LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Volidax
(lisdexamfetamine dimesilate)

SE/H/2184/01-03/DC

This module reflects the scientific discussion for the approval of Volidax. The procedure was finalised on 2022-12-20. 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 Volidax, 30 mg, 50 mg, 70 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 for Volidax, 30 mg, 50 mg and 70 mg, Capsule, hard, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) with DE, DK, FI, IS, NL and NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Elvanse, 30 mg, Capsule, hard authorised in Denmark since 2013, with Shire Pharmaceuticals Ireland Limited as marketing authorisation holder.

The reference products used in the bioequivalence studies are Elvanse, 20 mg and 70 mg, Capsule, hard from Germany with Shire Pharmaceuticals Ireland Limited as marketing authorisation holder.

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 dimesylate are well known. As lisdexamfetamine dimesylate 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)
Since Volidax is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

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

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted two bioequivalence studies comparing the lisdexamfetamine dimesylate capsules with the reference product Elvanse.

Pharmacokinetic properties of the active substance

Absorption: After oral administration, the pharmacologically inactive prodrug lisdexamfetamine dimesylate is rapidly absorbed from the gastrointestinal tract of healthy adults and children (6 to 12 years) with ADHD, thought to be mediated by the high capacity PEPT1 transporter. The absolute oral bioavailability of lisdexamfetamine is approximately 100%. After absorption, lisdexamfetamine dimesylate is converted to the active drug dexamfetamine, which occurs by metabolism in blood primarily due to the hydrolytic activity of red blood cells.

In 18 children (6 to 12 years) with ADHD, the Tmax of dexamfetamine was approximately 3.5 hours following single-dose oral administration of lisdexamfetamine dimesylate either 30 mg, 50 mg, or 70 mg administered after an 8-hour overnight fast. The Tmax of lisdexamfetamine dimesylate was approximately 1 hour.

Food does not affect the observed AUC and Cmax of dexamfetamine in healthy adults after single-dose oral administration of lisdexamfetamine dimesylate 70 mg capsules but prolongs Tmax by approximately 1 hour (from 3.8 hours at fasted state to 4.7 hours after a high fat meal). After an 8 hour fast, the AUCs for dexamfetamine following oral administration of lisdexamfetamine dimesylate in solution and as intact capsules were equivalent. There are no restrictions with respect to food in the SmPC of the originator.

Linearity: Linear pharmacokinetics of dexamfetamine after single-dose oral administration of lisdexamfetamine dimesylate have been established over the dose range of 30 mg to 70 mg in children aged 6 to 12 years. AUC of lisdexamfetamine is non dose-linear, with a greater than proportional increase in AUC and Cmax with increasing dose. This would appear to be due to differences in the clearance of lisdexamfetamine (i.e. conversion to dexamfetamine) and not to dose non-linearity of bioavailability. Presumably there is a degree of saturation of the metabolising enzymes in the red blood cells that may reduce the clearance of lisdexamfetamine at higher doses. This is not problematic as kinetics for the active drug dexamfetamine is essentially dose linear.

Elimination: The plasma elimination half-life of lisdexamfetamine typically averaged less than one hour in studies of lisdexamfetamine dimesylate in volunteers. The half-life of dexamfetamine is 11 hours. The pharmacokinetics of dexamfetamine, as evaluated by clearance, is similar in children (aged 6 to 12) and adolescents (aged 13 to 17) ADHD patients, and healthy adult volunteers after correcting for body weight.

Study ACT-20066 (20 mg)

Methods

This was a single-dose, two-way crossover study conducted in 32 healthy volunteers, comparing lisdexamfetamine dimesylate, 20 mg, hard capsule with Elvanse, 20 mg, hard capsule under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of lisdexamfetamine (inactive prodrug, main analyte) and dexamfetamine (active drug, supportive analyte) were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2021-07-27 and 2021-09-04.

There were 3 drop-outs during the study, with acceptable reasons for withdrawal.

Results

The results from the pharmacokinetic and statistical analysis are presented in Tables 1 and 2 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for lisdexamfetamine, n=29.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**9.97 ± 4.570**	**10.09 ± 4.943**	**0.83 (0.67 - 1.75)**
Reference	**10.15 ± 5.406**	**10.13 ± 5.835**	**1.00 (0.83 - 1.75)**
***Ratio (90% CI)**	**100.95 (92.25 - 110.46)**	**103.09 (91.13 - 116.63)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for dexamfetamine, n=29.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**340.39 ± 71.113**	**19.67 ± 3.481**	**3.33 (2.33 - 5.00)**
Reference	**332.54 ± 73.324**	**19.56 ± 3.600**	**3.33 (2.00 - 8.00)**
***Ratio (90% CI)**	**102.83 (98.14 - 107.75)**	**100.81 (98.25 - 103.45)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

Study ACT-20067 (70 mg)

Methods

This was a single-dose, two-way crossover study conducted in 32 healthy volunteers, comparing lisdexamfetamine dimesylate, 70 mg, hard capsule with Elvanse, 70 mg, hard capsule under fasting

conditions. Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of lisdexamfetamine (inactive prodrug, main analyte) and dexamfetamine (active drug, supportive analyte) were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2021-07-27 and 2021-09-01.
There were 7 drop-outs during the study, with acceptable reasons for withdrawal.

Results
The results from the pharmacokinetic and statistical analysis are presented in Tables 3 and 4 below.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for lisdexamfetamine, n=25.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**52.39 ± 16.823**	**44.35 ± 13.026**	**1.00 (0.83 – 1.75)**
Reference	**54.28 ± 22.620**	**44.43 ± 18.203**	**1.25 (0.83 - 1.75)**
***Ratio (90% CI)**	**99.81 (93.96 – 106.02)**	**104.18 (94.53 – 114.80)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for dexamfetamine, n=24.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1220.12 ± 212.727**	**69.72 ± 14.317**	**3.33 (2.33 - 7.00)**
Reference	**1259.95 ± 232.622**	**71.11 ± 13.907**	**3.33 (2.33 - 5.00)**
***Ratio (90% CI)**	**97.37 (94.11 – 100.74)**	**97.76 (95.80 – 99.75)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

Significant pre-dose concentrations of dexamfetamine were detected for one subject in both periods of study ACT-20067; hence dexamfetamine data from this subject was excluded from the pharmacokinetic study results for dexamfetamine. However, since no baseline concentrations were detected for lisdexamfetamine in this subject, no effect on the subject´s lisdexamfetamine plasma profile was expected. As a precautionary measure though, pharmacokinetic and statistical analysis for lisdexamfetamine was also performed after the exclusion of the subject´s lisdexamfetamine data. The exclusion of these data had no impact on the study results.

In both studies ACT-20066 and ACT-20067, bioequivalence was to be concluded if for AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for lisdexamfetamine, which is the parent analyte and inactive prodrug. The pharmacokinetic data of the active drug dexamfetamine was provided as supportive evidence of comparable therapeutic outcome. This approach is acceptable, and all results fell within the conventional acceptance range.

A biowaiver was sought for the additional strengths of 30 and 50 mg.

Discussion and overall conclusion
The bioequivalence studies and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Absence of studies with the additional strengths of 30 and 50 mg is acceptable, as all conditions for biowaiver for additional strengths, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled. From a pharmacokinetic point of view, it is sufficient to establish bioequivalence with only the highest strength, as the pharmacokinetics of lisdexamfetamine is non dose-linear, with a greater than proportional increase in AUC and Cmax with increasing dose, and the pharmacokinetics of dexamfetamine is linear between 20 mg and 70 mg. The test product does however not fulfil the requirements for quantitative proportionality for all strengths, and therefore a bracketing approach is used, i.e. bioequivalence studies have been performed on the highest and lowest strengths, 70 mg and 20 mg, which also have the largest differences with regards to quantitative proportional composition.

Based on the submitted bioequivalence studies, the applied lisdexamfetamine dimesylate capsules are considered bioequivalent with Elvanse.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Since bioequivalence with the originator product is demonstrated, additional data is not necessary.

Risk Management Plan
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 Volidax.

Safety specification

The MAH has submitted the version 1.1 RMP dated 2022-07-04 and proposed the following summary safety concerns:

Important identified risks	• Intentional drug misuse, abuse and diversion • Growth retardation and developmental delay in children and adolescents • Psychosis/Mania • Hostility/Aggression • Depression
Important potential risks	• Serious cardiovascular events (including arrhythmias, ischaemic cardiac events, cardiomyopathy, sudden death) • Cerebrovascular disorders (ischaemic and haemorrhagic stroke) • Syncope • Suicidality • Off-label use • Neonatal effects on growth (via lactation)
Missing information	• Safety in pregnant women • Safety in the elderly • Long-term safety (cardiovascular and cerebrovascular effects) in adults

Assessor's comment: the suggested summary of safety concern is aligned with the RMP of the reference product Elvanse, published on CMDh website, dated March 2020. This is considered acceptable.

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and in accordance with the originator the applicant has proposed follow-up questionnaires, which is acknowledged. No additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

The reference product has two additional pharmacovigilance studies stated in their RMP. However, since this is a generic application, these studies are not conditioned here since the product should follow the reference product and update the product information in line with the reference product, when required. Therefore, the applicants proposed pharmacovigilance plan is considered acceptable.

Risk minimisation measures

Routine risk minimisation is suggested, and as additional RMM they will provide educational material. The safety concerns addressed by the educational material include:

- Intentional drug misuse, abuse and diversion
- Growth retardation and developmental delay in children and adolescents
- Psychosis/Mania
- Hostility/Aggression
- Depression
- Serious cardiovascular events (including arrhythmias, ischaemic cardiac events, cardiomyopathy, sudden death)
- Cerebrovascular disorders (ischaemic and haemorrhagic stroke)
- Suicidality
- Off-label use
- Safety in Pregnant Women

Please refer to section VI.3 of this Overview concerning details of the conditioned educational material.

The risk minimisation measures are aligned with the RMP of the reference product Elvanse and is therefore considered acceptable.

The submitted Risk Management Plan, version 1.1 signed 2022-07-04 **is considered acceptable**. Please refer to section VI.3 of this Overview concerning details of the conditioned educational material.

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 PL was English. Assessment of the User Testing is attached in Appendix I.
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.

In conclusion, the user test is considered acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Volidax is found adequate. There are no objections to approval of Volidax from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk ratio is considered positive, and the application is therefore recommended for approval.

Please refer to section VIII.3 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:

  - **Checklist 1: Prescriber checklist before prescribing Lisdexamfetamine**
    The checklist is designed to support the prescriber in the appropriate initiation of lisdexamfetamine dimesylate in a child aged six years and above, or adults (in countries with approval for the adult use), with attention-deficit/hyperactivity disorder (ADHD);

  - **Checklist 2: Prescriber checklist for ongoing monitoring during Lisdexamfetamine 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 treatment -** The chart is designed to support you in the ongoing monitoring of lisdexamfetamine 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).

Leaflet for patient use:
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 accepted it.

Potential for non-medical use and diversion of prescription stimulant medications leaflet

- Educational leaflet for use by patients and their parents/guardians

The key elements of the educational material are in line with those of the originator. This is considered acceptble.

VII. APPROVAL

The decentralised procedure for Volidax, 30 mg, 50 mg, 70 mg, Capsule, hard was positively finalised on 2022-12-20.

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