LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Lisdexamfetamin MEDICE
(lisdexamfetamine dimesilate)

SE/H/2700/001-006/DC

This module reflects the scientific discussion for the approval of Lisdexamfetamin MEDICE. The procedure was finalised at 2026-01-21. 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

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Lisdexamfetamin MEDICE, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, Capsule, hard.

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

II. EXECUTIVE SUMMARY

II.1 About the product

Lisdexamfetamine dimesylate is a pharmacologically inactive prodrug. After oral administration, lisdexamfetamine is rapidly absorbed from the gastrointestinal tract and hydrolysed primarily by red blood cells to dexamfetamine, which is responsible for the drug's activity.

Amfetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action of amfetamine in ADHD is not fully established, however it is thought to be due to its ability to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

Lisdexamfetamine has been approved in EU since 2007 and it belongs to the pharmacotherapeutic group: Centrally Acting Sympathomimetics, ATC code: N06 BA12.

II.2 General comments on the submitted dossier

The applications for Lisdexamfetamin MEDICE, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, capsule, hard, are Generic Art. 10(1) applications submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK, DE and NL 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 Takeda Pharma A/S as marketing authorisation holder.

The reference products used in the bioequivalence study are Elvanse, 20 mg, capsule, hard, and Elvanse, 70 mg, capsule, hard, from Germany with Takeda Pharmaceuticals International AG Ireland Branch as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in CMS IT: Elvanse, capsule, hard, authorised in SE, with Takeda Pharmaceuticals International AG Ireland Branch as marketing authorisation holder. Year of authorisation for each strength is listed in the table below:

Strength	Year of auth.
20 mg	2015

30 mg	2013
40 mg	2015
50 mg	2013
60 mg	2015
70 mg	2013

The justification to use this product is based on RMS's own files. The ERP information was circulated during the validation period.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

GCP
A statement on the application of appropriate GCP standards in the submitted studies has been provided.

No issues regarding GCP have been identified. The clinical facility was inspected by the ES authority in year 2015 without any critical finding, and the bioanalytical facility was inspected by the UK authority in 2019 without any critical finding related to bioanalytical activity. No inspection of the submitted bioequivalence studies is deemed necessary.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

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.

Drug 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.2 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, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
The default Fpen was used in the Phase I PECsw calculation and the PECsw is 0.35 µg/L indicating the need to proceed to a Phase II assessment with supplementary studies. The applicant did not find any relevant pre-existing ERA or existence of previously performed studies. A request for data sharing was sent to the originator however without any response.

The Applicant commits to conducting the necessary studies to support an ERA for the active substance lisdexamphetamine in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use, with due date 21st January 2034.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted two bioequivalence studies comparing lisdexamfetamine dimesylate 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 dexamfetamin 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, 40, 50 and 60 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, 40, 50 and 60 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. However, the test product did 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. Since that bioequivalence is shown for 20 mg and 70 mg, waiving studies with the additional strengths 30, 40, 50 and 60 mg is acceptable from a pharmacokinetic point of view.

For quality aspects of biowaiver, see the quality assessment report.

Based on the submitted bioequivalence studies, Lisdexamfetamine dimesylate is considered bioequivalent with Elvanse.

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

Pharmacovigilance system
Proposed MAH : Medice Arzneimittel Pütter GmbH & Co.K
The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

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 Lisdexamfetamin MEDICE.

Part II Safety specification
The MAH has submitted the version 0.2 RMP dated 20-MAY-2025 and proposed the following summary safety concerns:

Summary of 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

The suggested summary of safety concern is aligned with the RMP of the reference product Elvanse, published on CMDh website, dated March 2020.

Part III Pharmacovigilance Plan

Routine pharmacovigilance is suggested and in accordance with the originator.
The applicant has proposed follow-up questionnaires when needed and this is agreed since there are no questionnaires conditioned in the reference product.

Part V 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.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.2, dated 20 May 2025 **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.

Periodic Safety Update Report (PSUR)
Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Lisdexamfetamin MEDICE is found adequate. There are no objections to approval of Lisdexamfetamin MEDICE, 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 is considered positive, and the application is therefore recommended for approval.

Please refer to section VII.3 for information about the condition regarding educational tools.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

The Applicant commits to conducting the necessary studies to support an ERA for the active substance lisdexamphetamine in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use, with due date 21st January 2034.

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

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

Draft key messages of the additional risk minimisation measures

- **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, with 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 with ADHD;
- **Chart for ongoing monitoring during lisdexamfetamine treatment** - The chart is designed to support the prescriber in the ongoing monitoring of lisdexamfetamine therapy in children aged six years and above or in adults with ADHD.

Leaflet for patient use:

In addition to the checklists and chart above, there is also a leaflet provided for use by patients.

- *Potential for non-medical use and diversion of prescription stimulant medications leaflet*
  - Educational leaflet for use by patients and their parents/guardians

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

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.

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. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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