LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Elvanse Vuxen
(lisdexamfetamine dimesilate)

SE/H/1825/04-06/DC

This module reflects the scientific discussion for the approval of Elvanse Vuxen. The procedure was finalised on 2022-11-18. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Elvanse Vuxen, 20 mg, 40 mg, 60 mg, capsule, hard.

The active substance is lisdexamfetamine dimesilate. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application is an extension, addition of new strengths, of the previously authorised product Elvanse Vuxen, 30 mg, 50 mg, 70 mg, capsule, hard, marketed by Shire Pharmaceuticals Ireland Limited since 2015.

The application for Elvanse Vuxen, 20 mg, 40 mg, 60 mg, capsule, hard, is submitted according to Article 8(3) of Directive 2001/83/EC. The applicant, Shire Pharmaceuticals Ireland Limited applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, DE, DK, ES, FI, IS and NO as concerned member states (CMS).

Potential similarity with orphan medicinal products

According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of lisdexamfetamine are well known. As lisdexamfetamine is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Elvanse Vuxen is intended to replace other similar products already on the market and the approval of Elvanse Vuxen would not result in an increase of the total quantity of dexamfetamine released into the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Elvanse Vuxen from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
Pharmacokinetic properties of the active substance

Basic information about the pharmacokinetic properties is provided in the current SmPC text section 5.2 (Note: Pharmacokinetic SmPC text is not subject to any changes within the current line extension Application).

The Applicant has discussed two clinical studies in the Clinical Overview Addendum in order to support the line extension to include 20, 40 and 60 mg dose strengths for adult patients (see the table below).

Study	Doses Included	Indication
SPD489-121	20 mg	healthy adult Japanese and Caucasian subjects
SPD489-310	20, 30, 40, 50, 60, 70 mg	pediatric subjects with ADHD

SPD489-121 was a Phase I clinical study which provided PK data in healthy adult subjects after the single 20 mg dose for both lisdexamfetamine and its pharmacologically active metabolite d-amphetamine. Furthermore, the corresponding PK data were also obtained after multiple once daily oral doses of 20, 50 and 70 mg. Importantly, PK data from this clinical study were previously assessed, and therefore no detailed regulatory re-assessment of PK data was performed for the purpose of the present line extension Application.

SPD489-310 was a Phase III clinical study in paediatric patients with age span 6-12 years. No PK samples were collected from this study. As such, no PK exposure comparisons was made with other clinical studies in adults. All paediatric patients had an initial oral dose of 20 mg and were titrated to achieve desired therapeutic effect with doses up to 70 mg (see also more details in the Clinical Efficacy). The results of this Phase III pediatric study supported the authorization of 3 additional TAK-489 dose strengths: 20, 40, and 60 mg, equivalent to 5.9, 11.9, and 17.8 mg d-amfetamine base, respectively.

In addition, the Applicant states the following pharmacokinetic information in the present Clinical Overview Addendum:

The pharmacological profile of lisdexamfetamine and the pharmacologically active metabolite d amphetamine have been well characterized in studies enrolling children, healthy adults, and adults

with a history of stimulant abuse. These studies have demonstrated that oral administration of TAK-489 resulted in a predictable d-amphetamine PK profile with low intra-subject and inter-subject variability. The d-amfetamine $AUC_{0-\infty}$ and C_{max} generally behaved in a linear, dose-proportional manner. The weight normalized d-amfetamine $AUC_{0-\infty}$ is similar for children and adults, with tmax and t½ consistent across age groups.
In Study SPD489-121, mean AUC_{τ} and C_{max} for d-amfetamine behaved in a linear, dose-proportional manner across the dose range studied (20-70 mg) for healthy adult Japanese and Caucasian subjects. For lisdexamfetamine and d-amfetamine, the plasma concentration versus time curves were generally similar in shape for Japanese and Caucasian subjects in the single-dose period (TAK-489 20 mg) and at each TAK-489 dose level during the multiple-dose period (TAK-489 20, 50, and 70 mg). In Study SPD489 121, the observed differences in C_{max} and AUC for lisdexamfetamine and d-amfetamine were likely due to differences in weight. On average, Japanese subjects in the TAK-489 group were approximately 17% lighter than Caucasian subjects in the TAK-489 group. It is noted that weight-corrected means for CL/F and CLR were similar in the 2 ethnic groups.
The CL/F and t½ for d-amfetamine were generally consistent across the dose range studied and were similar in Japanese and Caucasian subjects. There was no unexpected accumulation of d-amphetamine in Japanese or Caucasian subjects. TAK-489 was absorbed, metabolized, and excreted in a similar manner in Japanese and Caucasian subjects.

Furthermore, as a part of the present line extension application, the Applicant has also performed the statistical modelling approach to estimate the efficacy of the 20 mg dose in adults. E_{max} model provided the best fit of the data for all three clinical studies included in the modelling (i.e., study NRP104.301 in children aged 6 to 12 years, study NRP104.303 in adults and study SPD489-305 in adolescents aged 13 to 17 years). The dose response curves indicated that the change from baseline in ADHD-RS score (i.e., primary endpoint in these clinical studies) increased as the dose increased from 0 to 70 mg. Overall, the efficacy in adult and adolescent patients tended to be less than that in children, which could be attributed to higher body weight and lower PK exposure compared to children patients. However, the estimated absolute ADHD-RS total score for 20 mg in adults was -14.93, which implied a potential clinical benefit for some of the adult patients.

Of final note, the 3 newly proposed strengths (20 mg, 40 mg and 60 mg) in the present line extension application for adults are identical to previously authorized strengths for Elvanse in children from 6 years and up: 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg, SE/H/1839/001-006 (line extension approved April 2015). Therefore, the composition of the newly proposed strengths and their quantitative proportionality are not questioned in the present application from a pharmacokinetic point of view.

Pharmacodynamics
The active substance belongs to the pharmacotherapeutic group Centrally Acting Sympathomimetics (ATC code: N06 BA12) and is a pharmacologically inactive prodrug. After oral administration, lisdexamfetamine is rapidly absorbed from the gastrointestinal tract and hydrolysed primarily by red blood cells to d-amfetamine (dexamfetamine), which is responsible for the drug's activity.

Amphetamine appears to exert its pharmacological effects in the central nervous system (CNS) by increasing the availability of naturally occurring amines that have important functions in nerve terminals. Amphetamine increases synaptic levels of dopamine (DA), norepinephrine (NE), and serotonin (5-HT) through multiple mechanisms. It promotes the release of DA, NE, and 5-HT into the extraneuronal space, and also inhibits the reuptake of DA and NE into the pre-synaptic nerve terminal resulting in prolonged residency of these neurotransmitters in the synaptic cleft.

RMS Comment
Lisdexamfetamine is hydrolysed primarily by red blood cells to d-amfetamine. The stimulant activity of d-amfetamine appears to relate to blockade of norepinephrine and dopamine reuptake in the central nervous system, resulting in increased levels of monoamine neurotransmitters in the synaptic cleft.

Clinical efficacy

Post-marketing data
The approved doses for adult patients in Canada and the United States include 20, 30, 40, 50, 60 and 70 mg. In these countries there is significant use of the 20 mg dose: approximately 16.7% and 7.3% of the prescriptions in Canada from July 2018 to January 2022 and the United States from March 2019 to February 2022, respectively, see data in **bold** in **Table 1**.

Table 1 Number of LDX prescriptions written by physicians in Canada and the United States for 20 mg to 70 mg strengths for adult patients

			Canada[a]		United States[b]	
Age	Strength	Form	n	%	n	%
Adult	**20 MG**	**Capsule**	**855,102**	**16.7**	**1,536,108**	**7.3**
Adult	30 MG	Capsule	1,274,683	24.9	3,678,469	17.5
Adult	**40 MG**	**Capsule**	**1,259,807**	**24.7**	**4,219,240**	**20.1**
Adult	50 MG	Capsule	870,098	17.0	4,239,574	20.2
Adult	**60 MG**	**Capsule**	**759,757**	**14.9**	**3,177,790**	**15.1**
Adult	70 MG	Capsule	90,642	1.8	4,132,370	19.7
TOTAL			5,110,089	100	20,983,551	100

[a]From July 2018 to January 2022
[b]From March 2019 - February 2022
Source: IQVIA NPA Monthly, IQVIA Extended Insights Monthly
Note: The above data included both patients with ADHD and patients with Binge Eating Disorder, of which a vast majority are patients with ADHD based on the overall marketing experience in these two countries.

According to the Applicant, the proposed recommendation for 20 mg starting dose "*When in the judgment of the clinician a lower initial dose is appropriate, patients may begin treatment with 20 mg once daily in the morning*" can be found in the Product Information approved in e.g. Australia, Canada, Singapore and Switzerland:

- in section 4.2 subsection *Treatment of ADHD* page 3 of the Australian PI;
- in section Recommended Dose and Dosage Adjustment subsection *Attention Deficit Hyperactivity Disorder (ADHD)* page 27 of the Canadian Product Monograph;
- in section 2.3 *Dosage for Treatment of ADHD* page 2 of the Singapore PI.
- in section *Dosage* of the Swiss Approved information for professionals.

RMS comment
It is noted that the 20 mg strength is used in adults with ADHD in North America, and that the recommendation for 20 mg starting dose "*When in the judgment of the clinician a lower initial dose is appropriate, patients may begin treatment with 20 mg once daily in the morning*" is included in the Product Information in several countries e.g. Australia, Canada, Singapore and Switzerland.

Clinical efficacy data
As the line extension dose strengths of 40 and 60 mg are bracketed by the approved dose strengths for adults of 30, 50, and 70 mg, their efficacy profile is not expected to differ from the dosages currently approved, and in principle no further assessment of efficacy should be needed.

As the 20 mg dose is lower than the current lowest dose of 30 mg for adults, efficacy aspects are discussed. The 20 mg dose was included in a pediatric dose-finding study: SPD489-310, previously assessed (UK/H/3326/001-003/DC and SE/H/1839/001-006, line extension April 2015). The previous assessments of this study will not be repeated. For clarity, some data from study SPD489-310 are briefly discussed, data related to the 20 mg dose underlined:

Open-label pediatric efficacy and tolerability, dose-ranging, dose-optimization study (SPD489-310) in 6-12 year old subjects.
The primary objective was to assess the efficacy and tolerability of 6 dose strengths (20, 30, 40, 50, 60, and 70 mg) when children aged 6-12 years diagnosed with ADHD were dosed to optimal effect. The study duration was 7 weeks open label, consisting of a 5-week optimization phase and a 2-week maintenance phase. All 318 subjects began treatment at a dose of 20 mg. During the optimization phase, the dose strength for each subject was titrated weekly by a 10 mg increment until an optimal dose was reached, to a maximum dose of 70 mg.

The primary efficacy analysis evaluated mean change in the ADHD-RS-IV total score from baseline, to endpoint defined as the last post-baseline treatment visit for which a valid ADHD-RS-IV total score was observed. The percentage of subjects considered “improved” on the CGI-I scale was assessed as a secondary efficacy analysis. The efficacy assessments were validated measures of ADHD core symptoms or functional outcomes as required in the Guideline on the clinical investigation of medicinal products for the treatment of ADHD; (EMEA/CHMP/EWP/431734/2008).

Population Studied
A total of 318 children aged 6-12 years with ADHD were enrolled. The Safety Population included the 317 (99.7%) subjects who received at least 1 dose of LDX. The intent-to-treat (ITT) population included the 316 (99.4%) subjects who received at least 1 dose of LDX and had at least 1 post-baseline assessment of the primary measure of efficacy (ADHD-RS-IV total score).
Overall, 278 subjects (87.4%) completed the study; 40 (12.6%) discontinued before study completion. Thirteen (4.1%) discontinuations were due to adverse events (AEs). Two (0.6%) subjects discontinued due to lack of efficacy or response.

Demographics and Baseline Conditions
Subjects in the Safety Population had a mean (standard deviation [SD]) age of 9.1 (1.9) years, a mean (SD) weight of 77.6 (22.3) pounds, and were predominantly male (70.7%) and white (70.7%). Most subjects had the combined ADHD subtype (81.7%). Baseline ADHD-RS-IV mean (SD) total score was 41.2 (6.9).

Efficacy results
The primary efficacy result was the change in ADHD-RS-IV total score from baseline at endpoint (Day 49, or the last observation carried forward for subjects who discontinued early). The mean change from baseline at endpoint was statistically significant, as was the mean change from baseline at all visits (key secondary result). A significant ($p<0.0001$) reduction was seen at Visit 1, indicating that 20 mg may be an effective dose strength.

For all subjects in the ITT population, ADHD-RS-IV total scores were significantly ($p<0.0001$) reduced from Baseline to endpoint by a mean (SD) of -28.6 (10.9). Statistically significant ($p<0.0001$) changes from baseline were observed at each post-baseline visit, from Visit 1 through Visit 7. The mean (SD) changes from baseline to Visit 7 were: -30.1 (8.9), -32.9 (8.9), -30.8 (8.0), -29.6 (9.1), -28.1 (11.2), and -24.1 (12.5) for doses 20, 30, 40, 50, 60 and 70 mg.

The 20 mg dose strength was the final dose for 35 (11.0%) of the 317 subjects in the study, while the 40 mg and 60 mg dose strengths were the final dose strengths for 61 (19.2%) and 47 (14.8%) of subjects, respectively.

During the study, the investigator could decrease the dose strength by 1 level if necessary, and if the subject tolerated the reduced dose and maintained ADHD symptom control then the subject remained in the study. For each dose, the percentage of subjects who were down-titrated to their final dose strength is presented in Table 3. For example, of the 35 subjects with final dose strength of 20 mg, 24 (68.6%) subjects remained at that dose throughout the study, and 11 (31.4%) subjects were down-titrated from the 30 mg dose strength.

Table 3 demonstrates that the 20, 40, and 60 mg dose strengths were used for down-titration. It is noted that efficacy was associated with every dose strength in this study.

Table 3. Summary of Maximum Dose by Final Dose (Safety Population, Study SPD489-310)

	N=317 Final Dose					
	20 mg (N=35)	**30 mg (N=71)**	**40 mg (N=61)**	**50 mg (N=70)**	**60 mg (N=47)**	**70 mg (N=33**
Maximum Dose	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
20 mg	24 (68.6)	0	0	0	0	0
30 mg	11 (31.4)	56 (78.9)	0	0	0	0
40 mg	0	15 (21.1)	51 (83.6)	0	0	0
50 mg	0	0	10 (16.4)	61 (87.1)	0	0
60 mg	0	0	0	9 (12.9)	43 (91.5)	0
70 mg	0	0	0	0	4 (8.5)	33 (100.0

Note: Percentages indicate how many patients remained on their maximum dose as the final dose and how many were down-titrated one dose level. Source: SPD489-310, Table 214a

All subjects were rated at least moderately ill on the Clinical Global Impressions of Severity (CGI-S) at baseline. At endpoint, at all dose strengths, the majority (284 [89.9%]) of subjects were rated “improved” (ie, rated “very much improved” or “much improved”) on the CGI-I.

Each of the dose strengths 20, 40, and 60 mg was associated with improvement in ADHD symptoms at endpoint and at every study visit compared to baseline as measured by the ADHD-RS-IV total score for those subjects who remained enrolled in the study.

Furthermore, each of these 3 strengths was associated with improvement in global functioning as measured by the CGI-I. It is noted that all 6 dose strengths were used by the investigators in the study to optimize subject response from an efficacy and tolerability perspective according to the dose-optimization paradigm.

In summary, efficacy of the dose 20 mg for a proportion of children is established in the pediatric approval in 2015. The pediatric data alone could not demonstrate efficacy for a dose of 20 mg in adults. Further the second submitted study SPD489-121 provides data from healthy adults only. Therefore additional supporting data have been submitted.

Statistic modelling data

The Applicant has provided additional discussion based on statistic modelling. All three candidate models (E_{max}, Linear and Logistic) were statistically significant ($p<0.001$) for a dose response between LDX and ADHD-RS for each of 3 selected studies (children NRP104.301), adolescent SPD489-305 and adult NRP104.303). The maximum drug-induced effect (E_{max}) model provided the best fit of the data for all three studies. Subsequently, efficacy for the 20 mg dose was estimated using the E_{max} model.

Figure 1: placebo-adjusted estimated efficacy (ADHD-RS) of the 20 mg dose in children (NRP104.301), adolescent (SPD489-305) and adult (NRP104.303) patients based on the E_{max} model. All estimated means and 95% confidence intervals were on the left side of zero, which indicate they favour the 20 mg dose. The efficacy in adult and adolescent patients was less than that in children, which may be due to their higher body weight and lower PK exposure.

Figure 1 Forest plot of estimated efficacy differences between 20 mg and placebo arms

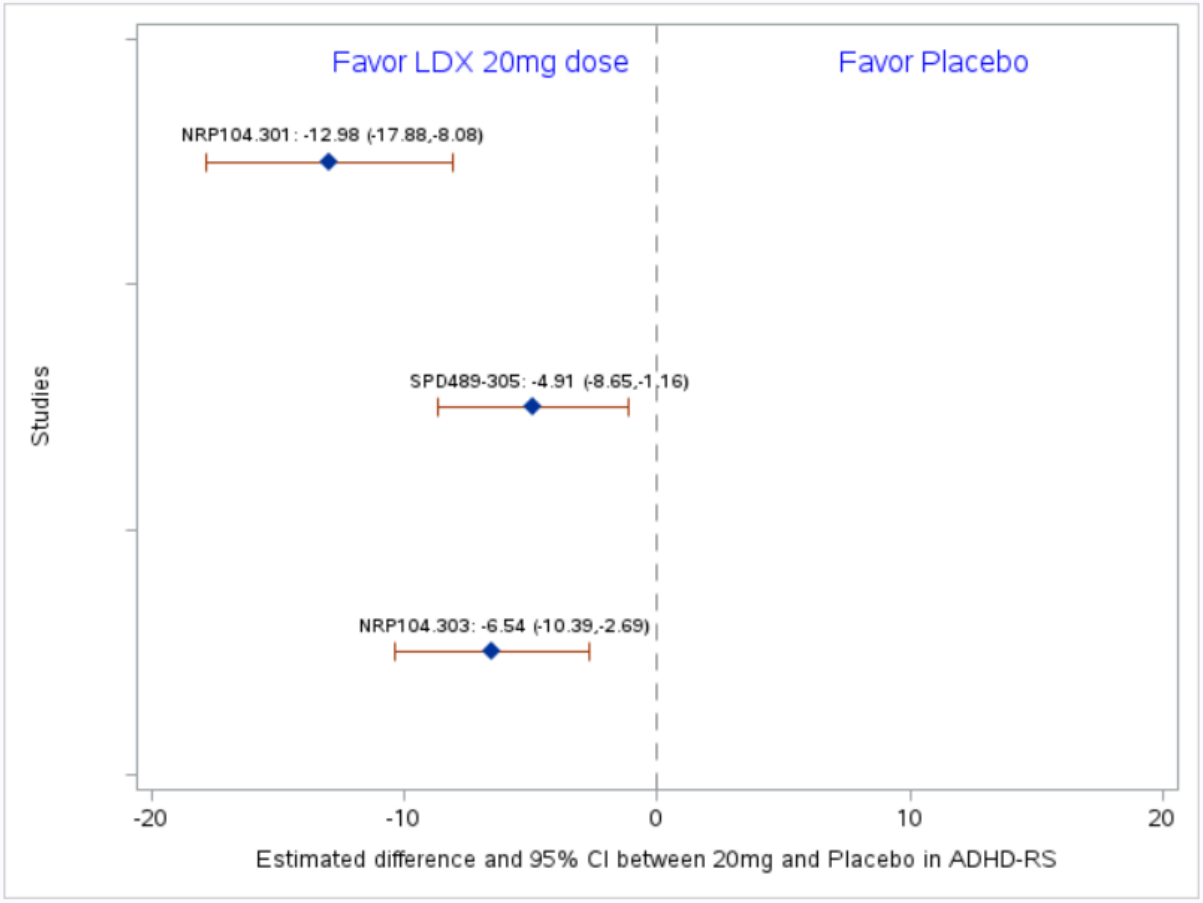
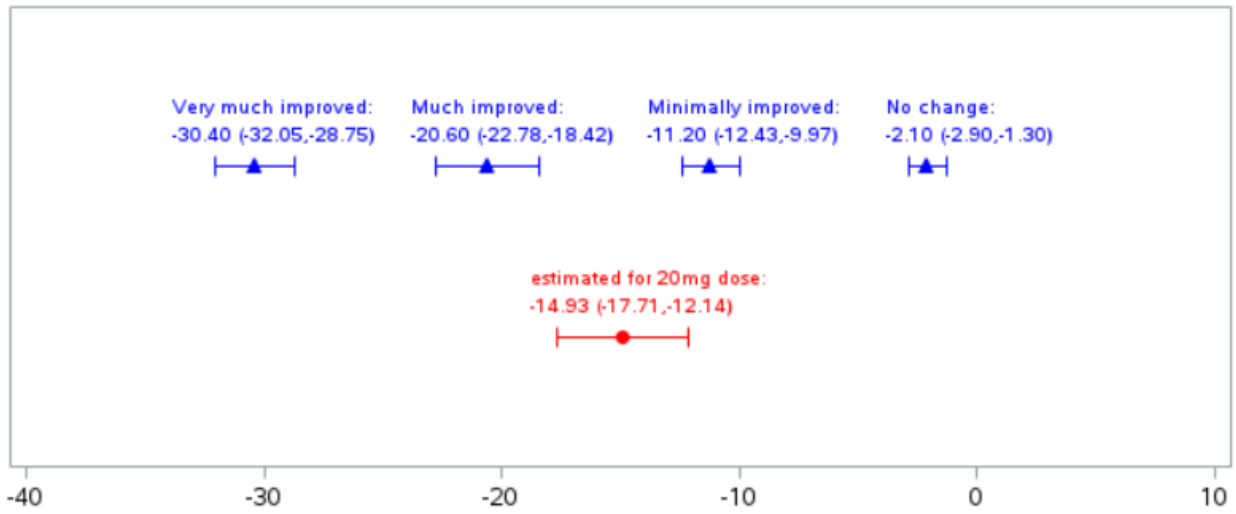


Figure 2: estimated ADHD-RS score change from baseline for the 20 mg dose in adult patients, plotted relative to the score changes as reported in (Goodman D 2010). In that paper, the ADHD-RS score changes were linked to the Clinical Global Impression – Improvement levels as assessed by the clinicians. The data indicate that the estimated efficacy measured by ADHD-RS Total Score change from baseline falls in between the CGI-I categories “Minimally improved” to “Much improved” (Goodman D 2010).

Figure 2. Mapping of absolute ADHD-RS total score changes from baseline at endpoint by CGI-I levels at endpoint



Note: 'Very much improved', 'Much improved', 'Minimally improved' and 'No change' refer to CGI-I levels, and the corresponding numbers are means of ADHD-RS score changes from baseline (with 95% Confidence Intervals, derived from Goodman et. al. 2010. 'Estimated for 20 mg dose: -14.93 (-17.71, -12.14)' are the corresponding E_{max} model-based estimates in adult population, based on the NRP104.303 study.

Clinical expertise letter

The Applicant has submittted additional clinical discussion referring to a Clinical expert letter.

RMS comment:

In the RMS view, the expert letter provide support for clinically observed efficacy in a significant proportion of adult patients with ADHD.

In modern treatment of ADHD, individual dose titration is of central importance. It is also important to enable over time fine adjustments of the dose, according to a range of other factors, e.g. levels of physical activity, levels of work- or studyload, status of comorbidities if any, co-medications if any, and so forth). In a clinical perspective, the proposed new range of strengths for adults adds flexibility of clinical relevance for the initial dose titration and for fine tuning over time as well.

The current application is an extension application for addition of the new strengths 20 mg, 40 mg and 60 mg to the authorised Elvanse Vuxen (30 mg, 50 mg and 70 mg). The new range of strengths for adults is identical to the since 2015 approved strengths 20-70 mg for Elvanse in children 6-18 years of age with ADHD. The suggested new posology for Elvanse Vuxen in section SmPC 4.2 is identical to the approved 4.2 wordings for Elvanse in children 6-18 years of age with ADHD.

The SmPC section 4.2 Elvanse Vuxen proposed update reads as underlined, with no other changes: *"The starting dose is 30 mg taken once daily in the morning. When in the judgment of the clinician a lower initial dose is appropriate, patients may begin treatment with 20 mg once daily in the morning. The dose may be increased by 10 or 20 mg increments, at approximately weekly intervals. Tradename should be administered orally at the lowest effective dosage."*

The new strengths (20, 40, 60 mg) add the option for dose titration increments of 10 mg (currently 20 mg). Through increased flexibility this will enhance a more precise tuning of dosage. From this perspective, the application could be considered clinically relevant. The recommended starting dose for adults will remain 30 mg as currently approved. The new 20 mg capsule will only add the option as

of clinicians judgement to start on a lower dose (20 mg) than currently approved for adults (30 mg). The proposed 4.2 wordings are consistent with this.

Pediatric data alone could not demonstrate efficacy for a dose of 20 mg in adults. The second submitted study SPD489-121 provides data from healthy adults only. Additional data include statistic modelling in support for efficacy of the 20 mg dose in adults. Other supporting data include significant prescription of the 20 mg dose to adults with ADHD in North America, and similar PI wordings in some countries as is proposed in this application. Consistent with this, also the provided view of clinical expertise could support efficacy of the 20 mg strength.

In conclusion on the 20 mg strength, multiple data sources support there is clinically relevant efficacy in a proportion of adults with ADHD.

Overall the RMS propose that efficacy of the new strengths 20, 40, 60 mg in adults with ADHD could be considered established from combined multiple data sources.

Clinical safety

The safety profile associated with LDX in the submitted 7-week study SPD489-310 enrolling children with ADHD aged 6-12 years and doses from 20 to 70 mg was consistent with the known safety profile, as assessed for pediatric approval (UK/H/3326/001-003/DC and SE/H/1839/001-006, line extension April 2015).

The previous assessment of this study will not be repeated. In summary, the majority of treatment-emergent adverse events (TEAEs) in SPD489-310 were mild or moderate in severity, and no differences due to age or sex have been noted. The most frequently reported TEAEs (decreased appetite, weight decreased, insomnia, irritability, headache, abdominal pain upper, initial insomnia, affect lability, nausea, vomiting) were those typically associated with LDX therapy in both adult and pediatric patients. These TEAEs were nonserious and are known adverse reactions that reflect side effects commonly associated with stimulant use. Mean increases in blood pressure and pulse rate in this 7-week study were well within the range of the known safety profile, as was the mean change in body weight.

Single dose 20 mg study in healthy adults

In the second submitted study SPD489-121 (A Phase 1, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single and Multiple Doses of SPD489 in Japanese and Caucasian Healthy Adult Subjects), the Safety Analysis Set included 28 exposed adults 18-55 ys of age:

12 Japanese LDX exposed subjects and 3 Placebo subjects; 16 Caucasian LDX exposed subjects and 3 Placebo subjects. Exposure followed the schedule:

- Days 4-8: LDX 20mg or placebo
- Days 9-13: LDX 50mg or placebo
- Days 14-18: LDX 70mg or placebo

The adverse events for the single 20 mg dose are shown in **Table 4**. These events were all considered related to the investigational product by the investigator. All were mild in severity.

TABLE 4. SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS IN STUDY SPD489-121 (SINGLEDOSE PERIOD)

	Placebo		LDX (20 mg)	
	Japanese	**Caucasian**	**Japanese**	**Caucasian**
Number of subjects	**3**	**3**	**12**	**16**
No. of TEAEs reported	1	0	7	3
No. (%) of subjects with TEAEs	1 (33.3)	0 (0.0)	4 (33.3)	1 (6.3)
No. (%) of subjects with TEAEs related to investigational product	0 (0.0)	0 (0.0)	4 (33.3)	1 (6.3)
No. (%) of TEAEs leading to discontinuation	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)

TEAE=treatment-emergent adverse event

Source: SPD489-121 CSR

Common adverse events

In study SPD489-121, the majority of TEAEs in the LDX groups were events known to be associated with stimulant treatment (eg, headache, dizziness, insomnia, decreased appetite). Adverse event profiles were generally similar in Japanese and Caucasian subjects. All but 2 of the TEAEs were mild in severity; 2 TEAEs were of moderate severity.

The most commonly reported TEAEs in study SPD489-310 were consistent with stimulant therapy and with the well-established safety profile of LDX. Although the dose optimization study design does not permit an independent dose to dose comparison, as compared to a completely randomized design, it better reflects a real world dosing situation; and results from this study indicate that subjects needing higher doses of LDX to treat ADHD symptoms did not appear to present increased TEAEs. Stimulant-related TEAEs tend to be short-lived and therefore the largest percentage of subjects experiencing a TEAE was observed at the starting dose (20 mg).

Deaths and SAE

No deaths or serious adverse events (SAEs) occurred during study SPD489-121.

Discontinuations due to TEAE

In study SPD489-121, one Japanese subject was discontinued on Day 4, after receiving the single 20 mg dose of LDX on Day 1 and prior to entering the multiple-dose period, as a result of increased blood pressure. These elevations were considered mild and related to the investigational product by the investigator. These increases were not typical of LDX-related increases in vital signs, in that they occurred later after dosing (ie, 12 hours post-dose) and lasted longer after dosing (ie, 72 hours) than would be predicted by the well-established PK of d-amfetamine. These elevations were still in evidence at the subject's final assessment. Attempts to obtain additional medical history and follow-up information for this subject were unsuccessful. The outcome of this TEAE is unknown.

Additional safety data relevant to the 20 mg dose

The Applicant have submitted additional data regarding potential safety information relevant to the 20 mg dose are extrapolated from three placebo (PBO)-controlled trials (NRP104-301, -303 and -305). The available data from placebo, 30 mg, 50 mg and 70 mg treatment arms, included a total of 808 patients (i.e., 30 mg [n=268], 50 mg [N=267], 70 mg [N=273] and placebo [N=211]). None of the studies had events with fatal outcome.

Adverse events (AEs) (%) by study and treatment arm are summarized in below **Table 2**.

Table 2 Adverse Events (%) by Study (N=3) and Treatment Arm

	Total AEs (%)				
Study Number	PBO	30mg	50mg	70mg	Total
NRP104-301	48.6%	71.8%	70.3%	84.9%	68.4%
NRP104-303	61.3%	76.5%	78.6%	83.6%	76.9%
NRP104-305	58.4%	65.4%	68.8%	71.8%	68.7%
	Total severe AEs (%)				
Study Number	PBO	30mg	50mg	70mg	Total
NRP104-301	0	4.2%	5.4%	5.5%	3.7%
NRP104-303	3.2%	4.2%	4.3%	4.9%	4. 3%
NRP104-305	2.6%	1.3%	1.3%	2.6%	1.7%
	Total related AEs (%)				
Study Number	PBO	30mg	50mg	70mg	Total
NRP104-301	26.4%	67.6%	59.5%	78.1%	56.6%
NRP104-303	37.1%	63.9%	68.4%	73.0%	63.8%
NRP104-305	27.3%	53.8%	53.2%	57.7%	54.9%

Across the above three studies, AEs (i.e., total, severe and related) were proportionately highest in the 70 mg treatment arm. The percentage of total related and severe AEs were comparable between the 30 mg and 50 mg treatment arms. There was a clear association between dose and AEs in the 30 mg and 50 mg treatment arms compared to the 70 mg treatment arm. Details from each clinical trial were provided in Appendix.

Summary of safety

Treatment-emergent AEs in pediatric study SPD489-121 for doses including 20 mg were consistent with the established safety profile of LDX.

Based also on extrapolations from three placebo controlled trials (NRP104-301, -303 and -305) it is proposed to conclude that the 20 mg dose would not likely have a higher proportion of AEs (i.e., total, severe or related) compared to the 30 mg and 50 mg doses.

RMS comment:

The submitted study SPD489-121 provides data for reported TEAEs after one-dose exposure of 20 mg LDX for 5 days. Additional data extrapolated from three placebo (PBO)-controlled trials (NRP104-301, -303 and -305) were submitted.

It is proposed by the RMS to conclude that likely the 20 mg dose would not be associated to a higher proportion of AEs (i.e., total, severe or related) as compared to the 30 mg and 50 mg doses.

Risk Management Plan

The current approved lisdexamfetamine (LDX) EU Risk Management Plan (RMP) version 5.0 (approved on 2021-10-22, EU procedure num.: SE/H/1825/01-03/IB/23) covers all the strengths for Elvanse (20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg). The RMP version 5.0 applies equally to the Elvanse Vuxen strengths and therefore this is cross-referenced within this application. The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Elvanse Vuxen. Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The submitted Risk Management Plan, version 5.0 approved 2021-10-22 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the package leaflet was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The proposed new range of strengths for adults is identical to the current range of the pediatric approval (Elvanse). For adults this will add flexibility, for initial dose titration and for fine adjustments over time. The new 20 mg capsule will add the option, as of clinicians judgement, to start on a lower dose (20 mg) than currently lowest approved for adults (30 mg). The new 40 and 60 mg dose strengths are bracketed by the current dose strengths with established efficacy and safety profile in adults.

For the 20 mg strength, multiple data sources appear to support efficacy in a proportion of adults with ADHD. The data include statistic modelling, prescription data from North America, relevant examples of PI from some countries, and clinical expert letter. There were no new or unexpected safety findings from the data related to the 20 mg dose. No new safety information related to exposure could be expected on this dose level.

Overall it is considered that the new strengths 20, 40 and 60 mg will provide benefit for patients from a more precise dosage and enhanced flexibility of dosage. The safety profile and the efficacy profile for LDX are considered to remain unchanged.

The quality of Elvanse Vuxen is found adequate. There are no objections to approval of Elvanse Vuxen, from a non-clinical and clinical point of view. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

Please refer to section “List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC” for information about the conditions regarding educational material.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**
  The educational material should contain the following key elements:

  The checklists, charts and forms can be obtained from the website: www.ldxguide.com,

  - ***Checklist 1: Prescriber checklist before prescribing Lisdexamfetamine dimesylate (LDX)***- The checklist is designed to support the prescriber in the appropriate initiation of Lisdexamfetamine dimesylate in a child aged six yearsand above, or an adults (in countries with approval for the adult use), with attention-deficit/hyperactivity disorder (ADHD);
  - ***Checklist 2: Prescriber checklist for ongoing monitoring during Lisdexamfetamine dimesylate (LDX) treatment*** – The checklist is designed to support the prescriber in the ongoing monitoring of Lisdexamfetamine dimesylate therapy in children aged six years and above, or in adults (in countries with approval for the adult use) with attention-deficit/hyperactivity disorder (ADHD);
  - ***Chart for ongoing monitoring during Lisdexamfetamine dimesylate (LDX) treatment***- The chart is designed to support you in the ongoing monitoring of LDX therapy in children aged six years and above or in adults (in countries withapproval for the adult use) with attention-deficit/hyperactivity disorder (ADHD).

    In addition to the checklists and chart above, there is also a leaflet provided for use by patients, which is made available in countries where the health authorities have acceptedit.

    Potential for nonmedical use and diversion of prescription stimulantmedications leaflet- Educational leaflet for use by patients and their parents/guardians

VII. APPROVAL

The decentralised procedure for Elvanse Vuxen, 20 mg, 40 mg, 60 mg, Capsule, hard was positively finalised on 2022-11-18.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se