Medicines and Healthcare products Regulatory Agency (MHRA)
Market Towers
1 Nine Elms Lane
London
SW8 5NQ

Regarding withdrawal of the harmful drug Yentreve

21 May 2007

Yentreve was approved 11 August 2004 for treatment of incontinence [1]. Manufacturer is Eli Lilly. It is *exactly the same substance* (duloxetine) that is sold as an antidepressant by Lilly, under the name Cymbalta.

As the MHRA knows, Yentreve was never approved in the US. Eli Lilly withdrew its application in January 2005. In BMJ the reason was given: ***"The FDA said that studies of women using the drug for incontinence showed that the risk of suicidality among the women was twice that in the general population of middle aged women in the US."*** [2]

But in the UK it was approved.

How come the MHRA could approve Yentreve just some months before Lilly withdrew its application to the FDA?

According to newly revealed data Lilly, in its application to British (and other European medical agencies), concealed data about suicides and suicidality – and about the drug's inefficiency and other harmful effects.

Lilly chose not to include these negative data in its application in Europe. If all data would have been included it is very likely that Yentreve would have been as disapproved in Europe as it was in the US.

The MHRA now knows the facts but has not yet withdrawn Yentreve from the market.

Parts of the known story follow:

The 19-year-old Traci Johnson committed suicide in a clinical trial in February 2004. Data in media said this was in a trial of the antidepressant drug Cymbalta [3]. It was reported in Swedish media in connection with the news that FDA was issuing warnings for suicide risks with antidepressants. A professor in the Swedish Medical Products Agency (MPA) gave the following calming words about the suicidality: that it was "a sign of betterment, that the drug works", for depressed persons [4].

There was only one problem. Traci Johnson was *not* depressed and she did *not* take part in a study of a drug to be marketed for depression (Cymbalta). She was healthy and took part in a study of Yentreve – to be marketed for urinary incontinence.

The results of the study Johnson took part in were approved for publication on Lilly's web site first 16 November 2006 – the last subject (patient) visit in the study was 18 March 2004. It took Lilly more than 2,5 years to publish the summary of the data [5].

Data from another European agency say this suicide was *not* known, or part of the Lilly submitted material, at the time of approval of Yentreve, in August 2004.

Neither were full data about suicidality and other harmful effects from another study of Yentreve part of the submitted material. This study, with last subject visit 27 February 2003, was approved for publication first 10 October 2006 – 3,5 years (!) after the last subject visit [6]. The MHRA did not have access to all data at the time of approval of Yentreve, and thus did not know that Lilly had failed to show any positive effect of Yentreve compared to placebo after 36 weeks ("failed to demonstrate a long-term difference in health outcomes").

What Lilly succeeded to *show* was that Yentreve caused harmful effects. In the study 224 patients got Yentreve and 227 got placebo. A comparison between reports about mental problems showed that 67 women in the Yentreve group developed some form of such problems, opposed to 30 in the placebo group. Under the heading "Nervous System Disorders" it was reported that 78 women in the Yentreve group experienced such an effect during the study, as opposed to 34 women in the placebo group.

The above study had been ongoing for *36 weeks*. The studies forming the basis for the application of Yentreve in Europe were mainly three studies of *12 weeks* – where the company had shown some effect above placebo and where the harmful effects had not yet shown up to any greater extent. But the full data from the failed study that had been ongoing for *36 weeks* was not part of the application despite the fact that the last subject visit was *27 February 2003* – 1,5 years before the approval of Yentreve.

This means that women in UK are now subjected to a drug the American authorities could not approve due to harmful effects – and anyone familiar with the normal procedures of the FDA knows that *much* is required in form of inefficiency and harmful effects before that agency disapproves an application.

It means that the FDA gained access to data about safety risks with Yentreve (as above) *after* the MHRA approved the drug based on biased data (even if the harmful effects in the SPC is impressive enough).

And it gets even worse – because today the MHRA knows the whole story, but the information why Eli Lilly withdrew the application in the US is classified. Letters from Eli Lilly explaining the reason the drug was disapproved is available to the agency – but not to the public. Lilly could be hurt if the information was officially released.

Isn't it time for the agency to live up to the principle *"we take any necessary action to protect the public promptly if there is a problem"?*

Isn't it time to admit that the approval was a mistake and withdraw Yentreve from the market?

Janne Larsson
Writer
Snöbollsgränd 22
129 45 Hägersten
Sweden
janne.olov.larsson@telia.com

[1] *Yentreve,* SPC, http://emc.medicines.org.uk/
[2] BMJ, *FDA warns that antidepressants may increase suicidality in adults,* 9 July 2005, http://www.bmj.com/cgi/content/full/331/7508/70-b?etoc
[3] New York Times, *Despite Missteps, Eli Lilly Is a Hard Stock to Bet Against,* 25 February, 2004, (published on) http://psychrights.org/News/NYTimes2-25-04onEliLilly-Zyprexa.htm
[4] Aftonbladet*, "Självmordstankar - tecken på tillfrisknande",* 23 March 2004, http://www.aftonbladet.se/vss/nyheter/story/0,2789,451839,00.html ; and *Nu varnar USA för lyckopillren,* http://www.aftonbladet.se/vss/nyheter/story/0,2789,451837,00.html
[5 Eli Lilly, clinical trial, *Study F1J-LC-HMCG A Placebo-Controlled Study of the Electrophysiological Effects of Supratherapeutic Doses of Duloxetine on the QT Interval,* approved summary 16 November 2006, http://www.lillytrials.com/results_files/yentreve/yentreve_summary_6867.pdf
[6] Eli Lilly, clinical trial, *Study F1J-MC-SBBA Title of Study: Prospective Outcomes of Duloxetine in Usual Naturalistic Care in Women with Stress Urinary Incontinence,* approved summary 10 October 2006, http://www.lillytrials.com/results_files/yentreve/yentreve_summary_3171.pdf