LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Dexatin
(dexamfetamine sulfate)

SE/H/2484/01-03/MR

This module reflects the scientific discussion for the approval of Dexatin. The procedure was finalised on 2023-11-21. 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 Dexatin, 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 Dexatin, 5 mg, 10 mg, 20 mg, tablet, is submitted according to Article 10a of Directive 2001/83/EC. The applicant, Abboxia AB, applies through the Mutual Recognition Procedure with Sweden acting as reference member state (RMS) and DK, FI and NO as concerned member states (CMS).

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

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

Pharmacodynamic, pharmacokinetic and toxicological properties of dexamfetamine are well known. As dexamfetamine 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 Dexatin will be used to substitute for other approved dexamfetamine-containing products, 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 Dexatin from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
No pharmacokinetic studies have been perfomed with Dexatin. The Applicant has submitted in vitro dissolution data for Dexatin demonstrating very rapid dissolution, which is pivotal. In addition, the Applicant has submitted comparative in vitro dissolution data to an approved product that is available on the market (Attentin).

Absorption
No study examining the absolute bioavailability of either *d*- or racemic amfetamine was reported in the published literature. Serum peak plasma concentrations of dexamfetamine are achieved approximately 2-4 hours after oral administration of a dexamfetamine IR tablet.

Distribution
The fraction of dexamfetamine bound to plasma proteins is approximately 20%, and the main binding protein is albumin. The apparent volume of distribution is 4-5 L/kg.

Elimination
Dexamfetamine and its metabolites are mainly excreted in the urine. The excretion of amfetamine depends on urinary pH. 48 h after administration of 10 mg dexamfetamine, 57% and 7% of the dose was excreted as unchanged parent compound, in acid (pH 4.5 – 5.6) and alkaline (pH 7.1 – 8.0) urine, respectively.

The terminal half-life of dexamfetamine is approximately 8-12 hours in healthy adults. A half-life of approximately 7 hours has been reported in children aged 5-12 years.

Dexamfetamine is mainly metabolized through N-deamination and oxidation into the corresponding benzoic acid derivatives which are further conjugated with glycine and excreted as the corresponding hippuric acids and hydroxylation in position 4 of the aromatic ring generating p-hydroxyamfetamine followed by conjugation of the phenol group with sulphate or glucuronic acid. In the minor metabolic pathway, the oxidation at the β-carbon of the side chain leads to the formation of norephedrine; oxidation of the in the aromatic ring results in the formation of hydroxynorephedrine, which is one of the pharmacologically active metabolites.

The enzymes involved in the metabolism have not been clearly defined. CYP2D6 seems to be involved in the formation of 4-hydroxyamfetamine.

Interactions
Concomitant use of MAO-inhibitor can cause hypertensive crisis. Dexamfetamine is contraindicated

in patients treated with non-selective, irreversible MAO-inhibitor or within 14 days after discontinuing MAO-inhibitor.

Since the CYP enzymes involved in the metabolism of dexamfetamine is not known, concomitant treatment with potent CYP-inhibitors or -inducers should be with caution.

It is not known if dexamfetamine inhibits or induces CYP enzymes *in vivo*. Concomitant administration with CYP substrates with a narrow therapeutic interval should be with caution.

Urinary acidifying and alkalinizing agents increase respective decrease the urinary excretion of dexamfetamine. Gastrointestinal alkanizing agents increase the absorption of of dexamfetamine, whereas gastrointestinal acidifying agents decrease the absorption of dexamfetamine.

Dexamfetamine has shown to inhibit OCT1 and OCT2 *in vitro*. The clinical relevance of this interaction is unclear.

Special populations
There is limited or no information of the pharmacokinetics of dexamfetamine in most of the special populations. The systemic exposure of dexamfetamine might be increased in patients with renal and hepatic impairment as compared to patients with normal renal/hepatic function after administration of dexamfetamine IR tablets. Dexamfetamine should therefore be used with caution in these patient groups by carefully titrating the dose.

No major conclusions can be drawn regarding the effect of gender, race and body weight. Since Dexatin will be individually titrated potential differences in the exposure due to these covariates is handled. Thus, it is supported that no dose-adjustments are necessary based on gender, race and body weight.

Discussion on the pharmacokinetics
This is an application according to Article 10a well-established use. As this is a complete application, the bibliography should cover all aspects of pharmacokinetics needed to make a complete characterisation of the disposition of the compound. For a WEU application establishing a link between the applied for product and the literature data used to support efficacy and safety is crucial.

The basic pharmacokinetic parameters of dexamfetamine are sufficiently described by the Applicant. Oral dexamfetamine IR formulations have been used in the clinical efficacy and safety studies reported in the literature. However, the compositions of the formulations are not known, and therefore these might be different from other approved products such as Attentin/Amfexa, which was used in the *in vitro* dissolution experiments.

Based on the data provided by the Applicantdexamfetamine cannot be classified as a BCS class I substance (high solubility and high permeability). However, it seems to be a substance in the borderline of BCS class I. BCS class I drugs generally represent a low-risk group of compounds in terms of the potential for excipients to affect absorption. BCS class III substances (high solubility with incomplete absorption) could be eligible for a biowaiver provided certain prerequisites are fulfilled regarding product composition and *in vitro* dissolution.

The excipients in Dexatin are not considered to have an impact on the oral bioavailability of dexamfetamine or on GI motility. The *in vitro* dissolution experiment indicates a very rapid dissolution of Dexatin (fulfilling dissolution criteria for a BCS class III based biowaiver). Dexamfetamine is not considered to be a substance with a narrow therapeutic index, and the dose is titrated until optimal clinical effect is achieved. Thus, Dexatin can be expected to behave similarly as the IR formulations used in the literature, considering the high solubility of the active substance, the rapid dissolution of the tablet and the absence of excipients expected to affect bioavailability. The comparison to the approved product Attentin further supports that other IR

formulations with dexamfetamin can also be expected to dissolve rapidly.

The application can be recommended for approval from a pharmacokinetic point of view.

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.

Pharmacodynamics
Amfetamines are psychoactive substances with stimulant, euphoric, anorectic, and in some cases, emphathogenic, entactogenic, and hallucinogenic properties. The compounds with amphetaminic structure derive from the β-phenylethylamine core structure and are kinetically and dynamically characterized by easily crossing the blood–brain barrier, to resist brain biotransformation and to release monoamine neurotransmitters from nerve endings.
Due to the structural similarity with monoamine neurotransmitters, amfetamines act as competitive substrates at the membrane transporters of norepinephrine (NET), dopamine (DAT), and serotonin (SERT), reducing the reuptake of endogenous neurotransmitters, and inducing the reverse transport of endogenous neurotransmitters, and hence non-exocytotic neurotransmitter release. Amfetamines also promote dopamine and serotonin release from storage vesicles and prevent the uptake into vesicles, thus increasing the cytoplasmic concentrations of the neurotransmitter and making them more readily available for reverse transport.

The Applicant has provided a pharmacodynamic summary describing the primary and secondary pharmacology, referenced to original scientific data on the subject.
The effect of *d*-amfetamine on neurotransmitter presence in the synaptic cleft is sufficiently described, summarising studies in which dopamine release and response following *d*-amfetamine administration. Of high importance with regards to the proposed indication of Dexatin for children and adolescents, specific pharmacodynamic studies on children have been included.
No dose-response studies could be found including *d*-amfetamine. One study with a racemic mixture of amfetamine showed a significant dose-related decrease of hyperactive/impulsive ADHD symptoms. However, two other clinical studies failed to show a clear dose-response relationship when lisdexamfetamine was studied in children with ADHD. The Applicant concludes that no evident dose-response relationship can be concluded, and the dose of *d*-amfetamine needs to be adjusted individually, which is considered acceptable by the MPA.

The pharmacodynamic interactions with other substances have been well described by the Applicant. The exact degree of the dependence of *d*-amfetamine metabolism on other CYP enzymes is not known, therefore co-administration of potent inhibitors or inducers of CYP enzymes should be made with caution.

Known genetic alterations that can lead to a different PD response to *d*-amfetamine intake have also been thoroughly described by the Applicant, referring to original published data.

Well-established use
For an application according to Article 10a of Directive 2001/83/EC, WEU, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use for the claimed therapeutic indication within the European Union for at least ten years, with recognised efficacy and an acceptable level of safety.

The Applicant has reviewed existing guidelines in Europe and presented a discussion and a tabulated summary of the recommendations for ADHD treatment with *d*-amfetamine. Immediate release *d*-amfetamine is mostly considered as a second-line option due to the higher abuse potential as compared to the longer acting prodrug, lisdexamfetamine.

Since the first MA of *d*-amfetamine for treatment of ADHD in children, new treatment alternatives have been developed and guidelines have been subjected to amendments. A clear consensus about the current place of dexamfetamine in the treatment paradigm of ADHD in children is currently lacking. In Sweden, it is considered that dexamfetamine should only be used in children and adolescents in case of insufficient response to methylphenidate.

Clinical efficacy

The Applicant has provided 8 publications as main studies to support clinical efficacy for the indication applied for. Two of the studies had study sites in Europe and the other main efficacy studies referred to were conducted outside Europe.

Furthermore, the applicant has included supporting studies performed in children diagnosed with hyperactivity disorder, or minimal brain disorder based on criteria not defined by the appropriate DSM, or that have improper study design.

Most of the selected main studies follow the EMA guideline on the clinical investigation of medicinal products for the treatment of ADHD (EMEA/CHMP/EWP/431734/2008) with regards to diagnosis and inclusion criteria (DSM), choice of active comparator (methylphenidate), and efficacy endpoints (Connor's and ADHD Symptom Rating Scales). The primary endpoints in the selected main studies, regarding both the symptomatic and the functional aspects of ADHD have been discussed by the Applicant and the majority of the studies used outcome measures for both symptomatic and functional primary endpoints, according to the recommendations in the guideline.
Moreover, the applicant has included a relevant discussion about the paediatric population, which is the intended treatment population for Dexatin, and also discussed the inhomogeneous distribution of gender in the main studies as well as the lack of data regarding race, which is endorsed.

Overall, the submitted Summary of Clinical Efficacy is sufficiently well compiled and included original clinical data to support the sought indication. The main studies all showed significant efficacy on the measured outcomes for dexamfetamine treatment of ADHD in children and adolescents. Although there are several limitations in the selected studies, these have been sufficiently discussed by the Applicant.

Additional studies investigating the efficacy of *d*-amfetamine administered as enantiopure drug following long-term administration could not be retrieved from the public domain by the Applicant. Information was instead retrieved from published studies on the prodrug lisdexamfetamine, and the Applicant has summarized the results from two studies.
The lack of long-term studies investigating the effect of *d*-amfetamine on children with ADHD is acknowledged by the MPA. An observational study with *d*-amfetamine showed significant effects at 6 and 12 months in children 6-17 years, while limited support can be drawn from lisdexamfetamine trials for the long-term clinical effect of *d*-amfetamine.

In response to posed concerns, the Applicant has also summarized the limited amount of available data for dexamfetamine in the main studies concerning comparing different age groups and potential differences in the clinical significance of the results. The MPA acknowledges the pharmacodynamic equivalence of lisdexamfetamine and dexamfetamine in terms of the active moiety, as concluded in a previous procedure (EMA/353952/2014), and the data presented by the Applicant are considered sufficient to support the proposed paediatric dosing recommendations.

In line with the proposed posology and based on a summary of the dosing utilised in the main studies, this includes a starting dose of 5 mg and a maximum dose of 20 mg.

This is endorsed.

Clinical safety
According to the applicant, the safety profile of *d*-amfetamine, when used in the claimed indication, is well established. The most common adverse reactions to *d*-amfetamine are reduced appetite, abdominal pain, insomnia or irritability, though serious adverse reactions such arrythmia and cardiac arrest are also known. The pharmacological basis for most of the adverse reactions to *d*-amfetamine resides mostly in its effect on dopamine and norepinephrine turnover being responsible for the stimulant effects on the cardiovascular, gastrointestinal, and nervous system.

Randomised controlled trials retrieved from the published domain in order to assess the efficacy of *d*-amfetamine in the claimed indication (i.e., treatment of ADHD) are inconsistent in reporting the encountered adverse events (AE). Of the 14 controlled trials retrieved, 9 studies either not provided any safety information at all or reported adverse events without their frequencies. A number of 5 identified trials provided appropriate numerical data upon which a safety analysis could be carried out.

AEs are presented in a tabulated form of the pooled reported adverse events from all the published studies assessed for clinical efficacy and safety. The applicant acknowledges the limitation of the data since information on specific adverse events available in published studies is not complete.
The limited extent of patient exposure with exposure rates has further been presented in a tabulated form. The studies presented in Summary of clinical efficacy were chosen to be representative for the controlled exposure to the drug to an extent appropriate for a sound assessment of the drug's level of safety. These studies included 624 subjects accounted as randomized to receive at least one oral dose of *d*-amfetamine across a range from 5 mg to 40 mg/day in case of children and of these subjects 64,7% were exposed for 1 month or less. The data on long-term exposure is limited and this information has been included in SmPC section 4.4.

The Applicant has provided a tabulated summary of what type of AEs that lead to withdrawal. Overall, the numbers are higher than those reported for placebo, but comparable to those of the active comparators and no new or unexpected safety issues were identified.

The published literature search also yielded a number of clinical trials and pharmaco-epidemiological studies specifically designed to assess specific risks related to the known pharmacological effects of *d*-amfetamine. Established risks associated to *d*-amfetamine, or generally amfetamine use, include cardiovascular effects, as well as effects on appetite, weight gain, the nervous system and overdose. Of note, the Applicant chose Attentin / Amfexa 5 mg, 10 mg, 20 mg tablets (Medice, DE) as a product representative for marketed drugs containing the same active substance. Attentin was subject to a referral due to perceived risks of diversion and abuse associated with this medication. The conclusion was that CHMP acknowledged that there is a risk of abuse and dependence with *d*-amfetamine, however it concluded that the risk minimisation measures proposed to mitigate this risk were adequate. Information proposed by the MPA to assure measures to mitigate the risk of abuse and dependence has been appropriately added to the SmPC by the Applicant.

A lack of meaningful laboratory data is noted. It could be the case that it is not available in the literature, and this has been accepted for other products.

Overall, the applicant has presented a sufficient overview of clinical data with original references investigating cardiovascular risks, effect on energy intake, body weight and growth, effect on mood and emotion, effect on sleep, and drug abuse, all relevant for dexamfetamine treatment in children and adolescents.

Risk Management Plan
The MAH has submitted a risk management plan, version 0.2 signed 4 January 2023, 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 Dexatin.

Safety specification

Proposal of safety concerns in the RMP version 0.2:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Drug abuse, misuse, diversion and dependence Cardiovascular disorders (arterial hypertension, arrhythmias, cardiac ischaemia, and cardiotoxicity) Psychiatric disorders (including depression, suicidality, aggression, psychosis) Growth and development restriction
Important potential risks	None.
Missing information	Long-term safety (cardiovascular, growth, neurological, cognition and psychiatric)

The summary of safety concerns is considered acceptable.

Pharmacovigilance Plan

No pharmacovigilance plan on additional Pharmacovigilance activities have been proposed by the Applicant, which is accepted. Routine pharmacovigilance is considered acceptable.

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Drug abuse, misuse, diversion and dependence	Routine risk minimisation measures: SmPC section 4.4 PL section 2 Additional risk minimisation measures: Guide for Healthcare Professionals Guide for Carers	None
Cardiovascular disorders	Routine risk minimisation measures:	None
	SmPC sections 4.3, 4.4 and 4.8 PL section 2 and 4 Additional risk minimisation measures: Guide for Healthcare Professionals	
Psychiatric disorders	Routine risk minimisation measures: SmPC section 4.3, 4.4 and 4.8 PL section 2 and 4 Additional risk minimisation measures: Guide for Healthcare Professionals	None
Growth and development restriction	Routine risk minimisation measures: SmPC section 4.4 and 4.8 PL section 2 and 4 Additional risk minimisation measures: Guide for Healthcare Professionals	None

The proposed additional risk minimisation activities are acceptable.

Summary of the RMP

The submitted Risk Management Plan, version 0.2 signed 4 January 2023 is considered acceptable.

It is endorsed that the company proposes to implement additional risk minimisation measures according to VI.3. The use of additional RMMs through an educational programme is agreed and considered a condition for the marketing authorisation.

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 MPA;
- 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.

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

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The present Marketing Authorization Application for Dexamfetamine sulfate 5 mg, 10 mg, 20 mg tablets, is submitted as per Article 10a of Directive 2001/83/EC, i.e., a well-established use (WEU), application.

The Applicant has established a sufficient bridge between the dexamfetamine IR formulations used to support clinical efficacy/safety and their own formulation.

The data from the presented main studies in combination with the additional supportive studies could be considered to be sufficient for proving the efficacy of dexamfetamine for treatment of children and adolescents 6-17 years of age.

The applicant has furthermore presented a sufficient safety overview of clinical data with original references investigating cardiovascular risks, effect on energy intake, body weight and growth, effect on mood and emotion, effect on sleep, and drug abuse, all relevant for dexamfetamine treatment in children and adolescents.

Please also see requested risk minimisation measures below.

In conclusion, the benefit/risk of this product is considered positive and the application is thus found approvable.

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

The marketing authorization holder (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.

Additional risk minimisation measures (including educational material)

The educational material should contain the following key elements:

- The Summary of Product Characteristics
- Guide for healthcare professionals
  - Relevant information of the safety concern(s) addressed by the aRMM (e.g. seriousness, severity, frequency, time to onset, reversibility of the AE as applicable)

- Details of the population at higher risk for the safety concern addressed by the aRMM (e.g. contraindications, risk factors, increased risk by interactions with certain medicine)
- Details on how to minimise the safety concern addressed by the aRMM through appropriate monitoring and management (e.g. what to do, what not do, and who is most likely to be impacted according to different scenarios, like when to limit or stop prescribing/ingestion, how to administer the medicine, when to increase/decrease the dosage according to laboratory measurements, signs and symptoms)

- The patient information pack:
- Patient information leaflet
- Patient/carer guide:
  - A description of the correct use of Dexatin name and the risk for drug misuse, abuse, diversion and dependence associated with its use

VII. APPROVAL

The mutual recognition procedure for Dexatin, 5 mg, 10 mg, 20 mg, Tablet was positively finalised on 2023-11-21.

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

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