LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Lisdexamfetamine FrostPharma (lisdexamfetamine dimesilate, lisdexamfetamine, dexamfetamine)

SE/H/2587/01

This module reflects the scientific discussion for the approval of Lisdexamfetamine FrostPharma. The Public Assessment Report was written in 03-2024 by the previous RMS MT after initial procedure MT/H/0619/001 and is attached at the end of this document. RMS transfer from MT to SE was completed 2024-03-27. For information on changes after this date please refer to the module 'Update'.

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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

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Public Assessment Report

Scientific discussion

Lisdexamfetamine Aristo 10mg/ml oral solution
Lisdexamfetamine FrostPharma 10mg/ml oral solution
Lisdexamfetamine Adalvo 10mg/ml oral solution

Lisdexamfetamine dimesylate

MT/H/0618/001/DC

MT/H/0619/001/DC
MT/H/0620/001/DC

Date: 21.03.2024

This module reflects the scientific discussion for the approval of Lisdexamfetamine 10mg/ml oral solution. The procedures were finalised at day 210 on the 8th February 2024. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Lisdexamfetamine Aristo 10mg/ml oral solution, Lisdexamfetamine FrostPharma 10mg/ml oral solution, Lisdexamfetamine Adalvo 10mg/ml oral solution from the MAH.

The product is indicated for*:*

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.

Treatment must be under the supervision of a specialist in childhood and/or adolescent behavioural disorders. Diagnosis should be made according to DSM criteria or the guidelines in ICD and should be based on a complete history and evaluation of the patient. Diagnosis cannot be made solely on the presence of one or more symptoms.

The specific aetiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use of medical and specialised psychological, educational, and social resources.

A comprehensive treatment programme typically includes psychological, educational and social measures as well as pharmacotherapy and is aimed at stabilising children with a behavioural syndrome characterised by symptoms which may include chronic history of short attention span, distractibility, emotional lability, impulsivity, moderate to severe hyperactivity, minor neurological signs and abnormal EEG. Learning may or may not be impaired.

The product is not indicated in all children with ADHD and the decision to use the drug must be based on a very thorough assessment of the severity and chronicity of the child's symptoms in relation to the child's age and potential for abuse, misuse or diversion.

Appropriate educational placement is essential, and psychosocial intervention is generally necessary. The use of lisdexamfetamine should always be used in this way according to the licensed indication.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Pharmaceutical form: The product is presented as oral solution

Formulation: Lisdexamfetamine dimesylate (API) and sodium methyl parahydroxybenzoate, sodium propyl parahydroxybenzoate, sodium dihydrogen phosphate dihydrate, disodium hydrogen phosphate dihydrate, propylene glycol, saccharin sodium, hydrochloric acid, sodium hydroxide and purified water as excipients.

Container Closure System: The product is packed in amber glass (type III) of 100 ml nominal capacity and sealed with a childproof and tamper evident plastic cap. The drug product is administered with the aid of a CEmarked oral syringe. A press-in bottle adapter is also provided.

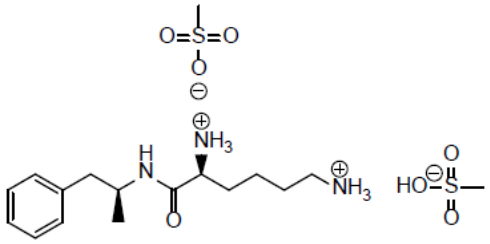
II.2 2.2 Drug Substance

INN; Lisexamfetamine dimesylate

Chemical Features:

Chemical (IUPAC) Name	(2*S*)-2,6-diamino-*N*-[(2*S*)-1-phenylpropan-2-yl]hexanamide;methanesulfonic acid
Molecular Formula	$C_{17}H_{33}N_3S_2$
Molecular Weight	455.5g/mol

Structural Formula



The specifications are adequately included in the dossier.

The manufacturing process has been sufficiently described. The proposed starting materials are acceptable. A full description of the steps has been adequately provided.
The drug substance manufacturer is covered by an Active Substance Master File (ASMF). The structure of Lisexamfetamine dimesylate has been described and characterised.

Stability studies are acceptable. Results of stability testing are provided in accordance to ICH Q1A.
Appropriate stability studies have been performed supporting a suitable retest period for the drug substance when stored in the proposed packaging.

II.3 Medicinal Product

Pharmaceutical development:
The development of the product has been described; The excipients are common pharmacopoeial excipients. The choice of excipients is justified, and their functions explained.. The formulation studies are suitable.

Manufacture of the product:

The manufacturing process and controls are well described. The applicant has carried out validation studies on batches of drug product. The manufacturing process is considered a standard one.

Quality control of drug product
The product specifications cover appropriate parameters for this dosage form; the control tests and specifications for drug product have been adequately drawn up. Analytical methods are adequately described together with validations of the analytical methods. Batch analysis data is presented on all process validation batches. Batch analytical data presented comply with the proposed finished product specifications have been submitted.

Stability
The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. The proposed shelf-life and storage conditions for the drug product as proposed by the applicant are now acceptable. The results confirmed a shelf life of 18 months when stored in the original package below 30°C. The in-use shelf-life is 30 days.

III. NON-CLINICAL ASPECTS

III.1 Introduction: Pharmacology, Pharmacokinetics, Toxicology

Lisdexamfetamine (LXD) is a centrally acting sympathomimetic. It is a prodrug of dexamphetamine which is a central nervous system (CNS) stimulant. The lisdexamfetamine parent compound does not bind to the sites responsible for the reuptake of noradrenaline and dopamine *in vitro* and is not thought to contribute to the pharmacological effects. After oral administration, lisdexamfetamine is rapidly absorbed from the gastrointestinal tract and hydrolysed primarily in whole blood to *d*-amphetamine, which is thought to be responsible for the drug's activity.

Pharmacodynamic, pharmacokinetic and toxicological properties of lisdexamfetamine are well known. As lisdexamfetamine is a well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Lisdexamfetamine dimesylate 10mg/ml oral solution is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is deemed acceptable by the RMS.

IV. CLINICAL ASPECTS

IV.1 Introduction

Lisdexamfetamine dimesylate is a well-known active substance with established efficacy and tolerability. A clinical overview, based on scientific literature, has been provided. This is acceptable and well justified.
The applicant has submitted a comparative bioequivalence study protocol which is discussed below.

IV.2 Pharmacokinetics

The bioequivalence study was a two stage, randomised, single centre, open-label, balanced, two-period, two sequence, single dose, crossover comparative oral bioavailability study to establish comparative bioequivalence of lisdexamfetamine dimesylate 10mg/ml oral solution and the reference Elvanse 70mg hard capsules.

The objective of the study was to compare the rate and extent of absorption of both products and to monitor the adverse events to ensure the safety and tolerability of a single dose of Lisdexamfetamine 70mg.

There were no other screening or post-study laboratory results outside of normal range that were deemed clinically significant by the Investigator.

The two treatments were well tolerated by the subjects (in both periods) enrolled in the study. The adverse events mentioned above are all included in the SmPC and there are no new concerns arising from this study. The two products had similar safety profiles.

The 90% confidence intervals calculated for the primary parameters C_{max} and AUC_{0-t} for Lisdexamfetamine fall within the 80.00 – 125.00% acceptance range after single dose administration under fasting conditions.

Table 3.1.1 Pharmacokinetics data for Lisdexamfetamine in Study LDA-BESD-02-LBS/20

Pharmacokinetics Parameters	Arithmetic Mean (+/-SD)	
	Test product	Reference product
$AUC_{(0-t)}$ (ng·hr/mL)	42.839 ± 14.494	47.715 ± 18.104
$AUC_{(0-\infty)}$ (ng·hr/mL)	43.796 ± 14.475	49.018 ± 17.712
C_{max} (ng/mL)	37.565 ± 13.795	39.621 ± 15.859
T_{max} (hr)[1]	1.000 [0.750-2.000]	1.250 [0.750-2.670]

[1]Median, (Min, Max)

Table 3.1.2 Pharmacokinetics data for Dexamfetamine in Study LDA-BESD-02-LBS/20 (for supportive information)

Pharmacokinetics Parameters	Arithmetic Mean (+/-SD)	
	Test product	Reference product
$AUC_{(0-t)}$ (ng·hr/mL)	1127.584 ± 198.468	1153.751 ± 212.988
$AUC_{(0-\infty)}$ (ng·hr/mL)	1206.492 ± 222.448	1220.491 ± 232.309
C_{max} (ng/mL)	64.226 ± 12.694	64.733 ± 12.265
T_{max} (hr)[1]	2.670 [1.500-6.000]	3.000 [2.000-6.000]

Table 3.3.1 Bioequivalence evaluation of Lisdexamfetamine in Study LDA-BESD-02-LBS/20

Pharmacokinetics parameter	Geometric Mean Ratio Test/Ref[1]	Confidence Intervals	CV%
$AUC_{(0-t)}$ (ng·hr/mL)	91.483	84.06% - 99.56%	19.066
C_{max} (ng/mL)	96.930	88.19% - 106.54%	21.351

[1] Calculated using least-squares means

Table 3.3.2 Bioequivalence evaluation of Dexamfetamine in Study LDA-BESD-02-LBS/20 (for supportive information)

Pharmacokinetics parameter	Geometric Mean Ratio Test/Ref[1]	Confidence Intervals	CV%
$AUC_{(0-t)}$ (ng·hr/mL)	98.051	94.30% - 101.95%	8.728
C_{max} (ng/mL)	99.068	96.93% - 101.25%	4.880

[1] Calculated using least-squares means

IV.3 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 Lisdexamfetamine dimesylate 10mg/ml oral solution.

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)

IV.4 Discussion on the clinical aspects

The bioequivalence study is considered to be approvable and the benefit/risk ratio is positive. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed.

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 PIL 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

Lisdexamfetamine dimesylate 10mg/ml oral solution has a proven chemical-pharmaceutical quality and are generic forms of Elvanse 70mg hard capsules. Elvanse 70mg hard capsules is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Lisdexamfetamine 10mg/ml oral solution with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8th February 2024 with 2 post approval commitments which do not fall under Article 21a/22 Directive 2001/83/EC

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