To Dr Ian Hudson, Chief Executive of MHRA

The approval of Ritalin for adults – where did all the aggression go?

4 August 2014

Dear Dr Hudson,

I hope you are willing to receive also this communication, even if you made it clear that you "consider this correspondence closed". The point is that I am not in this letter asking one single question, I am not asking for any information.

Instead the purpose with this letter is to *inform the MHRA about the fact that Novartis succeeded to hide/get rid of almost all instances of aggression in its clinical trial of Ritalin LA for adults.*

In your answer 21 July **http://jannel.se/AnswerDr.HudsonJuly14.pdf** you made it clear that "the MHRA has not been involved in any work sharing assessment concerning Ritalin LA in any other European member state."

This seemed to indicate that all questions in my earlier letters (see here from 16 March **http://jannel.se/MHRA.Concerta3.pdf** and here from 4 July **http://jannel.se/RitalinLetterMHRA.pdf**) were irrelevant. The assessment and possible approval of Ritalin LA for adults in UK seemed not to be a question. Until I asked: Please confirm the fact that Novartis *has not* submitted an application about Ritalin LA for adults *in UK*.

Then I got invited into the world of extreme secrecy when your Executive Assistant Christina Martin today writes that "the MHRA neither confirms nor denies that it holds information falling within the description specified in your request".

I simply assume that Novartis after its successful application in the countries being "on board with adult ADHD" http://www.ft.com/intl/cms/s/2/8b721a20-b8e9-11e2-a6ae-00144feabdc0.html now has submitted its application based on the same studies as in the German application (shared with Ireland, Sweden, Norway, Denmark, Finland, Austria, Hungary, Portugal, Luxembourg, France, Belgium).

As I have said in my earlier letters the MHRA presented important data about the findings of **aggression** in the studies of Concerta. To reiterate:

> MHRA, leading the European investigation about Concerta concluded: **"A *causal* relationship with Concerta was established for aggression, tics and depression."** [Italic added.] (Preliminary Variation Assessment Report, July 2010 page 112, http://jannel.se/PVAR.Concerta140710.pdf)
>
> The investigation showed that in the three Janssen-submitted, double-blind studies (3013, 02-159 and 3002) **"13 of the 596 subjects receiving Concerta … were withdrawn for aggression-related adverse events (vs. none receiving placebo)".** (Page 65, Preliminary Variation Assessment Report, Concerta, July 2010, see also FVAR, page 12, 26 April 2011.)
>
> These 13 persons suffered so ***severe*** aggression that they had to be taken out of the trials. *None* of those on placebo suffered such serious aggression that they had to end the trials.

> The investigation also showed that a total of **71 out of 596 subjects (11.9%) from the Concerta group had suffered aggression (compared to 17 persons, 5.5%, from the placebo group).** In the combined studies of Concerta in adults (placebo-controlled, and others) **202 of a total of 1369 subjects, 14.8%, suffered aggression. [10]** (See FVAR, page 12, 26 April 2011.)
>
> In the investigation it was concluded: **"The main new safety concern from the study data is around the frequency of psychiatric adverse events and that this is often de novo [new]. Of note is the incidence of anxiety but also rates of depression and aggressive and hostile behavior are raised."** (See Preliminary Variation Assessment Report, page 66.)

And we come to "the same pharmacological substance" Ritalin and the assessment reports of the studies submitted by Novartis to European medical agencies. I have earlier http://jannel.se/RitalinLetterMHRA.pdf described the 58 pages long Swedish assessment report and that we nowhere in the document could find specifics about "aggression" – all about it was gone.

I now want to invite you to read the 118 pages long "Final Worksharing Assessment Report" from 31 January 2014 – the document from the German medical agency BfArM, forming the basis for the approval of Ritalin in European countries.

I am sure Novartis has sent this assessment report to the MHRA to make the handling of the application easier. So you have it available.

And if we work hard we can (page 89) see **that *2 persons* in the Ritalin group (N=542) ended the studies due to aggression (in the 9 week double blind study) – compared with 13 of the 596 persons in the Concerta group; see above.**

And we can also find (page 82) **that 7 persons in total (!) in the Ritalin group had suffered aggression in the 9 weeks long double blind study.**

This means that 71 of 596 persons (11.9%) from the Concerta group had suffered aggression in the studies analyzed by the MHRA, compared to 7 persons of 542 (1,3%) from the Ritalin group in the studies analyzed by BfArM.

We have an 815% higher risk to suffer aggression from Concerta than from Ritalin!!

I really hope the MHRA can dig deeper and ask the questions to Novartis: Where did you hide all the aggression? How did you get rid of it?

I count on the MHRA to do that.

Yours sincerely,

Janne Larsson
Reporter
Sweden

From: Chief Executive
Sent: Monday, August 04, 2014 9:28 AM
To: 'Jan Larsson'

Subject: RE: (Simple confirmation) MHRA and the approval of Ritalin for adults – where did all the aggression go?

Good morning

The MHRA neither confirms nor denies that it holds information falling within the description specified in your request. The duty in Section 1(1)(a) of the Freedom of Information Act 2000 does not apply, by virtue of Section 43(Commercial interests)and Section 41 (Information provided in confidence) of that Act. This should not be taken as an indication that the information you requested is or is not held by the MHRA.

Section 41 is an absolute exemption and requires no consideration of the public interest, except to say that we consider any pending applications submitted to the MHRA to have the necessary quality of confidence such that to disclose that information would be considered an actionable breach.

Section 43 is a qualified exemption that requires a consideration of the public interest. The MHRA does not consider there is any overriding public interest in releasing information we may or may not hold on a pending application and considers that the release of such information will cause commercial harm by providing competitors with information of approximately how far a medicinal product is from market.

Best wishes

Christina Martin on behalf of Dr Ian Hudson

From: Jan Larsson [mailto:jan.olov.larsson@telia.com]
Sent: 01 August 2014 11:40
To: Chief Executive
Cc: Hudson, Dr Ian; Martin, Christina
Subject: (Simple confirmation) MHRA and the approval of Ritalin for adults – where did all the aggression go?

Dear Dr Hudson,

I would be happy if you could just confirm what I take up below (it was not clear in your earlier answer).

Yours sincerely,
Janne Larsson
Reporter
Sweden

From: Jan Larsson

Sent: Monday, July 21, 2014 1:53 PM
To: Chief.Executive@mhra.gsi.gov.uk
Cc: Ian.Hudson@mhra.gsi.gov.uk
Subject: MHRA and the approval of Ritalin for adults – where did all the aggression go?

Dear Dr Hudson,

Thank you for your clarifying answer.

Novartis said on page 1 in the attached document (Cover letter): “The current application is submitted via an informal worksharing procedure, as agreed by the CMD(h) in July 2012, which includes all European (EU) countries where Ritalin LA *[Long Acting]* is currently registered.” In other words Novartis explains that the application is submitted in *ALL* European countries “where Ritalin LA is currently registered”.

You now say that Ritalin LA is NOT registered in UK (for children). Thus “The MHRA has not been involved in any work sharing assessment concerning Ritalin LA in any other European member state.” This is fine.

But as you well understand my questions below about *aggression,* in connection with Concerta and Ritalin, are *fully valid* also if Novartis has chosen to submit an application for Ritalin LA in UK via a “national procedure”.

So please confirm the fact that Novartis *has not* submitted an application about Ritalin LA for adults *in UK*. (With that confirmation you are fully justified to “consider this correspondence closed”.)

Yours sincerely,

Janne Larsson
Reporter
Sweden

From: Chief Executive
Sent: Monday, July 21, 2014 12:54 PM
To: Jan Larsson
Subject: RE: MHRA and the approval of Ritalin for adults – where did all the aggression go?
Good morning Mr Larsson

Please find attached Dr Hudson’s response. We now consider this correspondence closed.

Here is the answer from Dr Hudson: http://jannel.se/AnswerDr.HudsonJuly14.pdf

All best wishes

Christina Martin
Executive Assistant to Dr Ian Hudson
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Medicines and Healthcare Products Regulatory Agency
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From: Jan Larsson [mailto:jan.olov.larsson@telia.com]
Sent: 04 July 2014 09:16
To: Hudson, Dr Ian
Cc: MHRA Customer Services

Subject: ACTIVE WITH IH: MHRA and the approval of Ritalin for adults – where did all the aggression go?

To Dr Ian Hudson, Chief Executive of MHRA

4 July 2014

The approval of Ritalin for adults – where did all the aggression go?

Dear Dr Hudson,

As you may remember I wrote to you in February and March about MHRA and the scandal with the ADHD drug Concerta **http://jannel.se/MHRA.Concerta3.pdf**

I made the "prophecy" that several drug regulatory agencies in Europe, who had allowed alarming levels of off label prescription for adults, like Sweden, would ***have to*** make sure that we quickly forgot the Concerta scandal. And the best way to do that would be to push through ***another*** application of methylphenidate for adults – like Ritalin. And to then claim "that we now have evidence".

I said that we could expect Novartis to have learned from the failed Concerta submission, and to design more "smart" studies, showing its drug Ritalin (in all important aspects the same as Concerta) to be "safe and effective". We could expect that the submitted studies would get a positive assessment this time – no embarrassing questions – and suddenly the concealed and alarming Concerta results could be expected to no longer exist!

We have now arrived at that point.

It has been a secret up to now how Novartis planned its conquest of Europe, or as Financial Times said, how to get everyone "on board with adult ADHD" http://www.ft.com/intl/cms/s/2/8b721a20-b8e9-11e2-a6ae-00144feabdc0.html . We have not known in which countries the application was submitted or via which procedure. We know now.

Novartis succeeded to get through some kind of "informal worksharing procedure", as there was *"currently no legal basis"* for a formal worksharing procedure. As the Swedish Medical Products Agency stated in its assessment report:

> "The worksharing procedure included all European (EU) countries where Ritalin LA is currently registered. As Ritalin LA is registered via national procedures in EU, there is currently no legal basis in EU for using 'formal' worksharing procedure for nationally registered products."

We also know that Germany was leading this "informal worksharing procedure".

I have read the Swedish "investigation" about Novartis' submitted studies, and as expected – no embarrassing questions. Much could be said about it, but at this point I only want to take up one important, even vital aspect.

Where did all the aggression go?

As you know MHRA, leading the European investigation about Concerta concluded: **"A *causal* relationship with Concerta was established for aggression, tics and depression."** [Italic added.] (Preliminary Variation Assessment Report, juli 2010 page 112, http://jannel.se/PVAR.Concerta140710.pdf)

The investigation showed that in the three Janssen-submitted, double-blind studies (3013, 02-159 and 3002) **"13 of the 596 subjects receiving Concerta … were withdrawn for aggression-related adverse events (vs. none receiving placebo)".** (Page 65, Preliminary Variation Assessment Report, Concerta, July 2010, see also FVAR, page 12, 26 April 2011.)

These 13 persons suffered so ***severe*** aggression that they had to be taken out of the trials. *None* of those on placebo suffered such serious aggression that they had to end the trials.

The investigation also showed that a total of **71 out of 596 subjects (11.9%) from the Concerta group had suffered aggression (compared to 17 persons, 5.5%, from the placebo group).** In the combined studies of Concerta in adults (placebo-controlled, and others) **202 of a total of 1369 subjects, 14.8%, suffered aggression. [10]** (See FVAR, page 12, 26 April 2011.)

Clear evidence also emerged in the studies that Concerta could ***cause*** **anxiety and agitated conditions in adults – "evidence for the risk of new-onset anxiety, tension and agitation". "Adult studies have identified anxiety as a very common risk in adults."** (See Preliminary Variation Assessment Report, page 117.)

In the investigation it was concluded: **"The main new safety concern from the study data is around the frequency of psychiatric adverse events and that this is often de novo [new]. Of note is the incidence of anxiety but also rates of depression and aggressive and hostile behavior are raised."** (See Preliminary Variation Assessment Report, page 66.)

MHRA asked for and Janssen submitted (January 2011, Response Document) the following illuminating table over adverse events in the Concerta studies:

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)

We would of course expect a similar picture in the clinical trials of Ritalin for adults.

And so we take a look at the comparable table in the Swedish investigation of Ritalin for adults. It looks like this (National Type II variation – Overview, page 35, 16 July 2014):

III.3.4.1 Adverse events

Table 20 Number (%) of patients with AEs during Period 1 by System Organ Class (Safety Analysis Set for Period 1) – Study D2302

	Ritalin LA 40 mg N=180 n(%)		Ritalin LA 60 mg N=181 n(%)		Ritalin LA 80 mg N=181 n(%)		All Ritalin LA N=542 n(%)		Placebo N=180 n(%)	
Primary system organ class										
Any primary system organ class	**131**	**(72.8)**	**134**	**(74.0)**	**136**	**(75.1)**	**401**	**(74.0)**	**108**	**(60.0)**
Blood and Lymphatic System Disorders	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.2)	0	(0.0)
Cardiac Disorders	15	(8.3)	24	(13.3)	24	(13.3)	63	(11.6)	1	(0.6)
Ear and Labyrinth Disorders	5	(2.8)	7	(3.9)	8	(4.4)	20	(3.7)	4	(2.2)
Endocrine Disorders	1	(0.6)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Eye Disorders	4	(2.2)	5	(2.8)	6	(3.3)	15	(2.8)	4	(2.2)
Gastrointestinal Disorders	67	(37.2)	61	(33.7)	68	(37.6)	196	(36.2)	29	(16.1)
General Disorders and Administration Site Condition	30	(16.7)	33	(18.2)	33	(18.2)	96	(17.7)	27	(15.0)
Immune System Disorders	1	(0.6)	0	(0.0)	2	(1.1)	3	(0.6)	0	(0.0)
Infections and Infestations	42	(23.3)	28	(15.5)	34	(18.8)	104	(19.2)	40	(22.2)
Injury, Poisoning and Procedural Complications	6	(3.3)	5	(2.8)	6	(3.3)	17	(3.1)	2	(1.1)
Investigations	12	(6.7)	10	(5.5)	24	(13.3)	46	(8.5)	6	(3.3)
Metabolism and Nutrition Disorders	40	(22.2)	49	(27.1)	49	(27.1)	138	(25.5)	13	(7.2)
Musculoskeletal and Connective Tissue Disorders	10	(5.6)	12	(6.6)	10	(5.5)	32	(5.9)	11	(6.1)
Nervous System Disorders	63	(35.0)	59	(32.6)	52	(28.7)	174	(32.1)	45	(25.0)
Psychiatric Disorders	58	(32.2)	63	(34.8)	67	(37.0)	188	(34.7)	25	(13.9)
Renal and Urinary Disorders	1	(0.6)	2	(1.1)	2	(1.1)	5	(0.9)	0	(0.0)
Reproductive System and Breast Disorders	3	(1.7)	5	(2.8)	6	(3.3)	14	(2.6)	2	(1.1)
Respiratory, Thoracic and Mediastinal Disorders	6	(3.3)	8	(4.4)	12	(6.6)	26	(4.8)	4	(2.2)
Skin and Subcutaneous Tissue Disorders	16	(8.9)	18	(9.9)	21	(11.6)	55	(10.1)	11	(6.1)
Vascular Disorders	6	(3.3)	6	(3.3)	5	(2.8)	17	(3.1)	1	(0.6)

Source: [D2302-Table 12-8]

We can see, for the first 9 weeks, that "Psychiatric Disorders" are lumped together, with 188 persons (34.7%) in the Ritalin group affected by these, compared to 25 (13.9%) in the placebo group.

But *nowhere* in the 58 pages long Swedish "investigation" can we read specifics about what comprised these psychiatric disorders. We find nothing at all in the document about "aggression". We find nothing about ***"new safety concerns"*** for aggression, hostile behavior, anxiety, depression.

While the assessment of the Concerta studies showed: **"A *causal* relationship with Concerta was established for aggression, tics and depression",** we find nothing at all about this in the Swedish document.

So in some way the Swedish authorities together with Novartis succeeded to get rid of, or not go further with, these serious adverse effects, which *must have been* about the same in the studies of Ritalin as in the studies of Concerta. And which could have – as for Concerta – formed the basis for disapproval of the application. How this was done is not clear at the moment. Maybe we have a case of "recoding" the adverse events, like the famous renaming of suicide attempts by pharmaceutical companies, instead calling them "emotional lability". Anyhow the Swedish authorities could not "afford" to ask too many questions about this.

What did the MHRA do about it?

At the moment I don't know how much of the text in the Swedish assessment report is copied from the text originated by the Reference Member State (RMS), Germany, leading the handling of Novartis' application.

And we come to the role of MHRA and my questions to you:

1. Did MHRA "handle" *aggression*, and other serious adverse events, in the same way as the Swedish authorities did? (In other words, not at all.)

2. If so, how could MHRA, considering what the agency knew about the harmful effects of the almost identical drug Concerta, fail to go further with the investigation about this manipulation of data?

3. If MHRA actually challenged the manipulated data about adverse effects in Novartis' application for Ritalin, I assume the agency arrived at the same conclusion as in the Concerta investigation – that the drug could *not* be approved. I would be happy to get a copy of that important assessment report.

Yours sincerely,

Janne Larsson
Reporter
Sweden