To: PRAC Lead Ulla Wändel Liminga
Copy: Lead Member State Assessor Medical Products Agency (MPA)
Copy: Pharmacovigilance Risk Assessment Committee (PRAC)

A contribution to the forthcoming Periodic Safety Update Report (PSUR) assessment report for lisdexamfetamine (Elvanse/Vyvanse) aimed to be completed September 2024

Sweden is the Lead Member State for the assessment of the yearly Periodic Safety Update Report (PSUR) for lisdexamfetamine (Elvanse/Vyvanse) in Europe.

The PSUR (February 2023-February 2024) has been submitted by the Marketing Authorization Holder (MAH) Takeda Pharmaceuticals. The data lock point for the current PSUR from the MAH was February 2024. It can be expected that the assessment report from Sweden is completed and accepted with recommendations by the Pharmacovigilance Risk Assessment Committee (PRAC), EMA, this autumn.

The vital safety data below is submitted as a contribution to the work with the assessment report.

It concerns the safety signal of ***Suicidality*** and compares the earlier safety data submitted by the MAH (Takeda) with the data that has emerged in Sweden about suicidality for the age group 10-19 years.

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2024-07-04

Data from the Lead Member State PSUR assessment reports about the safety signal *Suicidality*

In the earlier Lead Member State PSUR assessment report, completed with recommendations by the Pharmacovigilance Risk Assessment Committee (PRAC), EMA, 29 September 2022, we found some *global data* about reported adverse events of ***suicidality*** in connection with Elvanse/Vyvanse[1].

The MAH (Takeda) was in this report (p. 5) directed to submit data about *suicidality* in its *next* PSUR (-February 2023). It was written: *"Issues to be addressed in the next PSUR"* [-February 2023]:

> "A cumulative review of suicidality should be provided. Clinical trials, relevant post marketing safety data bases and the literature should be searched, and all relevant preferred terms should be included. Relevant cases should be summarised in tabular format, with particular focus on dechallenge and rechallenge cases. Based on this review, a discussion on the need for an update of the product information should be provided, with proposed wording if applicable."

And we go to the figures submitted by Takeda over ***suicidality*** in connection with Elvanse/Vyvanse in the latest PSUR (-February 2023). We find the following on page 45[2]:

Figure 3. Distribution of Cases Reporting a Possible/Probable Causality and Background of 839 SRE Cases Over the Years

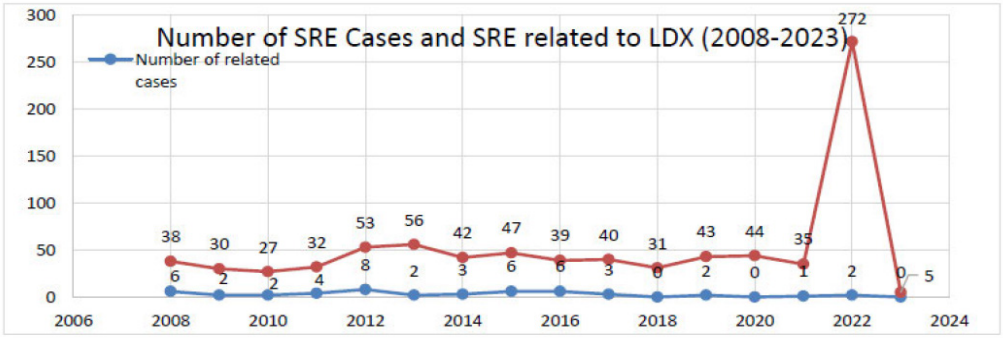


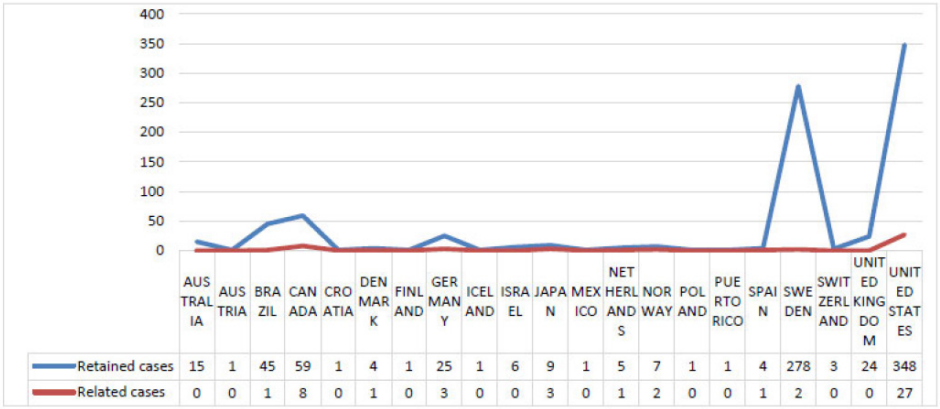
Figure 3 shows annual frequency case distribution for overall SRE and for related SRE to LDX during the period 2008 (IBD) to 15 September 2022. The number reported of overall SRE cases as well as those with potential relationship to LDX were stable.

This is a diagram over Suicidality Related Events (SRE) reported to Takeda's *the Global Safety Data Base, GSDB, since 2008.*

[1] PRAC PSUR assessment report, lisdexamfetamine, 29 September 2022
[2] PRAC PSUR assessment report, lisdexamfetamine, 28 September 2023

The company makes the comment: "This peak was driven by cases from Sweden."

Figure 1. Distribution of SRE Cases reporting a Possible/Probable Causality and Background of 839 Cases with SRE by Country



	AUSTRALIA	AUSTRIA	BRAZIL	CANADA	CROATIA	DENMARK	FINLAND	GERMANY	ICELAND	ISRAEL	JAPAN	MEXICO	NETHERLANDS	NORWAY	POLAND	PUERTO RICO	SPAIN	SWEDEN	SWITZERLAND	UNITED KINGDOM	UNITED STATES
Retained cases	15	1	45	59	1	4	1	25	1	6	9	1	5	7	1	1	4	278	3	24	348
Related cases	0	0	1	8	0	1	0	3	0	0	3	0	1	2	0	0	1	2	0	0	27

In Figure 1 we see the peak in Sweden. And Takeda makes the comment:

> "The peak … is triggered by receipt of a high number of cases from Sweden Poison Information Center (all with insufficient information for assessment of causality)."

Takeda's handling of the *Suicidality* data

"The peak" is of obvious reasons hard for Takeda to make nothing of. Yet the company succeeds very well. Looking on the figures above we see 278 reports from Sweden – of which 240 are for the years 2021-2022.

Let's look at the "reporting rate" of *Suicidality* in connection with Elvanse/Vyvanse in the Nordic countries, *since* 2008: Danmark 4, Finland 1, Iceland 1, Norway 7 = **13** and Sweden = **278**!

Takeda is listing "839 SRE Cases Over the Years" *since* 2008 – globally. And little Sweden contributes with 278 of these cases, 33% (278/839).

The sales of Elvanse/Vyvanse worldwide is estimated to be **3800 million USD for 2022**[3], and for Sweden **68 million USD** for the same year[4]. The sales in Sweden makes up **2%** of the global sales of the drug (68/3800).

We can say that with the *same* reporting rate of suicidality in other countries as in Sweden, the number of cases for **2021-2022 alone** would be **12 000** – instead of **67**! (See figure 3 above with 240 reported cases from Sweden and 67 from the rest of the world for 2021-2022.) The reporting rate for the rest of the world would be 0,6% of that in Sweden for these two years (67/12 000).

But now, let's see what the company does with the 278 reported cases from Sweden (where 240 were for the years 2021-2022). In Figure 1 we see: only 2 (!) of the cases are considered as "Related cases". In this – what we can call The Big Subtraction Game – 276 cases are deducted and only 2 are left, as being "related". How is this done?

[3] The Global Drug sales of Vyvanse (2019 - 2026, USD Millions) - GlobalData
[4] Data released by the Swedish Dental and Pharmaceutical Benefits Agency.

First, the cases that are considered “not related” to the intake of Elvanse are removed. That means minus 132 cases. These deductions can be divided as follows: **a)** The cause can be attributed to the patient's history or diagnosed condition; **b)** The cause can be attributed to other psychotropic drugs that the patient is taking. It is even so that **c)** the cause of the patient's suicidal condition can be attributed to significant stress factors (such as "home eviction") And so 132 cases disappeared.

That leaves 707 cases (of the original 839). The subtraction continues. This time, it is explained that 658 (!) of these cases are "unassessable", as there is not enough data in the reports to assess a possible or probable causal relationship. Now only 49 of the 839 cases remain, which, in the language used, "cannot be excluded and which were therefore assessed as probable or possible". 49 cases of "15 504 763 – 22 810 069 patient-years" (in the report said to be the exposure of Elvanse/Vyvanse).

And for Sweden only 2 cases of the 278 remained as “related”.

This is how Takeda handles the *suicidality* signal in connection with its drug. Meaning, that “no signal” is found for Elvanse to have a *causal* relation to *suicidality*.

The handling of the *Suicidality* data by the lead member state (LMS, Sweden) and concerned member states (CMS, other European countries)

First the work of responsible officials at the Medical Products Agency (MPA) in Sweden should be acknowledged. Important safety data about Elvanse and *suicidality* has *for the first time* been compiled and included in adverse event reports, for the years 2021-2022. This is “the peak” referred to by Takeda in the figures above. (*See more about data for 2023 in the section Late Breaking Information later in this report*).

All these reports, 240 for the years 2021-2022, are “medically confirmed” by Health Care Professionals. They *all* concern young persons in the age group 10-19. They *all* concern young persons taken to an emergency unit in a hospital due to taking an overdose of Elvanse with a self-destructive purpose. *All* of these reports are to be considered serious as they involve hospitalization.

In the assessment report ***PRAC Periodic Safety Update Report assessment* for Elvanse** 28 September 2023[5], the LMS, Sweden, is in section 7 on page 86 commenting on the “large proportion of cases” from Sweden:

> “The large proportion of cases reported from the Swedish Poison Information Center is the result of a focused effort to report cases of overdose of ADHD medications. It is in that sense a type of stimulated reporting.”

We can see that the “focused effort”, the “stimulated reporting”, meant that 240 young persons who had taken overdoses of Elvanse with a self-destructive purpose and who were committed to hospital, earned serious adverse event reports.

And we can see that this “focused effort”, this “stimulated reporting” was *not* taking place in other countries. In fact the reporting of this kind of incidences was not, and has never been, reported and included in Takeda’s Global Data Base of adverse events about suicidality.

[5] PRAC PSUR assessment report, lisdexamfetamine, 28 September 2023

As these cases most definitely *exist* – they are not dreamed up – we can say that this reporting is an honest effort to, for the first time, describe the actual reality in this area.

However the laudable reporting actions from responsible officials at the MPA were not met with an appropriate response by the Swedish officials (Lead Member State, LMS) writing the assessment report, and could obviously not be understood and handled by the Concerned Member States (CMS).

Instead of requiring a focused reporting effort in the next safety report, by the medical authorities in other countries, the assessors from Sweden *downgrade* the importance of the findings of the MPA officials who compiled the adverse event reports.

It is said (p. 86): "that generalisation to other countries of this type of safety concern may not be self-evident, since this relates to behavioural patterns that may vary between countries and over time." Yes, it is true, it is *not* "self-evident" that the total number of cases in other countries would be 12 000, but it *is* self-evident that the total number of cases in all other countries is *not* 67 – see above about Takeda's handling of data.

In downplaying *the clear and shining safety signal of suicidality* from the Swedish data in connection with the intake of Elvanse, the Swedish assessors are also shifting the attention from the drug to this "vulnerable population" – meaning that the probable suicidal or suicidality enhancing effect of the drug is blamed on the patients' "disease characteristics". Quote (p.75): "It is of importance for the current discussion that according to the DSM-V criteria for ADHD – 'By early adulthood, ADHD is associated with an increased risk of suicide attempt, primarily when comorbid with mood, conduct, or substance use disorders'."

And so comes the recommended solution (p.86), to "educate patients/caregivers on proper storage and disposal of unused medicinal product".

But with this the attention is *further* diverted to, what "Member State 2" – The Netherlands (not even agreeing to this simple recommendation) writes (p.86):

> "The proposed warning is not considered specifically needed for this product. Most drugs can be potentially harmful for an unintended receiver and storing a medicinal product in a safe space is considered common practice."

The use of the wording "unintended receiver" emphasizes a blindness to the fact that a *huge* majority of the teenagers taking an overdose of Elvanse with a self-destructive purpose *was prescribed the drug by psychiatrists.*

And as expected, we can read (p. 74) that the manufacturing pharmaceutical company Takeda, considers that the signal of *suicidality* in connection with Elvanse is "refuted":

> "It is thus concluded that the cumulative evidence up to the DLP [Data Lock Point] and the signal regarding the relationship between exposure to LDX [Lisdexamfetamine, Elvanse] and development of SRE [Suicidal Related Events] is refuted. This risk is therefore considered sufficiently addressed through the information provided in the current labelling material. This topic will undergo re-assessment as new information becomes available."

And the assessors from the Lead Member State, Sweden, agree:

> **"Suicidality**
> **The signal was refuted by the MAH and this is agreed."**

The Swedish data was not given attention, no "focused effort" to compile similar data about *suicidality* from other countries was ordered, and so it can be expected that instead of a total number of 12 000 cases of overdoses with a self-destructive purpose, the number will again, in the coming report, be around 67 – *from all other countries combined*.

Late-breaking information about the safety signal *Suicidality* for Elvanse / Vyvanse in Sweden for the age group 10-19

After the data lock point (February 2024) more data has emerged in Sweden about the safety signal *suicidality* in connection with Elvanse/Vyvanse, for the age group 10-19.

This information has now been finalized in adverse event reports by the Swedish MPA, should now have been included in Takeda's Global Safety Base, and must be taken into account in the process of the new Lead Member State PSUR assessment report[6].

We find in the *new* adverse event reports 140 *new* cases of overdoses of Elvanse with a self-destructive purpose for the age group 10-19 for 2023, for Sweden.

This in addition to the 240 adverse event reports submitted for 2021-2022 for the same population.

Where *all* these adolescents wound up in emergency units, and where *all* of these cases were reported by health care personnel from these units.

It is my hope that the vital safety data above from Sweden can be an important contribution to the new assessment of the safety data about *suicidality* connected with Elvanse/Vyvanse.

Respectfully submitted for inclusion and evaluation in the forthcoming assessment report.

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[6] The Adverse Event Reports are available from the Swedish MPA, and can be released after an FOIA request.