CBG MEB

Public Assessment Report

Scientific discussion

Dexamfetaminesulfaat DMB 5 mg, tablets

(dexamfetamine sulphate)

NL License RVG: 115446

Date: 4 April 2018

This module reflects the scientific discussion for the approval of Dexamfetaminesulfaat DMB 5 mg, tablets. The marketing authorisation was granted on 13 May 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Dexamfetaminesulfaat DMB 5 mg, tablets from Tiofarma B.V.

The product is indicated as part of a comprehensive treatment programme for attention-deficit/hyperactivity disorder (ADHD) in children and adolescents aged 6 to 17 years when response to previous methylphenidate treatment is considered clinically inadequate. A comprehensive treatment programme typically includes psychological, educational and social measures.
Diagnosis should be made according to DSM-5 criteria or the guidelines in ICD-10 and should be based on a comprehensive multidisciplinary evaluation of the patient.
Dexamfetamine is not indicated in all children with ADHD and the decision to use dexamfetamine 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.
Treatment should be under the supervision of a specialist in childhood and/or adolescent behavioural disorders
A comprehensive description of the indications and posology is given in the SmPC.

This national procedure concerns a generic application claiming similarity with reference medicinal product Dexamfetamine sulphate 5 mg tablets from MAH Auden Mckenzie (Pharma Division) Ltd. since 6 June 2008 in the United Kingdom. The early originator was Dexedrine tablets of MAH Smith Kline & Franch (licencing in 1985, renewal in 1990). The original dossier and license was later transferred to MAH Auden Mackenzie.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Dexamfetaminesulfaat DMB is a white to off-white, round tablets with the inscription ‘DAE 5’. Each tablet contains 5 mg dexamphetamine sulphate

The tablets are packed in PVC/PVDC and aluminium blisters

The excipients are: stearic acid (E570), acacia gum (E414), lactose monohydrate, light liquid paraffin, maize starch, sucrose, talc (E553 B) and purified water

II.2 Drug Substance

The active substance is dexamphetamine sulphate, an established active substance, described in the United States Pharmacopeia (USP) and British Pharmacopoeia (BP), however not described the European Pharmacopoeia (Ph. Eur.). It is a white to off-white solid, soluble in water, slightly soluble in alcohol and insoluble in ether. The synthetic process uses racemic amphetamine. One form is isolated and processed to become the S enantiomer of amphetamine sulfate. The active substance does not show polymorphism.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The active substance is manufactured by a wet granulation manufacturing process which is adequately described. The starting material is acceptable as it is a sufficiently simple molecule and the process steps from hereon downstream described include the optical conversions leading to the defined, optically active drug substance.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monographs in the BP and USP. Batch analytical data demonstrating compliance with this specification have been provided for 2 batches.

Stability of drug substance
Stability data on the active substance have been provided for 7 batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 48 months when stored in the proposed packaging without any special storage conditions.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The formulation is qualitatively and quantitatively identical to the reference product. Both products have identical formulations, manufacturing processes and quality control. Therefore, no development studies with the formulation are performed.
No bioequivalence study has been performed; a biowaiver has been proposed based on *in vitro* equivalence data with the reference product, including comparative dissolution data. The results of the dissolution study show that the product exhibit a high solubility. All profiles show more than 85% of dexamphetamine sulphate released within 15 minutes in water and in media at pH 1.0, 4.5 and 6.8; f2 calculations are therefore not necessary. Overall, the pharmaceutical development is considered acceptable.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines. It is considered to be a standard process, comprising wet granulation followed by tablet processing. Process validation data on the product have been presented for 2 production scaled batches in accordance with the relevant European guidelines.

Control of excipients
All excipients comply to the Ph. Eur. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, disintegration time, mean weight, uniformity of mass, hardness, friability, identification, assay, related substances, uniformity of dosage units, microbial purity and dissolution. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from 2 batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for two batches in accordance with applicable European guidelines. On basis of the data submitted, a shelf life was granted of 6 months when stored in the proposed blister. The labelled storage condition is: “Store below 25°C”. The results of the photostability study showed that the product can be considered light resistant.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
The excipients lactose monohydrate and stearic acid are of animal origin. The milk as source for the lactose monohydrate is collected from healthy animals in the same conditions as milk collected for human consumption. The stearic acid is derived from tallow category 3 source and complies to the TSE guideline/directives. Therefore, compliance with the Note for Guidance on Minimising the Risk of

Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Dexamfetaminesulfaat DMB has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Dexamfetaminesulfaat DMB 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.2 Discussion on the non-clinical aspects

This product is a generic formulation of Dexamfetamine sulphate 5 mg tablets which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Dexamphetamine sulphate is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the MEB agrees that no further clinical studies are required.

IV.2 Pharmacokinetics

Biowaiver
No bioequivalence study has been carried out. Instead, a biowaiver was requested. *In vitro* comparison demonstrate the equivalence of the test product Dexamfetaminesulfaat DMB 5 mg, tablets (Tiofarma BV, NL) and the reference product Dexamfetamine sulphate 5 mg tablets (Auden Mackenzie, UK). Since the proposed generic medical product and the reference medicinal product are manufactured at the same site and are qualitatively and quantitatively identical, a biowaiver has been granted.

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 Dexamfetaminesulfaat DMB.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Drug abuse, misuse and diversion • Cardiac and cardiovascular disorders incl. increased blood

	pressure / hypertension, arrhythmias • Cardiomyopathy • Increased risk of depression • Increased risk of aggressive / hostile behaviour • Psychotic reactions e.g. hallucination (visual, auditory, skin sensation), mania • Withdrawal syndrome • Growth and developmental, e.g. anorexia • Serious skin reactions
Important potential risks	• Ischaemic / serious cardiovascular events, e.g. myocardial infarction, sudden death, cyanosis, QT prolongation • Cerebrovascular disorders e.g. stroke (ischaemic and haemorrhagic) • Migraine • Raynauds syndrome • Suicidal ideation • Tics / Tourette / dystonia • Repetitive behaviours • Seizures • Growth and development; e.g. sexual maturation, neonatal growth (via lactation) • Neonatal toxicity e.g. cardio-respiratory toxicity • Carcinogenicity • Off-label use
Missing information	• Long term safety (cardiovascular, growth, neurological, cognition and psychotic) • pregnancy

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product. No new clinical studies were conducted. The product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PIL) has been performed on the basis of a bridging report making reference to Amfexa 5 mg tabletten (N License RVG 110336). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Dexamfetaminesulfaat DMB 5 mg, tablets has a proven chemical-pharmaceutical quality and is a generic form of Dexamfetamine sulphate 5 mg tablets. This is a well-known medicinal product with an established favourable efficacy and safety profile

Since both the reference and current product are manufactured at the same site and are qualitatively and quantitatively identical, no bioequivalence study is deemed necessary. A biowaiver has been granted.

In the Board meeting of 2 April 2015 , the proposed indication was discussed. After several changes, the Board considered the final indication approvable.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Dexamfetaminesulfaat DMB with the reference product, and have therefore granted a marketing authorisation. Dexamfetaminesulfaat DMB was authorised in the Netherlands on 13 May 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
Variation A.1 Variation A.5.a	– Change in the name and/or address of the marketing authorisation holder – Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites); the activities for which the manufacturer/importer is responsible include batch release				