Open Letter V, to Dr Ian Hudson, Chief Executive of MHRA

18 February 2016

ADHD drugs – MHRA and the Concerta scandal – a summary

Dear Dr Hudson,

Thank you for the answer dated 10 February 2016.

We can now summarize the Concerta scandal and the MHRA:s handling of it:

- In July 2010 the MHRA assessment of Concerta for adults was given this comment by the Dutch medical agency: **"We fully support the position of the RMS [Reference Member State, UK] that the B/R [benefit/risk] of Concerta in the proposed indication [adults] is negative…"** In May 2011 the MHRA gave the following final directive to the manufacturer, Janssen, about the prescription of Concerta to adults: **"The usage [of Concerta for adults] may not increase in this time period [up to October 2011]."** (All data and references in my letters below.)

- The MHRA and Janssen "made a deal": Janssen should make sure that Concerta was *not* prescribed to adults in Europe, and the MHRA did make sure that Janssen didn't have to warn about the alarming safety data in the trials of Concerta on adults – after all no adults would be prescribed Concerta.

- But the prescriptions of Concerta to adults exploded and the MHRA got reliable and exact data about this exploding prescription in Sweden. The Agency did not act in any way to enforce what was decided when Concerta was disapproved for adults. The prescriptions continued to explode.

- As CEO of the MHRA you made the following promise: **"We will continue to monitor European and international patient exposure and any new information on benefits and risks of methylphenidate through Periodic Safety Update Reports."** The facts in this case show something else.

- When asking (FOIA request) for the Periodic Safety Update Report about Concerta submitted by Janssen for the period October 2012-October 2013, the Swedish MPA (15 February 2016) says it can't be released. It is not finalized, it is being assessed, and the release of the data in the report would threaten Sweden's relations with other countries; "impair the possibilities for Sweden to take part in the international cooperation".

- So the obvious question was: When did Janssen submit this important Periodic Safety Update Report for Concerta, for the period October 2012-October 2013? And so the truth is revealed: **Janssen submitted this safety report 19 December 2013! This means that the MHRA has been sitting on this report for over 2 years, without getting it finalized. Without getting any actions done based on the safety data in the report.**

- With this and all references in my earlier letter I have **a)** shown that the MHRA has concluded that the harms of a psychiatric drug (Concerta) clearly outweighs the potential benefit of the drug for adults, and thus should not be used. I have **b)** proven that the MHRA has failed to take any action to enforce the conclusions of its own assessors, and **c)** that the MHRA has been sitting on an important Periodic Safety Update Report for Concerta, for over 2 years.

- And the final action in burying this scandal seems to be what you now let us know in your letter: **There will be no finalized specific Periodic Safety Update Report for Concerta.** We will never see the reliable and exact data about the exploding prescriptions of Concerta to adults in Sweden – in violation of what was decided – in any assessment report from the MHRA. And why? Because, as you say, all the different methylphenidate drugs (Concerta, Ritalin, Medikinet …) will now be handled in ONE Periodic Safety Update Single Assessment Procedure, supposed to be released in June.

- **Or do you, Dr Hudson, really want us to believe that we in the coming report will be able to read about this: that your assessors in 2010 found that the harms of Concerta outweighed the potential benefit of the drug for adults; the conclusion that the prescription must not increase to adults; the exact data about the exploding prescriptions after that point – with Janssen selling the drug in Sweden for adults for over 500 million SEK (!); decisive actions to immediately curb the prescriptions of Concerta to adults with legal actions against the pharmaceutical company if this does not happen?**

Yours sincerely,

Janne Larsson
Reporter
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Medicines & Healthcare products Regulatory Agency

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Janne Larsson
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Sent by email: janne.olov.larsson@telia.com

10 February 2016

Dear Mr Larsson

Thank you for your email dated 26 January 2016 regarding your update of prescribing Concerta to adults in Sweden, emailed to MHRA in October 2015.

The MHRA can only reiterate that issues of prescribing practice in Sweden are for the relevant professional bodies in Sweden. We will not be making any further comments to you on prescribing practices in Sweden.

We will take your concerns regarding patient exposure into account during the Periodic Safety Update Single Assessment Procedure (PSUSA/00002024/201510).

Yours sincerely

Dr Ian Hudson,
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Open Letter IV, to Dr Ian Hudson, Chief Executive of MHRA

11 October 2015

ADHD drugs – MHRA and the Concerta scandal – an update

Dear Dr Hudson,

In the beginning of 2014 you received and answered my earlier letter about the Concerta scandal and the pharmaceutical company Janssen. This is to give an update to you and your Pharmacovigilance Department about the situation.

To recap: The methylphenidate drug Concerta was in your investigation found to have "negative benefit/risk balance" for adults; should *not* be prescribed. And so eager was Janssen to make sure that the negative data in the Concerta trials on adults did not reach the public that the company, in its document from January 2011, 29 times repeated a version of the statement: **"The Company no longer seeks an extension of the indication to include adults with ADHD** [i.e. does not any longer seek approval of Concerta for adults]**."** And: **"The Company therefore considers that no further action** [i.e. issued warning text] **is necessary."** http://jannel.se/Concerta.Janssen.Response.11.01.2011.pdf

You made a deal with Janssen, basically saying:

> **You [Janssen] make sure that Concerta is not prescribed to adults in Europe, and we make sure that you don't have to warn about the alarming safety data in your trials of Concerta on adults.**

And we can for sure say that you kept *your* part of the agreement. But Janssen didn't keep its part at all. The agreement in the Final Variation Assessment Report from May 2011 was: **"The usage [of Concerta for adults] may not increase in this time period."** [1] (The first period being October 2010-October 2011.) But as you know from my earlier letters (full background below) Janssen *made sure* that the usage of Concerta for adults *exploded* in this and later time periods.

The very reason I take this up with the *MHRA* again is that UK *is* the Reference Member State for Concerta in Europe and supposed to follow up what happened with the decision in the Final Variation Assessment Report. The follow-up is done via Periodic Safety Update Reports (PSURs) where the company, Janssen, gives data to be evaluated by MHRA (after comments from member states), and ends in safety recommendations from the drug regulator. You wrote in your earlier letter (below): **"We will continue to monitor European and international patient exposure and any new information on benefits and risks of methylphenidate through Periodic Safety Update Reports."**

But as I have stated earlier we have seen *nothing* of this, the monitoring of "patient exposure" has been non-existent in the Periodic Safety Update Reports – as if Janssen has had the intention to avoid giving data about the continued increased prescriptions of Concerta to adults. And the MHRA and other involved drug regulatory agencies have allowed this lack of information. We can safely say that the only reliable "patient exposure" data (nationally) about Concerta for adults, sent to the MHRA, are the data sent by me – exact information directly received from the good, exact Swedish national registers. This means

that even the Swedish Medical Products Agency, having access to all needed data, have failed to submit data in the follow-up process.

And we come to the updated information about the prescription of Concerta to adults in Sweden. Keep in my mind that it was agreed in the beginning of 2011 that the prescription of Concerta to adults "may *not* increase". Keep in mind that Janssen and the MHRA made it very clear that "**those patients with ADHD who would be considered for continuation of treatment into adulthood *must* have previously been treated with methylphenidate and continue to show adequate response and acceptable tolerability."** [Emphasis here.] No other adults could be considered.

We listen to what Mikael Själin, Medical Affairs Director for Janssen in Sweden, had to say in Swedish Radio (SR) about the prescription of Concerta in Sweden, 31 August this year (translated) [2]:

> **"As I understand it, almost half of the use [of Concerta] is for adult patients. And it is likely teenagers continuing, as you can do, up in adult age. But in all likelihood, it is also a large number of adults who are newly prescribed Concerta, and that is a use not supported by the Medical Products Agency, and neither do we stand behind it."**

We should shake our heads in disbelief. Here we have the Medical Affairs Director for a company selling its drug to adults for 616+64=**680[1] million SEK (53 million GBP) in the years 2011-2014,** [3] and the Director, with all his daily information about sales, does not know for whom the drug was sold in these four years, and does not "stand behind" sales for adults?

Let's help Janssen find out a bit better. A fast check with the Swedish authorities gives the result that Concerta (and its generic form, for 2014) was sold for 1157 million SEK (92 million GBP) in 2011-2014. For children 477 million SEK, for adults 680 million SEK. **This means that the "off label" sales for adults was 59 % of the total sales of the drug. For the year (2011), when the sales was not to increase, it went from 112 million SEK (2010) to 142 million SEK (2011), to 166 million SEK (2012), to 180 million SEK (2013) and to 128+68=192 million SEK (2014) – an increase with 71% from 2010.**

We have total sales figures for the drug in the country comparable with the annual income of 5,000 citizens, and the responsible Medical Affairs Director pretends that he really does not know who got sold what and for how much.

Let's help Janssen find out even more. We send some simple questions to the helpful staff at the National Board of Health and Welfare, having access to the Swedish Prescribed Drug Register. And we get the exact data **that 40,952 unique adults (19+) got Concerta in 2011-2014.**

We also want to find out **the number of unique adults *newly* prescribed Concerta,** meaning the number of adults who had *not* got the drug before the age of 19. We remember from

[1] In 2014 Janssen had lost it patent on Concerta. For that year the sales was 128 million SEK; the generic form of Concerta, marketed by Sandoz, was sold to adults for 64 million SEK, in total 192 million SEK that year. The same rules governing Janssen's Concerta would apply for the generic version. In the later data about number of prescriptions to adults the two are combined for 2014.

the agreement between the drug regulatory agencies and Janssen that the *only* persons who could be considered for prescription after the age of 18 was those who had "previously been treated with methylphenidate and continue to show adequate response and acceptable tolerability". And the National Board of Health and Welfare can tell us about that too:

> **The data say that 29,226 adults were *newly* prescribed Concerta in the years 2011-2014, meaning that 29,226/40,952, or 71% of all adults prescribed Concerta belonged to the category *newly* prescribed[2].**

Of course Janssen in Sweden had access to this easily found information, and many, many more details about the development of the sales activities. Yet the Medical Affairs Director pretends in national radio that he has only some vague impressions of what has been sold.

And what about the Medical Affairs Director knowing about the sales of the drug to adults for 680 million SEK (53 million GBP) these four years and saying: "… **it is a use not supported by the Medical Products Agency, and neither do we stand behind it".**

It was much more than half of the total sales of the drug, and the company knew about it from the very first month after the agreement with the MHRA *not* to increase the sales to adults, with the very clear promises that the *only* adults prescribed Concerta would be those who had been treated before the age of 19. And so the sales increased year after year (2011-2014), until at last Janssen had sold Concerta to adults for 680 million SEK – without standing behind it!

We heard Janssen's Medical Affairs Director say that the use of Concerta described above was "not supported by the Medical Products Agency". Your Pharmacovigilance Department should take a look at the comments from the MPA in the Periodic Safety Update Reports. Do they find *any* action from the MPA to handle Janssen's illegal marketing activities and to curb the exploding off-label prescription of Concerta? Do they find *anything at all* indicating that the MPA doesn't "stand behind" this serious violation of the rules? Do they find *any data* from Sweden (like the data above) useful for the Department's assessment of the report?

Of course, these are rhetorical questions; the MPA has in actual fact assisted Janssen in its illegal marketing of Concerta. Instead of informing doctors about the data and conclusions in the Concerta investigation the MPA has, as I wrote in my earlier letter, spread these falsehoods:

> **"Stimulants are effective in about 70% of [adult] patients with ADHD in controlled trials."** And: **"Stimulants … improves ... anger outbursts, mood swings."** And: **"Side effects are usually mild and transitory ..."** http://www.biomedcentral.com/1471-244X/10/67

This is what all Swedish doctors get to know, what they believe in – and what they say to their patients. This fraudulent marketing is what is behind the exploding prescription of a

[2] The so called "wash-out period" chosen by the National Board of Health was from 31 July 2005, meaning that the persons calculated as "newly prescribed" had not got a prescription in the time 31 July 2005-31 December 2010.

drug found to have a "negative benefit/risk balance" for adults; a drug that should *not* be prescribed.

The **MPA** – **Jane Ahlqvist Rastad**, with a prominent position also in the EMA, CHMP – has also recently appointed the Key Opinion Leaders **Ylva Ginsberg** and **Johan Franck** to propose new medical guidelines for the treatment of adults with ADHD.

Ginsberg and Franck can be said to be our national representatives for what the Texas prosecutor said 2008 in the famous case against Janssen, when he claimed that the company acquired *"key opinion leaders", "advisors"* and *"experts",* and provided inducements including *"research funding", "consulting fees"* and *"enhanced professional reputation"* to these *"experts",* to get *"biased research in favor"* of Janssen's drug. [4] A full description of Janssen's (and Johnson & Johnson's) illegal activities, including the Texas case, can be read in the new article America's Most Admired Law Breaker. [5] Law enforcement agencies in Europe would have much to gain comparing the data in the Texas case with Janssen's marketing activities for Concerta.

I think the MHRA also finds it interesting that psychiatrist Ylva Ginsberg was Janssen's clinical investigator in Study 3013 and Study 3002 – both part of Janssen's, by the MHRA, disapproved application to get Concerta approved for adults. We find **Ginsberg and Janssen** saying (Study 3013) that **Concerta "provided overall benefits in the treatment of adults with ADHD",** and that **the study showed "treatment was well tolerated".** [6] We find the **drug regulatory agencies** saying that Study 3013 (13 weeks) was **"clearly a failed study"** and that **"the lack of demonstrated efficacy coupled with the safety issues, especially cardiovascular safety (potential long-term effects of increase in BP [blood pressure]), abuse potential, and psychiatric/aggression AEs** [Adverse Events] **render the B/R** [Benefit/Risk] **negative for the proposed indication",** concluding: **"A causal relationship with Concerta was established for aggression, tics and depression."** [7] We can conclude that Ginsberg and Janssen misrepresented the actual result of the study and *"concealed and failed to disclose information about safety"* (quote from the Texas case). And with that background, in addition to other huge conflicts of interest in the area, [8] Ginsberg was appointed to propose new medical guidelines for the treatment of adults with ADHD in Sweden.

Johan Franck has together with Ylva Ginsberg been the leading force behind the escalating prescription of high doses of Concerta and other methylphenidate drugs to prisoners in Sweden. On his advice the MPA is now accepting prescription of huge doses of methylphenidate and amphetamine to amphetamine addicts ("with ADHD"). Doses of 300 mg- methylphenidate and 250 mg- dexamphetamine is "acceptable". [9] In 2013 Franck/Konstenius published a study supposed to show that "methylphenidate treatment reduces attention deficit hyperactivity disorder symptoms and the risk for relapse to substance use in criminal offenders with attention deficit hyperactivity disorder and substance dependence" [10], a highly misleading presentation. It has taken several court decisions and three critical decisions from the Swedish Parliamentary Ombudsmen (JO) to get the researchers in this area to understand what the good Swedish Freedom of Information Act actually means, and that the real research results are not their own property. So it is now possible to show raw data from the study and how the researchers had

turned a disastrous result into a success. [11] As Franck now is writing guidelines for the Medical Products Agency in this area we can wonder if his conclusions from 2007 about the miracles with methylphenidate will be visible in the final paper from the Agency: “When you take psychostimulants something happens that kind of streamlines the traffic in the brain. Suddenly you can read a book, listen, talk, communicate. One can be quiet and wait for his turn.” [12]

And we can ask the question: Is it true, as the Medical Affairs Director for Janssen says, that the MPA *does not* support the prescription of Concerta to adults in Sweden? If so, wouldn’t it be possible to show this in another way than to appoint the strongest proponents for such prescriptions to write national guidelines?

I have been informed by the Swedish MPA that the safety work in Europe about Concerta is led by the MHRA – and that the effective actions are supposed to come from that leadership. With the above data known to your Pharmacovigilance Department we should be able to read the correct information about the prescription in Sweden in the next Periodic Safety Update Report for Concerta.

Let me also repeat what I said last year about the warnings issued to patients. Do you think Dr Hudson that psychiatrists give this honest information – that was found in your investigation – to their adult patients and that this “sales talk” is how Janssen has sold its drugs to adults for 680 million SEK in Sweden?

> **“I will prescribe Concerta to you. However you should know that Concerta in the Company’s best studies had no positive effects after 5 weeks, while *causing* quite some serious harmful ones. Like aggression, depression, anxiety, psychosis, heart disorder. Just so you understand: They have proven that you very likely will not get anything positive out of Concerta after 5 weeks, and that everything after that point is on the minus side. And all this comes from an extensive investigation led by MHRA.”**

In my earlier letters I have given more evidence about Janssen’s criminal marketing activities resulting in the scene described above. The data in your agreement with company has not reached doctors and the public. Instead the Key Opinion Leaders, hired by the pharmaceutical company, have been misleading the public, saying that the drug is effective in “about 70% of [adult] patients”, with “mild and transitory” side effects.

I am now repeating my request that you *counter* the misleading marketing campaign from Janssen about Concerta and actually tell European doctors, patients, politicians and the media what was proven in the investigation led by the MHRA.

I am expecting the MHRA to finally do something *effective* to handle this scandal – we have tens of thousands of patients in Europe right now who are subjected to the *harmful effects* of a drug that you have disapproved, without informing them.

Yours sincerely,

Janne Larsson
Reporter
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[1] MHRA, Final Variation Assessment Report, FVAR, 26 May 2011, http://jannel.se/FVAR.Concerta260511.pdf
[2] Felix och medicinerna (Felix and the medication), SR (Swedish Radio), Vetandes värld, 31 August 2015, 12:20, http://sverigesradio.se/sida/avsnitt/597962?programid=412
[3] e-Hälsomyndigheten, Prescriptions of ADHD drugs in Sweden 2008-2014.
[4] State Prosecutor Greg Abbott, "Plaintiff's Second Amended Petition," December 12, 2008, http://jannel.se/texas-janssen-complaint.pdf
[5] Brill, America's Most Admired Law Breaker, The Huffington Post, September 2015, http://highline.huffingtonpost.com/miracleindustry/americas-most-admired-lawbreaker/
[6] Casas, Rösler, Kooij, Ginsberg, Ramos-Quiroga, Heger, Berwaerts, Dejonckheere, van der Vorst, Schäuble. Efficacy and safety of prolonged-release OROS methylphenidate in adults with attention defi cit/hyperactivity disorder: A 13-week, randomized, double-blind, placebo-controlled, fixed-dose study. *The World Journal of Biological Psychiatry*, 2011; Early Online, 1–14. http://www.ncbi.nlm.nih.gov/pubmed/22106853
[7] MHRA, Preliminary Variation Assessment Report, Concerta, July 2010 http://jannel.se/PVAR.Concerta140710.pdf ; MHRA, Final Variation Assessment Report, Concerta Day 90, 26 April 2011 http://jannel.se/FVAR.Concerta.Day90.260411.pdf ;MHRA, Final Variation Assessment Report, Concerta, 26 May 2011, http://jannel.se/FVAR.Concerta260511.pdf
[8] Declaration of Conflicts of Interest (Swedish text), Ylva Ginsberg, 4 January 2015, http://jannel.se/GinsbergConflictsOfInterest.pdf
[9] (MPA) Läkemedelsverket, (Notes from the meeting, text in Swedish), Minnesanteckningar från möte på Läkemedelsverket, 13 April 2010, http://jannel.se/minnesanteckningLVapril2010.pdf
[10] Konstenius M, Jayaram-Lindström N, Guterstam J, Beck O, Philips B, Franck J. Methylphenidate for ADHD and Drug Relapse in Criminal Offenders with Substance Dependence: A 24-week Randomized Placebo-controlled Trial. *Addiction*; 4 October 2013. http://onlinelibrary.wiley.com/doi/10.1111/add.12369/abstract
[11] Larsson, Research fraud, prisoners and ADHD drugs in Sweden, 10 October 2015, http://jannel.se/ResearchFraudADHDprisoners.pdf
[12] (Text in Swedish) Oberoende, Vem vågar skriva ut narkotika till en narkoman, 1/2007, http://rfhl.se/riks/images/rfhl/oberoende/arkiv/oberoende1-07.pdf

Open Letter III, to Dr Ian Hudson, Chief Executive of MHRA

16 March 2014

ADHD drugs – MHRA and the Concerta scandal

Dear Dr Hudson,

First I must say I really appreciate getting an answer from you personally. It is important that the information I have given about the Concerta scandal is fully known at the top of MHRA.

Of course I am not, in your answer, expecting you to agree with me, to admit that MHRA has done anything wrong, or to announce some effective actions from the Agency to handle what I have described. I could at best hope that you read the information and acknowledge that you have done so, while at the same time via my open letter informing politicians and media about the scandal.

As you know the Dutch medical agency, CBG, in July 2010 wrote that it *agreed* with MHRA about the assessment of Concerta for adults:

> **"We fully support the position of the RMS [Reference Member State, UK] that the B/R [benefit/risk] of Concerta in the proposed indication [adults] is negative…" (Day 100-comments NL)**

It was at that time also clear that Concerta actually ***caused*** aggression, depression and tics. To quote from the MHRA assessment:

> **"A causal relationship with Concerta was established for aggression, tics and depression."**

I think you agree with me that the table over adverse events presented by Janssen in January 2011, on the request of MHRA, was very clear (see my earlier letter) – and ***alarming***. Here we have the answer from Janssen (with the table on page 84) and a summary of the adverse events reported in Janssen's own studies of Concerta for adults:

> **Response Document from Janssen (Johnson & Johnson) from January 2011**
> **http://jannel.se/Concerta.Janssen.Response.11.01.2011.pdf**

I don't think, Mr Hudson that you actually have read this document, forming the agreement between MHRA and Janssen about such vital issues as the need for information about what emerged in Janssen's studies of Concerta on adults. If you had, it would be hard to state, as you do in your answer below, that adults are being fully informed about the risks identified in Janssen's studies.

Probably this is the first time that Janssen's "Response Document" is made fully known to the media, politicians and the public in general. Everyone can now verify that Janssen, in the "Response Document" 29 times (!!) repeats a version of the statement: **"The Company no longer seeks an extension of the indication to include adults with ADHD."** And: **"The Company therefore considers that no further action is necessary."**

I would advise you, Mr Hudson, before answering *this* letter, to actually take a look at Janssen's document. In it you will – at these 29 points – see what MHRA and Janssen actually agreed to. After that you cannot any longer state that adults receiving Concerta are being informed about what you and Janssen know.

Do you actually think Mr Hudson that psychiatrists say the following to their adult patients?

> **"I will prescribe Concerta to you. However you should know that Concerta in the Company's best studies had no positive effects after 5 weeks, while *causing* quite some serious harmful ones. Like aggression, depression, anxiety, psychosis, heart disorder. Just so you understand: They have proven that you very likely will not get anything positive out of Concerta after 5 weeks, and that everything after that point is on the minus side. And all this comes from an extensive investigation led by MHRA."**

Of course that would be impossible as MHRA has not communicated the results of the investigation in any official publication reaching doctors and the public.

No, what doctors and patients are being told is another message – a false, misleading and deceitful message from psychiatrists sponsored by Janssen and other pharmaceutical companies.

Don't you personally think it is bizarre that Janssen's sponsored psychiatrists could tell the media, the scientific community and the public the following, two months after the company from MHRA got to know that the Concerta application for adults "should be refused"?

> **"Stimulants are effective in about 70% of [adult] patients with ADHD in controlled trials."** And: **"Stimulants … improves ... anger outbursts, mood swings."** And: **"Side effects are usually mild and transitory ..."** http://www.biomedcentral.com/1471-244X/10/67

Without MHRA doing anything to correct the falsehoods.

These falsehoods are widely distributed in Sweden – and are behind the explosion in the prescription of Concerta to adults. The Medical Products Agency has, in the old and new version of Läkemedelsboken [The Pharmaceutical Book] spread what these psychiatrists have written in their Consensus Statement. This is what all Swedish doctors get to know, what they believe in – and what they say to their patients.

I suppose the situation is the same in UK, with the group member Professor Philip Asherson "advising" the National Institute for Health and Clinical Excellence (NICE) about the good effects of Concerta and about "the mild and transitory" side effects.

You write in your letter: "I understand that you have been in correspondence with other parts of the Agency on these matters." Yes, I have been in contact with the unit for "**Vigilance and Risk Management of Medicines".**

I had earlier read the final assessment of the latest Periodic Safety Update Report (PSUR) for Concerta, from MHRA and the Drug Utilisation Study (DUS) 2011 for Methylphenidate, from the manufacturers – and I could not believe my eyes.

Here we had MHRA stating: **"The usage [of Concerta] may not increase in this time period"** (October 2010-October 2011) http://jannel.se/FVAR.Concerta260511.pdf and then no follow-up whatsoever about this in the PSUR!

Here we had the manufacturers of methylphenidate in Europe giving false information about the prescription of methylphenidate in Sweden in the DUS 2011.

So I thought the reason for MHRA's lack of effective follow-up was false data or no data about the exploding prescriptions of methylphenidate in Sweden. In order to correct that I got several Swedish agencies to send the true data directly to the unit in MHRA handling these matters.

However that did not change anything. I am still waiting for effective actions from this unit.

The latest assessment of the Periodic Safety Update Report for Concerta is soon to be released. It will be very revealing and will answer the question if MHRA *now* has followed up, analysed and recommended effective actions in this area.

It is a bit funny to read in your letter that the exploding prescriptions in Sweden are a matter for the Swedish Medical Products Agency, not for MHRA. Especially considering the fact that

the information I get from the Swedish MPA is that the security work about Concerta is led by MHRA – and that the effective actions are supposed to come from that cooperation.

So Mr Hudson, you have a full-fledged medical scandal in your lap. MHRA is *sitting* on the information that a drug proven negative for effect and positive for harm is being heavily marketed and sold to the population (adults) for which it was *disapproved*. The Key Opinion Leaders, hired by the pharmaceutical company, are lying to the public, saying that the drug is effective in "about 70% of [adult] patients", with "mild and transitory" side effects.

I am now expecting you *counter* the misleading marketing campaign from Janssen about Concerta and to actually tell doctors, patients, politicians and the media what was proven in the investigation led by MHRA.

I am expecting MHRA to finally do something *effective* to handle this scandal – we have tens of thousands of patients in Europe right now who are subjected to the *harmful effects* of a drug that you have disapproved, without informing them.

Yours sincerely,

Janne Larsson
Reporter
Sweden
janne.olov.larsson@telia.com

From: MHRA Customer Services

Sent: Thursday, March 06, 2014 5:05 PM

To: 'jan.olov.larsson@telia.com'

Subject: RE: ADHD drugs - MHRA and the Concerta scandal

Dear Mr Larsson,

Thank you for your e-mail of 14 February. I apologise for the delay in responding. I understand that you have been in correspondence with other parts of the Agency on these matters.

I note the action taken against Johnson & Johnson in the USA in relation to risperidone (Risperdal). We work within a different legal framework in the EU. The Marketing Authorisation Holder of Concerta are subject to advertising regulations as set out in Title VIII of Directive 2001/83/EC and are enforced on a national basis within the EU.

As you state in your letter, the public assessment report concerning the variation to include the initiation of treatment of adults diagnosed with ADHD provides information for the general public and is available on the MHRA website. The current Summary of Product Characteristics (SPC) and Patient Information leaflet (PIL) for Concerta does allow use in adults if treatment withdrawal has not been successful when an adolescent has reached 18 years of age, however continued treatment of adults should be reviewed regularly.

The SPC also lists adverse events that are observed in adults who participated in clinical trials, which may also be relevant for children and adolescents. All adverse effects are also listed in the PIL as side effects, written in a language that is easily understood by the layperson.

Both documents contain warnings for all patients (regardless of age) about the risk of underlying mental disorders which can be altered by treatment with methylphenidate. Healthcare professionals and patient carers are directed to monitor patients for adverse events and take the necessary action.

I appreciate that you have concerns about the number of adults treated with methylphenidate, particularly in Sweden. Any concerns about clinical practice and prescribing outside of the licence in Sweden are matters for the MPA and the Swedish medical professional bodies. We will continue to monitor European and international patient exposure and any new information on benefits and risks of methylphenidate through Periodic Safety Update Reports.

Your sincerely,

Dr Ian Hudson

From: Jan Larsson [mailto:jan.olov.larsson@telia.com]
Sent: 14 February 2014 12:02
To: Hudson, Dr Ian
Cc: mailto:%22info@mhra.gsi.gov.uk%22@hosting-e.gsi.gov.uk; nice@nice.org.uk

Open Letter II, to Dr. Ian Hudson, Chief Executive of the MHRA

14 February 2014

ADHD drugs – MHRA and the Concerta scandal

Thank you for the answer (below) on behalf of Dr. Ian Hudson, CEO of the MHRA.

It seems as if my important information is not coming across, so I will try to be a bit more clear in my response.

As you know Johnson & Johnson (and its subsidiary Janssen) in November 2013 agreed with the U.S. Department of Justice to pay 2.2 billion USD, mainly for the illegal marketing of the psychiatric drug Risperdal. The Attorney General of the United States, Eric Holder, said at the press conference presenting the agreement, "these are not victimless crimes" [1].

Let's also look at the case in Texas, where Janssen in early 2012 had to pay 158 million USD [2]. In that case we can, with the words from the State Prosecutor, look at specific examples of *"sophisticated strategies and tactics to disseminate misrepresentations"*, *"a variety of marketing tools disguised as medical education, scientific research and patient advocacy literature"* that the pharmaceutical company used, and how the *company "concealed and failed to disclose information about safety"* of the drug (Risperdal); how it acquired *"key opinion leaders", "advisors"* and *"experts",* and how the company provided inducements including *"research funding", "consulting fees"* and *"enhanced professional reputation"* to these *"experts",* to get *"biased research in favor"* of Janssen's drug. (The quotes from the Complaint against Janssen in Texas [3].)

Let's compare this with Janssen's actions to market and sell Concerta to adults in Europe, despite the agreement with the MHRA and other European drug regulatory agencies *not* to do this.

I refer in my letter below to the secret internal MHRA documents about the Concerta investigation; the documents revealing that Concerta was found to have "negative

benefit/risk balance" for adults. I am glad that MHRA now has made the most important of these documents available to the public, even if it is *very* hard to find it. But here it is: http://www.mhra.gov.uk/home/groups/l-unit1/documents/websiteresources/con2033483.pdf

The MHRA assessment document about Concerta to adult is dated **14 July 2010**. Janssen had the information that the Concerta application for adults "is not approvable" and "should be refused" (page 18 in the document) in July. But at the same time Janssen sponsored "The European Network Adult ADHD", to produce one for Concerta (methylphenidate) *positive Consensus document,* which the pharmaceutical company could then use in their marketing of Concerta for adults [4]. The group wrote in the document: "We thank Janssen-Cilag who provided support for meeting costs of the European Network Adult ADHD."

So despite knowing about the ***disapproval*** of the Concerta application, the company permitted publication of completely opposite data about the *good effects* and *mild adverse effects* of Concerta in adults in the group's *Consensus document.* The publication of the wide spread document about the good effects of methylphenidate (Concerta, Ritalin) for adults, was done **3 September 2010,** 2 month after MHRA informed the company that the Concerta application "should be refused".

Here is a comparison of the data that emerged in the European study of Concerta, and what was stated in the Consensus document:

Consensus document: "stimulants are by far the best studied and most effective treatment for ADHD." "Stimulants are effective in about 70% of [adult] patients with ADHD in controlled trials."
The European study: "B/R [Benefit/Risk] of Concerta in the proposed indication is negative". Overall, the conclusion of Janssen´s submitted studies were that the company could not demonstrate a beneficial effect even short-term (after seven or thirteen weeks).

Consensus document: "Stimulants … improves ... anger outbursts, mood swings."
The European study: "A causal relationship with Concerta was established for aggression, tics and depression."

Consensus document: "Side effects are usually mild and transitory ..."
The European study: "The lack of demonstrated efficacy coupled with the safety issues, especially cardiovascular safety (potential long-term effects of increase in BP [blood pressure]) abuse potential, and psychiatric/aggression AEs [Adverse Events] render the BR [Benefit/Risk] negative for the proposed indication."

Consensus document: "Importantly, both clinical studies and clinical experience support the view that methylphenidate does not lead to stimulant or drug addiction. On the contrary, it has been shown to have a neutral or reducing impact on substance abuse and the risk of relapse."
The European study: "It is assessed there is a significant abuse and diversion risk with Concerta." "... the misuse/abuse potential of methylphenidate is considered a major safety concern: in combination with the concerns regarding the reliability of the diagnosis, adults may try to get diagnosed for ADHD to retrieve methylphenidate in a legalised manner."

Janssen's experts concluded that Concerta (methylphenidate) is the **"first choice medication treatment"** for adults with ADHD **"based on an extensive and still growing body of data on efficacy and safety".** Janssen knew at the time of publication that neither efficacy nor safety was considered to exist for Concerta for adults. Despite that, the company allowed the above false marketing messages to be disseminated to doctors and authorities.

In the group we could also find prominent European psychiatrists, among them **Professor Philip Asherson** (U.K.), advisor to the National Institute for Health and Clinical Excellence (NICE), and a member of the group writing the guidelines for treatment of adults with ADHD in U.K.

The investigation by MHRA and other European agencies showed:

- The combined studies showed that Concerta had no significant positive effects for adults and that the drug caused a number of serious adverse effects, Concerta had a "negative benefit/risk balance" for adults;

- The submitted studies gave clear evidence that Concerta could ***cause*** anxiety and agitated conditions in adults ("evidence for the risk of new-onset anxiety, tension and agitation");

- The submitted studies gave clear evidence of the abuse potential and of the risk of diversion of Concerta;

- A ***causal*** relationship was established for Concerta for aggression, tics, and depression;

- No warnings were to be issued about the fact that it had been proven that Concerta could cause anxiety, agitated conditions and aggression in adults, ***for the simple reason that Concerta should not be prescribed to adults***;

- Concerta could ***only*** be prescribed to adults who before the age of 18 had received methylphenidate (Concerta, Ritalin) and who were judged to have had an "adequate response and acceptable tolerance", ***and*** for which a withdrawal of the drug had been tried without success. The pharmaceutical company Janssen-Cilag declared that it agreed to the following conditions: **"those patients with ADHD who would be considered for continuation of treatment into adulthood *must* have previously been treated with methylphenidate and continue to show adequate response and acceptable tolerability."** [Emphasis here.] No other adults could be considered.

In other words MHRA agreed with Janssen that the company did not need to issue warnings about what emerged in the clinical studies on adults. The company did not need to issue data about the lack of positive effects and the harmful effects proved in Janssen's own studies. MHRA said basically that Janssen did not need to tell this:

Table 59. Number (%) of Subjects With an Important Adverse Event by Adverse Event Category of Special Interest and by Treatment Group
(CONCERTA EU SCS: All Treated Subjects Analysis Set)

Adverse Event Categories of Special Interest	Placebo (N=309) n (%)	DB CONCERTA (N=596) n (%)	Total CONCERTA (N=1369) n (%)
Total no. subjects with Adverse Events	87 (28.2)	307 (51.5)	815 (59.5)
Hypertension	12 (3.9)	32 (5.4)	136 (9.9)
Tachycardia	0	36 (6.0)	81 (5.9)
Raynaud's phenomenon	2 (0.6)	3 (0.5)	6 (0.4)
Psychosis/mania	3 (1.0)	17 (2.9)	45 (3.3)
Anorexia	23 (7.4)	174 (29.2)	394 (28.8)
Migraine	6 (1.9)	7 (1.2)	25 (1.8)
Repetitive behaviours	0	1 (0.2)	1 (0.1)
QT prolongation	1 (0.3)	0	4 (0.3)
Arrhythmias	11 (3.6)	80 (13.4)	240 (17.5)
Cerebrovascular disorders	0	1 (0.2)	1 (0.1)
Aggression	17 (5.5)	71 (11.9)	202 (14.8)
Hostility	0	3 (0.5)	11 (0.8)
Depression	32 (10.4)	100 (16.8)	270 (19.7)
Suicidality	0	1 (0.2)	3 (0.2)
Tics/tourette's syndrome/dystonias	4 (1.3)	25 (4.2)	72 (5.3)
Carcinogenicity	0	0	5 (0.4)
Withdrawal syndrome	0	1 (0.2)	1 (0.1)

From Janssen's "Response Document" (page 84) to the MHRA, 11 January 2011.

In the Company's three best (!) studies of Concerta on adults, the ones chosen for Janssen's application, the following harmful events emerged in the short-term studies (up to 13 weeks), where Concerta was compared to placebo:

- **The persons who received Concerta had a 270% increased risk for heart disorders in form of Arrhythmias;**
- **The persons who received Concerta had a 116% increased risk for Aggression;**
- **The persons who received Concerta had a 62% increased risk for Depression;**
- **The persons who received Concerta had a 225% increased risk for neurological disorders in form of Tics/Dystonias;**
- **The persons who received Concerta had a 190% increased risk for Psychosis/Mania;**
- **The persons who received Concerta had a 295% increased risk for Anorexia;**

And what happened?

After the initial assessment from MHRA (14 July 2010), that Concerta was to be *disapproved* for adults, Janssen and its sponsored psychiatrists issued the misleading data in the Consensus document (2 September 2010).

In January 2011 Janssen declared that the company will withdraw its application – and made the agreement with MHRA *not to* issue warnings about the proven harmful effects.

MHRA agreed with Janssen that Concerta was *not* to be prescribed to adults in Europe. The Agency made the following clear in the Final Variation Assessment Report (FVAR p. 9) from May 2011: (for the period October 2010-October 2011): "The usage [of Concerta] may not increase in this time period." [5]

And Janssen just continued to market and sell Concerta to adults in Europe as if the assessment by MHRA had never been done. In Sweden the company increased its sales of Concerta for adults from 112 million SEK (10.5 million GBP) in 2010 to 180 million SEK (17.0 GBP) in 2013; an increase with 60% (!!) since the drug was disapproved for adults [6].

MHRA is handling the Periodic Safety Update Reports (PSURs) for Concerta in Europe. These reports show that *no effective actions* have been taken by the Agency to enforce the agreements in the years after the disapproval.

***Tens of thousands* of adult patients in Sweden and the rest of Europe have been misinformed and misled about the effects and harmful effects of the drug. MHRA has done nothing to make the real results of Janssen's studies (as written above) known to the patients, while allowing the company and its sponsored psychiatrists to use *"a variety of marketing tools"* to push the drug out on "the adult market".**

So there you have the Concerta scandal. What is MHRA going to do about it?
Yours sincerely,

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[1] Department of Justice, Comments by Attorney General, Eric Holder, 4 November 2013, http://www.justice.gov/iso/opa/ag/speeches/2013/ag-speech-131104.html
[2] The New York Times, "J. & J. to Pay $ 158 Million to End Suit Filed by Texas" January 19 2012, http://www.nytimes.com/2012/01/20/business/johnson-johnson-settles-risperdal-claim-in-texas.html
[3] State Prosecutor Greg Abbott, "Plaintiff's Second Amended Petition," December 12, 2008, http://jannel.se/texas-janssen-complaint.pdf
[4] Kooij et al, "European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD", *BMC Psychiatry,* September 3, 2010, http://www.biomedcentral.com/1471-244X/10/67
[5] MHRA, Final Variation Assessment Report, FVAR, 26 May 2011, http://jannel.se/FVAR.Concerta260511.pdf
[6] e-Hälsomyndigheten, Prescriptions of ADHD drugs in Sweden 2008-2013, http://jannel.se/N06BA.pdf