To the European Commission (DG SANCO)
Copy: European Medicines Agency, EMEA (Committee for Medicinal Products for Human Use, CHMP)

5 March 2010

Pharmaceutical companies – calling themselves the "Consortium" – are preventing long-term safety studies of methylphenidate (Ritalin, Concerta) in Europe

A request for decisive actions from the European Commission to initiate required safety actions about methylphenidate products

This is a request to the Commission to take decisive actions to prevent the manufacturers of methylphenidate products from stopping or delaying the needed safety actions decided upon by the Commission 27 May 2009 **[1]**. (This request is addressed to Directorate-General for Health and Consumer Affairs as I understand these questions are now to be handled there.)

It can in general be expected that the involved pharmaceutical companies would try to prevent any and all studies with the potential of proving that long-term use of methylphenidate products is harmful. A very good example of this approach is also the confidential report ***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 the report:

> "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")."

This document, presented by the "Consortium", can 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 is clearly to delay needed safety actions for methylphenidate drugs.

I really hope that the analysis below can be of value for the Commission in preventing the manufacturers from stopping or delaying the needed safety actions.

It took two years for the EMEA (2007-2009), after the referral from the European Commission, to recommend the safety actions put forward in January 2009, and decided upon by the Commission 27 May 2009 **[1]**.

Part of the Conditions for continued Marketing Authorisation (p. 65-68 Annex IV to the Commission decision) was for the manufacturers of methylphenidate products to do the following:

> "The MAHs [Marketing Authorisation Holders] committed to provide a detailed feasibility assessment for a scientifically valid, welldesigned and suitably powered long-term safety study to examine specific endpoints for the following outcomes:
>
> i) adverse cognitive outcomes
> ii) adverse psychiatric outcomes (e.g. mood disorders, hostility and psychotic disorders)
>
> The MAHs will consider including predominantly EU-based data, and the feasibility assessment will also comment on what non-EU sources of data could be used as an alternative. If the feasibility assessment shows that a scientifically valid, well-designed and suitably powered study is viable, then the MAHs commit to provide a detailed protocol. The proposed follow-up duration of at least 5 years for individual subjects will be considered. Within the 5-year follow-up, particular emphasis will be placed on assessing the effects of a cumulative exposure of at least 18 months. Because this is a noninterventional study, the MAH's will have no control over actual prescribing practices. The proposed patient enrolment age will be as young as possible consistent with the age restrictions of the label (i.e. children aged 6 years or more). The preferred design would be a prospective, cohort study. The MAHs agree to evaluate suitable comparator groups."

The first question that comes to mind when reading this is: Did the European Commission and the EMEA really believe that the manufacturers would conclude that it was possible to do such a study? Wasn't the end result clear from the beginning: The manufacturers would conclude that they *cannot* (should not) do such a study or even a study of a similar nature; they would probably even explain that such studies were unnecessary.

The future development has shown that the manufacturers did exactly the above and that the involved authorities now have to act decisively to handle the efforts by the manufacturers to stop all follow-up actions of safety risks.

The 4 November 2009 the pharmaceutical company Novartis (representing the Consortium) submitted the 18 pages long report ***Feasibility Assessment of a Study of Long-term Effects of Methylphenidate on Cognition and Psychiatric Outcomes***. It was addressed to Members of The Committee for Medicinal Products for Human Use (CHMP) within the European Medicines Agency (copy to the British Medicines and Healthcare products Regulatory Agency, MHRA).

A request to get the report from the European Commission (Enterprise & Industry) is answered 25 January 2010:

> "Your request for access to documents should be addressed to EMEA."

But earlier efforts to get the report from the EMEA had been met with the answer:

> "Clinical study reports, including raw data submitted to the European Medicines Agency are considered confidential…Therefore they cannot be released to researchers or the public at large." (17 December 2009)

Continued requests were met with:

> "…this is not a document produced or received by the Agency". (20 January 2010)

And finally 26 February a long answer about my request was sent. In this answer it was stated:

> "You indicate in your email that this report is addressed to all CHMP members. However, I would like to clarify that there is not currently an on-going procedure involving the scientific committees of the European Medicinse Agency regarding methylphenidate containing products for which this document is part. In that respect *any such submission to the CHMP members is not relevant* as, *would they have received this document*, it was not in their capacity as members of a scientific committee of the Agency." (Emphasis added.)

This means that the document was first seen as confidential, then it didn't exist and then it was not relevant even if it *would have been* received by the CHMP members of the EMEA. Obviously at least the *manufacturers* of methylphenidate in Europe (the "Consortium") were convinced that it *was* relevant to send this important document to *all* the CHMP members.

The EMEA in its letter above refer to the member states (in the European Union) "on which rests the final responsibility to ensure that the conditions as defined in Annex IV are fulfilled". But earlier contacts with the Medical Products Agency (MPA) in Sweden have shown that this national ageny has done nothing about the safety follow-ups ordered by the Commission 27 May 2009. It is very unlikely that the Swedish MPA would do something with the report from the Consortium. The *manufacturers* addressed its letter to the EMEA (all CHMP members) and the national authorites do not think they should investigate the matter and give an answer to the report.

But the Swedish Medical Products Agency has via a court order now been forced to release the (earlier) confidential Feasibility Assessment report in all its parts.

This is truly a remarkable document – which is now made public **(see link in the end).**

Questioning the very basis for the actions by the CHMP and the Commission – and the new warnings in the SPC (Summary of Products Characteristics)

In the new warning section of the SPC for all methylphenidate products in Europe it is stated:

> **"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."
>
> **"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."

The ***causal*** role for methylphenidate products in inducing psychotic reactions, mania, aggression and hostility has been proven in many studies. The long 2006 report from FDA reviewers about this subject, followed by an article in the journal Pediatrics, contain very convincing data about these effects of methylphenidate **[2]**, **[3]**. It has taken many years to get the warnings out about these harmful effects. Many children have been considered psychotic and put on heavy antipsychotic drugs – with even more harm produced – when the actual fact was that they experienced harmful reactions from methylphenidate drugs. Many children have experienced new or exacerbated aggressiveness as a result of taking stimulant drugs, which in turn have put them and people around them in danger.

But when the manufacturers now explains for the European authorities that they don't intend to do any long-term studies of psychiatric adverse effects (e.g. mood disorders, hostility and psychotic disorders) they go so far that they even negate the well-known effects described above. In the Feasibility Assessment under the heading *Summary and overall conclusions* (p. 11) the Consortium says:

> "The available observational studies, which were systematically reviewed and included in this feasibility assessment - some of which were published recently and were not available when the requirement for a long-term safety study to investigate the potential signals was discussed within CHMP - ***do not indicate any signal of worsening of psychiatric symptoms or cognition during treatment with MPH*** and even suggest a beneficial long-term effect of MPH on the course of psychiatric disorders and cognitive function over time." [Emphasis added.]

Blaming the harmful effects of the drugs on the children's "underlying diseases"

The main method used by the Consortium to prevent the safety actions is the "comorbidity trick". This means that *any and all* adverse reactions from the drugs are explained away as signs of a "co-occuring disease". As the Consortium says (p. 3): "It is well established that ADHD co-occurs with other psychiatric disorders". The list that follows is very long: "disruptive behavioral disorders such as oppositional defiant disorder, conduct disorder; and mood disorders such as depression, bipolar disorder; and anxiety disorders."

Many references are made to Dr. Joseph Biederman – the father of pediatric bipolar disorder, and subject to Congressional investigations in the US – and his colleagues, Wilens, Spencer and Faraone. So for example we get to know that it has been found that 26% (!!) of the children with ADHD also can have bipolar disorder.

The Consortium wants to say that when a child on methylphenidate exhibits agitation or mania it should directly be seen as the "co-occuring disease" bipolar disorder popping up. Meaning in turn that they now have something *more* for which psychiatric drugs needs to be prescribed. This time heavy antipsychotic drugs, like Risperdal, Invega, Clozaril, Seroquel and Zyprexa.

No references are of course made in the Feasibility Assessment Study to the extensive FDA report from 2006 **[2]** where it is explained in the Executive Summary/Introduction:

> "**The most important finding of this review is that signs and symptoms of psychosis or mania, particularly hallucinations, can occur in some patients with no identifiable risk factors, at usual doses of any of the drugs currently used to treat ADHD.** Current approved labeling for drug treatments of ADHD does not clearly address the risk of druginduced signs or symptoms of psychosis or mania (such as hallucinations) in patients without identifiable risk factors, and occurring at usual dosages. In addition, current labeling does not clearly state the importance of stopping drug therapy in any patient who develops hallucinations, or other signs or symptoms of psychosis or mania, during drug treatment of ADHD. We recommend that these issues be addressed."
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> "For drugs currently approved for ADHD treatment, no risk factors were identified which could account for the majority of reports of psychosis-related events… **in the overwhelming majority of cases (roughly 90% overall), the patient had no prior history of a similar condition."** [Emphasis added.]
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> "Numerous postmarketing reports of aggression or violent behavior during drug therapy of ADHD have been received, most of which were classified as non-serious, although approximately 20% of cases overall were considered life-threatening or required hospital admission… No specific risk factors for aggression or violent behavior were identified in this analysis… **a striking majority (80 to 90% overall) of patients identified in this review had no prior history of similar events.** Several cases describing positive rechallenge were reported for each of the drugs included in this analysis. Consideration should be given to stopping the medication in patients who develop aggressive or violent behavior during drug therapy of ADHD." [Emphasis added.]

Whereas the FDA reviewers clearly could see that these children had "no prior history of a similar condition", "no prior history of similar events", and that the reactions did "occur in some patients with no identifiable risk factors, at usual doses", the manufacturers (the Consortium) tell that it is impossible to say anything about these reactions, as they "are part of the natural course of the disease [ADHD]".

The FDA reviewers told that "In many patients, the events resolved after stopping the drug" [dechallenge], and that "Positive rechallenge (i.e., recurrence of symptoms when drug is re-introduced) is considered a hallmark for causality assessment of drug-induced adverse effects. Cases which include a positive rechallenge were reported by the Sponsors for each of the drugs included in this analysis, and were also identified in the FDA AERS [Adverse Event Reporting System] analysis." This extensive review finally led to the warnings in the new SPC text for methylphenidate products in Europe.

The clear and simple observations by the FDA reviewers are in sharp contrast with what the Consortium tells in its report – no mentions are made in the report about *any* problem whatsoever from the drugs, all problems lie *within* the child; the real problems are said to be the "underlying diseases" showing up as "part of the natural course" of ADHD! One could wonder after having read the aggressive report from the Consortium: Have there *ever* been any adverse reactions from these drugs?

Distorted description of the MTA study

The Consortium is (p. 7) describing the 8 year follow-up in the MTA study as "strongly supportive for the absence of harm due to MPH [methylphenidate] treatment" and that the results "actually suggest that there is evidence of a beneficial effect of ADHD treatment approaches" [with methylphenidate].

Professor William Pelham, in the MTA Cooperative Group, had this to say about the above description in a mail:

> "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. The literature review in this document is not comprehensive and draws a conclusion with respect to long-term beneficial effects on academic outcomes that can only be drawn with respect to acute, not long-term effects of stimulants."

The new Australian ADHD study about long-term outcomes associated with stimulant medication

The 16 February the Western Australia Government released the Raine ADHD study **[4]**, and presented it with the following words:

> "The ADHD Study, the first of its type in the world, found that long-term use of drugs such as Ritalin and dexamphetamine may not improve a child's social and emotional well-being or academic performance."

And from the study itself:

> "In children with ADHD, ever receiving stimulant medication was found to increase the odds of being identified as performing below age-level by a classroom teacher by a factor of 10.5 times (compared to never receiving stimulant medication)."

And even if the effects of methylphenidate on cardiovascular function is not part of this letter to the Commission or part of the report from the Consortium the following finding in the Australian government report should really convince the European authorities that decisive actions must be taken right away to protect the children:

> "The results also indicated that between the age of 8 and 14 years there may be an effect of stimulant medication on diastolic blood pressure above and beyond the wellestablished immediate short-term effects on cardiovascular function. The finding that consistent use of medication was associated with an average elevation 10mmHg at 14-years of age indicates that the long-term cardiovascular implications of stimulant medication-use need to take a high priority when determining directions for future research."

The Australian report and its conclusions should also most definitely be compared with the following words (p. 11) from the Consortium:

> "[new data] do not indicate any signal of worsening of psychiatric symptoms or cognition during treatment with MPH and even suggest a beneficial long-term effect of MPH on the course of psychiatric disorders and cognitive function over time."

In summary the report from the Consortium can only be seen 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 report has been sent to all members of CHMP of the EMEA but the agency does not consider that it has anything to do with this and refer the matter to the national authorities. And these have most likely acted as the Swedish Medical Products Agency and done nothing about the matter.

I request that the Commission take whatever actions necessary to get these safety follow-up studies started right away.

See: ***Feasibility Assessment of a Study of Long-term Effects of Methylphenidate on Cognition and Psychiatric Outcomes***, **http://jannel.se/Consortium_ADHD-drugs.pdf**

Janne Larsson
Reporter
janne.olov.larsson@telia.com
(Snöbollsgränd 22
129 45 Hägersten
Sweden)

[1] The European Commission, Decision and Appendixes about methylpenidate products, from 27 May 2009; Appendixes found in different languages on http://www.ema.europa.eu/htms/human/referral/article31/methylphenidate.htm
[2] 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
[3] 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
[4] Raine ADHD Study: *Long-term outcomes associated with stimulant medication in the treatment of ADHD in children,* February 2010, http://www.health.wa.gov.au/publications/documents/MICADHD_Raine_ADHD_Study_report_022010.pdf