

Public Assessment Report

Scientific discussion

Lisfaveen

(lisdexamfetamine dibesilate)

SE/H/2640/01-06/DC

This module reflects the scientific discussion for the approval of Lisfaveen. The procedure was finalised at 2025-09-11. For information on changes after this date please refer to the module ‘Steps taken after the finalisation of the initial procedure - Summary’.

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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 Lisfaveen, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, Capsule, hard.

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

II. EXECUTIVE SUMMARY

II.1 About the product

Pharmacotherapeutic group: Centrally Acting Sympathomimetics, ATC code: N06BA12.

Mode of action

Lisdexamfetamine 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.

Claimed indication

As part of a comprehensive treatment programme for attention deficit/hyperactivity disorder (ADHD) in children aged 6 years and over when response to previous methylphenidate treatment is considered clinically inadequate.

Also indicated as part of a comprehensive treatment programme for attention deficit/hyperactivity disorder (ADHD) in adults with pre-existing symptoms of ADHD in childhood.

II.2 General comments on the submitted dossier

The application for Lisdexamfetamin MEDICE, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, capsule, hard, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and 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, capsule, hard, 30 mg, authorised in UK since 2013, with Takeda Pharmaceuticals International AG Ireland Branch as marketing authorisation holder.

The reference product used in the bioequivalence study is Elvanse, capsule, hard, 20 mg and 70 mg, from DE with Takeda GmbH as marketing authorisation holder.

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.

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

No issues regarding GCP have been identified. The clinical and the bioanalytical facilities were inspected by the DK authority in 2017 and UK authority in 2019, without any critical findings. No inspection of the submitted bioequivalence studies is needed.

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)

Since Lisdexamfetamin MEDICE 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 Lisdexamfetamin MEDICE from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics

To support the marketing authorisation application the applicant has conducted two bioequivalence studies (20 mg and 70 mg) comparing Lisdexamfetamin MEDICE with the reference product Elvanse, as the composition of the applied product is not dose proportional over the range of strengths.

Pharmacokinetic properties of the active substance

Absorption: After oral administration, 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.

Food does not affect the observed AUC and C_{max} of dexamfetamine in healthy adults after single-dose oral administration of 70 mg of lisdexamfetamine dimesylate but prolongs T_{max} by approximately 1 hour (from 3.8 hours at fasted state to 4.7 hours after a high fat meal). Therefore, there are no restrictions with respect to food in the SmPC of the originator.

Linearity: AUC of lisdexamfetamine is non dose-linear, with a greater than proportional increase in AUC and C_{max} with increasing dose. Linear pharmacokinetics of the active drug, dexamfetamine after single-dose oral administration of lisdexamfetamine dimesylate was established over the dose range of 30 mg to 70 mg in children aged 6 to 12 years.

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.

Study 2797, 20 mg strength

Methods

This was a single-dose, two-way crossover study conducted in 40 healthy volunteers, comparing Lisdexamfetamine dimesylate, 25.4 mg, hard capsule with Elvanse (lisdexamfetamine dimesylate), 20 mg, hard capsule under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 8 hours post-dose. Plasma concentrations of lisdexamfetamine were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t} and C_{max} . The study was conducted between 2024-01-10 and 2024-02-16.

Results

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

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ SD, $t_{\max}$ median, range) for lisdexamfetamine, n=40.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	9.96 $\pm$ 4.11	8.70 $\pm$ 3.18	1.00 (0.67-2.50)
Reference	10.38 $\pm$ 6.67	9.57 $\pm$ 5.90	0.94 (0.67-2.00)
*Ratio (90% CI)	100.40 (94.52-106.64)	96.27 (87.31-106.15)	-
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*

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 %.

Study 2798, 70 mg strength

Methods

This was a single-dose, two-way crossover study conducted in 40 healthy volunteers, comparing Lisdexamfetamine dibesylate, 89.1 mg, hard capsule with Elvanse (lisdexamfetamine dimesylate), 70 mg, hard capsule under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 8 hours post-dose. Plasma concentrations of lisdexamfetamine were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2024-01-15 and 2024-03-12.

Results

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

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ SD, $t_{\max}$ median, range) for lisdexamfetamine, n=39.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	59.67 $\pm$ 16.11	47.27 $\pm$ 16.81	1.00 (0.83-2.00)
Reference	60.23 $\pm$ 21.38	47.22 $\pm$ 18.82	1.00 (0.67-2.50)
*Ratio (90% CI)	101.86 (95.29-108.90)	101.66 (93.12-110.98)	-
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*

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%.

A biowaiver was sought for the additional strengths of 30, 40, 50 and 60 mg.

Discussion and overall conclusion

The bioequivalence studies and the 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.

Elvanse capsules contain lisdexamfetamine dimesylate. The applied product has a different salt of the active substance, lisdexamfetamine dibesylate. Differences in the salt form may change the pH-solubility profile of the active substance and bioequivalence under normal fasting conditions may not ensure bioequivalence in a gastric pH-altered situation e.g. in the presence of an acid reducing agent or achlorhydria. Therefore, an additional bioequivalence study with concomitant treatment of an acid reducing agent is necessary unless this study may be waived with a scientific justification demonstrating that bioequivalence in a gastric pH-altered situation can be expected. Comparative dissolution profile was shown for the test and reference product. Thus, no additional bioequivalence study with acid reducing agent is necessary.

Based on the submitted bioequivalence studies, Lisdexamfetamin MEDICE is considered bioequivalent with Elvanse.

As the composition of the applied product is not dose proportional over the range of strengths, the applicant conducted the bioequivalence studies with 20 mg and 70 mg strength, differing most in composition. Absence of studies with the additional strengths of 30, 40, 50 and 60 mg is acceptable, as all conditions for biowaiver for additional strength(s), as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled.

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 Puetter GmbH & Co. KG

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 RMP version 0.3 RMP dated 2025-08-25 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 most recent RMP version of the reference product Elvanse, version 5.0. This is considered acceptable.

Part III Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

The reference product also has follow-up questionnaires for some adverse events, but since these are not conditioned it is considered sufficient with routine only for these generic applications.

Part V Risk minimisation measures

Routine risk minimisation is suggested, and as additional RMM educational material in the form of a Physician's guide to prescribing will be provided. 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 VII.3 of this Overview concerning details of the conditioned educational material.

Part VI Summary of the RMP

The Summary of the RMP is endorsed.

Conclusion RMP assessment

The submitted Risk Management Plan, version 0.3 signed 2025-08-25 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 the educational material including Prescriber checklist, sections 1 and 2, Chart for monitoring therapy and Patient guide.

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

N/A

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:

- Prescriber checklist, sections 1 and 2
- Chart for monitoring therapy
- Patient guide

Checklist 1: Prescriber checklist before prescribing lisdexamfetamine dibesylate

The checklist is designed to support the prescriber in the appropriate initiation of lisdexamfetamine

dibesylate in a child aged six years and 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 dibesylate treatment

The checklist is designed to support the prescriber in the ongoing

monitoring of lisdexamfetamine dibesylate 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 dibesylate treatment

The chart is designed to support you in the ongoing monitoring of lisdexamfetamine dibesylate 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).

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 nonmedical 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

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Elvanse SE/H/1839/01-03 regarding both content and layout.

The bridging report submitted by the applicant has been found acceptable.

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
-	-	-	-	-	-