention of a trial of therapy withdrawal

o 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.

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

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.

Company Response

The Company confirms it can accept the revised wording proposed by the Reference Member State (RMS) to sections 4.2, 4.8 and 5.1 of the SmPC.

With respect to the RMS request to delete reference to continued treatment into adulthood in section 4.4, the Company believes that some guidance would be useful as the current text could cause confusion. Therefore the Company proposes to include the following statement in section 4.4 of the SmPC. This statement has also been included in section 4.2 as proposed by the RMS.

Use in adults

Safety and efficacy have not been established for the initiation of treatment in adults or for the routine continuation of treatment beyond the age of 18 years of age. Methylphenidate is not licensed for use in adults with ADHD. Safety and efficacy have not been established in this age group.

The following amendment is also made to the RMS suggested wording to the PIL:

'When treatment was 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.'

All amendments to the EU product information are shown as tracked changes at module 1.3.1.

RMS Assessment
The RMS accepts the preferred position of FR and NL to use the harmonised wording in section 4.2 and address the issue establishing the need for continued therapy in section 4.4. The MAH have indicated they are content with both forms of wording. **Point Resolved.**

2.2 RMS Comment 2 – SmPC section 4.4

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.

Company Response
The Company no longer seeks an extension of the indication to include adults with ADHD, and considers no further action is necessary for this point.
In line with the proposed SmPC, those patients with ADHD who would be considered for continuation of treatment into adulthood must have previously been treated with methylphenidate and continue to show an adequate response and acceptable tolerability. Adult patients who continue to receive CONCERTA and thus have previously tolerated treatment with methylphenidate would not be expected to be at a substantially increased risk of new-onset anxiety, agitation, and tension relative to children and adolescents. Therefore it is unlikely that these symptoms would emerge for the first time in individual patients with ADHD who continue to receive CONCERTA into adulthood.

RMS Assessment The MAH's point is accepted. **Point resolved.**

2.3 RMS Comment 3 – Suicidality

Suicidality: The MAH will be asked further details on the handling of Subject A10056, a 29-year-old woman, in Study 3013. [Subject A10056] had a history of major depressive disorder (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.

Company Response
The full narrative is provided at Attachment I, in addition the Company wishes to clarify the below points:
(i) Timing of the events:
Subject A10056 was randomly assigned to the 54-mg dose group. Treatment with the 36-mg dose was initiated on March 4 and the dose increased to 54 mg as per the protocol at a scheduled visit on March 10. At the visit on March 10, anxiety, irritability, and panic attacks were reported as AEs with a date of onset of March 5, i.e. one day after initiation of treatment and 5 days before the increase in dose to 54 mg. The onset of the AEs one day after the first dose of study drug on March 5 was not a sufficient reason for the investigator to discontinue double-blind treatment. The protocol did not allow for any "dose adjustments" to manage these types of AEs.
The last scheduled visit that the subject attended was on April 10th 2008, i.e. before the onset of suicidal ideation. There was no scheduled visit on April 15th 2008. The subject was not admitted to hospital on April 15th 2008 because of the suicidal ideation (nor was there an unscheduled visit). The first time that the onset of suicidal ideation was reported by the subject to a medical professional was on April

20th 2008, i.e. at the time of hospitalization for suicide attempt. At that time, the subject reported that suicidal thoughts had started 5 days earlier and that the anxiety initially reported as an AE on March 10 had increased after the increase in dose to 54 mg on March 10. The increase in severity of anxiety was not reported by the investigator as a separate AE; instead, the investigator elected to provide this information as part of the narrative in the SAE (serious adverse event) report (as reflected in the CIOMS report).
(ii) Diligence in seeking follow-up information:
In addition to the standard data queries, additional follow-up occurred between the study team and the medical monitor, Dr Steffen Heger, on February 10, February 12 and July 27 2009, and between the medical monitor and the investigator, Dr. Pendse, seeking additional information to document the SAE on March 9, 2009.

RMS Comments
The MAH have clarified that the suicidal ideation was not reported prior to the attempt. **Point resolved.**

3 Assessment of Day 115 Comments from CMS

3.1 France Comment 1
Based on provided data, we support the RMS that, a mention may be added in SPC to allow the continued use of CONCERTA from adolescence into adulthood for individual patients. However, start of treatment with CONCERTA in adults is not appropriate.
We support the MAH's proposal for section 4.2 as it is more appropriate than the RMS's wording
"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 in adults is not appropriate".
Company Response
As stated in the response to Comment 1 from the RMS, the Company confirms that it can accept the revised wording proposed by the RMS for section 4.2. The proposed SmPC in section 1.3.1 submitted with this response therefore retains the wording proposed by the RMS.
However, the Company also considers that the text it proposed in response to the PVAR and which is favored by the AFSSAPS and MEB to still be appropriate, as it is in line with a corresponding statement in the SmPC of Strattera (atomoxetine).

RMS Comment
As concluded in point 2.1, the RMS accepts the preferred position of FR and NL to use the harmonised wording in section 4.2 and address the issue establishing the need for continued therapy in section 4.4. The MAH have indicated they are content with both forms of wording. **Point Resolved.**

3.2. France Comment 2
However [with respect to proposed section 4.2 wording], one can question how the MAH will make sure that a given adult who is prescribed MPH had been treated with the drug during the childhood or adolescence and benefited from it. France is of opinion that the MAH should comment this point.
Company Response
The CONCERTA SmPC is the basis of information for healthcare professionals on how to use CONCERTA safely and effectively. The proposed wording in section 4.2 only provides for continued treatment into adulthood for patients in whom treatment withdrawal was not successful. Therefore any patient who receives continued treatment with CONCERTA into adulthood must have been treated with CONCERTA in adolescence who continues to show an adequate response and acceptable tolerability.

Furthermore, section 4.2 of the proposed SmPC states "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"

RMS Comment
The RMS assesses that additionally an attempted withdrawal should be made to establish the need for continued treatment and this precaution can be made in section 4.4. **Point resolved.**

3.2 France, Comment 3
In case the variation is approved, we are of opinion that the MAH should commit to conduct a drug utilisation study to determine patients' characteristics (age, gender, history of ADHD....) in real-life setting. Indeed, off-label use in adults who had not been previously treated by MPH during childhood (i.e. initiation of treatment in adults) is a potential risk with MPH.

Company Response
As part of its follow-up measures following the Article 31 referral for methylphenidate (EMEA/H/A/31/886), the Company currently provides drug utilization reports annually with the PSUR.
Within these reports, prescription data are characterised by age, gender, diagnosis and prescriber medical specialty. In addition, data are provided on the duration of therapy prior to discontinuation by specific age ranges including 19 years of age and above.

RMS comment Although the drug utilisation reports mentioned by the MAH do capture 'patient age on prescription', it is important to be certain that these utilisation studies will fully address the risks of off-label use with Concerta from 1) newly prescribing methylphenidate to adults with ADHD (i.e. adult first-time MPH users) and 2) prescribing MPH to adults with ADHD that has only been initially diagnosed in adulthood. Data should also be collected on the exact reason for prescribing in adulthood (i.e. whether it was continued into adulthood because treatment withdrawal was unsuccessful, or any other reason). The MAH should confirm that the utilisation studies performed will specifically characterise all of the risks described here. A further response from the MAH resolves this issue.

Further Response from MAH Company Response

The IMS Drug Utilisation Study conducted as a follow-up measure under the Article 31 procedure for methylphenidate products in the EU is reported annually in December (2008-2013) with the PSUR and includes analyses using the IMS disease analyser database. This comprehensive patient database includes real-life observational patient data including specific data collected in France allowing the monitoring of the age of treatment initiation and duration of treatment over time. The age of treatment initiation and duration of methylphenidate therapy is calculated using the patient's first ever methylphenidate prescription and their last prescription. Patient age is recorded both at commencement and end of therapy.

RMS Comment The analysis of drug utilisation data described by the MAH should allow an estimate to be made of the age of onset of ADHD in adult patients being prescribed the drug (assuming that time of initiating the drug is close to the time of first diagnosis of ADHD) and of the pattern of use over time. Although there are some important limitations to the interpretation of this data, the methods described by the MAH can be considered adequate for the time being, for estimating the size of the populations using Concerta off-label as described in the question. If, upon evaluation of the annual utilisation data, it is considered that the extent or type of off-label use of Concerta observed is of particular concern and warrants further evaluation, further studies may be required. **Point resolved**

Prescriptions recorded in the age range '+ 19 years' therefore reflect adult patients who were prescribed methylphenidate for treatment initiation in adulthood. Use of methylphenidate in both patient populations described above (i.e. i and ii) are therefore captured in this age category within the annual DUS report.

The annual drug utilisation data will therefore allow comparison of the proportion of prescriptions that result in initiation of methylphenidate therapy in adults year on year, both in adults who were diagnosed with ADHD as children and those who were first diagnosed with ADHD in adulthood.

3.3. France, Comment 4

In section 4.4, caution on cardiovascular status in adults should be reinforced, as increased blood pressure and cardiovascular effects may have different implications in this older population.

Company Response

The Company proposes inclusion of the following wording in section 4.4 under the cardiovascular status sub-heading. Please note that this proposed wording (underlined) is based on wording proposed by the Netherlands Health Authority (please refer to NL CMS Comment 2 below):

'Cardiovascular status

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

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

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

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

RMS comment

The MAH have now added a further warning to section 4.4. **Point resolved.**

3.4 France Comment 5

PSUR: In case the variation is approved, the next PSURs should include a specific analysis in adult population.

Company Response

The Company commits to provide a cumulative report of adult cases (18 years of age and older) received in the Global Medical Safety worldwide safety database, up to 10th October 2011 with the next annual PSUR (11th October 2010 through 10th October 2011). This PSUR is planned to be submitted on 9th December 2011 and will be assessed under a worksharing procedure UK/H/PSUR/0068/003.

RMS comment The usage in adults may not increase in this time period. The MAH should commit to cumulative adult reports with each PSUR. The MAH have now committed to this. **Point resolved.**

3.5 France Comment 6

RMP assessment: We previously mentioned (day 85) that Routine pharmacovigilance was not considered sufficient to monitor drug abuse and drug dependence, especially in this new population (i.e. adults).
The MAH was requested to put in place proactive pharmacovigilance measures. No answer has been provided to this comment that is however of importance.

Company Response

The current CONCERTA Risk management plan (version 3, 30 November 2010) identifies 'Drug abuse and drug dependence' as an important potential risk with use of CONCERTA. Central to the minimisation of this potential risk is the CONCERTA SmPC.
Section 4.2 of the SmPC states that patients should be monitored for the risk of diversion, misuse and abuse of methylphenidate. Additional warnings are provided in section 4.4 regarding misuse.
An educational tool (physician's guide and checklists) has also been developed for methylphenidate containing products following the Article 31 referral. The objective of this tool is to educate physicians on the use methylphenidate according to the safety sections of the SmPC. The current checklist for monitoring of ongoing therapy includes a reminder to document any indication of abuse, misuse or diversion and a reference to the guidance given in section 4.4 of the SmPC.
This educational tool is currently being reviewed by European Health Authorities prior to Implementation

RMS comment The MAH are not pursuing a new indication but there may be increased usage in adults associated with the new posology. This will be dealt with through the PSURs and the above educational tool. **Point resolved.**

3.6 France Comment 7

Long term data (efficacy and safety) are lacking and are of concern especially in subjects initiating the treatment in their childhood or adolescence and going on the treatment while adults. Therefore, depending on the results of the drug utilisation study, a long-term follow-up of those patients could be considered.

Company Response

The Company no longer pursues an indication for the treatment of adults with ADHD. Proposed wording in section 5.1 of the SmPC states that a randomized withdrawal study failed to demonstrate continued efficacy in the longer term.

RMS comment The need for a further study will be reviewed following the results of the data on drug utilisation. **Point resolved.**

3.7 Netherlands, Comment 1

The conclusion of the RMS is endorsed that efficacy is weak but that the available evidence would justify wording in section 4.2 regarding continued treatment in adults who were successfully treated in childhood/adolescence. However, NL supports the text for section 4.2 as proposed by the company:
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 in adults is not appropriate. There appears to be no compelling reason to deviate from the text as agreed for Strattera (atomoxetine), and a harmonised approach is therefore preferred.
Company Response
As stated in the response to Comment 1 from the RMS, the Company confirms that it can accept the revised wording proposed by the RMS for section 4.2. The proposed SmPC in section 1.3.1 submitted with this response therefore retains the wording proposed by the RMS.
However, the Company also considers that the text it proposed in response to the PVAR and which is favored by the MEB and AFSSAPs to still be appropriate, as it is in line with a corresponding statement in the SmPC of Strattera (atomoxetine).

RMS Assessment
As concluded in point 2.1, the RMS accepts the preferred position of FR and NL to use the harmonised wording in section 4.2 and address the issue establishing the need for continued therapy in section 4.4. The MAH have indicated they are content with both forms of wording. **Point Resolved.**

3.8 Netherlands Comment 2
It is agreed with the RMS that there is a clear safety signal with respect to cardiovascular risk (increase in blood pressure) and risk of aggression. The RMS concludes that these risks are already appropriately addressed in the current SPC. This is not fully supported, as increased blood pressure and of aggression in adults might be having different implications for adults than for children. Therefore it is proposed to add a warning text regarding these risk to the SPC under section 4.4. I.e. (underscored text to be added):
Cardiovascular status
'... The short- and long-term clinical consequences of these cardiovascular effects in children and adolescents are not known, but the possibility of clinical complications cannot be excluded as a result of the effects observed in the clinical trial data. Especially when treatment during childhood/adolescence is continued into adulthood. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate....'
Aggressive and 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, especially when treatment during childhood/adolescence is continued into adulthood, 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.'
Company Response
The Company agrees to the proposed changes to the product information under the 'cardiovascular status' sub-heading. Please see proposed text in the Company response to the French Comment 4.
The Company does not accept the proposed wording under the 'Aggressive and hostile behaviour' sub-heading.
In line with the proposed SmPC those patients with ADHD who would be considered for continuation of treatment into adulthood must have previously been treated with methylphenidate and continue to show an adequate response and acceptable tolerability. Adult patients who continue to receive CONCERTA and thus have previously tolerated treatment with methylphenidate would not be expected to be at a substantially increased risk of new-onset aggressive and hostile behaviour relative to children and adolescents. Therefore it is unlikely that these symptoms would emerge for the first time in individual patients with ADHD who

continue to receive CONCERTA into adulthood.
All amendments to the EU product information are shown as tracked changes at module 1.3.1.

RMS comment
The MAH have added the emphasised warning to cardiovascular status. The MAH have declined to add the same wording to aggressive and hostile behaviour. Since the warning is referring to initiation of therapy the additional wording does not make sense. **Point resolved.**

3.9 Netherlands Comment 3

The wording proposed by the RMS for section 5.1 is endorsed, but it is proposed to add a sentence indicating that a randomized withdrawal study has failed to demonstrate continued efficacy on the longer term.

Company Response
The Company accepts the proposal to make an amendment to section 5.1 with regard to the failed randomized withdrawal study. The following wording is proposed:
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. Some short-term efficacy has been demonstrated for CONCERTA XL in a dosage range of 18 to 72 mg/day, but this has not been consistently shown beyond 5 weeks. A randomized withdrawal study (N=45) failed to demonstrate continued efficacy over a one month-period following long-term treatment.

RMS comment
The proposed addition by the NL adds important information for the prescriber and explains further the reasons for not indication the use of MPH in adults. **Point resolved.**

3.10 Netherlands, Comment 4

Where relevant, the PIL needs to be amended taking the above comments into account.

Company Response
A minor amendment is made to the RMS proposed wording. Please refer to response to RMS Comment 1. Amendments to the patient information are shown as tracked changes at module 1.3.1.

RMS comment
The wording for the PIL is acceptable. **Point resolved.**

3.11 Norway Comment 1

The Norwegian Medicines Agency (NoMA) agrees with the overall conclusion of the RMS and is therefore prepared to grant a marketing authorisation for the following wording in section 4.2 (as proposed by the RMS) for Concerta XL, provided that the SPC comments below are taken into consideration:
"***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."

RMS Comment
This is addressed above in the proposed SPC wording for sections 4.2 and 4.4. **Point resolved.**

3.12 Norway Comment 2
It is suggested that the need for further treatment of these adults should be reviewed regularly and undertaken not less frequently than 2 years.

Comment: What is the rationale behind 2 years? We suggest that the review should take place once a year as is already recommended for children and adolescents.
Due to that efficacy of Concerta has not been consistently shown beyond 5 weeks, the frequency for reviewing long-term use of Concerta in adults should be discussed.

RMS Comment
This has been changed to annual to keep consistency with the advice for children and adolescents. **Point resolved.**

3.13 Norway Comment 3
Section 5.1
More details should be stated about the performed studies (the failed study 3013, the borderline failure study 02-159 and the successful study 3002).

RMS Comment
Further information has been added and a cross-reference from 4.2. **Point resolved.**

3.14 Norway Comment 4
We support the SPC comments from CMS NL regarding cardiovascular status and aggressive and hostile behaviour.

RMS Comment
Please see above. **Points resolved.**