CBG MEB

Public Assessment Report

Scientific discussion

Betahistine Sandoz 8 mg, 16 mg and 24 mg, tablets

(betahistine dihydrochloride)

NL/H/3706/001-003/DC

Date: 4 January 2019

This module reflects the scientific discussion for the approval of Betahistine Sandoz 8 mg, 16 mg and 24 mg, tablets. The procedure was finalised on 23 January 2018. 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 Member States have granted a marketing authorisation for Betahistine Sandoz 8 mg, 16 mg and 24 mg, tablets from Sandoz B.V.

The product is indicated for the treatment of Menière's syndrome, symptoms of which may include vertigo (often associated with nausea and/or vomiting), tinnitus and hearing loss.

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

This decentralised procedure concerns a generic and hybrid application claiming essential similarity with the innovator product Betaserc 8 mg tablets which has been registered Abbott Healthcare Products since 8 July 1970.

The concerned member state (CMS) involved in this procedure was Germany.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC for the for the 8 mg and 16 mg strength. For the 24 mg strength the application is made following the procedure according to Directive 2001/83/EC as amended, article 10(3) so called hybrid application in The Netherlands (RMS) and in CMS Germany according article 10(1).

II. QUALITY ASPECTS

II.1 Introduction

- Betahistine Sandoz 8 mg is a white, round, flat uncoated tablet and plain on both sides. Each tablet contains 8 mg of betahistine dihydrochloride.
- Betahistine Sandoz 16 mg is a white, round, biconvex, uncoated tablet and scored on one side with embossing "I" on either sides of the score and plain on the other side. Each tablet contains 16 mg of betahistine dihydrochloride. The tablet can be divided into equal doses.
- Betahistine Sandoz 24 mg is a white, round, biconvex, uncoated tablet and scored on one side with embossing "II" on either sides of the score and plain on the other side. Each tablet contains 24 mg of betahistine dihydrochloride. The tablet can be divided into equal doses.

The tablets are packed in PVC/PVDC/Al foil blisters or HDPE bottles with a PP screw closure with an induction seal liner.

The excipients are: citric acid anhydrous, microcrystalline cellulose (PH-102), mannitol, silica, colloidal anhydrous and talc.

II.2 Drug Substance

The active substance is betahistine dihydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Betahistine dihydrochloride is very soluble in water, soluble in ethanol (96%), practically insoluble in 2-propanol. The active substance is very hygroscopic. Polymorphism is not known and has not been observed.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and is in line with the CEP. Batch analytical data demonstrating compliance with this specification have been provided for 3 full scaled batches.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

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 choice of excipients is justified and their functions explained. Adequate data has been provided, in accordance with the Ph. Eur. test on subdivision of the 16 mg and 24 mg tablets, which demonstrates that the tablets can be broken into two equal halves at release and at the end-of-shelf life.
A bioequivalent study has been performed between the 24 mg test product and the 24 mg reference product. The comparative dissolution data provided for the 24 mg tablets support the results obtained in the bioequivalence study. To support the Biowaiver of Strength for the 16 and 8 mg tablets, comparative dissolution profiles have been provided in accordance with the Guideline on the Investigation of Bioequivalence.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines. It is a straight forward and common process, namely the tablets are manufactured by a wet-granulation technique. Process validation data on the product have been presented for three pilot scaled batches in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
All excipients comply with the Ph. Eur. The 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 description, identification, dissolution, water content, related substances, assay, uniformity of content and microbial limits. 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 three pilot scaled 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 three pilot scaled batches stored at 25°C/60% RH (36 months), 30°/65% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. A photostability study showed that the product is not sensitive to light. Consequently, it is acceptable that no additional storage condition concerning light has been adopted. On basis of the data submitted, a shelf life was granted of 36 months without special storage conditions. Sufficient data has been provided to support the in-use period of the HDPE container for 70 days.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Betahistine Sandoz 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 Betahistine Sandoz 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 Betaserc 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 member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Betahistine dihydrochloride 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 member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Betahistine Sandoz 24 mg, tablets (Sandoz B.V., NL) is compared with the pharmacokinetic profile of the reference product Betaserc 24 mg tablets (Abbott Healthcare Products, Finland).

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

Betahistine has a high permeability, high solubility and linear pharmacokinetics. In principle, a biowaiver for the additional strengths can be applied if bioequivalence can be shown between the 24 mg of the test and reference product and the following criteria according to the Guideline on the investigation of bioequivalence are met:

a) the pharmaceutical products are manufactured by the same manufacturing process
b) the qualitative composition of the different strengths is the same
c) the composition of the different strengths are quantitatively proportional
d) in-vitro dissolution data demonstrating similarity between the two strengths.
e) pharmacokinetic linearity of the drug.

In this case all requirements have been met and therefore the biowaiver has been accepted.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 26 healthy male subjects, aged 23-43 years. Each subject received a single dose (24 mg) of one of the 2 betahistine dihydrochloride formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 hours after administration of the products.

The design of the study is acceptable. According to the SmPC, the tablets should be taken preferably with food. This advice is based on improvement of gastric tolerability. For immediate release tablets, fasting is the most sensitive condition to measure bioequivalence. It is therefore accepted that the study was performed under fasted conditions.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

One subject withdrew from the study. Therefore, 25 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of betahistine under fasted conditions.

Treatment N=25	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	4069 ± 905	4157 ± 955	826 ± 170	0.53 (0.33 - 2.5)
Reference	3976 ± 897	4068 ± 949	778 ± 170	0.75 (0.50 - 2.5)
***Ratio (90% CI)**	1.02 (0.99 – 1.05)	--	1.07 (0.99 – 1.15)	--
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity **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 concentration				

**ln-transformed values*

Conclusion on bioequivalence studies:

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Betahistine Sandoz is considered bioequivalent with Betaserc.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 Betahistine Sandoz.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Hypersensitivity reactions

	- Clinical intolerance in bronchial asthma patients - Gastrointestinal disorders - Off-label use (including pheochromocytoma)
Important potential risks	None
Missing information	- Use in paediatric population (<18 years of age) - Use in pregnancy and lactation

The member states 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 Betaserc. No new clinical studies were conducted. 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. This generic medicinal product can be used instead of the reference product.

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 test consisted of: a pilot test followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. 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

Betahistine Sandoz 8 mg, 16 mg and 24 mg, tablets from Sandoz B.V have a proven chemical-pharmaceutical quality and are generic and hybrid forms of Betaserc 8 mg tablets. Betaserc 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.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Betahistine Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 January 2018.

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