To: European Medicines Agency, EMA
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ADHD: Strattera Death Count Continued – 137 Reports of Deaths, 57 were Children

The European Medicines Agency has not received the 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 only interested in 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:

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

137 cases of death with Strattera *involved* reported to FDA 2004 – March 2010.

57 children and teenagers have died, 28 of them committed suicide. See http://jannel.se/StratteraDeath5.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 as you know 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* – and then we have 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.*

Let's look at the cases of death reported for Strattera.

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 over 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: 57 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) 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 deaths 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 very 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/enterprise/pharmaceuticals/eudralex/vol-9/pdf/vol9a_09-2008.pdf)

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

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?

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 "apparant 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)".

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 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 conslusion 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 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 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.

I would like to know what the European Medicines Agency intends to do with reference to the data presented in this report.

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