European Commission (Health and Consumer Policy, DG Sanco)

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Actions in Sweden in violation of the legally binding rules about ADHD drugs (methylphenidate) decided by the Commission

This is a report about violations of the legally binding rules for prescription of Concerta and other methylphenidate drugs in Sweden. It focuses on the prescription of Concerta to adults. It describes how the pharmaceutical company Janssen-Cilag has violated the conditions for continued marketing authorisation and how the national medical authorities have failed to enforce the decision of the Commission from 27 May 2009. [1] These violations are now resulting in a major threat to the safety of the public.

In May 2009 the European Commission decided about *the conditions to be fulfilled* by the pharmaceutical companies producing ADHD drugs (methylphenidate) *in order to get continued marketing authorisation.* **[1]** It has been clarified by the Commission: "The decision is legally binding on Member States." (letter by Mr. Stefan Führing, 25 July 2009)

Part of the decision from the Commission is the harmonised Summary of Product Characteristics (SPC) for all methylphenidate products. All parts of the SPC are legally binding for the member states. They cannot, as stated by the Commission (Mr. Führing), "go beyond these requirements".

It was stated in Annex II of the decision page 34: "It is an amphetamine-like drug that has controlled drug status, which imposes restrictions on prescribing and handling." Parts of the prescription restrictions were for adults, where it was said (Annex III, SPC page 44): "Methylphenidate is not licensed for use in adults in ADHD. Safety and efficacy have not been established in this age group." Of this reason the *restrictions* in prescription were (p. 43): "Treatment must be initiated under the supervision of a specialist in childhood and/or adolescent behavioural disorders." And p. 43: "Treatment must be under the supervision of a specialist in childhood behavioural disorders."

However the Swedish Medical Products Agency, MPA, (Ahlqvist Rastad) did not accept these legally binding prescription restrictions and used the judicial section (Nordback, Lindström) to argue against the restrictions. The MPA argued that the national prescription rules – LVFS 2008:11 – from December 2008, were to be applied. These rules stated that *all* psychiatrists (also for adults) were allowed to initiate and supervise treatment with methylphenidate.

The matter was handled by Mr. Terberger from the Commission (Head of Unit SANCO C8). I am not aware of any legal instruments or other policy tools used to enforce the legally binding prescription restrictions, and the MPA has continued to apply the nationally decided wide prescription rules.

This resulted in the following situation in Sweden:

In 2009 the prescription (in Defined Daily Doses, DDD) of Janssen-Cilag's methylphenidate drug Concerta *to adults* increased with 49% (!), from 3 101 150 to 4 623 442. Janssen-Cilag's sales of Concerta *to adults* increased from 53 million SEK (2008) to 79 million SEK (2009). **[2]**

As Janssen-Cilag did not change their marketing efforts, through Key Opinion Leaders (KOL:s) and sponsored advocacy groups (mainly the patient group Attention), assisted by the nationally decided generous prescription rules from the MPA, the prescription of Concerta to adults continued to increase in 2010.

In that year the prescription (in Defined Daily Doses, DDD) of Concerta *to adults* increased further, now with 42% (!), from 4 623 442 to 6 589 035. Janssen-Cilag's sales of Concerta *to adults* increased from 79 million SEK (2009) to 113 million SEK (2010). **[2]** As seen in the reference document the same pattern goes for other methylphenidate products.

The disapproval of Janssen-Cilag's application of Concerta to adults

In February 2010 Janssen-Cilag turned in an application to the European medical agencies to get Concerta approved for adults.

The UK Medicines and Healthcare products Regulatory Agency (MHRA) handling the application found after an extensive investigation **that Concerta could NOT be approved for adults.**

With that it could no longer be said that "safety and efficacy" for Concerta (and other methylphenidate products) had "not been established in this age group" (as stated in the SPC). Instead we could now say, as also stated in Preliminary Variation Assessment Report from July 2010 in the European investigation, **"that the B/R [Benefit/Risk] of Concerta in the proposed indication [adults] is negative".**

In other words, it was now proven that the harm caused by the drug exceeded any potential positive effects.

In May 2011 the European investigation was completed and a final agreement was presented in a Final Variation Assessment Report for Concerta. **[3]**

It can be summarized as follows:

- The combined studies showed that Concerta had no significant positive effects for adults and that the drug caused a number of serious adverse effects, Concerta had a "negative benefit/risk balance" for adults;

- The submitted studies gave clear evidence that Concerta could ***cause*** anxiety and agitated conditions in adults ("evidence for the risk of new-onset anxiety, tension and agitation");

- The submitted studies gave clear evidence of the abuse potential and of the risk of diversion of Concerta;

- A ***causal*** relationship was established for Concerta for aggression, tics, and depression;

- No warnings were to be issued about the fact that it had been proven that Concerta could cause anxiety, agitated conditions and aggression in adults, ***for the simple reason that Concerta should not be prescribed to adults*** ;

- Concerta could ***only*** be prescribed to adults who before the age of 18 had received methylphenidate (Concerta, Ritalin) and who were judged to have had an "adequate response and acceptable tolerance", ***and*** for which a withdrawal of the drug had been tried without success. The pharmaceutical company Janssen-Cilag declared that it agreed to the following conditions: **"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 adequate response and acceptable tolerability."** [Emphasis here.] No other adults could be considered.

It was decided (FVAR p. 9) the following for Concerta in Europe (for the period October 2010-October 2011): **("The usage [of Concerta] may not increase in this time period.")** **[3]**

But the opposite happened in Sweden.

In 2011 the prescription of Concerta to adults (19+) in Sweden increased with 25%, according to official data from Apotekens Service AB (Pharmacy Services Company). **[2]**

This means that Janssen-Cilag sold Concerta *to adults* for 113 million SEK in 2010, and increased the sales to adults up to 142 million SEK in 2011. The prescription in DDD to adults increased from 6 589 035 in 2010 to 8 290 329 in 2011. **[2]** 61% of all methylphenidate prescription (DDD) to adults was for Concerta. **[2]**

Instead of taking action to fulfil the requirements of prescription of Concerta to adults (as agreed in FVAR 26 May 2011) the pharmaceutical company *increased* its sales volume of Concerta *to adults* with 25% for 2011.

Instead of informing doctors and patients that Concerta should **NOT** be used for adults, explaining what the European assessment of the studies showed, the pharmaceutical company announced the European disapproval of Concerta as a successful ***approval*** of the drug.

Janssen-Cilag is stating in its promotional material to health care personnel: "Concerta is now – as the only methylphenidate drug – approved for continued treatment in adult age!" **[4]** (In Swedish)

The company is in other words turning the *disapproval* of the application for Concerta to adults into a unique *approval* of the drug for continued treatment in adult age.

As for 2011 we can, with access to the Prescription Drug Registry of the National Board of Health and Welfare, say: **57 % (!!) of the prescriptions for methylphenidate in Sweden 2011 were for adults 20+. (DDD for 0-19 was 9 570 246; DDD for 20+ was 12 808 417). [5]**

I have in earlier letters to the Commission given data about the alarming diversion and abuse of methylphenidate resulting from the violations of the conditions for continued marketing authorisation.

With the additional data above I hope the Commission will initiate effective procedures in order to handle these violations. It is stated in the Mission Statement on the web site of the Directorate-General for Health and Consumers: "We are open to using both binding legal instruments and other policy tools that bring effective results."

I have no doubts that instruments and tools must exist to enforce the decisions by the Commission, and I hope these will now be applied to handle the situations described above.

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References:

[1] The European Commission, Decision and Appendixes about Methylphenidate Products, from 27 May 2009. http://ec.europa.eu/health/documents/community-register/html/ho11401.htm
[2] Apotekens Service AB (Pharmacy Services Company), prescription of ADHD drugs in Sweden 2007-2011, http://jannel.se/ADHD.droger2007-2011.pdf
[3] MHRA, *Final Variation Assessment Report, FVAR*, Concerta, 26 May 2011,
[4] Janssen-Cilag, Promotional letter, January 2012, http://www.janssen.se/content/backgrounders/janssen-cilag.se_swe/eNewsletters/concerta/ADHD_01_SE_01-2012.html
[5] The National Board of Health and Welfare, The Prescription Drug Registry http://192.137.163.49/sdb/lak/val.aspx