LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Dexfarm
(dexamfetamine sulfate)

SE/H/2344/01-03/DC

This module reflects the scientific discussion for the approval of Dexfarm. The procedure was finalised on 2024-03-27. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Dexfarm, 5 mg, 10 mg, 20 mg, Tablet.

The active substance is dexamfetamine sulfate. 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 Dexfarm, 5 mg, 10 mg, 20 mg, tablet, 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) and DK, FI, NL, NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Attentin, 5 mg, tablet, SE/H/1719/001 (former UK/H/5007/001) authorised in Sweden since 2014, with Medice Arzneimittel Pütter & Co as marketing authorisation holder.

Potential similarity with orphan medicinal products
N/A.

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 dexamfetamine sulfate are well known. As dexamfetamine sulfate 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 Dexfarm 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 Dexfarm from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics

Pharmacokinetic properties of the active substance
Absorption
Dexamfetamine is highly lipophilic and rapidly absorbed from the gastrointestinal tract. The pharmacokinetics of the tablets was measured in 18 healthy subjects. Following the administration of one 5 mg tablet of dexamfetamine, average maximal plasma concentrations (C_{max}) of 11.5 ng/mL were achieved at approximately 1.5 hours.

According to the SmPC of the originator, the effect of food on the absorption of dexamfetamine has not been studied. Therefore, it is recommended that the product should be taken in a standardised manner in relation to the timing of meals, i.e. that doses should be given at the same times, relative to the time of meals, on each day, preferably with or immediately after meals.

Elimination:
Amfetamine is primarily excreted in the urine; however, tubular reabsorption is relatively high due to its lipophilic properties. The elimination of amfetamine is pH-dependent, i.e. at low pH about 80% of the amfetamine may be eliminated in the unaltered form within 24 hours; in alkaline urine, there are only 2– 3% of the amfetamine which will be eliminated as free amfetamine. The extent of bioavailability of the tablets was measured in 18 healthy subjects. The average plasma half-life (t1/2) was 10.2 hours.

BCS-based biowaiver
The application is based on a Biopharmaceutical Classification System (BCS) based biowaiver and no bioequivalence study has been submitted.

According to the applicant, only limited data can be found on the absorption and permeability of dexamfetamine sulfate in the literature. The applicant concludes, based on the presented data, that dexamfetamine sulfate is a highly soluble drug, but due to the limited data available on the absorption it is classified as a BCS class III drug in this biowaiver as a precaution. The applicant does however consider dexamfetamine sulfate to be borderline BCS class I/class III.

According to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr), a BCS class III-based biowaiver is applicable for an immediate release product if the drug substance is not considered to have a narrow therapeutic index and has been proven to exhibit high solubility and limited absorption (BCS class III). Also, *in-vitro* dissolution characteristics of the test and the reference product should be very rapid and excipients that might affect bioavailability should

be quantitatively and qualitatively the same and all other excipients should be qualitatively the same and quantitatively very similar.

Discussion and overall conclusion
Although the applicant has not discussed the therapeutic index of dexamfetamine, it can be concluded that dexamfetamine does not have narrow therapeutic index.

It can also be concluded that the drug substance has been proven to exhibit high solubility, but high permeability has however not been demonstrated by the applicant. As it has not been demonstrated that the extent of absorption is above 85%, dexamfetamine is considered as a BCS class III substance in this application.

The criteria for quantitative similarity for BCS class III drugs are fulfilled in accordance with ICH M9 guideline.

The quality criteria for biowaiver (solubility and dissolution) have also been fulfilled. Similar *in vitro* dissolution characteristics of the test and the reference product has been demonstrated.

In conclusion, the justification for a BCS (Biopharmaceutics Classification System) based biowaiver can be accepted.

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.

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 Dexfarm.

Part II Safety specification
The MAH has submitted the version 1.2 RMP dated 2024-01-04 and proposed the following summary safety concerns:

Important identified risks	• Myocardial infarction, sudden death, serious ischaemic cardiac or cardiovascular disorder, cardiomyopathy • Stroke, TIA and other cerebrovascular accidents • Psychiatric disorders (including psychotic symptoms, suicidality, aggression and hostility, depression, anorexia nervosa/anorectic disorders) • Tic/Tourette's/dystonia • Decreased rate of growth and development • Drug abuse, misuse and diversion • Dependence • Withdrawal syndrome
Important potential risks	• Off label use
Missing information	• Long-term safety (cardiovascular, neurological, cognition and psychotic)

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

The reference product has non-conditioned follow-up questionnaires for AE involving abuse, misuse, diversion, dependence and pregnancy. This ongoing application does not have these questionnaires in the RMP, which can be agreed for a generic application.
In addition, the reference has additional pharmacovigilance studies, but since this is a generic application following the reference product, these studies are, and should not, be conditioned here.

In conclusion, the suggested routine pharmacovigilance is endorsed.

Part V Risk minimisation measures
The aRMM is in line with those of the reference product.

Part VI Summary of the RMP
The summary of the RMP is acceptable.

RMS conclusion of the RMP assessment
The submitted Risk Management Plan, version 1.2 signed 2024-01-04 **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.

V. USER CONSULTATION

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 Attentin 10 mg/20 mg tablets, UK/H/5007/001/DC concerning content and Kaliumklorid Orifarm 750 mg depottabletter, DK/H/2347/001 concerning layout.

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

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Please see key elements of the conditioned aRMM according to art 21a of Directive 2001/83/EC, in section VIII.3.

The quality of the generic product, Dexfarm, is found adequate. There are no objections to approval of Dexfarm, from a non-clinical and clinical point of view. The absence of bioequivalence studies is

acceptable. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

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 aRMM material should contain the following key elements:

Physician educational material:
- The Summary of Product Characteristics
- Prescriber checklist
- Guide for healthcare professionals

Prescriber checklist:
- Lists of tests to be conducted for the initial screening and monitoring of the patient
- Special warnings and precautions for use
- Measurement recording chart

Guide for healthcare professionals:
- Information on <invented name>, including the approved indication according to the SmPC
- Remarks on the importance of reporting of adverse events
- Details on how to minimise the risk of drug abuse / drug dependence, drug misuse and diversion, and off-label use (signs and symptoms, patient screening and monitoring)

The patient information pack:
- Patient information leaflet
- A parent/carer guide
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Parent/carer guide:
- A description of the important identified/potential risks associated with the use of <invented name> namely: drug abuse / drug dependence, drug misuse and diversion, off-label use
- A description of the signs and symptoms of the identified/potential risk of drug abuse / drug dependence, drug misuse and diversion, and off-label use
- A description on how to prevent the important identified/potential risks of drug abuse / drug dependence, drug misuse and diversion, and off-label use

Assessor's comment: the key elements listed in the RMP are in accordacne with those of the reference product.

VII. APPROVAL

The decentralised procedure for Dexfarm, 5 mg, 10 mg, 20 mg, Tablet was positively finalised on 2024-03-27.

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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)

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