To: European Commission (Health and Consumer Policy, DG Sanco)
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Confidential document shows Janssen-Cilag gives false and misleading data in the application for Concerta to adults

I have just come across a document, part of the application for Concerta to adults in Europe. It is of so highly confidential nature that the Swedish Medical Products Agency (MPA) says it can't release *any* part of it, as this would threaten the relations between United Kingdom (UK) and Sweden. UK being the country in Europe handling the application from Janssen-Cilag (Johnson & Johnson).

The document, a so called Risk Management Plan (RMP), written by Janssen-Cilag and describing the risks with the drug Concerta and what the company should do to lessen these risks, contains wildly false and misleading data. It is submitted to the UK medical authority MHRA (Medicines and Healthcare products Regulatory Agency).

I am quite sure the Commission wants to be fully informed about this case. The data in the document are forming the basis for the decision by the European medical agencies in the Concerta case. And the data very clearly show one thing: The pharmaceutical company has not adhered to and does not intend to fulfil the conditions for continued marketing authorisation decided by the Commission 27 May 2009. **[1]**

The document is showing that we are now at the point where Concerta and other methylphenidate products should be withdrawn from the market in Europe – and very far away from a situation where Concerta could be approved also for adults.

I have in december 2010, before getting access to the confidential document, taken up this affair with the MHRA. I have described that Janssen-Cilag is not adhering to and fulfilling the conditions set up in the Commission decision 27 May 2009, and how this relates to the current application from the company. The MHRA has not taken this seriously. Instead the agency has brushed off the facts with the following PR statement:

> "Please be assured that the MHRA and other European regulatory authorities are fully committed to ensuring that all safety concerns for methylphenidate products are subject to robust pharmacovigilance assessments and that the best possible regulatory action is taken in a proportionate manner, based on a critical appraisal of all the evidence and taking into account the benefits of treatment, according to national and European pharmacovigilance legislation." (MHRA, e-mail 17 December 2010)

This is for sure an empty statement considering the fact that the MHRA obviously has accepted the false data in the new version of the RMP from 30 November 2010, presented by Janssen-Cilag and described below.

I have earlier presented another confidential document in this affair for the Commission. This was the now infamous paper *Feasibility Assessment of a Study of Long-term Effects of Methylphenidate on Cognition and Psychiatric Outcomes* (30 October 2009), written by the pharmaceutical companies manufacturing methylphenidate in Europe. As stated in that document: "This information is provided on behalf of the following Marketing Authorisation Holders for methylphenidate-containing medicinal products in the EU: Novartis, Johnson & Johnson, Shire, Medice and Laboratorios Rubió (also referred to as the "Consortium")."

That document could only be characterised as an aggressive effort to explain why long-term studies about adverse psychiatric outcomes of methylphenidate treatment *could not and should not* be done, together with *distorted facts* about the beneficial long-term outcomes of drug treatment. The intention with the feasibility assessment study was clearly to delay needed safety actions for methylphenidate drugs.

See link to that document and an analysis of its content in my earlier letter to the Commission. **[2]** **http://jannel.se/letter_Consortium_ADHD.pdf** As a result of my letter the Commission took the matter to the EMA, but nothing effective was done by the EMA or the MHRA.

Instead we can now see *the same* false and misleading data being used in the just submitted Risk Management Plan (RMP) from November 2010. Janssen-Cilag has included ***exactly the same data and evaluations***, in the new RMP as they used in the aggressive effort to explain why no effective safety studies could be done, in the Feasibility Assessment Report. And what makes this even worse – the MHRA has obviously accepted these data and wants us to believe that they are "evidence" used in the "robust pharmacovigilance assessments" of Concerta (see letter from MHRA above).

I have fully described the false and misleading data presented by Janssen-Cilag in the *earlier* RMP (version 2), in my letter to the Commission from August 2010 **[3]** **http://jannel.se/Application-Concerta-Adults.pdf**

I took up that the point of off-label use, misuse, abuse and diversion (as listed in the decision of the Commission) were very important in the application for using Concerta for adults in Europe – meaning that the non-execution of the required actions on this point – and the data that had emerged – *in themselves* were enough for disapproving the application from Janssen-Cilag.

The fact was that Janssen-Cilag had not only not done anything effective on this point, but the company had also submitted easily verified false information to the medical authorities in Europe.

In the *current* RMP the data about off-label use are excluded, in the version I have access to. I would however estimate that the company is continuing to provide easily verified false information. In the earlier RMP (version 2) the company tried to convince the European medical authorities that "**the vast majority (94.0%) of retail prescriptions of CONCERTA were prescribed to children and adolescents between the ages of 6 and 20 years",** saying that off-label use was not a problem at all in Europe. The facts were however that **45 % (!) of the prescriptions for methylphenidate in Sweden 2009 were for off-label use, for adults,** meaning that

the situation with this narcotic drug is already now out of control. I suppose the Commission will compare the data in my earlier report from August with the data presented in the current RMP.

Explaining away the proven harmful effects of mania, psychotic reactions, aggression and hostility

I want to end off with an example of the dangerous distorted facts presented in the *new* RMP, taken from the part 1.3.1.3 *Long-Term Psychiatric Effects,* page 28- in the report.

Janssen-Cilag is claiming the following about the long-term positive effects of Concerta (methylphenidate) and about "the absence of an adverse psychiatric outcome" shown with the treatment. The company claims (pp. 29-30) studies:

> "…consistently show no evidence of worsening of psychiatric symptoms during treatment with methylphenidate",
> "even point in the direction of an improvement of behavioural symptoms over time";
> (for long-term effects in the MTA study) "a beneficial effect on the course of comorbid psychiatric disorders over time",
> "although … it might be difficult to conclude that the beneficial effects seen years later in the study is entirely due to methylphenidate treatment",
> "the data available are strongly supportive for the absence of harm due to methylphenidate";
> "In summary the results of the long-term observational data are in line with the patterns known from clinical trials and substantiate the absence of an adverse psychiatric outcome of methylphenidate treatment and support a positive benefit risk assessment of treatment in children with ADHD".

I would guess the Commission has objections to these claims, having concluded in the Decision (Annex III) from 27 May 2009 (p. 47) **[1]**:

> **Emergence of new psychotic or manic symptoms**
> ***Treatment-emergent psychotic symptoms (visual/tactile/auditory hallucinations and delusions) or mania in children and adolescents without prior history of psychotic illness or mania can be caused by methylphenidate at usual doses***. If manic or psychotic symptoms occur, consideration should be given to a possible causal role for methylphenidate, and discontinuation of treatment may be appropriate. [Emphasis added.]
>
> **Aggressive or hostile behaviour**
> ***The emergence or worsening of aggression or hostility can be caused by treatment with stimulants.*** Patients treated with methylphenidate should be closely monitored for the emergence or worsening of aggressive behaviour or hostility at treatment initiation, at every dose adjustment and then at least every 6 months and every visit. Physicians should evaluate the need for adjustment of the treatment regimen in patients experiencing behaviour changes. [Emphasis added.]

It is, in other words, ***very clear*** that methylphenidate ***even in the short-term*** can cause psychotic symptoms, mania and aggressive behaviour/hostility. This is now even the text in the SPC for all methylphenidate products.

The facts are – as the Commission knows – that the extensive FDA review from 2006 and the article by Mosholder et al in Pediatrics from 2009 gave an entirely different picture from the one presented by the company. **[4, 5]** This review by itself disproves almost everything claimed in this part of the RMP.

In addition, in one of the studies (Cherland and Fitzpatrick, 1999), said by Janssen-Cilag to "show no evidence of worsening of psychiatric symptoms during treatment with methylphenidate", the conclusion, when six of ninety-eight children in the study "developed psychotic or mood-congruent psychotic symptoms during treatment", was: "Awareness of the potential for psychotic side effects from stimulant medications is important when prescribing for children". **[6]**

Also the presentation in the RMP of the long-term positive results of the MTA study is wildly misleading. In the 3 years follow-up of the MTA study it was in actual fact concluded that **"medication use was a significant marker not of beneficial outcome, but of deterioration**. That is, participants using medication in the 24-to-36 month period actually showed increased symptomatology during that interval relative to those not taking medication." [Emphasis added.] **[7]** In the paper describing the follow-up at 6 and 8 years it is stated, contrary to what Janssen-Cilag is explaining in the RMP, that **medication use "was associated with worse hyperactivity/impulsivity and ODD [Oppositional Defiant Disorder] symptoms and CIS [Cognitive Impairment Scale] impairment … at 6 years".** [Emphasis added.] **[8]**

Professor William Pelham, in the MTA Cooperative Group, had this to say in a mail about the statements in the earlier Feasibility Assessment Report (statements which are now repeated in the current RMP):

> "The statements about the latest long-term outcome paper from the MTA are inaccurate. The paper actually concluded that there is no evidence for long-term benefit of stimulants from the MTA follow up (see discussion section in attached paper [MTA 8 years]). In another MTA paper not yet published, it is reported that there ARE negative long-term adverse effects on growth. Thus, the MTA is consistent with the entire rest of the literature, from which there are no data that support a conclusion that there are long-term benefits of stimulants on any outcome." (Pelham, December 2009)

See the document itself: ***Risk Management Plan Concerta, version 3.0 from 30 November 2010***, **http://jannel.se/RMP3-Concerta30Nov2010.pdf**

It must now be very clear that Janssen-Cilag (Johnson & Johnson) is not adhering to and fulfilling the conditions for continued marketing authorisation decided by the Commission. The company must be informed that the marketing authorisation for Concerta is about to be withdrawn.

It must also be very clear that the application for approval of Concerta for adults must be disapproved.

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[1] The European Commission, Decision and Appendixes about methylphenidate products, from 27 May 2009; Decision and Appendixes: http://jannel.se/anx_55708_en.pdf
[2] Larsson, *A request for decisive actions from the European Commission to initiate required safety actions about methylphenidate products*, 5 March 2010, http://jannel.se/letter_Consortium_ADHD.pdf
[3] Larsson, *Regarding Janssen-Cilag's application to get Concerta approved for adults in Europe,* 21 August 2010, http://jannel.se/Application-Concerta-Adults.pdf
[4] FDA, *Psychiatric Adverse Events Associated with Drug Treatment of ADHD: Review of Postmarketing Safety Data*, 3 March 2006, http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4210b_11_01_AdverseEvents.pdf
[5] Mosholder et al, Hallucinations and Other Psychotic Symptoms Associated With the Use of Attention-Deficit/Hyperactivity Disorder Drugs in Children *PEDIATRICS* Vol. 123 No. 2 February 2009, pp. 611-616 (doi:10.1542/peds.2008-0185)
http://pediatrics.aappublications.org/cgi/content/full/123/2/611
[6] Cherland E (1999), Fitzpatrick R. Psychotic side effects of psychostimulants: a 5-year review. *Can J Psychiatry* 1999;44:811-813, http://www.ncbi.nlm.nih.gov/pubmed/10566114
[7] Jensen PS (2007), Arnold LE, Swanson JM, et al. 3-Year Follow-up of the NIMH MTA study. *J Am Acad Child Adolesc Psychiatry* 2007;46(8);989-1002. http://www.jaacap.com/article/S0890-8567(09)61550-1/abstract
[8] Molina BSG, Hinshaw SP, Swanson JM, Arnold LE, Vitiello B, Jensen PS, Epstein JN, Hoza B, Hechtman L, Abikoff HB, Elliott GR, Greenhill LL, Newcorn JH, Wells KC, Wigal T, Severe JB, Gibbons RD, Hur K, Houck PR, and the MTA Cooperative Group. The MTA at 8 years: Prospective follow-up of children treated for combined type ADHD in the multisite study. *Journal of the American Academy of Child and Adolescent Psychiatry*. May 2009,
http://www.jaacap.com/article/S0890-8567(09)60066-6/abstract