To: PRAC Lead Ulla Wändel Liminga
Copy: Lead Member State Assessor Medical Products Agency (MPA)
Copy: Pharmacovigilance Risk Assessment Committee (PRAC) 6 June 2023

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

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 2022-February 2023) has now been submitted by the Marketing Authorization Holder (MAH) Takeda Pharmaceuticals. The data lock point for the current PSUR from the MAH was February 2023. 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.

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

In the latest Lead Member State PSUR assessment report, completed with recommendations by the Pharmacovigilance Risk Assessment Committee (PRAC), EMA, 29 September 2022, we find *global data* about reported adverse events of ***Suicidality*** in connection with Elvanse/Vyvanse.

We find the data under the heading ***Suicidality*** on page 33 of the report. Takeda refers to its Global Safety DataBase (GSDB) and gives a table – presumably and acknowledged by the Swedish Medical Products Agency (MPA) – made up from the *global reporting* of these adverse events.

We can in the table see that Takeda has registered *18 adverse events of suicidality for adolescents 12-17 years* for the one-year period (February 2021-February 2022).

In total and for all age groups the MAH registered ***162 event of Suicidality*** (excluding 100 cases of reported depression). Of the total figure of 262 events 69 were seen as serious.

For the sake of comparison with the safety data that has emerged from Sweden we look at the terms *Intentional overdose* and *Intentional self-injury.* We find that the MAH reports: *"Intentional overdose (n=**13**/262)"* and *"Intentional self-injury (n=**4**/262)"* – internationally for all age groups.

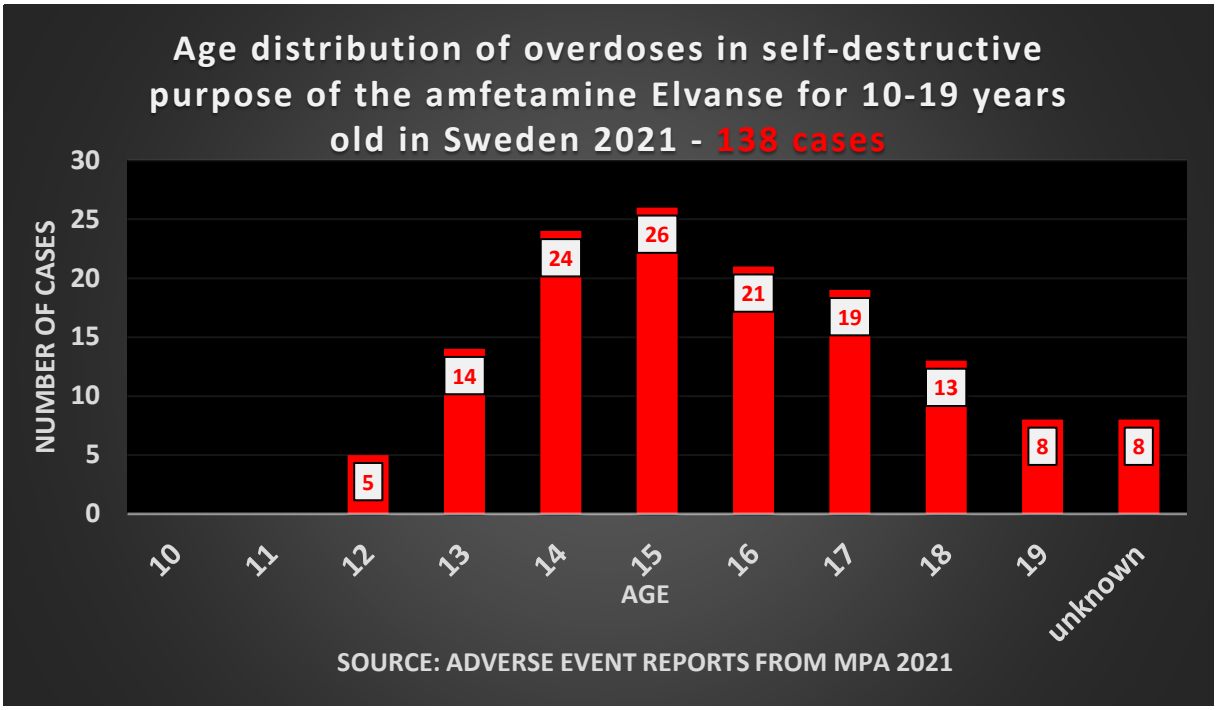
The relevant parts of the PSUR assessment report under the heading *Suicidality* can be found in the ***Appendix*** to this report.

A comparison of the safety data that has emerged in Sweden, about the signal *Suicidality* and Elvanse / Vyvanse for the age group 10-19, with the international data

A review of the adverse event reports about *Suicidality* connected with Elvanse/Vyvanse for the age group 10-19 years old for 2021, produced by the Swedish Medical Products Agency (MPA), gives the following results.

*The MPA has produced **138** adverse event reports about Suicidality for adolescents 10-19 for 2021, for Elvanse/Vyvanse. All* these adverse event reports were categorized as *"Intentional overdose"*, and *"Intentional self-injury"* (including 5 cases of suicide attempt).

The age distribution of these cases can be seen in the diagram below:



These **138** cases of *Suicidality* from 2021, *could* have been included in the Lead Member State PSUR assessment report completed 29 September 2022, but was produced by the MPA first in December 2022 and January 2023.

Meaning that these cases are supposed to be part of the PSUR now under assessment.

We note that the MAH reported: *"Intentional overdose (n=**13**/262)"* and *"Intentional self-injury (n=**4**/262)" – internationally for all age groups.*

We note that Sweden has reported ***138** cases of "Intentional overdose/"Intentional self-injury" – for the age group 10-19, for 2021.*

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

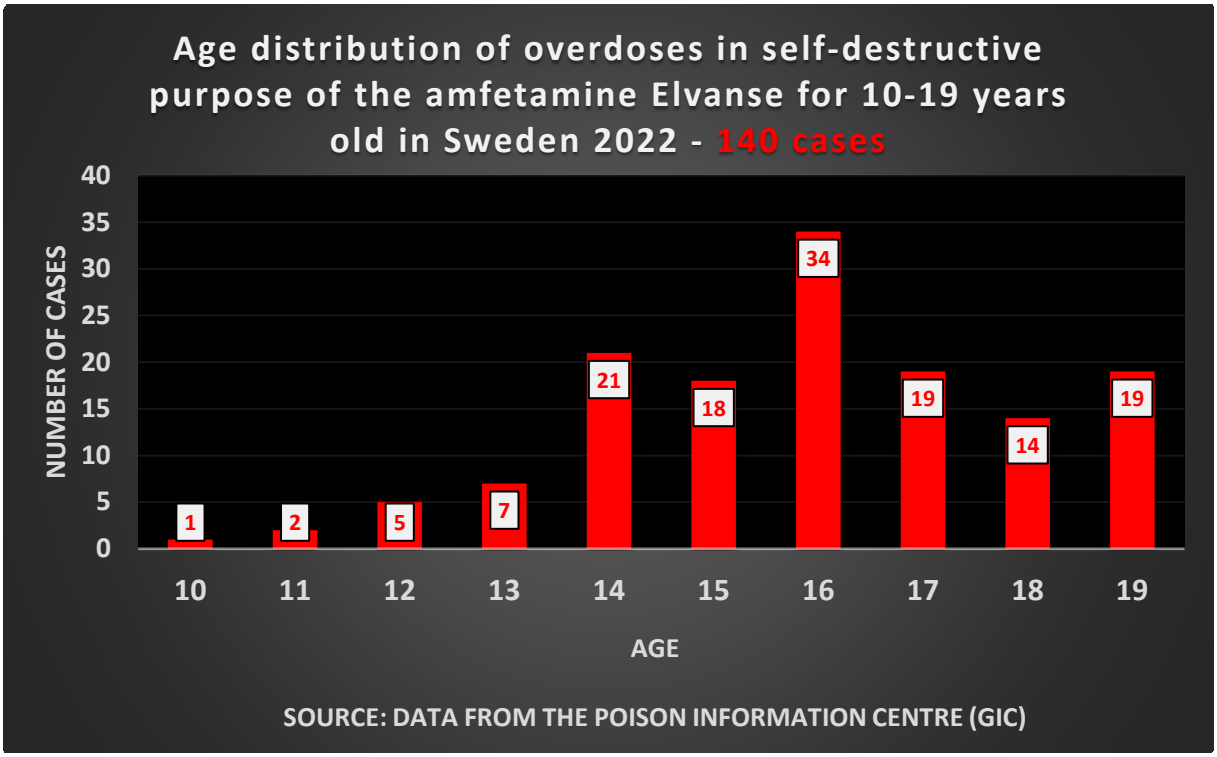
After the data lock point (February 2023) more data has emerged in Sweden about the safety signal *Suicidality* in connection with Elvanse/Vyvanse, for the age group 10-19.

This information has yet to be finalized in adverse event reports by the MPA, but should be taken into account in the process of the new Lead Member State PSUR assessment report.

We find in case data from the Swedish Poison Information Centre (GIC) *140 cases of overdoses in self-destructive purpose for the age group 10-19 for 2022.*

All these cases are reported by health care personnel from emergency units, taking care of the adolescents.

The age distribution of these cases can be seen in the diagram below:



And again, we note that the MAH reported: *"Intentional overdose (n=**13**/262)"* and *"Intentional self-injury (n=**4**/262)" – internationally for all age groups for 2021.*

And that this late-breaking information says that Sweden has reported ***140*** *cases of "Intentional overdose/"Intentional self-injury"* for the age group 10-19, for 2022.

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

The cumulative review of *Suicidality* ordered in the Lead Member State PSUR assessment report

In the Lead Member State PSUR assessment report (page 6) the MAH has been ordered to do a cumulative review of *Suicidality*. It is said:

> "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."

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

As an end note: The attention in the evaluation of the data above should also go to the difference in exposure to Elvanse/Vyvanse, internationally and in Sweden. We see in the Lead Member State PSUR assessment report, that the exposure for the drug is estimated to be *2,298,542 Patient Years for 2021 – while we for Sweden find that 24 198 adolescents got the drug for 2021.*

Respectfully submitted for inclusion in the forthcoming assessment report.

Jan Larsson
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EMA/670459/2022
Pharmacovigilance Risk Assessment Committee (PRAC)

Lead Member State PSUR assessment report

Active substance(s): lisdexamfetamine

Procedure No.: PSUSA/00010289/202202

Data lock point: 22.02.2022

Status of this report and steps taken for the assessment[1]			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	02 June 2022	02 June 2022
☐	Lead Member State preliminary assessment report (AR)	01 Aug 2022	29 July 2022
☐	MS/PRAC members and MAH comments	31 Aug 2022	30 Aug 2022
☐	Lead Member State updated assessment report following comments	15 Sept 2022	15 Sept 2022
☐	Oral explanation	N/A	N/A
☒	PRAC recommendation	29 Sept 2022	29 Sept 2022

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date

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Declarations

☒ The assessor confirms that this assessment does **not** include non-public information, including commercially confidential information (e.g. information shared by other competent authorities or organisations, reference to on-going assessments, development plans (including Scientific Advice/Protocol assistance), pharmacovigilance inspections), irrespective from which entity this was received*.

Whenever the above box is un-ticked please indicate the section and page where the confidential information is located here: ☐

Seriousness:	2/20 events were non-serious and 18/20 events were serious.
Gender:	11/20 events were reported in females, 8/20 events were reported in males, and for 1/20 events, gender was unknown.
Source:	3/20 events were reported from post marketing study, 17/20 events were reported from spontaneous sources.
Patient age:	12/20 events were in adults (18 to <65 years old), 6/20 events were in adolescents (13 – 16 years), 1/20 event was in elderly population (unknown age) and patient age was unknown in 1/20 event.
Company causality assessment:	3/20 events were assessed as not related and 17/20 events were assessed as related.
Event outcome:	2/20 events were not resolved, 7/20 events were resolved, 3/20 events were resolving, and outcome for 8/20 events were unknown. No events were reported with fatal outcome.
Reported PTs:	The reported events were: Loss of consciousness (n=12/20), Syncope (n=6/20), Presyncope (n=2/20).

Of the total 20 events reported, 18 events were serious and 2 were non-serious.

Of the 18 serious events reported, more than 1 suspect drug was reported in 8 events, concomitant medications in 6 events and no further information was available in the remaining 4 events. Positive dechallenge was reported in 3 events. Action taken in response to the events was dose not changed (n=4), drug withdrawn (n=7) and unknown (n=7).

Clinical trial sources: There were no events reported from Company sponsored trials during the reporting period.

Conclusion: The CCDS contains precautionary language that "patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation". No new or significant information was identified from these cases of syncope.

Lead Member State assessment comment:

The number of reported cases has doubled from 10 to 20 events compared with the previous reporting period. The EU SmPC lists syncope as an ADR at a frequency of "Uncommon" for both paediatric- and adult patients. Syncope is an Important potential risk in the EU RMP.

Suicidality

A search of company GSDB was conducted using the following search criteria: SMQ (Narrow) Depression and suicide/self-injury.

Post-marketing data and other sources: During the reporting interval, 230 case reports (262 events) were received for this risk. The event details are further characterized as follows:

Seriousness:	193/262 events were non-serious and 69/262 events were serious.
Gender:	85/262 events were reported in female, 84/262 events were reported in male, and for 93/262 events, gender was unknown/not reported.
Source:	31/262 events were reported from post marketing study, and 231/262 events were reported from spontaneous sources.
Patient age:	97/262 events cases were in adults (18 to <65 years old), 15/262 events were in children (8 – 11 years), 18/262 events were in adolescents (12 -17 years), 6/262 events were in elderly population (65 – 72 years) and patient age was unknown in 126/262 events.
Company causality assessment:	19/262 events were assessed as not related and 243/262 events were assessed as related.
Event outcome:	2/262 events were fatal, 5/262 events were not resolved, 24/262 events were resolved, 9/262 events were resolving, and outcome of 222/262 events were unknown.
Reported PTs:	The reported events were: Depression (n=100/262), Depressed mood (n=54/262), Suicidal ideation (n=37/262), Discouragement (n=16/262), Intentional overdose (n=13/262), Suicide attempt (n=8/262), Feeling of despair (n=7/262), Decreased interest (n=4/262), Intentional self-injury (n=4/262), Depressive symptom (n=3/262), Self-injurious ideation (n=3/262), Agitated depression (n=2/262), Completed suicide (n=2/262), Major depression (n=2/262), Suicidal behaviour (n=2/262), Activation syndrome (n=1/262), Dysphoria (n=1/262), Feeling guilty (n=1/262), Feelings of worthlessness (n=1/262), and Suspected suicide attempt (n=1/262).

Of the 262 events, fatal outcome was reported for 2 events. The reported PTs were Completed suicide (n=2). The age groups for the fatal events were adults (n=1) and unknown age group (n=1). Of the 2 events, 1 event was reported in female patient, and 1 event in male patient. The information available was insufficient for comprehensive medical assessment.

Case [redacted]: This case concerned male patient of unknown age from Australia who committed suicide (completed suicide) while on therapy with LDX at 20 mg once daily for an unknown indication. Medical history and concomitant medications were not reported. No further information or autopsy details were provided.

Company comment: The company assessed the event of Completed suicide as unlikely related to LDX. The event was more consistent with the underlying mental health disorder.

Case [redacted]: This case concerned a [redacted]-year-old female patient from US who committed suicide (completed suicide) while on therapy with LDX at 70 mg at an unspecified frequency for unknown indication. Medical history and concomitant medications were not reported. No further information or autopsy details were provided.

Company comment: The company assessed the event of Completed suicide as unlikely related to LDX. The event was more consistent with the underlying mental health condition of the patient.

Of the 262 events, 9 events were reported to be life-threatening. The reported PTs were Suicide attempt (n=5), Depression (n=1), Intentional self-injury (n=1), Suicidal ideation (n=1), and Suspected suicide attempt (n=1). The age groups for the life-threatening events were adolescents (n=2), adults (n=3) and patients of unknown age (n=4). Of the 9 events, 3 events were reported in female patients, 3 events were reported in male patients and gender was unknown for 3 patients.

In most of the events (n=6), the reported event was confounded by underlying condition of ADHD. For 1 event, co-suspect drugs (diazepam, xyrem, trazodone, omeprazole, linzess, minoxidil, tagamet, meloxicam) was assessed as the contributing factor. In the remaining 2 events, the information available was insufficient for comprehensive medical assessment.

Out of rest of the 251 events, 131 events were confounded by the underlying conditions (ADHD, depression, anxiety disorder, sleep disorder, binge eating, oppositional defiant disorder, bipolar

disorder, Tourette's disorder, schizophrenia, mental disorder, insomnia, autism spectrum disorder, post-traumatic stress disorder).

For remaining 112 events, event start date was not provided, hence, the temporal relationship could not be established for these events. In the remaining 8 events, at least 1 confounding concomitant medication, past history was reported.

A review of cases in the safety database did not indicate new information on this risk. This safety issue will continue to be monitored via routine pharmacovigilance; no additional activities are required at this time.

Clinical trial sources: There were no events reported from Company sponsored trials during the reporting period.

Conclusion: The CCDS lists depression as an ADR and states that, prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. No new or significant information was identified from these cases of suicidality.

Lead Member State assessment comment:

Suicidality:

The total number of reported cases (262 cases, 69 serious) is slightly greater as compared to the previous reporting period (207 cases, 51 serious). 9 events were reported to be life-threatening. In general, the information provided in the case-reports is very limited and precludes making any conclusions. Despite the causes, suicidality is an Important potential risk in the EU RMP and should be continued to be monitored and presented in the next PSUR.

Nevertheless, the presentation by the MAH is quite limited; for instance information on de-challenge and re-challenge cases is missing.

It is also noted that for dexamfetamine, *Suicidal behaviour (including completed suicide)* is included in section 4.8 of the SmPC as a very rare ADR.

For the next PSUSA; a cumulative review of suicidality should be provided. See further Section 4.

Off label use

A search of company GSDB was conducted using the following search criteria: TMQ off-label use. Please refer to Appendix 11 for the list of PTs under the TMQ Off label use.

Post-marketing data and other sources: During the reporting interval, 574 case reports (593 events) were received for this risk. The event details are further characterized as follows: