Renowned Psychiatry Professor Helped Forest Labs Cover up Bad Results of Antidepressant in Children

The U.S. Department of Justice has sued the pharmaceutical company Forest Labs about the marketing of the antidepressant Celexa for use by children. It's an affair about bribery, illegal marketing and cover-up of a drug trial with negative results. The company has set aside $170 million to settle the civil aspects of the matter with the government. That does not cover the potential criminal law violations. What has not been told is the important role played by the renowned European Professor of Psychiatry Dr. Anne-Liis von Knorring in this affair. She not only helped the company to cover up the bad results of her clinical trial of Celexa, she also actively misled doctors and the public about it.

On 25 February 2009 the New York Times told that the Department of Justice sued the pharmaceutical company Forest for many millions **[1]**. Forest is a partner to the European company Lundbeck and markets its antidepressants Celexa (Cipramil in Europe) and escitalopram (Lexapro) in the United States (basically two versions of the same drug).

The article in NYT said that Forest defrauded the government of millions of dollars – the company illegally marketed Celexa for unapproved uses in children and teenagers. The basis for the complaint by the Department of Justice is a concealed European study of Celexa for children ("the Lundbeck study"). Top Forest executives were aware of the results but did not for several years reveal the negative result, including the fact that the drug could cause children to become suicidal. Instead the company heavily promoted the results from another study that was supposed to show that the drugs gave positive results when used in the treatment of children.

The concealed European study was performed by the renowned Psychiatry Professor Anne-Liis von Knorring, child psychiatrist, consultant to the National Board of Health and Welfare and to the Medical Products Agency in Sweden. Professor von Knorring and her co-researcher, the country's foremost advocate of antidepressants for children, child psychiatrist Gunilla Olsson are among the small selected group who have known the outcome of the concealed study, since around year 2000.

The facts are as follows

In the U.S., pharmaceutical companies can get a six month extension of the patent for a drug if they are carrying out trials of the drug in children and adolescents. A half-year extension of the patent on Celexa (ending 2002) would be worth *very* much for Forest (and Lundbeck). In order to obtain such an extension, Forest on 18 April 2002, submitted two studies in children and adolescents to the U.S. Food and Drug Administration. At the same time it sought to get Celexa approved for children and adolescents.

In the complaint from the Department of Justice, we can read that the FDA 15 July 2002 approved the application for Forest's *patent extension* – based on the two studies on children – a six month extension of the patent on Celexa for adults (during which time no other drug company could produce the same drug).

But when it came to the application for *approval of Celexa for children* FDA rejected this, on 23 September 2002. To understand the rest of the story it is necessary to know that the FDA rules say that a *refusal and the reasons for this* is confidential information - they notified *only* the pharmaceutical company in question, not anyone else.

It was first 6 years later, with the complaint by the Department of Justice, when FDA's rejection of the application and the reasons for it became publicly known.

In the complaint – which was made known through a press release **[2]** – we can on page 12 read the FDA's assessment of "the Lundbeck study" (Professor Anne-Liis von Knorring's European study), and that this study ...

> **"...is a clearly negative study that provides no support for the efficacy of citalopram [Celexa] in pediatric patients with [major depressive disorder]. [3]**
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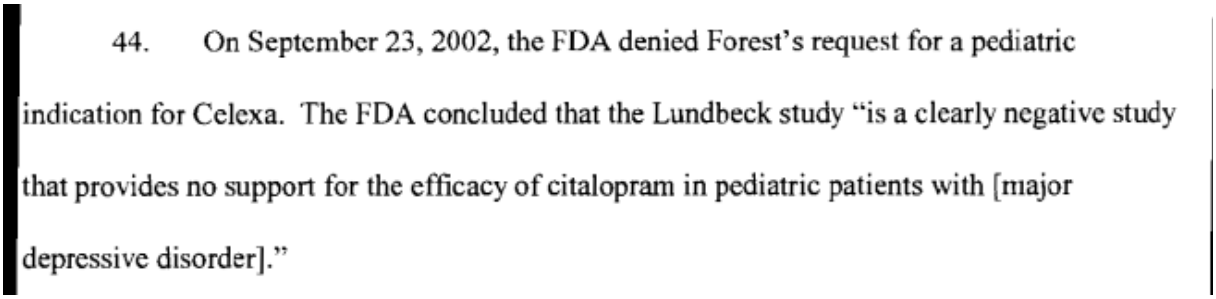
> **[Read the entire complaint via the link in the end.]**



44. On September 23, 2002, the FDA denied Forest's request for a pediatric indication for Celexa. The FDA concluded that the Lundbeck study "is a clearly negative study that provides no support for the efficacy of citalopram in pediatric patients with [major depressive disorder]."

One can also on page 11 read that "the Lundbeck study" besides being negative, i.e., **"... it did not show Celexa to be any more effective than placebo in treating pediatric depression"**, *also* showed that ...

> **"14 of the patients taking Celexa attempted suicide or reported suicidal ideation (i.e., contemplation of suicide), compared to only 5 patients taking placebo. Under one statistical test, this result was "significant", and, under another statistical test, it was "borderline significant"."**

depression, but the Lundbeck study was negative, *i.e.*, it did not show Celexa to be any more effective than placebo in treating pediatric depression. Furthermore, in the Lundbeck study, 14 of the patients taking Celexa attempted suicide or reported suicidal ideation (*i.e.*, contemplation of suicide) compared to only 5 patients taking placebo. Under one statistical test, this result was "significant," and, under another statistical test, it was "borderline significant."

In the complaint one can read how Forest hid the results of the Lundbeck study and instead "aggressively marketed" a study of Celexa by the American psychiatrist Karen Wagner – a study that was supposed to show that Celexa was safe and effective for children. When reading the rest of this article bear in mind that the half year extension of the patent for Celexa in the U.S. was worth **$485 million (!)**, (see p. 14 of the complaint) for the company.

51. Although Forest submitted the Lundbeck study to the FDA in 2002 in order to seek a six-month extension of patent exclusivity for Celexa (which Forest later valued at $485 million), Forest failed otherwise to disclose the negative study beyond a small group of its senior executives. At the same time, Forest aggressively promoted the Wagner study, thereby relaying the false impression that the only available pediatric data on Celexa was positive.

One can (p. 21-22) read how the pharmaceutical company paid the child psychiatrist, Dr. Jeffrey Bostic, $750.000 for the years 2000-2006, as compensation for his promotion of the company's antidepressants. Bostic made over 350 presentations of the drugs, in 28 states, where many of the presentations were about the use of the drugs for children. (Compare this with the information below how the company Lundbeck, in Europe described how Psychiatry Professor Anne-Liis von Knorring and Child Psychiatrist Gunilla Olsson, travelled "around the country" [Sweden] to market antidepressants - also for children.)

One can (p. 20-21) read how the company's dealers got doctors to prescribe Celexa for children (based on the "positive" study senior management had decided should be aggressively marketed), and (p. 21) how the company arranged "education" of physicians - which was only slightly disguised promotional events. (Compare this with the information below how Lundbeck described the country-wide "education" of doctors in Sweden.)

One can (p. 29-30) read how Forest paid major psychiatric opinion-leaders' fishing trips, visits to luxury restaurants and other events. (Compare this with how Swedish psychiatric opinion leaders were invited to the French Riviera by Lundbeck and other pharmaceutical companies, and the way in which they declared their commitment to future cooperation.)

So what did Lundbeck and its paid psychiatric opinion leaders in Sweden do?

The concealed study that is the basis for the complaint in the U.S. is the clinical trial of Celaxa (Cipramil) on children, done by Psychiatry Professor Anne-Liis von Knorring, and sponsored by Lundbeck.

The study began in 1996 in Sweden, was extended to various European countries (Finland, Norway, Denmark, Switzerland, Germany and Estonia), and ended around 2000. Anne-Liis von Knorring led the study, and had as her primary co-researcher at the University Hospital in Uppsala, the child psychiatrist Gunilla Olsson.

Anne-Liis von Knorring and Gunilla Olsson knew early of the results of the study and must have known all about them when the FDA made its conclusion that the study "is a clearly negative study that provides no support for the efficacy of citalopram [Celexa] in pediatric patients with [major depressive disorder]" in 2002. Even if Lundbeck according to the complaint thought also negative data should be published they did not do so.

So what did Lundbeck, von Knorring and Gunilla Olsson tell doctors, media and patients?

Lundbeck publishes the magazine Transmittorn (The Transmitter). In number 2 of the magazine from 1999 the "new child psychiatry" is presented. In the editorial, by Psychiatry Professor Jan Wålinder, Chairman of the Lundbeck Foundation **[4]**, this incredible assessment is made: "One in four children/adolescents are suffering from a mental disorder." **[5]** It is further said:

> "Around the country they have travelled, the child and adolescent psychiatry lecturing team with Professor Anne-Liis von Knorring in the lead. … they met with crowded halls. Lundbeck's symposium series 'The ages of the brain' and the first four sessions on child and adolescent psychiatry has attracted such attention and interest that the organizers had to reschedule for larger lecture halls for a couple of rounds."

As seen Lundbeck is very enthusiastic about a tour that can be compared with the lecturing tour by Dr. Jeffrey Bostic over 28 U.S. states, as described in the complaint by the U.S. Department of Justice.

Gunilla Olsson conveys, in the same issue of the Lundbeck magazine, the view of Celexa and other antidepressants that was presented by the lecturing team. She says:

> "We know today that treatment of depression with **SSRIs work equally well in young and adult depression patients**. As in so many other medical situations, it is **important that the depression is given treatment and care as early as possible**, not least because all the serious consequences to be avoided. "[Emphasized here.] **[6]**

Olsson gives this statement while being a leading researcher in the study that according to the FDA showed the *negative* results cited earlier. She says this about psychotropic drugs which are not approved for children.

The negative result of the Lundbeck study was known to the FDA and to senior Forest executives in April 2002; *and earlier by Anne-Liis von Knorring/Gunilla Olsson.*

Although Anne-Liis von Knorring was aware of the negative results early on, she did not make them publicly known. On the contrary, almost *two years* after Forest had submitted the *negative* results from "the Lundbeck study" to the FDA (April 2002), Professor von Knorring publicly, in the Swedish Medical Journal, *described the study in a completely different, positive way*. In connection with some positive studies about antidepressants for children mentioned in the article in the journal it is said: "In addition, a study of Cipramil [Celexa] is in the pipeline to be completed, a study in which Anne-Liis von Knorring herself has been a coordinator. The study is not yet published." One can assume that von Knorring did not tell the reporter about the results submitted to the FDA in 2002. Professor von Knorring then makes the following remarkable statement (where one also gets the idea that the study is not quite finished):

> "The only side effects we have seen with Cipramil [Celexa] in these populations are an increased frequency of fatigue. **The increased frequency of suicidal thoughts, as some other types of drugs have had as side effects, we have not been able to see in our study.** The study includes 240 patients aged 13-18 years and our study is **possibly too small for results to be completely reliable, it may need to be further expanded.**" [Emphasized here.] **[7]**

This is what the Department of Justice writes in the complaint – compare this with von Knorring's statement above:

> **"14 of the patients taking Celexa attempted suicide or reported suicidal ideation (i.e., contemplation of suicide), compared to only 5 patients taking placebo."**

At the same time von Knorring in the article in the Swedish Medical Journal transformed the increased risk of suicide, as reported for antidepressants, to an expected and even *positive* effect, when she said: "This sort of side effect is often part of the treatment of depressions as the treatment leads to that the patient gets energy to do things that the depression earlier prevented. As hurting oneself."

Professor von Knorring concluded in the Journal "that today probably there is still an under-prescription of SSRIs for adolescents with depression". And she did these statements shortly after the English Medical Agency, MHRA, in December 2003, with the exception of Prozac, *banned* the use of all antidepressants for children.

A few months later, in April 2004, Anne-Liis von Knorring went to the Scandinavian College of Neuro-Psychopharmacolgy (SCNP), to one by the manufacturers of antidepressants sponsored luxury conference on the French Riviera. The conference agenda included, as a declaration of loyalty to pharmaceutical companies: *"We are looking confidently into the future and our continuous cooperation."* **[8]** And one of the areas they had cooperated very well in was, as seen above, to cover up negative research findings and to fraudulently promote antidepressants for children, although these were not approved for pediatric use. "The Lundbeck study", after extensive editing work by "statistical experts" on the company, ultimately got published, in June 2006 **[9]** – 4 years (!) after the results were submitted to the FDA. And in the hands of "statistical experts" it almost looked like a positive study.

In the complaint by the U.S. Department of Justice one can read (p. 20) about the fraudulent arguments that Forest's dealers used to get doctors to prescribe Celexa for children. Let's compare this with what psychiatrist Gunilla Olsson, one of the main researchers in the concealed and negative Celexa study, has said over the years about giving unapproved antidepressants to children:

> "With the SSRIs, we now have a good chance to break depressions quickly ... For the [young] to accept and carry out a treatment they need to have knowledge about medicine function, both biologically and symptomatically."
> Serotonin in Psychiatry, No. 1, 1999.
>
> "The newer drugs for depression, SSRIs (Selective Serotonin Reuptake Inhibitors), works equally well for adolescents and adults and are easy to use."
> Advice for young people, Net Doctor, quote from version 1 January 2001.
>
> "There are several reasons to medicate young people. If you do not treat they risk losing much. An untreated depression can also turn into a deep depression and become prolonged. At worst, it can lead to suicide. "
> Pfizer press release, 27 September, 2002
>
> "It is still so that too few teenagers get needed medicine." "Despite the difficulty of getting studies done one has been able to demonstrate that the drugs have effects without serious side effects."
> We can not afford to lose our young, the newspaper Aftonbladet, 22 August 2003.
>
> "... Stress leads to the degeneration of neurons and the medicines we use today can protect cells and help them grow again."
> The book Depression i tonåren, (Depression in Adolescence), 2004
>
> "... Antidepressants are effective and in many cases can quickly get the depression to go", "The drugs are not risky to use."
> Newspaper Dagens Nyheter, 24 November 2004

No actions have been taken by judicial agencies in Sweden to investigate the activities of Lundbeck, Anne-Liis von Knorring or Gunilla Olsson.

Instead Professor Anne-Liis von Knorring has just recently been given the position of external expert in the independent government agency "The Swedish Council on

Health Technology Assessment" **[10]**, to give advice about the medical treatement of children with ADHD diagnoses.

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[6] Olsson, Den förrädiska depressionen hos barn och ungdom (summaries of lectures), *Transmittorn 2*, 1999 http://www.transmittorn.com/nr_7/art6.htm
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[8] Program for 45th-Annual and 4th Mediterranean Meeting; SCNP.
[9] Anne-Liis von Knorring et al., A Randomized, Double-Blind, Placebo-Controlled Study of Citalopram in Adolescents With Major Depressive Disorder, Brief Report, June 2006, *Journal of Clinical Psychopharmacology*, http://www.ncbi.nlm.nih.gov/pubmed/16702897
[10] SBU, website http://www.sbu.se/en/