Johnson & Johnson PRD, a division of Janssen-Cilag

CONCERTA®
Prolonged-release tablets (18 mg, 27 mg, 36 mg and 54 mg)

Response to the 26 April 2011 Final Variation Assessment Report and Day 115 CMS comments

(Type II variation for Use of CONCERTA in Adults)

(Mutual Recognition Procedure, UK/H/0544/002/II/056)

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'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.

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.

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

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).

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 have 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 behavior' 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 behavior 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.

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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.**