Letter to: Assessor/Assessors for the ADHD drug Strattera,
Medicines and Healthcare products Regulatory Agency – MHRA

Copy: Sarah Morgan, Head of Pharmacovigilance Risk Management, MHRA
Copy: Professor Kent Woods, Chief Executive, MHRA
Copy: European Medical Agencies in Concerned Member States (CMS)

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The ADHD drug Strattera: The forgotten 700 cases of psychomotor hyperactivity

I have earlier this year given info to and requested answers from the MHRA about the ADHD drug Strattera (psychosis, instances of death and all the reported cases of "psychomotor hyperactivity"). This has been done in letters January 2,[1] March 9,[2] May 15,[3] and August 10 [4] . The response could not have been worse – not a single letter has been answered.

I therefore send this letter directly to the assessor/assessors for Strattera – as a service to the MHRA. I don't expect an answer to this letter. What is expected is that the assessors for Strattera just acknowledge the receipt of the information.

Already in the Periodic Safety Update Report (PSUR) nbr 5 (for the period 27th May 2005 – 26th November 2005) the assessors took up Lilly's review of Movement Disorders and the subject of psychomotor hyperactivity (pages 54-55). The assessors criticized Eli Lilly and the following information was given: **"... the MAH [Marketing Authorisation Holder] is requested to provide further clarification as to the criteria used for determining that the 700 reported cases of psychomotor hyperactivity were related to an exacerbation of the underlying ADHD which resulted in exclusion of these cases from this review." [1]**

What could be understood from this was that Lilly had received 700 reports classified as reports of "psychomotor hyperactivity" and that these were excluded from the analysis, with the explanation that they only were a sign of "exacerbation of the underlying ADHD".

This was remarkable in several ways. First of all 700 reports are *many* reports, and considering the accepted rate of underreporting they represent an incidence of

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[1] The ADHD drug Strattera – actions needed now http://jannel.se/letter.mhra.strattera.jan08.pdf
[2] The ADHD drug Strattera – an analysis of reports of drug induced mania, psychosis and hallucinations http://jannel.se/strattera.mhra.March.08.pdf
[3] Strattera: Eli Lilly gave false information about deaths from Strattera "treatment" http://jannel.se/Strattera.death2.pdf
[4] The ADHD drug Strattera and its harmful effects – where is the response from the MHRA? http://jannel.se/strattera.mhra.pdf

between 7000 and 70 000 cases. Secondly, accepting for a moment that ADHD is a valid medical disorder comparable to diabetes – which of course it isn't, based as it is only on subjective views, lacking any confirmable physical abnormality – this would mean that Lilly said that the "medication" (Strattera, supposed to be comparable to insulin) **worsened** the hyperactivity it was supposed to positively affect (induced more hyperactivity). In other words the drug was more than ineffective, it *worsened* the condition for which it was prescribed.

Even more serious, what Eli Lilly classified as "psychomotor hyperactivity" (an exacerbation of ADHD) should very likely, in many cases, **be classified as drug induced agitation, mania, hypomania or akathisia.**

In actual fact the definitions for "psychomotor hyperactivity", "agitation, psychomotor" and "akathisia" are the same, at least in The Medical Dictionary Online: "A feeling of restlessness associated with increased motor activity. This may occur as a manifestation of nervous system drug toxicity or other conditions." **[2]** So the question must be asked: What did the reporting physicians actually report?

The MHRA was asking Lilly for data about these 700 reported cases of "psychomotor hyperactivity" *after* the company had **withheld** this obviously sensitive information and classified it as "exacerbation of the underlying ADHD". The natural solution should have been for the agency to request all data about this security risk, followed by an independent review of the data. But this was not done.

So what happened? What was the eventual answer from Lilly?

The Periodic Safety Update Report (PSUR) nbr 5 was "finalized" in the beginning of 2007. *One year later*, March 2008, a preliminary assessment report for the answers from Lilly for different PSURs was released. Eli Lilly's answer was:

> 'In the initial Preferred Term search, *psychomotor hyperactivity* was included; however, after a screening review of the 700 cases found using this strategy it was determined this term was utilized to denote hyperactivity or exacerbation of ADHD disease state as opposed to de novo movement disorders. Therefore, this term was removed from the list and those cases were not used in the assessment. For the purpose of this document, the LSS database was searched for any atomoxetine spontaneous cases with reported *psychomotor hyperactivity*. A total of 729 cases were identified with 735 events reported. The increase of 29 cases is most likely attributed to the dynamic nature of the database and contains cases that received new/follow-up information after the original datalock in November 2005. Of these 735 events, 489 had the Lower Level Term (LLT) *Hyperactive* and 198 had the LLT *Hyperactivity*. **Hyperactivity is a hallmark symptom of ADHD, for which atomoxetine is approved to treat.** Of the 735 events of *Psychomotor hyperactivity*, 582 were in children and adolescents, 81 were in adult patients, and 66 had unknown age reported. Of the 735 events of *psychomotor hyperactivity* reported, only 4 were considered serious, and 255 also had *Drug ineffective* or *Drug effect decreased* as a reported event. **Lilly thus concludes that psychomotor hyperactivity is often a symptom of ADHD rather than a frank adverse drug reaction. A review of these cases would not have provided any relevant safety information.** [Emphasis added.]

Assessor's comments: The MAH should state whether any of the reported events of psychomotor hyperactivity *were reported along with terms that would reflect an aggravation or exacerbation of the symptoms of ADHD (e.g.* 'ADHD aggravated').

Obviously Lilly had realized its mistake, it's not good PR to claim that the drug was not only ineffective, but also *worsened* the "condition" for which it was approved. So in its answer Lilly now says: **"Lilly thus concludes that psychomotor hyperactivity is often a symptom of ADHD rather than a frank adverse drug reaction."**

In other words Lilly says that what is reported is *not an adverse reaction* at all, but the actual *indication* for which Strattera is approved – ADHD! This is really a remarkable strategy for explaining away the reports.

And the MHRA makes a new similar request (also in the *final* assessment report from May 2008), trying to get data. It has gone almost **three years** since the period for which Eli Lilly excluded the 700 reported cases (26th November 2002 – 31st October 2005) – and still the matter is not resolved.

In order to help the MHRA with its request a search has been done for **"psychomotor hyperactivity"** in FDA's database (MedWatch).

The search found 400 distinct Case + "Psychomotor Hyperactivity" reports for the years 2004-2007 – with Strattera marked as *Primary Suspect Drug*.

Lilly is explaining away the reports of "Psychomotor Hyperactivity" by saying: "…psychomotor hyperactivity is often a symptom of ADHD rather than a frank adverse drug reaction". This is really a bizarre argument to use in this case. After all the reports to the FDA are *Adverse Reactions Reports* where the reporting health care professional in many cases have noted the *indication* ADHD and "psychomotor hyperactivity" as the *adverse event,* with Strattera as the *Primary Suspect Drug.*

How can Lilly be allowed to claim that the adverse reactions reports are in actual fact reports that the persons have ADHD? - which is what they say with the statement "Lilly thus concludes that psychomotor hyperactivity is often a symptom of ADHD rather than a frank adverse drug reaction".

In 58 of the 449 individual safety reports – in 13% of the reports – a Positive Dechallenge is noted, and in 22 reports (5%) a Positive Rechallenge is noted.

This is of course a very strong signal that Strattera caused the noted adverse events – and it most definitely refutes Lilly's argument that what is seen in these reports is in actual fact the "underlying ADHD".

Please see a table for the FDA reports here:
http://www.psychdrugdangers.com/AtomoxetinePsychomotor.html or in the attached PDF file. (Note that the included table over suicidality and homicidality are just for *these* reports – as we know the *total* number of reports over suicidality for Strattera is now well above 1 000.)

Considering the similarity in definitions a table has also been made for the number of reports to FDA (2004-2007) of "Akathisia" and "Restless". The Positive Dechallenge for these is 33.6%.
Please see table here:
http://www.psychdrugdangers.com/AkathisiaRestless.html or in the attached PDF file.

Of use for the MHRA is also a table for "Agitation" with a 22% Positive Dechallenge. Please see table here: **http://www.psychdrugdangers.com/Agitation.html** or in the attached PDF file.

And see also the table for reported mania, hypomania in connection with Strattera. We find a 37% Dechallenge rate. And note in the Hypomania/Mania summary that 59 of the 84 Cases were reports from MDs; only 5 were from Consumers.
Please see table here:
http://www.psychdrugdangers.com/HypomaniaMania.html or in the attached PDF file.

With this the MHRA should have a very good starting point in its follow-up of Strattera and "psychomotor hyperactivity".

The high Dechallenge/Rechallenge rates noted above must answer many questions for the MHRA (answers that Lilly has avoided for a long time). They are important pointers to a causal relationship and are strongly suggestive that the drug was responsible.

Yours sincerely,

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References:
[1] MHRA, *Periodic Safety Update Report 5*, May 27, 2005 – November 26, 2005, finalized early 2007, pages 2, 54-63, http://jannel.se/PSUR5.excerpt.pdf
[2] Medical Dictionary Online, accessed September 9, 2008, http://www.online-medical-dictionary.org/