A Review of the approval of Concerta for adults in Europe

In 2010, the pharmaceutical company Janssen's application to have Concerta approved for adults was rejected, after a devastating investigation.
In 2022, the pharmaceutical company's new application was approved.
These are initial investigative questions about the affair and about the actions of the German Federal Institute for Drugs and Medical Devices, BfArM

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A Review of the approval of Concerta for adults in Europe

In 2010 , the British Medicines Agency (MHRA) led the European investigation into Janssen's application to have Concerta approved for treatment of adults. The MHRA was Reference Member State (RMS). After a devastating investigation for the pharmaceutical company, it was clear that the application would be rejected, and Janssen was forced to withdrew the application. Lack of efficacy, serious harmful effects, a high potential for abuse, had been demonstrated in the studies submitted by the pharmaceutical company. [1]

In 2021, Janssen submitted a new application to have Concerta approved for new adult admission. This time, the investigation was led by the German Medicines Agency BfArM. In 2022, Concerta was approved for *de novo* treatment of adults.

In the following I would like to question how the devastating investigation for Concerta to adults from 2010, a number of years later, could be turned into an approval of the drug. I want clear answers from BfArM, mainly about:

> **(a)** the damage revealed in the pharmaceutical company's double-blind randomised trials;
> **(b)** the high abuse potential identified in the first investigation but lost in the latter; and
> **(c**) the discrepancies (or suspected irregularities) detected as regards "discontinuation" of studies.

The harms revealed in the pharmaceutical company's double-blind randomized trials

In the assessment of the three ***double-blind randomized studies (3013, 02-159, 3002) that Janssen submitted in support of his application in 2010,*** some of the **conclusions of the investigation were:**

- **"the B/R [Benefit/Risk] of Concerta in the proposed indication is negative".**
- **"The lack of demonstrated efficiacy coupled with the safety issues, especially cardiovascular safety (potential long-term effects of increase in BP [blood pressure]), abuse potential, and psychiatric/aggression AEs render the B/R negative for the proposed indication."**
- "**A causal relationship with Concerta was established for aggression, tics and depression.**" [1]

Aggression

The summary of the 2010 studies for *aggression* showed that **11.9% (71/596) of subjects receiving Concerta reported under this category ("adverse event"), while the percentage for those receiving placebo was 5.5%** (**17**/309). Thus, those receiving Concerta were **116% more likely** to exhibit aggression-related behaviour during the studies (11.9/5.5), compared to those receiving placebo (**see Table 59 later in the text).**

In the report it was stated:
"**13 of the 596 subjects receiving Concerta ... were withdrawn for aggression-related adverse events (vs. none receiving placebo)**" [1] (See page 65, Preliminary Variation Assessment Report, Concerta, July 2010; see also FVAR, p. 12, 26 April 2011.)

When two additional double-blind randomised trials were added (3014, JPN-A01), **to the new 2021 application, the result in terms of *aggression* was that 9.7% (89/913) of subjects receiving Concerta were reported under this category ("adverse event"), while the percentage for those receiving placebo was 4.8% (30/625)**. Thus, those receiving Concerta were **102% more likely** to exhibit aggression-related behaviour during the studies (9.7/4.8), compared to those receiving placebo (**see Table 32 later in the text).**

A curious fact is that in the two additional studies, only **1 person (out of 317) in the Concerta group** discontinued the studies due to aggression-related effects, while in the previous three studies (more data on this in the section **Discontinuation/Withdrawal from the studies** below).

Based on the results of the combined double-blind studies and Concerta's stated causal role in terms of aggression, we could say that of the 19,216 adults who received Concerta in Sweden last year, 942 adults (9.7-4.8=4.9) would show aggression-related effects, which they would not have had without Concerta

Tics / Tourette syndrome / dystonia

The summary of the 2010 studies for *Tics/Tourette syndrome/dystonia* showed that **4.2% (25/596) of subjects receiving Concerta were reported under this category ("adverse event"), while the percentage for those receiving placebo was 1.3% (4/309).** Thus, those receiving Concerta were **223% more likely** to show effects in this category during the studies (4.2/1.3), compared to those receiving placebo (see Table 59 later in the text).

When two additional double-blind randomised trials were added, **in the new application in 2021, the result for Tics/Tourette syndrome/dystonia (Verbal or motor tics) was that 3.9% (36/913) of subjects receiving Concerta were reported under this**

category ("adverse event"), while the percentage for those receiving placebo was 0.8% (5/625). Thus, those receiving Concerta were **388% more likely** to show effects in this category during the studies (3.9/0.8), compared to those receiving placebo (see Table 32 later in the text).

Based on the results of the combined double-blind studies and Concerta's stated causal role in Tics, we could say that of the 19,216 adults who received Concerta in Sweden last year, 596 adults (3.9-0.8=3.1) would show such effects, which they would not have had without Concerta.

Depression

The summary of the studies on ***depression*** showed that **16.8% (100/596) of subjects receiving Concerta reported under this category ("adverse event"), while the percentage for those receiving placebo was 10.4% (32/309).** Thus, those receiving Concerta were **62% more likely** to show depression-related effects during the studies (16.8/10.4) compared to those taking placebo (see Table 59 later in the text).

When two additional double-blind randomised trials were added, in **the new application in 2021**, the result for ***depression*** was that **13.9% (127/913) of subjects receiving Concerta were reported under this category ("adverse event"), while the percentage for those receiving placebo was 6.2% (39/625).** Thus, those receiving Concerta were **124% more likely** to show depression-related effects during the studies (13.9/6.2), compared to those taking placebo (see Table 32 later in the text).

Based on the results of the combined double-blind studies and Concerta's established causal role in depression, we could say that of the 19,216 adults who received Concerta in Sweden last year, 1480 adults (13.9-6.2=7.7) would show depression-related effects, which they would not have had without Concerta.

Psychosis / mania

The summary of the 2010 ***psychosis/mania*** studies showed that **2.9% (17/596) of subjects receiving Concerta reported adverse event, while the percentage for placebo was 1.0% (3/309).** Thus, those receiving Concerta were **190% more likely** to show psychosis/mania-related effects during the studies (2.9/1.0), compared to those receiving placebo (see Table 59 later in the text).

When two additional double-blind randomised trials were added, **in the new 2021 application**, the result for ***psychosis/mania*** was that **2.3% (21/913) of subjects receiving Concerta were reported under this category ("adverse event"), while the percentage for those receiving placebo was 0.6% (4/625)**. Thus, those receiving

Concerta were **283% more likely** to show psychosis/mania-related effects during the studies (2.3/0.6), compared to those receiving placebo (see Table 32 later in the text).

Based on the results of the combined double-blind studies and Concerta's established causal role in psychosis/mania, we could say that of the 19,216 adults who received Concerta in Sweden last year, 327 adults (2.3-0.6=1.7) would show psychosis/mania-related effects, which they would not have had without Concerta.

Cardiovascular Disorders

The summary of the 2010 ***cardiovascular disorders*** studies showed that **6%** (36/596) of subjects receiving Concerta showed **tachycardia** ('heart arrhythmia') while the percentage for those receiving placebo was **0%** (0/309)**; 13.4**% (80/596) of subjects receiving Concerta had ***arrhythmias*** *(heart rhythm disorders)* while the percentage for those receiving placebo was **3.6%** (11/309); **5.4**% (32/596) of subjects receiving Concerta showed ***hypertension*** **(***high blood pressure),* while the percentage for those receiving placebo was **3.9%** (12/309). (See Table 59 later in the text.)

When two additional double-blind randomised trials were added, in the **new application in 2021**, the result for ***Serious Cardiovascular Events,*** as the title is in the current table, was that **9.5 % (87/913) of subjects receiving Concerta were reported under this category, while the percentage for those receiving placebo was 3.8% (24/625).** Thus, those receiving Concerta were **150% more likely** to have heart-related adverse effects during the studies (9.5/3.8) compared to those receiving placebo (see Table 32 later in the text).

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)

Table 32: Number and Percent of Subjects With At Least One Adverse Event Within Any Adverse Event Category of Special Interest by Treatment Group - Double-Blind and Overall CONCERTA Safety Analysis Set (CONCERTA EU SCS: Double-Blind Safety + Overall Concerta Safety Analysis Sets)

	Placebo (N=625)	DB Concerta (N=913)	Overall Concerta (N=1815)
Total no. subjects WITH ADVERSE EVENTS	121 (19.4%)	414 (45.3%)	970 (53.4%)
Aggression	30 (4.8%)	89 (9.7%)	240 (13.2%)
Cerebrovascular Disorders	0	1 (0.1%)	2 (0.1%)
Decreased Rate of Growth	0	0	0
Depression	39 (6.2%)	127 (13.9%)	309 (17.0%)
Drug Abuse/Drug Dependence	0	0	0
Neonatal Toxicity	0	0	0
Psychosis/Mania	4 (0.6%)	21 (2.3%)	56 (3.1%)
Reduced Weight Gain	40 (6.4%)	257 (28.1%)	534 (29.4%)
Seizures	0	0	0
Serious Cardiovascular Events	24 (3.8%)	87 (9.5%)	259 (14.3%)
Sexual Maturation Delayed	0	0	0
Suicidality	2 (0.3%)	3 (0.3%)	7 (0.4%)
Verbal or Motoric Tics	5 (0.8%)	36 (3.9%)	99 (5.5%)
Withdrawal Syndrome	0	1 (0.1%)	1 (0.1%)

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
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Abuse Potential

The 2010 European investigation into Concerta concluded:

"It is assessed there is a significant abuse and diversion risk with Concerta." [1]

Among the scientific studies that Janssen submitted as part of the 2010 application to have Concerta approved for adults were three so-called Abuse Potential Studies (12-302, 12-005, and 12-007). These were studies carried out *specifically* to determine the risk of abuse with Concerta. (See Appendix 1 for a brief review of these studies.)

And as above, the conclusion was: **"It is assessed there is a significant abuse and diversion risk with Concerta."** The results of these Abuse Potential Studies could also at the same time, without difficulty, be seen in "anecdotal evidence" from internet pages – here an excerpt of 103 pages with stories from Swedish users about the "euphoric effect" of Concerta and Ritalin. Lots of stories about Concerta and Ritalin in "therapeutic doses" giving an intoxication effect – which is greatly enhanced if you crush, snort and inject the drugs. (In Swedish) **http://jannel.se/concrit.Apr2010.pdf**

But what happened to this high Abuse Potential when Janssen submitted their new 244-page Clinical Overview on May 26, 2021, in the new application to have Concerta approved for adults? [2] What happened to the studies above, which were judged by the English and Dutch medicines authorities to show "a significant abuse and diversion risk"?

They are mentioned, as a historical reference, once in the 244-page document, without any mention of the assessment above. We are only told (p. 18): "In addition, a series of 3 clinical pharmacokinetic and pharmacodynamic studies were conducted in adults to evaluate

different aspects of abuse liability that may be related to CONCERTA XL (Studies 12-302, 12-005, and 12-007)."

Contrary to the above, the pharmaceutical company Janssen on "abuse potential", *in recent* studies in Japan (JPN-A01 , JPN-02) has come to the conclusion (p. 68): **"no apparent drug abuse potential was found in the CONCERTA XL group compared to the placebo group"**.(More on the Japanese studies, and suspected irregularities, later.)

Discontinuation / Withdrawal

The 2010 European investigation of Concerta described that **a high proportion** of subjects in the double-blind studies of Concerta were forced to discontinue /were withdrawn due to adverse effects.

So, for example, in the *three* studies submitted by Janssen (3013, 02-159 and 3002), "**13 of the 596 subjects receiving Concerta ... were withdrawn for aggression-related adverse events (vs. none receiving placebo".** [1] (See page 65, Preliminary Variation Assessment Report, Concerta, July 2010; see also FVAR, p. 12, 26 April 2011.) These 13 people suffered such severe aggression that they had to discontinue their intake of Concerta and withdraw from the studies. **None of those who received placebo suffered such severe aggression that they had to stop the studies.**

In the longest of the double-blind studies (3013), the MHRA stressed that **19% of subjects (34 out of 182) receiving Concerta discontinued the study due to adverse effects versus 2% in the placebo group.**

We can see the opposite of the above in the two double-blind studies that Janssen submitted in support of their new application.

Thus, in the previous three studies (3013, 02-159, 3002), 13 out of 596 subjects (2.2%) in the Concerta group had to discontinue the studies due to aggression-related side effects – compared to none in the placebo group. In Janssen's new studies submitted (3014, JPN-A01), only 1 in 317 subjects (0.3%) in the Concerta group discontinued due to aggression-related adverse events – and 1 person in the placebo group. [3]

The really strange thing emerges in Janssen's 8-week study in Japan, JPN-A01, where we can read in the words of the German Medicines Agency, "the extremely low drop-out rate" – only 5%. (The discontinuation rate in the Concerta group was 6.3%, the discontinuation rate in the placebo group was 4.3%.) [4] Where the Agency compares with the previous studies

where the discontinuation rate was up to 40% in the Concerta group and higher than in the placebo group. [4, p. 88]

And what was the reason for this extremely low drop-out rate? What could make the people in the placebo group stay in the study at this extremely high rate until its end? What could make the people in the Concerta group – given the harmful effects shown in other studies – stay in the study to this extremely high degree until its end?

The German authority refers to Janssen's arguments as a reason and writes: "**The extremely low drop-out rate in study JPN-A01 was explained by the MAH [Marketing Authorization Holder, Janssen] due to the lack of approved ADHD medications in adults in Japan at the time of the study** and due to the flexible dose titration regimen (leading to less discontinuation due to efficacy reasons)." (Bold here.)

The big difference would simply be that continuing the entire study was the only way for the subjects to be able to get any form of ADHD drug in Japan. And Janssen's actual answer confirms the matter. On page 33 of its 244-page Clinical Overview, the company writes:

> "MPH [Methylphenidate] had been approved for the treatment of children with ADHD in Japan, but there was no medication approved for adults with ADHD at the time of the study. Because of this situation, it could be considered that the motivation for patients to continue participation in this study was very high."

And further (after speculating about the titration):

> "Third, only patients who completed this initial study were eligible for enrolment in the open label long-term extension study"

And we are not surprised that the pharmaceutical company chose to conduct its additional study in Japan. More surprising is how BfArM can accept this as good scientific practice.

My questions to the Federal Institute for Drugs and Medical Devices, BfArM

I do not want to put BfArM in a situation of having to explain *the reasons why* it approved Janssen's new application without any critical questions whatsoever. My questions below are introductory and simple, they are formulated to give equally simple **YES or NO answers**.

1. Was BfArM aware of what I have brought up under the heading "harms revealed in the pharmaceutical company's double-blind randomized trials" – with the data in the table from 2010 and the table from 2021 – when it supported Janssen's new application?

2. Was BfArM aware of what I mentioned under the heading "Abuse Potential" – that Janssen, it seems, hid the stated *specific* studies on abuse potential and the conclusion from 2010, and replaced this with studies from Japan in which no difference in abuse potential was found between Concerta and placebo?

3. Was BfArM aware of what I have mentioned under the heading "Discontinuation/Withdrawal" – with the strange conditions that have been shown to prevail mainly around the double-blind study in Japan?

That said, I now just want to get a YES or NO to the questions above.

Best regards
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[1] MHRA, Preliminary Variation Assessment Report, Concerta, juli 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 maj 2011, http://jannel.se/FVAR.Concerta260511.pdf
[2] Janssen Research & Development, Clinical Overview, CONCERTA XL® for the *de Novo* Treatment of Adult Patients with Attention-Deficit/Hyperactivity Disorder, 26 maj 2021
[3] Janssen, Summary of Clinical safety, 6 maj 2021.
[4] BfArM, DE/H/6007/001-004/II/107, RMS's FVAR, Overall Conclusion and Benefit-Risk Assessment, 2021.

APPENDIX 1 ABUSE POTENTIAL STUDIES

Among the scientific studies that Janssen submitted as part of the 2010 application to have Concerta approved for adults were three so-called Abuse Potential Studies. These were studies carried out *specifically* to determine the risk of abuse with Concerta.

The first of these studies (Study 12-005) [1] (See Preliminary Variation Assessment Report, Concerta) was a double-blind, placebo-controlled study in which subjects (49, 18-48 years) were "healthy subjects with a history of recreational use of stimulants". The subjects had previously used cocaine (88%) and methamphetamine (25%). The study compared placebo, with Ritalin (IR, Immediate Release) 60 mg and Concerta, 108 mg. They used the Drug Rating Questionaire, Subject (DRQS-VAS) questionnaire, which mainly measured the degree of "Liking" in response to the question: "Do you like the drug effect you are experiencing now?" ("Do you like the drug effect you are feeling now?").

The conclusion of the assessment was: "The result clearly shows that although Concerta is not crushed (a more likely scenario in case of abuse), it produces a pleasant effect in this group of recreational drug users." As expected, Ritalin IR also gave this "pleasure effect", but there was no significant difference between the preparations.

The second of these studies (Study 12-007) was a double-blind, placebo-controlled, randomized study, in which the subjects (55) were "healthy normal adults with a history of mild (temporary) use of stimulants", comparing placebo, with Ritalin (IR) 50 mg, 90 mg, and Concerta 54 mg, 108 mg.

The agency wrote that Concerta would probably be crushed if you wanted to abuse the pill, *but* that "addiction potential" in this study was also proven for regular intake in the doses (108 mg and 54 mg).

The MHRA concluded that Concerta "had a positive effect on the 'Liking element' of DRQS [Drug Rating Questionaire Subject]... If the tablets are crushed, the effect is likely to increase. The amplification effect of other drugs of abuse is not known and it is known that spread [diversion] is a significant problem".

The third of these studies (Study 12-1302) was done on *active* drug users [people diagnosed with substance abuse] and the assessment (MHRA) was that in this group "it is unlikely that anyone would take Concerta in this way if they wanted to abuse it". In other words, these addicts would take other drugs if they had a choice, and would probably crush or take Concerta in another way if they were to take Concerta.

In summary, the studies submitted by Janssen showed the considerable abuse potential of Concerta at the usual dose, 54 mg, prescribed by psychiatrists. The English Medicines Agency was apparently surprised at the "pleasure effect" that these "therapeutic doses" gave the subjects. The "drug effect" that emerged led the English Medicines Agency to question what the *real* results were in other short-term studies when adults "with ADHD" were given Concerta.