To: European Medicines Agency (EMA)
Copy: Medicines and Healthcare products Regulatory Agency – MHRA, UK
Copy: The European Commission's Directorate General for Health and Consumer Policy (DG SANCO)
Copy: Media

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ADHD: Strattera Death Count Continued – 150 Reports of Deaths, 64 were Children

The European Medicines Agency has not received the new important data about instances of death in connection with prescriptions of the ADHD drug Strattera.

The reason is obvious: Eli Lilly, the manufacturer of Strattera, is explaining away all instances of death; the responsible medical agency, the UK MHRA, is accepting this and is not requiring that Lilly obtains and submits comprehensive information about all fatal cases.

This is where we stand today as regards deaths in connection with the ADHD drug Strattera:

122 cases of death with Strattera as *Primary Suspect Drug* reported to the FDA, 2004 - 2010. See http://www.lamplightersoftware.com/StratteraAll.html

150 cases of death with Strattera *involved* reported to the FDA 2004 –2010 and in Periodic Safety Update Reports from Lilly/MHRA.

64 children and teenagers have died, 31 of them committed suicide. See summary http://jannel.se/StratteraDeath6.pdf

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Every half year the UK medical agency MHRA is sending out so called Periodic Safety Update Reports (PSURs) to concerned European medical agencies about Strattera. These reports are forming the basis for the "safety work" around this drug. The data are supposed to be commented upon by the medical agencies in the countries where Strattera is approved. And then the report is finalized in UK, conclusions and required actions are issued.

But almost no comments are given from the 25 countries receiving these reports. And if one reads the PSURs about Strattera it is easy to understand why: Every medical agency involved must know that the data presented are more or less worthless, so why comment? Data, analyses and conclusions are from the *manufacturer of the drug Eli Lilly*, with the Scientific Assessor at the MHRA giving some comments to what Lilly has offered. If there is a "new safety signal" (meaning new harmful effects reported) Eli Lilly is being asked to give more data and to submit an analysis of the area for a later PSUR. And so, half a year to one year later Lilly submits a "review" of the "safety signal" – *doing what they can to make nothing of the harmful effects in question.*

One very good example of this "safety work": The "signal" that Strattera induces mania and psychoses with hallucinations in children. In October 2008 information about this was *finally* included in the European product information for Strattera. But *everything* around this "safety signal" was known already in March 2006, when FDA took the unusual step to issue a

very clear and honest report about psychosis, suicidality and aggression/hostility in connection with Strattera (and other ADHD drugs). Eli Lilly and MHRA delayed the warning text about this in Europe *for almost three years!* In December 2007 Lilly submitted *its own* "review" about Strattera and psychosis to MHRA – in fact only a long paper defending the drug, explaining away all evidence and blaming the effects on the children themselves. And then it took another year for MHRA to get the warning text out. **Read the incredible background story about this in the article *The ADHD drug Strattera – actions needed now*** http://jannel.se/letter.mhra.strattera.jan08.pdf where you also find a review of ***The forgotten 700 cases of psychomotor hyperactivity.***

But let's go back to all the cases of death reported for the drug.

The EMA and the European countries in which Strattera are marketed have *never* got any compilation over fatal cases in connection with Strattera from the responsible medical agency, the UK MHRA – much less a full independent review of these cases. Neither have they asked for such a compilation or review.

The children getting Strattera can be expected to be healthy normal children and in this group of "patients" *there should be extremely low morbidity and mortality.*

As seen above it is not: **64 children and teenagers getting Strattera "for ADHD" have died.** I think we can agree that this is quite a "safety signal"! (It should of course be noted that only a *fraction* of the serious harmful events caused by psychiatric drugs are reported to the medical agencies; the actual number of deaths can be expected to be much higher.)

I made a FOIA request to MHRA in November 2007 asking for the number of deaths reported for Strattera. The answer was – *the Agency didn't know.* They had to ask Eli Lilly.

In its answer, January 2008, Lilly said the company up to 30 November 2007 *"has identified 41 fatal cases in our safety database".* But as Lilly only accepted deaths reported by a "health care professional (HCP) or regulatory authority", 17 of these cases were right away deducted by the company. They did not count. In Lilly's words: *"Of the 41, only 24 were Adverse Drug Reactions (ADR) with fatal outcomes."*
(See the letters: Eli Lilly, Letter to the MHRA, January 2, 2008, (see last 3 pages of the document) http://jannel.se/FOI%2008-011.redacted.letters.Strattera.pdf , where Lilly makes a good job trying to convince MHRA not to release this information.)

The data from Lilly and MHRA didn't make sense as other data indicated that FDA had received at least 61 reports of death with Strattera as *Primary Suspect Drug,* 2004-2007. So how could Lilly state 41 fatal cases of which only 24 should be counted?

As MHRA didn't have any data about the number of children and adults who had died I submitted the information that could be found about this (via FDA and PSURs). This was done in May 2008. MHRA didn't answer. First in October the Scientific Assessor of the Vigilance and Risk Management of Medicines (VRMM) in MHRA sent a reply.

In the answer the Scientific Assessor stated:*"… in order to calculate the total number of reports with a fatal outcome* ***it is not simply a case of adding up reports with a fatal outcome*** *mentioned in our assessment reports of the PSURs [Periodic Safety Update Reports] and those available on the FDA website as these different sources may contain duplicate*

information." [Emphasis added.] (MHRA*, Re: letter of 9 September 2008 to "Assessor responsible for Strattera",* 1 October, 2008, **http://jannel.se/Reply.from%20MHRA.Assessor.October.pdf**)

This was of course true. But it was also very true that *much care* had been taken to *exclude* possible duplicates. It was quite easy to see that the data presented was NOT "simply a case of adding up reports with a fatal outcome".

From the MHRA letter it looked as if the Scientific Assessor had done some form of investigation to verify the data about the instances of death brought to the Agency's attention. The Assessor wrote: *"We have looked at the data you have sent us to see if they can add insight to the statutory sources of data we have received* ***and do not think that they are of benefit as we cannot verify their source or accuracy."*** (p. 3) [Emphasis added.]

This indicated that MHRA didn't know anything more about these cases in October 2008 than it knew in November 2007, when I first asked questions about the fatal cases!

I found this very strange as there are clear rules for pharmacovigilance in Europe – and *very strict requirements* for both the medical agencies and pharmaceutical companies in investigating reported serious adverse drug reactions – especially fatal drug reactions. I am of course referring to *Volume 9A of The Rules Governing Medicinal Products in the European Union.* (European Commission, *Volume 9A of The Rules Governing Medicinal Products in the European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use,* September 2008, **http://ec.europa.eu/health/documents/eudralex/vol-9/index_en.htm**)

In order to verify the MHRA's adherence to these rules I made a FOIA request to get the documents that ***should*** exist – had the Agency actually adhered to the rules. I referred very clearly to *all applicable* EU rules. **(See my FOIA request: *FOIA-request about deaths from Strattera treatment*,** 10 January 2009, **http://jannel.se/FOIA.strattera.death.pdf)**

And here is where it stopped. MHRA decided not answer this FOIA request. **The Agency found that asking for this information should be classified as "vexatious".** MHRA did not want to say anything about the documents requested. And the actual reason was of course: **The Agency had failed in its mission; it did not have the documents requested; the rules that all cases of death should be followed up and that comprehensive information should be obtained had simply not been adhered to.**

My investigation about Strattera has been ongoing since 2005 and I have been in contact with MHRA about the harmful effects of Strattera since early 2006. No matter how "vexatious" this can have been for the Agency the "vexatious effects" of the drug revealed in different documents are far worse. **Cardiac disorders, liver disorders, suicidality, aggression, mania, psychosis with hallucinations – and many cases of death –** how can a medical agency allow children to be subjected to this?

But even if MHRA has refused to release more documents about cases of death in connection with Strattera there has been other ways for obtaining data. **These documents prove that Eli Lilly is continuing its violation of the rules and that the MHRA is doing nothing about it.**

> **The "investigation" of the death of a 14-year old boy** who got **cardiac arrest** after having been 7 months on Strattera is a good example of the approach from Eli Lilly – and MHRA.

The boy got Strattera for 7 months, and then "the patient suddenly fell down, his face turned blue, and he experienced cardiac arrest". He died in the classroom. "The reporting physician stated that the event of sudden death was related to atomoxetine treatment."

It should be noted that the boy "had no apparent cardiovascular history and was not taking any concomitant medications"; it should be noted that "his physical development was normal and he was always very active and lively"; it should be noted that the boy "was taking atomoxetine until his death". In other words there were NO "apparent confounding factors".

Having read quite some of the earlier Periodic Safety Update Reports (PSURs) about Strattera I have at numerous occasions – more often than not – seen the causality assessments end up with statements like "these cases had confounding factors present such as concomitant medication or medical history" – and so the role of Strattera in inducing the harmful effect was either excluded or could not be assessed (the same would be the case for the other drugs present).

In the cases where there are no apparent confounding factors – meaning for example that the *only* possible toxic factor introduced into the life of the person was the drug – the causality assessments strangely enough often end up with the words "information was missing from reports preventing full causality assessment". And so the drug's role cannot be evaluated and *nothing* more is done.

And the last scenario is what we can view in the case of the death of this young boy.

Eli Lilly ends the report by concluding: *"This case report was extensively followed up at the time it was notified to Lilly but no further information was provided despite direct follow up with the physician reporter. Without the autopsy report or other additional information, it is difficult to further assess the relationship between atomoxetine treatment and the reported event."*

And the UK Assessor, not getting more than this, would tend to agree; the drug's role cannot be evaluated and *nothing* more is done.

But this time it turned out that the tragic case concerned a 14-year-old *Swedish* boy. Thus it was possible to verify the information submitted by Lilly, and to show it was incorrect.

The PSUR 12 covers the period 27 November 2008 - 26 May 2009, with "late-breaking information" included up to 25 June 2009. The approval date for the report from Lilly was 15 July.

However Eli Lilly stated in its report to the MHRA: *"The availability of the autopsy may take as long as 6 months."* (This ended the causality assessment; the "missing" autopsy report *could,* according to Lilly, have shown some earlier undetected illness explaining the death of the seemingly healthy boy.)

The facts are that the (summary) autopsy report is dated 2 March 2009 – *according to information from the Swedish MPA (having access to the report).* This means that Eli Lilly could have got information about the autopsy when writing the PSUR, and could have known that no underlying, earlier undetected disease was found at autopsy.

Of course the statement from Lilly saying that it was impossible to get the physician reporter to give more data about the case (if that really was needed) should have been put in question. Having reported all this information it would be very strange if the physician reporter didn't want to submit additional data.

***I* submitted the** above data – including data about the autopsy report to MHRA in November 2009, saying I hoped that the data would make it possible for MHRA to advance its investigation into this tragic death of a young healthy boy. I said that in this investigation the Swedish MPA could most definitely assist.

But MHRA was obviously not interested. When the **Reference Member State's *Final* Assessment Report (for PSUR 12)** was issued by MHRA and sent to all European Medical Agencies, **in July 2010**, MHRA had done nothing more to follow up on the case. The only thing written by the UK Assessor was (p. 9):

"The MAH should obtain further relevant information on this case, particularly autopsy findings (which were pending) and any other relevant test results."

FACTS: The boy died in February 2009. The autopsy report was dated 2 March 2009 – and right away available! The case got reported to the Medical Agencies (like FDA) in March 2009. And yet Eli Lilly claims that they can know nothing more about this case – and MHRA says in July 2010, *17 months after the boy died*, that Eli Lilly should try to obtain "autopsy findings (which were pending)".

And in the Reference Member State's *Final* Assessment Report (for PSUR *13*), issued 15 November 2010, there is nothing about this case – it became yet another case where Eli Lilly succeeded to convince MHRA that it was impossible to find the relevant data.

In addition to this, despite knowing the facts the Swedish Medical Products Agency did not make sure that MHRA corrected the false statements from Eli Lilly.

The "investigation" of the death of an 11-year old boy who died from **"ruptured cerebral aneurysm"** after having been on Strattera for some months is another good example of the approach from Eli Lilly – and MHRA.

Per background data directly from the family the boy was healthy and athletic when he died unexpectedly from a bleeding in his brain. The boy died in September 2008 and was reported to FDA in October 2008.

We can find that Lilly in its reporting in Periodic Safety Reports about this case considers it "unrelated" to Strattera use – using a conclusion in the adverse event report, that an uncle was also diagnosed with brain aneurysm rupture – giving the incredible conclusion that the reaction was "likely familial" !

And so the death of this healthy and athletic boy is not being further investigated.

Almost two years after the boy's tragic death, we find in the **Reference Member State's *Final* Assessment Report (for PSUR 11)**, issued by MHRA in July 2010, the following from the MHRA Assessor:

"Cerebrovascular outcomes are a Potential Risk in the Safety Specification of the RMP [Risk Management Plan] for atomoxetine and it is biologically plausible that a cascade of physiological events could be initiated by atomoxetine that could lead to serious clinical cerebrovascular outcomes, including in patients with pre-existing risk factors."

"Therefore, it would have been useful if the MAH had discussed this case in a more detail, as the family history of brain aneurysm in an uncle does not preclude a contributory role of atomoxetine in the events in the patient. The MAH should ensure they fully discuss cases where atomoxetine may have had a contributory role in the development of important potential/identified risks in patients with pre-existing risk factors such as family history."

And so no further investigation or assessment is to be done in this tragic case. Eli Lilly and MHRA can agree that they also in *this* case had "pre-existing risk factors" because an uncle also had died from bleeding in the brain! No further data about the reasons why this uncle died, or how his death *could* be related to the death of this young child, are given. The pharmaceutical company is quite happy to end the story at this point – no further investigations or warnings that Strattera can cause sudden death. And the Assessor from MHRA agrees: We end the investigation at this point. Even if "it is biologically plausible that a cascade of physiological events could be initiated by atomoxetine that could lead to serious clinical cerebrovascular outcomes", we end the case here with saying that an uncle also died from bleeding in the brain. And a simple advice is given to Eli Lilly, as if the company doesn't know this: "it would have been useful if the MAH had discussed this case in a more detail", and a recommendation is made for the future, to "fully discuss cases where atomoxetine may have had a contributory role".

And so we got yet another case where a child has died a sudden death in connection with Strattera treatment, and another case where Eli Lilly has succeeded to get away with it.

We can conclude that the EMA, MHRA, and thus the other European medical agencies, know as little today about all the cases of Strattera death as they did when I started to ask questions.

The only compilation of data in this area available for European medical agencies seems to be the one I have submitted – of which an updated version is found in this report.

No real effort has been done by MHRA, or requested by any other agency, to use the available immense resources to get full information about all these cases of death and to do an independent analysis of that information – *not leaving it up to the manufacturer to explain why Strattera didn't have anything to do with the deaths of all these children.*

The number of deaths is steadily increasing – and the responsible medical agencies have done nothing effective to put an end to that.

In an earlier answer from EMA about instances of death in connection with Strattera treatment (13 December 2010) I got to know that "in most cases it is the responsibility of the national competent authorities to act upon non-compliance of companies to meet their legal obligations for nationally authorised products or to undertake regulatory action as necessary". I also got to know: "Please note that in the case of Strattera, safety issues have been brought to the attention of the Pharmacovigilance Working Party [within the EMA] and this has subsequently led to discussions", and that "the Strattera product information for prescribers (the Summary of Product Characteristics) and patients (the Patient Information Leaflet) has been updated to include appropriate warnings to reflect the current safety profile of the medicine as per currently available data".

I hope a more careful reading of the report above can convince the European Medicines Agency that the national authorities, mainly MHRA, have *not* taken the expected responsibility "to act upon non-compliance of companies to meet their legal obligations".

I also hope the information presented above, showing that the number of deaths is steadily increasing, without anything effective done by the national authorities, can convince EMA or the European Commission's Directorate General for Health and Consumer Policy (DG SANCO), to actually DO something effective about it.

Please give me an answer with what is to be DONE about this disastrous situation.

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