7 August 2019

# ADHD drugs, MHRA and the Concerta scandal – suicides, suicide attempts and self-harm

Dear Dr Hudson,

It is time to end this long story before you step down as head of the MHRA in September. Included below are all my letters and the answers given.

**As you know this started in 2011** (see page 36) when a secret internal MHRA document revealed: The application to get the ADHD drug Concerta approved for adults was **refused**; Concerta was found to have "negative benefit/risk balance" for adults. In the final decision MHRA wrote to Janssen: "The usage [of Concerta for adults] may not increase in this time period." (2010-2011) We can say that the MHRA made a deal with Janssen: You 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. MHRA kept its promise; Janssen did not.

As I have documented in my letters, the sales for adults exploded. So for example Janssen sold Concerta for adults in Sweden for 680 million SEK (53 million GBP) in the years 2011-2014. The drug was found to have "negative benefit/risk balance" for adults – and the sales *exploded* to that age group! The MHRA did nothing about it. In Sweden the most prominent psychiatrist involved in this scam – Ylva Ginsberg – was even appointed by the Medical Products Agency (MPA) to write guidelines for the prescription of ADHD drugs to adults (see my Open Letter IV) and is now employed by the National Board of Health and Welfare as a "medical expert", to write new guidelines for the prescription of ADHD drugs to *children*.

**In my latest Open Letters (VI-X)** I have extensively taken up the alarming data about the children and adolescents (10-19) in Sweden who have made suicide attempts with *methylphenidate* or taken overdoses of the drug in some other self-destructive purpose in the years 2011-2018. **We now have 754 children and adolescents (10-19) (!) in that category (and 1074 for all ADHD drugs).** In my last letter (27 March 2019) I asked what we could expect to read about these children in the *coming* Periodic Safety Single Assessment Report (PSUSA) for methylphenidate (MPH) from MHRA and EMA. That report was finalised 14 June 2019. It is the same old story. The data from the pharmaceutical companies are a joke, and all the resulting assessments based on them (supposed to be a reflection of reality) are the same. Not only do the data represent a *miniscule* proportion of the actual scene, the companies make a fantastic job of *minimizing even that miniscule proportion.* When the companies have "analyzed" these cases, we have – as seen in the MHRA/EMA report – basically *nothing* left.

**I am sure you can agree with me when I say that this document shows some differences between the factual reality and the MHRA declaration: "We protect and improve the health of millions of people every day through the effective regulation of medicines and medical devices, underpinned by science and research."**

Yours sincerely,

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

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

27 March 2019

# ADHD drugs, MHRA and the Concerta scandal – suicides, suicide attempts and self-harm

## Comparing the data about suicidality and self-injurious behaviour in the new MHRA/EMA report about methylphenidate, 14 June 2018, with known data from little Sweden

Dear Dr Hudson,

As you remember I provided data from Sweden for the earlier Assessment Report (PRAC PSUR Assessment Report, 9 June 2017) about suicide attempts and self-injurious behaviour in connection with methylphenidate. My data were even included in the report, pages 61-63. We could on page 62 read:

> **463 children and adolescents (10-19) made suicide attempts with methylphenidate or took overdoses of the drug in some other self-destructive purpose in the years 2011-2015,** (data from the he Swedish Poisons Information Centre, GIC).
> http://jannel.se/Methylphenidate%20PSUSA.June2017.PRAC.AR.excerpt.pdf

In my earlier letters (below) we can read your statements that my information was "invaluable in the overall assessment" (even if providing "limited case by case detail"). We can also read that the assessors had *severe problems* handling these alarming data when comparing them to the data from the manufacturers (Marketing Authorization Holders, MAH). I could, based on the invaluable information from little Sweden state the following about the "no-figures" given by the MAHs:

> These figures are of course a joke, and all the resulting assessments based on them (supposed to be a reflection of reality) will be the same. Not only do they represent a *miniscule* proportion of the actual scene, the companies make a fantastic job of *minimizing even that miniscule proportion.* When the companies have "analyzed" these cases we have – as seen in the MHRA/EMA report – basically *nothing* left!

**In short:** I had proven that psychiatrists and other health care personnel didn't report the alarming data about suicidality and self-injurious behaviour coming to their attention and that authorities, like the Swedish MPA, with all its resources, allowed this to happen, making it easy for the pharmaceutical companies to explain away the harmful effects of the drugs.

I asked, without getting an answer, if you now would make sure that true and reliable data were included in the *new* assessment procedure, and if these reliable data were to take precedence over the false and unreliable data submitted by the pharmaceutical companies.

**So let's look at the latest report (1). What can we find about methylphenidate and self-injurious behaviour?**

We can find that ***a significant ongoing signal is self-injurious behaviour.***

And we find that the PRAC (Pharmacovigilance Risk Assessment Committee, EMA) – f*rom the data presented by the pharmaceutical companies* – arrived at the following conclusion:

> "Based on the data reviewed regarding self-injurious behaviour the PRAC considers that there is insufficient evidence to support further regulatory action at this time. However, the signal remains ongoing and should remain under close monitoring in future PSURs. Current labelling and risk minimisation measures are deemed appropriate."

We note that the PRAC says that "the signal remains ongoing", and that it "should *remain* under *close monitoring*" (my emphasis); with "remain" meaning "to continue in the same state or condition", and "close" meaning "very attentive; rigorous".

So what data, what *"close monitoring"*, have the pharmaceutical companies and the national authorities as the Swedish MPA submitted for this report?

Here (yellow marked) are the relevant parts covering *self-injurious behaviour* (from the 262 pages long report)
**http://jannel.se/methylphenidatePSUSA-00002024-201710PRAC%20Assessment%20Report.EXCERPT.pdf**

We can, under the heading **Self-injurious behaviour** on page 67, see that **Novartis** has found the following: *"**Three cases** of Ritalin and **one case** of Focalin were retrieved during the reporting period."* (1 November 2016 to 31 October 2017) The four cases leads Novartis to the following conclusion: *"Evidence for causality was identified to be weak. The RR [Reporting Rate] of current reporting interval is lower than previous reporting intervals and cumulative period."* We can see that **Mylan** (manufacturer of Methylphenidate Mylan) has found ***"no cases"*** of intentional self-injury, but recommends: *"MAH proposes to continue close monitoring."* **Janssen** (Concerta, OROS MPH), **Sandoz** (Sandoz Methylphenidate), **Orifarm** (Generics MPH Alternova), **MEDICE** (Medikinet) and **Shire** (Equasym) seem to have had nothing to say at all.

On page 123 of the report we find a table with figures about **Suicidal behaviour/Suicidality,** saying that the pharmaceutical companies had found **20 such cases** in this time period (1 November 2016 to 31 October 2017) **for the age group <18 years**.

**Let's compare this** to data from little Sweden.

(1) The third *Periodic Safety Single Assessment Report (PSUSA) for methylphenidate (MPH)*, 14 June 2018, with recommendations from Pharmacovigilance Risk Assessment Committee (EMA), presenting information for the reporting period 1 November 2016 to 31 October 2017.

**We can from the table below see that 101 children and adolescents (10-19) made suicide attempts with methylphenidate or took overdoses of the drug in some other self-destructive purpose in 2017 and 100 in 2018.** (Data from the he Swedish Poisons Information Centre, GIC.)

**Förfrågningar per år**

*Kopplade ärenden är exkluderade.*

Fr.o.m. *2011-01-01* T.o.m. *2018-12-31*

| | |
|---|---|
| Åldersgrupp | *10-19 år* |
| Förgiftningsmedel | *LN06BA02 / LN06BA04 / LN06BA09 / LN06BA12 / LÖ030020 / LC02AC02* |
| Frågeställare | *Alla* |
| Orsak | *Självdestruktiv handling* |
| Exponeringsväg | *Alla* |
| Risk | *Alla* |
| Råd | *Alla* |

| | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 |
|---|---|---|---|---|---|---|---|---|
| Atomoxetin | 19 | 11 | 22 | 10 | 16 | 20 | 17 | 18 |
| Dexamfetamin | | | | | 1 | | | 1 |
| Guanfacin | | | | | | 3 | 4 | 8 |
| Licenspreparat, amfetamin | | 1 | 1 | 1 | | | | |
| Lisdexamfetamin | | | | 11 | 24 | 33 | 73 | 51 |
| Metylfenidat | 96 | 86 | 98 | 102 | 81 | 90 | 101 | 100 |
| Totalt | 115 | 98 | 121 | 124 | 122 | 146 | 195 | 178 |

**NONE** of these **201 cases** were reported to the Swedish Medical Products Agency in an Adverse Even Report, **NONE** of these cases were part of the data submitted by the pharmaceutical companies to the MHRA/EMA, **NONE** of these cases were thus part of the Assessment Report – and **NONE** of these cases *will be part* of the currently prepared Assessment Report (for 2018).

**My concluding questions:**

Don't you think it is time for the Swedish MPA to *contribute* to the currently prepared Assessment Report (for 2018) instead of choosing – as documented in my earlier letters – *to make nothing* of all these serious cases from little Sweden?

Or should we in the upcoming report expect that the 100 reported cases for 2018 will be buried as effectively as the 101 cases for 2017? With the conclusion from MHRA/EMA of "low numbers" and "insufficient evidence" – while pretending to continue to keep "the signal" of self-injurious behaviour under "close monitoring".

Yours sincerely,

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

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

10 September 2017

# ADHD drugs, MHRA and the Concerta scandal – suicides, suicide attempts and self-harm

## With data from the new MHRA/EMA report about methylphenidate 9 June 2017

Dear Dr Hudson,

First I want to thank you for the inclusion in the latest MHRA/EMA report of my data from little Sweden about suicidality and self-harm in connection with methylphenidate.

In this excerpt from the final report (PRAC PSUR Assessment Report, 9 June 2017) my data from Sweden can be seen on pages 61-63. We find on page 62:

> **463 children and adolescents (10-19) made suicide attempts with methylphenidate or took overdoses of the drug in some other self-destructive purpose in the years 2011-2015,** (data from the he Swedish Poisons Information Centre, GIC).
> http://jannel.se/Methylphenidate%20PSUSA.June2017.PRAC.AR.excerpt.pdf

So we have *463* documented cases of suicide attempts/self-injurious behaviour for children 10-19 in the years 2011-2015 with methylphenidate from little Sweden, reported by me, a private citizen, from data obtained via FOIA requests to Swedish authorities.

To be compared with what *all* the manufacturers of methylphenidate products (Novartis, Janssen, Shire, Medice) report about the *total* number of suicides/suicide attempts/self-injurious behaviour with methylphenidate, for *all* countries world-wide, for (what it seems) *the last years* on pages 57-60.

I concluded in my earlier letter below (31 March 2017) that the MHRA/EMA assessment in this area will be based on false and completely unreliable data. And I was right as all interested readers can verify by comparing my figures with those from the pharmaceutical companies.

**Case in point:** Janssen (Concerta) reports (page 58) *77 cases of suicidal behaviour/self-injury and 8 completed suicides,* for the time period 31 October 2014-31 October 2016. In a table (page 60) we can find *195 cases of reported suicidality* (including 11 cases of suicide) with Concerta for a time period of *five* years (October 2011-October 2016). Janssen reports (in the underlying PSUR, forming the basis for the MHRA/EMA summary) a *cumulative figure of 43 suicides* with Concerta, from the International Birthdate of Concerta, 1 August 2000,
http://jannel.se/Methylphenidate%20PSUSA.June2017.PRAC.AR.excerpt.pdf

**Case in point:** Novartis (Ritalin) reports (in the underlying PSUR) 6 *cases of self-harm,* for the time period 1 November 2015-31 October 2016. The *54 cases* mentioned in the MHRA/EMA summary is found to be from a cumulative review – *almost from the beginning of time (!)* – from the International Birthdate of Ritalin, 6 October 1954. We can find the following data (in the underlying PSUR) – also from "the beginning of time": *233 cases of self-injury/suicide attempt/intentional overdose*, in addition to *40 reported suicides*.

**Allow me to be rude and say: Shit in – Shit out!** These figures are of course a joke, and all the resulting assessments based on them (supposed to be a reflection of reality) will be the same. Not only do they represent a *miniscule* proportion of the actual scene, the companies make a fantastic job of *minimizing even that miniscule proportion.* When the companies have "analyzed" these cases we have – as seen in the MHRA/EMA report – basically *nothing* left!

We can see (page 57) how Novartis explains away the 54 cases of self-harm (in some way separated from suicidality) by saying: "poorly documented", "additional risk factors", "underlying medical conditions", "concomitant medication", and they end up with *2 cases* (since 1954!) where "the causal role of Ritalin could not be ruled out".

**And in the middle of this** my data from little Sweden arrives. The data says that *463 children and adolescents in Sweden (10-19) made suicide attempts with methylphenidate or took overdoses of the drug in some other self-destructive purpose in the years 2011-2015, adding also 2016 we got the figure 553 children.* Included in my earlier letter below (but not in the assessment report) was the fact that only 3 (!) of these 553 cases had been reported to the Swedish Medical Products Agency (MPA), 0.5% of the cases!

Included in my earlier letter (but not in the assessment report) was also the fact that *33 persons* in Sweden committed suicide with methylphenidate in their body 2015. Adding the just released figures for 2016 (FOI request, National Board of Forensic Medicine) we get a total of **65 suicides on methylphenidate in the last two years in Sweden.** *None* of the cases was reported to the MPA!

Compare these 65 suicides from Sweden in 2 years with the 43+40=83 reported suicides from Janssen and Novartis for their drugs since the International Birthdate of Concerta and Ritalin.

**We can in the MHRA/EMA report see** that the assessors have a hard time handling the figures from Sweden. How can it be that *463 children* have been reported in this category for methylphenidate for little Sweden in five years, while Novartis reports *233 cases* for all ages, world-wide, since October 1954? How can it be that Janssen reports *77 cases* for all ages, world-wide for the last two years, while the corresponding figure for methylphenidate for the ages 10-19 for Sweden is *183* (for 2014-2015, see excerpt)?

The assessors don't know how to handle this, and so ask the Swedish MPA what to do with these figures. Remember, when reading below what happened, that the handling by the pharmaceutical companies (represented above by Novartis) is to claim say that the *quality* of the data reported to them is *so bad* that basically *nothing* is left after their analyses are done – 2 cases for Ritalin and self-harm since 1954! And even that was not "good enough"! Novartis tells us, via MHRA/EMA (page 57): "however these two cases did not fulfil the noteworthy case definition criteria". So we end up with 0 cases. And this is accepted by the MHRA/EMA!

The idea of the assessors to handle the disturbing figures from Sweden is obviously to invite the MPA (page 76) to do a similar job, as the one done by the pharmaceutical companies, of "making nothing" of the reported cases. We should, at this point, add that the Swedish MPA have contributed with, *absolutely no valuable data*, to the MHRA/EMA report. Shouldn't we expect the MPA, *with all its resources*, to give a lot more good data about the situations I have reported about the 463 children? Shouldn't we expect the MPA to use all the fantastic registers they have access to and make sure that Sweden *adds quality* to the European investigation with all its bad data? Instead the MPA explains to the worried assessors that they basically can ignore these 463 children!

**In its "contribution" to the report the Swedish MPA** says that the data (about the 463 children) "should be taken into consideration with caution … are based on the descriptions during the calls [to the Poisons Information Centre, GIC] and are not verified with healthcare records."

We get to know that GIC says that the specifics for a case "can vary from being very exact and precise … to pure guesses from people around the patient". As for the question about consequences of the intentional overdoses we are informed that one cannot always know if the consequence was hospitalization – even if the child was taken to the hospital in ambulance. Neither could one really know if the child had taken his/her personal medication or someone else's. And finally we are informed that the lack of such information [about other drugs or alcohol] in a case does not necessarily mean that e.g. alcohol or other drugs were not present." http://jannel.se/Methylphenidate%2520PSUSA.June2017.PRAC.AR.excerpt2.pdf

Why didn't the MPA try to get as much information as possible over to the MHRA/EMA about all these children, instead of using the Novartis approach above, of *making nothing* of all these serious cases?

- Why didn't the MPA require *all* data about these cases from the Poisons Information Centre (GIC)?
- Why didn't the MPA, as good as possible, cross check this information with other useful registers, like the Prescribed Drug Register and the National Patient Register?
- Why didn't the MPA in some effective way enforce the binding rules about reporting adverse events, including overdoses? After all 90% (73 of the 82 cases for 2016) came from Health Care Personnel (HCPs), and concerned children and adolescents requiring handling in emergency rooms; these cases should in other words be seen as *serious* adverse events.

If that had been done the MHRA/EMA would have known more *after* this assessment procedure than *before*!

**My concluding questions:**

1. Don't you think it is time for the MPA and MHRA/EMA to do *something*, knowing the true facts that 553 children and adolescents in Sweden made suicide attempts with methylphenidate or took overdoses of the drug in some other self-destructive purpose in the years 2011-2016? Instead of *doing nothing* and saying, as the MPA does (see letter below from 28 April): "The MPA is following the development and other available information and will signal/act when it is deemed correct to do so."
2. Will you now *request* that the Swedish MPA (with all its resources), for the next assessment procedure, is investigating and reporting the *full* data with *all relevant details* about suicidal behaviour and self-injury reported to the Swedish Poisons Information Centre (GIC) for *all age group*s and *all years*, crosschecking *all available registers* to get *the best quality data*?
3. Will you make sure that true and reliable data from trustworthy authorities in other concerned member states are also included in the assessment procedure, and that these reliable data are taking precedence over the false and unreliable data submitted by the pharmaceutical companies?

Yours sincerely,

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

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

28 April 2017

# ADHD drugs, MHRA and the Concerta scandal – suicides, suicide attempts and self-harm

## With data for the ongoing investigation about methylphenidate and self-harm

Dear Dr Hudson,

Thank you for your answer dated 4 April 2017. I really appreciate to hear that the information I have provided will be included in your assessment about of suicides, suicidality and self-harm in connection with methylphenidate. You have earlier (14 November 2016) also stated that the information I submitted in the area was "invaluable in the overall assessment" (even if providing "limited case by case detail").

I am now writing to inform you that the information submitted by me seems to be the only invaluable information from Sweden to be provided in relation to this issue.

My questions to the Swedish MPA and its PRAC Member (Liminga), about what important contributions we can expect from the MPA for this investigation, get a very disappointing answer. The Agency (Fornstedt Wallin) says in a letter dated 25 April: "The MPA is following the development and other available information and will signal/act when it is deemed correct to do so." The Agency also points out that the important information I have submitted has "limitations".

This answer tells me that you will get *no* contributions from the Swedish MPA in form of data relating to the issue of suicides, suicide attempts and self-harm (from the country with the best possibilities to do so). We can even ask if you will get any *comments* from Sweden; in the earlier assessment reports it seems as if Sweden has no interest, has nothing to say.

**I have identified** that "553 children and adolescents (10-19) made suicide attempts with methylphenidate or took overdoses of the drug in some other self-destructive purpose in the years 2011-2016." I have contributed with the information that 33 persons in Sweden committed suicide 2015 with methylphenidate in their blood at the time of death; 10 of these persons were in the age group 15-24.

**The MPA and the concerned pharmaceutical companies** (having the same information for Sweden) will contribute with *3 (!) adverse event reports* about suicide attempts/self-harm in connection with methylphenidate treatment (for the age group 10-19). The MPA will contribute with *0 cases of suicide* in connection with methylphenidate treatment.

I would say the contributions from the MPA have some serious "limitations", and I again hope you will request the data from the Agency that I asked for in my earlier letter (below).

Yours sincerely,

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

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

31 March 2017

# ADHD drugs, MHRA and the Concerta scandal – suicides, suicide attempts and self-harm

Dear Dr Hudson,

I should have come back much earlier, but the secrecy stamps from MHRA and the Swedish Medical Products Agency (MPA) have made it impossible to gain access to the important facts *about suicides, suicide attempts and self-harm in connection with methylphenidate treatment.*

It's first now, four month after your answer (below) that we can compare the data from the pharmaceutical companies with the reliable data from Sweden about suicides, suicide attempts and self-harm, revealed in my investigation.

**As you know** the manufacturers of methylphenidate (Concerta, Ritalin, Equasym, Medikinet) were ordered by the MHRA and the EMA Pharmacovigilance Risk Assessment Committee (PRAC) to *"undertake a cumulative review of all cases of self-injurious behaviour"* in connection with their products (1). These reviews were to be presented in the next Periodic Safety Update Reports (PSURs), to be submitted to the MHRA/EMA in the end of 2016.

We could thus, in these reports, expect to get *exact data* about *all* cases of self-injurious behaviour (including suicides and suicide attempts) in connection with methylphenidate prescription world-wide known to the companies, from the International Birth Date (IBD) of the products.

**As you also know** I have investigated the cases of "suicide attempts or overdoses in some other self-destructive purpose" in connection with ADHD drugs, presented to the Swedish Poisons Information Centre (GIC). This for the population of children and adolescents (10-19) for the years 2011-2015. The investigation revealed that we had *463 individual cases of "suicide attempts or overdoses in some other self-destructive purpose" for these young persons for methylphenidate in these five years!*

In your earlier letter you acknowledged the receipt of this information, and said it was "invaluable in the overall assessment of these events" though providing "limited case by case detail". You also said that these reports were "considered to be spontaneous occurring post-authorisation" and would be "taken into consideration in our ongoing monitoring of the issue of suicidal and self-injurious behaviour with methylphenidate".

It was of course very good to know that the information I had submitted was regarded as "invaluable" and was to be taken into consideration in the coming assessment by MHRA/EMA. But the assessment report from MHRA/EMA raised many serious questions requiring further investigation. We could for example in the assessment report read (page 25): *"Whilst overall the numbers of self-injurious reports may be low, self-injury can have serious consequences."*

Yes, self-injury can *indeed* have serious consequences, *but* what about *"overall the numbers of self-injurious reports may be low"*? I have revealed and presented alarming data about 463 individual cases (10-19) of self-injurious behaviour for methylphenidate in little Sweden (2011-2015) – not exactly a "low number"!

So what do the pharmaceutical companies actually report to the MHRA/EMA; what are the figures about suicides, suicidal behaviour and self-injury *forming the basis for the assessment* by the agencies? How could it be – considering my alarming data from little Sweden – that the instances of self-injury could be deemed to "be low" in the world-wide prescription of these drugs, from their birth?

## The secrecy stamp on reported suicides and self-harm

The secrecy stamp first made it impossible to get an answer to any of these questions.

The Swedish Medical Products Agency (MPA) got the Periodic Safety Update Reports (PSURs) from pharmaceutical companies in the beginning of 2017, but refused to release the data about the *number* of suicides, suicidal behaviour and self-injury in these reports. The MPA explained that the MHRA had objected to release the data about the *number* of reported cases of suicidal behaviour and/or self-harm contained in these reports.

It's been said (Goldacre, Bad Pharma, 2012) that drug regulatory agencies have *a "dangerous obsession with secrecy"*, and what could be a better example of this than putting a secrecy stamp on the cumulative number of suicides, suicide attempts and self-injurious behaviour reported by the manufacturers of methylphenidate drugs. Drugs that we know have been involved in 463 cases of "suicide attempts or overdoses in some other self-destructive purpose" for children and adolescents in Sweden.

The MPA even explained that the release of these data – *just the number of cases* – would cause disturbance in Sweden's relations with another country (UK)!

I don't know who at the MHRA decided that this information was sensitive to such a degree that it would hurt the relations between Sweden and the United Kingdom would it be released. What I *do* know is that it would have been impossible to compare the data reported by the pharmaceutical companies with my data from Sweden – had the MHRA and MPA been *successful* in their "dangerous obsession with secrecy".

## The newly updated investigation for Sweden

I have now updated my investigation for Sweden up to 2016 and can report:

- 553 children and adolescents (10-19) made suicide attempts with methylphenidate or took overdoses of the drug in some other self-destructive purpose in the years 2011-2016, (data from the he Swedish Poisons Information Centre, GIC).

- Only 3 (!) of these 553 cases were reported to the adverse events register at the MPA.

In your November letter you said the earlier data I gave, though "invaluable", provided "limited case by case detail". In order to give even more valuable data to the MHRA/EMA review I can provide the following data for the added 82 individual cases for 2016:

- 73 of the 82 cases (90%) came from Health Care Personnel (HCPs), and concerned children and adolescents requiring handling in emergency room; these cases should in other words be seen as *serious* adverse events.

- Only one (a 14-year old girl taking Ritalin) of these cases were reported, as required, to the adverse events register at the MPA.

- Concerta was the drug mentioned in 63 of the cases, Ritalin in 14, Medikinet in 8 and Equasym in 3.

- Some examples from the notes for individual cases:
  "hard to breath …heart beating",
  "14 of 18 mg Concerta",
  "feel strange and does not want to live anymore",
  "hope she will die",
  "pain in the heart and cannot breath properly",
  "18 of 54 mg Concerta",
  "hallucinating",
  "not possible get in contact with",
  "11 Concerta 54 mg with suicide purpose",
  "with suicide purpose".

It should be noted that the Swedish Poisons Information Centre (GIC) is an agency administratively *under* the Medical Products Agency (MPA). The MPA can without much effort make a full evaluation of all the 553 cases presented to the GIC for the years 2011-2016.

It should most definitely be noted, as mentioned earlier, that only 3 (!) of the 553 cases (0.5%) were reported to the adverse events register – all of them should have been reported.
In addition to the data above, about suicide attempts and self-injurious behaviour, we should add some words about the *number of completed suicides* in Sweden in connection with methylphenidate treatment. The main purpose with this note is to be able to *compare* the figures with those reported by the pharmaceutical companies.
We find for the year 2015:

- 33 persons in Sweden committed suicide with methylphenidate in their blood at the time of death; 10 of these persons were in the age group 15-24 (data from toxicology analyses done by the National Board of Forensic Medicine).

- *None* of these cases were reported to the adverse events register as a suspected adverse event.

## What did the pharmaceutical companies report to the MHRA/EMA?

And we come to *the data reported by the pharmaceutical companies to the MHRA/EMA.*

These are the figures about suicides, suicidal behaviour and self-injury forming the basis for the MHRA/EMA assessment.

The figures so sensitive that it would hurt the relations between Sweden and the United Kingdom would they be released.

The figures about *all* cases of self-injurious behaviour (including suicides and suicide attempts) in connection with methylphenidate prescription world-wide, known to the companies, from the International Birth Date (IBD) of the products.

### Completed suicides:

Concerta (Janssen) 43
Ritalin (Novartis) 40
Equasym (Shire) 23

### In total: 106

### Suicide attempts, self-injurious behaviour*:

Concerta (Janssen) 154-347
Ritalin (Novartis) 93-241
Equasym (Shire) 37-82
Medikinet (Medice) 21-39

### In total: 305-709

***** After long negotiations with the European Medicines Agency (EMA) I have finally got access to these figures. However EMA cannot give data about *the number of individual cases* for suicide attempts, suicidal behaviour, intentional self-injury, intentional overdose – only *the total of reported adverse events.* As *one* individual can fall in more than one of these categories I have had to report it as above. The number of reports of self-injurious behaviour (including all categories) is in other words *minimally* 305 and *maximally* 709.

These are the cases of suicides, suicidal behaviour and self-injury forming the basis for the MHRA/EMA assessment.

Let's make it even clearer by presenting these figures about methylphenidate and the ones from Sweden in a table:

| **Number of cumulative cases of self-harm world-wide reported by the pharmaceutical companies** | **Number of cases of self-harm Sweden for children and adolescents (10-19) 2011-2106** |
|---|---|
| 305-709 | 553 |
| **Number of cumulative cases of completed suicides world-wide reported by the pharmaceutical companies** | **Number of cases of completed suicides found in toxicological analyses in Sweden for 2015** |
| 106 | 33 |

## The MHRA/EMA assessment is based on false and completely unreliable data

I have with *limited* resources (the Freedom of Information Act) proved that the MHRA/EMA assessment is based on false and completely unreliable data.

I have also proved that the "dangerous obsession with secrecy" includes the hiding of these data about suicides, suicidal behaviour and self-injury – easily exposed as false if made public.

The MHRA/EMA is looking *in the wrong direction*, and can let the pharmaceutical companies conclude that the number of self-injurious reports is *low*, and so can continue to say that there are no reasons to be concerned.

**My concluding questions:**

1. Will you make sure that the updated information I have given about Sweden is right away included in the investigation and is given full attention?

2. Will you make sure that the Swedish MPA (with all its resources), for the current assessment procedure, is investigating and reporting the *full* data with *all relevant details* about suicidal behaviour and self-injury reported to the Swedish Poisons Information Centre (GIC) for *all age group*s and *all years*?

3. Will you make sure that true and reliable data from trustworthy authorities (like the Swedish GIC) in the concerned member states are included in the assessment procedure, and that these reliable data are taking precedence over the false and unreliable data submitted by the pharmaceutical companies?

Yours sincerely,

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

1. EMA/MHRA, "Lead Member State PSUR updated preliminary assessment report Methylphenidate", released in June 2016, http://jannel.se/methylphenidatePSUSA2015.pdf (see page 7).

Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Janne Larsson
Sent by email:

14 November 2016

Dear Mr Larsson

Thank you for your emails dated 31 July 2016 and 12 October 2016. Issues relating to the use of methylphenidate, and more specifically Concerta, in adults have been addressed in previous correspondence and I have nothing further to add.

You have noted that there is an overall concern regarding the issue of suicides, suicidality and self-harm in connection with methylphenidate.

To clarify, the independent analysis of suicidality undertaken by Life Science Services on behalf of five Market Authorisation Holders (MAHs) presented in Periodic Safety Update Single Assessment (PSUSA) assessment report dated 09 June 2016, examined those cases reported during clinical trials. The report identified cases of suicidality in the clinical trials in both methylphenidate and placebo-treated patients. This analysis did not take into account spontaneous post-authorisation reports.

The Pharmacovigilance Risk Assessment Committee (PRAC) considered the possibility that those patients involved the clinical trials would have been given greater emotional support than in normal clinical practice and hence the data would not necessarily be reflective of the pattern of reports from patient experience outside a clinical study. The current Summary of Product Characteristics (SmPC) and patient leaflet contains warnings of the risk of suicidal tendency. In a further evaluation, the PSUSA identified spontaneous reports of self-injury that may not be directly associated with suicidality; therefore PRAC agreed that the MAHs undertake a cumulative review of their spontaneous post-authorisation data to be provided in the next PSUR.

Cumulative patient exposure to methylphenidate medicines is extensive, exceeding 25 million patient years of treatment. Therefore individual numbers of cases observed are low in comparison to the overall patient exposure. In spite of this, the final PRAC conclusion remains that the reporting of these behaviours are a safety concern which require further review.

Thank you for the data that you have extracted from the Swedish poisons information centre (GIC) identifying 463 reports of self-destructive action. It should be recognised that the information taken from poison centres, whilst invaluable in the overall assessment of these events, also provide limited case by case detail. Regardless of this, the reports are considered to be spontaneous occurring post-authorisation. These would not routinely have been reported directly to the MAHs therefore the data you provided will be taken into consideration in our ongoing monitoring of the issue of suicidal and self-injurious behaviour with methylphenidate.

Yours sincerely



Dr Ian Hudson,
Chief Executive Officer
Medicines and Healthcare products Regulatory Agency
151 Buckingham Palace Road, London, SW1W 9SZ
www.mhra.gov.uk

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

31 July 2016

**(Those not familiar with this affair should start on page 19, letter 14 February 2014)**

## ADHD drugs – MHRA and the Concerta scandal – did this really happen?

Dear Dr Hudson,

I promised to get back to you after having received the follow-up reports about the ADHD drug Concerta. The reports have now been released via an FOI request, and I was right in everything.

Let's begin with uploading the reports we talk about:

**1.** First we have the Periodic Safety Update Report (PSUR) for Concerta (period 11 October 2012-31 October 2013), written by the manufacturer Janssen, and submitted to the MHRA in December 2013, released in June 2016 http://jannel.se/ConcertaPSUR12to013.pdf

**2.** Then we have the assessment report of that PSUR done by the MHRA as the "Lead Member State" for the concerned European countries, released in June 2016. (The assessment of Concerta was included in one assessment report for *all* methylphenidate products in Europe.) http://jannel.se/methylphenidatePSUSA2015.pdf

In your earlier letters, Dr Hudson, you let me know that "the safety of Concerta is being continuously monitored" and that you would take my concerns into account in the next assessment report (meaning the current report).

I challenged that statement, and I was absolutely right in doing this. For what do we find in the now issued reports?

We can read *nothing* in the Janssen PSUR and in new "Lead Member State PSUR updated preliminary assessment report Methylphenidate" about **a)** the fact that Concerta was found to be *ineffective and harmful for adults* by the MHRA assessors already in 2010, **b)** that Janssen's application about the drug for adults at that time was *turned down, rejected*. We can find **c)** *no* actions in the new assessment report enforcing the conclusions from the earlier assessors, **d)** *no* actions to curb the prescription of the drug. The pharmaceutical company did *not* follow the agreement, they just continued to sell the drug to the patient group for which it was *proven to be harmful* – resulting in *huge* profits. The MHRA has been sitting on Janssen's report for 2.5 years (!) before it could be accessed. So much for the "continuously monitored" safety of the drug!

Reading these reports it is as if this affair has never happened, as if the documents from the MHRA showing the harmful effects of the drug do not exist. And yet, everyone reading these 23 pages can with their own eyes see what the honest MHRA assessors earlier had written.

We could end at this point, the proof of your scandalous handling of this affair is clear to everyone reading these pages, but I want to make it even worse by commenting on some of the things *actually written* in the now released reports.

**Let's start,** Dr Hudson, by looking at the three studies of Concerta for adults submitted by Janssen to the MHRA (2010). The studies that were said to prove that Concerta was safe and effective for adults, forming the basis for Janssen's application to get Concerta approved for adults.

As you know, and as I have written extensively about in my earlier letters (see for example page 21 below), MHRA found that these studies showed **"that the B/R [benefit/risk] of Concerta in the proposed indication [adults] is negative…"** In other words Janssen had showed that the drug was ineffective and harmful for adults.

Let's look at **Study 3013** – the longest of the studies (13 weeks) submitted by Janssen. The MHRA assessors found that this 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."** In other words Concerta *caused* aggression, tics and depression.

At this point I want to refer you to the presentations of "the B/R [benefit/risk] of Concerta for adults" and of Study 3013, *done by Janssen* in its PSUR. I also want to take up how you have handled these points in your current assessment report.

We find that Janssen says that **Concerta "continues to have a favourable benefit-risk profile for ADHD in children and adults"** (page 185), that it is authorized for the treatment of ADHD in adults (page 183), that **the benefits of Concerta for adults "are supported by prospective, randomized, active-comparator controlled trials"** (page 185).

Can you, Dr Hudson, refer me to the points *in Janssen's PSUR* taking up what we know from the MHRA assessment of the drug for adults in Europe? I can't find anything about it.

Can you refer me to the points *in your current assessment report*, "Lead Member State PSUR updated preliminary assessment report Methylphenidate", where I can find data *correcting* the statements from Janssen *and data taking up what we know from the MHRA assessment of the drug for adults?* Where I can find data about how the company has handled the agreement with the MHRA: **"The usage [of Concerta for adults] may not increase …".**

And what does Janssen say about **Study 3013** in their PSUR – the study found by the MHRA to be **"clearly a failed study"**? We look at page 174 and can read that Study 3013 was one of the successful studies that **"formed the basis for the adult indication"**. On page 175 we can find more descriptions of the study. The passage is filled with words describing **the effect of Concerta as "statistically significantly superior to placebo"**, "statistical superiority over placebo was maintained", "significant improvements", and with a reanalysis showing "statistically significantly larger decreases … in the … ADHD symptoms … relative to the placebo group".

On page 184 we can find more data from Janssen along the same lines. The trials forming the basis for the ***rejection*** of Concerta for adults in Europe are transformed by Janssen to studies showing the **"favourable benefit-risk profile [of Concerta] for ADHD in … adults".**

I can understand that you have not acted on the distorted, manipulated data about the study presented in the article in World Journal of Biological Psychiatry, where Janssen and leading European psychiatrists said Study 3013 showed that **Concerta "provided overall benefits in the treatment of adults with ADHD",** and that **the study showed "treatment was well tolerated".** After all, pharmaceutical companies are free to present fraudulent study results in medical journals without intervention by drug regulatory agencies.

What I can't understand is how you can let Janssen get away with this distortion of facts in a report to the MHRA. I don't see any handling of these fraudulent descriptions in the "Lead Member State PSUR updated preliminary assessment report Methylphenidate". In case I missed something I would appreciate if you could refer me to a point, *where the valid MHRA evaluation of Concerta for adults is described*.

**Before I end this letter** I want to take up the subject of ***suicides, suicidality and self-harm in connection with methylphenidate,*** as this is one of the concerns taken up in your new assessment report.

I want to show that it would be quite easy to collect and evaluate data about harmful effects of the drugs, if it wasn't for the pharmaceutical companies' efforts *not to get* full data about them and to *explain them away* once collected – and for the drug regulatory agencies' acceptance of this system failure in collecting data and the false explanations.

I am talking about the "successful" pattern taken over from the tobacco industry: *Doubt is our product*. Create a lot of confusion and cause disbelief about clear harmful effects of the drugs; never accept a *causal* role for the drugs in inducing harm, always find "confounders"; always blame the patients' "underlying diseases" when the drugs cause harmful events.

The data in Janssen's PSUR and in your new assessment report are beautiful examples of this.

But let's stick to the subject of ***suicides, suicidality and self-harm in connection with methylphenidate.***

The first recommendation (page 7) in your new "Lead Member State PSUR updated preliminary assessment report Methylphenidate" reads:

> **"All MAHs [Marketing Authorisation Holders] are recommended to undertake a cumulative review of all cases of self-injurious behaviour. "** (-31 October 2016)

On page 25 in the report we can read: **"Whilst overall the numbers of self-injurious reports may be low, self-injury can have serious consequences."** The "low numbers" (cumulative) referred to for all methylphenidate products seem to be the ones listed on the same page.

We can for Ritalin/Concerta read: 21/36 [=57] reports of self-injurious behaviour; 19/29 [=48] intentional self-injury; 1/11 [=12] Dermatillomania [the repeated urge to pick at one's own skin]; 4/14 [=18] reports of self-injurious ideation. In total we get 135 reports of self-injury.

I must ask: Should we really believe that there are *only* 135 known reports about self-injury *cumulatively* for methylphenidate, now to be reviewed (or rather, explained away) by the manufacturers in the next PSURs (-31 October 2016)?

The MHRA and the EMA Pharmacovigilance Risk Assessment Committee (PRAC) do a good job of explaining away cases of suicides, suicidality and self-harm in the assessment report. We get to know (page 25): "It is known that concomitant psychoses may be apparent in patients with ADHD." We also get to know that "ADHD medicines may be associated with emergent *underlying* psychoses." [My emphasis.] And Janssen does an even better job in its PSUR (page 188): "ADHD patients are subject to inherent background risks for suicidal behaviour." Explain it all away and blame the harm caused on the patients' "underlying disease".

And so the manufacturers are invited to discuss these few cases of suicidality and self-injury in their next PSURs, and present their views to the MHRA and the EMA. Of course we know the results of that presentation (see the reference to the tobacco industry above: *Doubt is our product*).

**So I thought I should help the MHRA and EMA,** and present some data from Sweden concerning what is already known about suicides, suicidality and self-harm in connection with methylphenidate.

1. The Swedish Poisons Information Centre (GIC) is a national agency under the Medical Products Agency (MPA). GIC has presented information about the number of cases of **"suicide attempts or overdoses in some other self-destructive purpose"** in connection with ADHD drugs, for children 10-19, recorded 2011-2015. Here is the table made by the GIC: http://jannel.se/GIC2011to2015.pdf You can see that we have **463 cases of "suicide attempts or overdoses in some other self-destructive purpose" for methylphenidate in these five years!** In order to give a face to these children and to present further details about these cases I have described the 123 children for 2014, where 102 of them had taken methylphenidate. See these children here (Swedish, but easy to understand). http://jannel.se/ChildrenSelfHarmADHD2014.pdf

   Due to the complete system failure in reporting adverse events these children will *not* be visible at the MPA and the pharmaceutical companies can say they have *no data* about this. Case in point: Only 2 (!) of the 183 children, reported to the GIC for 2014-2015 as taking overdoses of methylphenidate in a self-destructive purpose, were subject to an adverse event report.

   So there you have it: 463 cases of self-injurious behaviour for methylphenidate for children 10-19 in 5 years in Sweden; 3.4 times the figure reported cumulatively for all patients word-wide in your assessment report!

2. As for ***suicides*** The National Board of Forensic Medicine in Sweden can report that toxicological investigations were done on 107 young persons (15-24 years) who had committed suicide in 2015 (almost all suicides are subject to toxicological investigation). And we find that **10 of the 107 young persons (9%) who committed suicide in 2015 had traces of methylphenidate in their blood at the time of the suicide.** And as you can guess, we find *no reports* about this at the Medical Products Agency. Even though a **causal relationship with methylphenidate was established for aggression, tics and depression.** After all, as the manufacturer has let the doctors know: "ADHD patients are subject to inherent background risks for suicidal behaviour."

Looking forward to your answer.

Yours sincerely,

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

To Dr Ian Hudson, Chief Executive of MHRA

10 March 2016

## ADHD drugs – MHRA and the Concerta scandal – final comments

Dear Dr Hudson,

Thank you for the answer dated 8 March 2016.

The MHRA assessors found the B/R [benefit/risk] of Concerta for adults to be negative, meaning Janssen's application was turned down, the drug found to be harmful and ineffective for adults.

Despite that the prescription to adults exploded. MHRA took no action to enforce the assessment conclusions and the pharmaceutical company Janssen has made *huge* profits in selling the drug for exactly the patients for whom it was found harmful and ineffective.

You now let me know: "The safety of Concerta is being continuously monitored".

We can be certain no one reading the full story about the Concerta scandal will agree with that.

This summer you will release a report supposed also to take up the following: "We will take your concerns regarding patient exposure into account during the Periodic Safety Update Single Assessment Procedure". (Letter 10 February 2016)

I am sure the report will not mention that Concerta was found to be ineffective and harmful for adults by the MHRA assessors in 2010. There will be *no* actions in that report enforcing the conclusions from the assessors, *no* actions to curb the prescription of the drug. We will neither find the reliable and exact data about the exploding prescriptions of Concerta to adults in Sweden, submitted to the MHRA.

I get back to you after having read the report.

Yours sincerely,

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

Medicines & Healthcare products Regulatory Agency

151 Buckingham Palace Road
London
SW1W 9SZ
United Kingdom

**www.gov.uk/mhra**

Janne Larsson
Sent by Email: jan.olov.larsson@telia.com

8 March 2016

Dear Mr Larsson

Thank you for your summary email dated 18 February 2016.

We have responded to you fully on multiple occasions on all the points that you have raised.

The safety of Concerta is being continuously monitored. The current Periodic Safety Update Single Assessment Procedure (PSUSA/00002024/201510) will examine patient exposure. Any new information on benefits and risks will also be reviewed during this procedure.

Current knowledge on the benefits and risks of Concerta are available to the public in language that is understandable to the lay person in patient leaflets, and to healthcare professionals in the Summary Product of Characteristics. As detailed in previous correspondence Concerta is not authorised for initiation of treatment in adults and the product information includes information about who should be treated as well as a warning that its safety and efficacy has not been established in adults.

The MHRA can only reiterate that issues of prescribing practice in Sweden are for the relevant professional bodies in Sweden.

We now consider this correspondence closed.

Yours sincerely



Dr Ian Hudson,
Chief Executive Officer
Medicines and Healthcare products Regulatory Agency
151 Buckingham Palace Road, London, SW1W 9SZ
www.mhra.gov.uk

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
Sweden
janne.olov.larsson@telia.com

Medicines & Healthcare products Regulatory Agency

151 Buckingham Palace Road
London
SW1W 9SZ
United Kingdom

**www.gov.uk/mhra**

Janne Larsson
Telia
Sweden
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,
Chief Executive Officer
Medicines and Healthcare products Regulatory Agency
151 Buckingham Palace Road, London, SW1W 9SZ
www.mhra.gov.uk

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
Sweden
janne.olov.larsson@telia.com

[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,

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

[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