LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Amdex
(lisdexamfetamine dimesilate)

SE/H/2723/001-006/DC

This module reflects the scientific discussion for the approval of Amdex. The procedure was finalised at 2026-02-18. 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 Amdex, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, Capsule, hard.

The active substance is dexamfetamine, lisdexamfetamine dimesilate, lisdexamfetamine. 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.

Mechanism of action
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. The prodrug, lisdexamfetamine, does not bind to the sites responsible for the reuptake of norepinephrine and dopamine in vitro.

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 Amdex, 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 the following concerned member states (CMS):
SE/H/2723/001-006 DC: IS

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 Sweden since 2013, with Takeda Pharmaceuticals International AG Ireland Branch as marketing authorisation holder.

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

European Reference Product (ERP)
SE/H/2723/001-006/DC
A European Reference Product is used in CMS IS: Elvanse, 30 mg, 50 mg, 70 mg, capsule, hard authorised in Sweden since 2013, with Takeda Pharmaceuticals International AG Ireland Branch as marketing authorisation holder and Elvanse, 20 mg, 40 mg, 60 mg, capsule, hard authorised in Sweden since 2015, with Takeda Pharmaceuticals International AG Ireland Branch as marketing authorisation holder.

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.

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 and the bioanalytical facilities were inspected by the EU Authorities AGES, DKMA and CBG in 2022, without any critical findings.

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 dimesylate are well known. As lisdexamfetamine dimesylate 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 product is a generic version of the reference medicine ELVANSE®. Only the active substance, dextroamphetamine (released from the prodrug lisdexamfetamine), is considered relevant for environmental assessment. An ERA document in line with the 2024 ERA-GL which identifies a previously regulatory approved ERA for a relevant active substance (for medical product: Elvanse, approved under the 2006 ERA-GL framework) as a reference ERA has been provided and is acceptable (a so called 'Art-10 ERA document'). The environmental exposure scenario of this medical product is sufficiently similar to that of the reference ERA (the same active ingredient, form, strength, route, dose, and patient population; no increased environmental exposure is expected) and new technical requirements introduced with the 2024 ERA-GL have been accounted for (no new ecotoxicological studies are necessary). It can be noted that the applicant did not get access to the reference ERA dossier from the data-owner but available public information was sufficient to submit an Art-10 ERA document. The reference ERA environmental risk conclusions (no risk) are considered applicable also for the present medical product.

Overall conclusion
The are no non-clinical/ERA concerns remaining.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted two bioequivalence studies (20 mg and 70 mg) comparing Amdex 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). There are no restrictions with respect to food in the SmPC of the originator.

Linearity: AUC and C_{max} of lisdexamfetamine increases more than proportional to dose in the dose range 20 mg to 70 mg. Linear pharmacokinetics of 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 2863 (20 mg)

Methods

This was a single-dose, two-way crossover study conducted in 34 healthy volunteers, comparing Dilida, 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 8 hours post-dose. Plasma concentrations of lisdexamfetamine 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 10th June and 1st August 2024.

Results

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

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for lisdexamfetamine in study 2863 (20 mg capsule), n=34.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**10.75 ± 3.73**	**9.05 ± 3.17**	**1.00 (0.67-2.75)**
Reference	**10.92 ± 4.35**	**9.42 ± 3.71**	**1.00 (0.83-1.50)**
***Ratio (90% CI)**	**99.77 (93.26-106.74)**	**96.44 (85.18-109.19)**	**-**
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 2864 (70 mg)

Methods

This was a single-dose, two-way crossover study conducted in 32 healthy volunteers, comparing Dilida, 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 8 hours post-dose. Plasma concentrations of lisdexamfetamine 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 13th June and 1st August 2024.

Results

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

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for lisdexamfetamine in study 2864 (70 mg capsule), n=32.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**70.88 ± 34.72**	**56.19 ± 27.63**	**1.01 (0.83-1.75)**
Reference	**72.34 ± 30.97**	**58.16 ± 33.28**	**1.00 (0.67-2.00)**
***Ratio (90% CI)**	**96.89 (90.86-103.32)**	**99.58 (91.87-107.93)**	**-**

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 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) and ICH M13A Guideline on bioequivalence for immediate-release solid oral dosage forms (EMA/CHMP/ICH/953493/2022). The bioanalytical methods were adequately validated.

The test product does 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 the 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, Amdex 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

SE/H/2723/001-006/DC Proposed MAH:
Williams & Halls ehf.: SE, IS

The Applicant has submitted an updated 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 Amdex SE/H/2723/001-006 DC.

Part II Safety specification
SE/H/2723: The MAH has submitted the version 0.3 RMP dated 2025-12-18 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

Having considered the data in the safety specification the assessor agrees that the safety concerns listed by the MAH are appropriate. The proposed summary of safety concerns is in line with the summary of safety concerns in latest version (v 5.0) of the RMP for the reference product Elvanse.

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested and in accordance with the originator, follow-up questionnaires is proposed concerning
- Cardiovascular ischaemic events
- Cerebrovascular events
- Sudden death
- Suicidality,

which is acknowledged. No additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested, and additional risk minimisation activities are proposed by the applicant in form of
- Physician’s checklist prior to starting treatment
- Physician’s checklist for ongoing monitoring during treatment

- Chart for ongoing monitoring of therapy
- Patient guide (only applicable to safety concern Intentional drug misuse, abuse and diversion)

for the following safety concerns:

- 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

For key elements for these additional risk minimisation measures see section VII.3 Proposed list of conditions pursuant to Article 21a or specific obligations pursuant to article 22 of Directive 2001/83/EC.

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

Conclusion RMP assessment
SE/H/2723: The submitted Risk Management Plan, version 0.3 signed 2025-12-18 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 products, Amdex, is found adequate. There are no objections to approval of Amdex, 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 applications are therefore recommended for approval.

Please refer to section V.2 for information about the condition regarding the educational tools (checklist 1, checklist 2, monitoring chart and educational leaflet).

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

Post approval commitments
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:

  - Checklist 1: Prescriber checklist before prescribing lisdexamfetamine dimesylate
  - Checklist 2: Prescriber checklist for ongoing monitoring during lisdexamfetamine dimesylate treatment
  - Chart for ongoing monitoring during lisdexamfetamine dimesylate treatment
  - Potential for non-medical use and diversion of prescription stimulant medications Leaflet.

  Education material components:
  - **Checklist 1: Prescriber checklist before prescribing lisdexamfetamine dimesylate.**

The checklist is designed to support the prescriber in the appropriate initiation of lisdexamfetamine dimesylate in a child aged six years and above, or an adult (in countries with approval for the adult use) with attention-deficit/hyperactivity disorder (ADHD).

- **Checklist 2: Prescriber checklist for ongoing monitoring during lisdexamfetamine dimesylate 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 an adult (in countries with approval for the adult use) with ADHD.

- **Chart for ongoing monitoring during lisdexamfetamine dimesylate treatment**
The chart is designed to support you in the ongoing monitoring of lisdexamfetamine dimesylate therapy in children aged six years and above, or an adult (in countries with approval for the adult use) with 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 non-medical use and diversion of prescription stimulant medications leaflet**
Educational leaflet for use by HCPs, 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 for procedures, SE/H/2723/001-006/DC, on the basis of a bridging report making reference to Elvanse, SE/H/1839/01-03 (the readability test was done when UK was RMS in UK/H/3326/001-03/DC).
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
-	-	-	-	-	-