COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Betahistine 2Hcl Accord 24 mg, tablets

(betahistine dihydrochloride)

NL/H/4000/001/DC

Date: 30 June 2020

This module reflects the scientific discussion for the approval of Betahistine 2Hcl Accord 24 mg, tablets. The procedure was finalised at 15 November 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 2Hcl Accord 24 mg, tablets, from Accord Healthcare Ltd.

The product is indicated for the treatment of Ménière's disease defined by the following three key symptoms

- Vertigo (with nausea/vomiting),
- Hearing loss (hard of hearing)
- Tinnitus

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

This mutual recognition procedure concerns a generic application claiming essential similarity with the product Betaserc 24 mg tablets (originally marketed by Abbott Ges.m.b.H, now BGP Products Ges. M.b.h.), authorised in Austria in 2001. In addition, reference is made to Betaserc authorisations in the individual member states.

The MAH already holds marketing authorisations for Betahistine Accord 8 mg tablet, and Betahistine Accord 16 mg tablet in some countries. Both products were granted an MA in the RMS on 16 February 1999. Dossier and the product information (SmPC, PL, Labelling) were harmonised following a mutual recognition procedure in 2011 (NL/H/2045/001-002/MR).

The concerned member states (CMS) involved in this procedure were Austria, Bulgaria, Czech Republic, Germany, Estonia, Spain, Finland, France, Italy, Lithuania, Latvia, Poland, Romania, Slovenia, Slovak Republic and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Betahistine 2Hcl Accord is a white to off white, round, biconvex, uncoated tablet with inscription 'GRI' on one side and a break line on other side. Each tablet contains 24 mg betahistine dihydrochloride. The tablet can be divided into equal doses.

The tablets are packed in PVC-PVdC/Aluminium blisters.

The excipients are: lactose monohydrate, povidone K25, anhydrous citric acid (E330), maize starch, microcrystalline cellulose, crospovidone (Type B) and hydrogenated vegetable oil.

II.2 Drug Substance

The active substance is betahistine dihydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Betahistine dihydrochloride is a white or slightly yellow powder, very hygroscopic. It is very soluble in water, soluble in ethanol (96%), practically insoluble in 2-propanol. The active substance does not possess asymmetric carbon atoms. No polymorphs are known.

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 Ph.Eur.

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 meets the requirements of the monograph in the Ph.Eur. and additional requirements listed on the CEP. Batch analytical data demonstrating compliance with this specification have been provided for five 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.

Two bioequivalence studies have been provided. Comparative dissolution studies were performed of the test and reference product used in the bioequivalence studies, in the media as recommended in the Guideline of Bioequivalence. The results show similar dissolution profiles between the proposed Betahistine dihydrochloride 24 mg tablets and the reference product as used in the bio-equivalence study.

Manufacturing process

The manufacturing process consists of sifting, dry mixing, granulation, drying, blending, lubrication and compression and has been validated according to relevant European guidelines. Process validation data on the product have been presented for two batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with their corresponding Ph.Eur. or British Pharmacopoeia monograph. 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 description, average weight of tablet, identification, resistance to crushing, loss on drying, subdivision of tablets, uniformity of dosage units, dissolution, related substances, assay and microbial examination. 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 two batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

The conditions used in the stability studies are according to the ICH stability guideline. Based on the provided stability data, the proposed shelf-life of 2 years and storage condition “This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture.” are acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

None of the excipients used in this formulation are of human or animal origin except lactose monohydrate. Lactose is derived from milk, which is sourced from healthy animals in the same conditions as milk collected for human consumption. There is no risk of transmissible spongiform encephalopathy (TSE) and bovine spongiform encephalopathy (BSE) associated with the excipients.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Betahistine 2Hcl Accord 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 2Hcl Accord 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 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 a bioequivalence study with the 24 mg tablets strength. The studies are discussed below.

IV.2 Pharmacokinetics

The MAH conducted bioequivalence studies in which the pharmacokinetic profile of the test product Betahistine 2 HCl Accord (Accord Healthcare B.V., NL) is compared with the pharmacokinetic profile of the reference product Betaserc (Abbott Healthcare SAS, France.).

Design
An open label, balanced, randomised, two-treatment, two-period, two-sequence, single dose, two-way crossover, oral bioequivalence study was carried out under fasted conditions in 35 healthy adult male subjects. Each subject received a single dose (24 mg) of one of the 2 betahistine formulations. After an overnight fast of at least 10 hours, the subjects were

orally administered the single dose sitting posture with 240 mL of water at an ambient temperature.
A washout period of 6 days was maintained between the successive dosing days.

A total of 22 venous blood samples were collected in each period at pre-dose and 0.167, 0.333, 0.50, 0.667, 0.833, 1.00, 1.167, 1.333, 1.50, 1.75, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00 and 24.00 hours post dose administration.
The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

After absorption, betahistine is almost completely metabolised into the inactive metabolite 2-pyridylacetic acid (2-PAA). Plasma samples were therefore analysed for the inactive metabolite 2-PAA content. Measuring the metabolite instead of the parent drug is justified because no unchanged betahistine has been detected in human plasma or urine.

According to the SPC, the tablets should be taken with food. This advice is based on improvement of gastric tolerability. According to the literature food does not interact with absorption. 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.

Results
Two subjects were withdrawn from the study on medical grounds and two subjects withdrew their consent. Therefore, a total of 31 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 inactive metabolite 2-PAA under fasted conditions.

Treatment N=31	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**	**$t_{1/2}$ (h)**
Test	3776.306 ± 712.066	3894.245 ± 729.565	757.631 ± 124.211	0.833 (0.500-1.500)	4.35 ± 0.88
Reference	3705.671 ± 683.395	3829.039 ± 694.085	735.420 ± 111.961	0.667 (0.333 – 1.500)	4.29 ± 0.93
***Ratio (90% CI)**	1.02 (0.99 – 1.05)	1.02 (0.99 – 1.05)	1.03 (0.98 – 1.08)	---	---
CV (%)	6.9	6.8	11.0	---	---

$AUC_{0-\infty}$	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
$t_{1/2}$	half-life
CV	coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Betahistine 2Hcl Accord 24 mg, tablets is considered bioequivalent with Betaserc 24 mg tablets.

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 2Hcl Accord.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	- Hypersensitivity reactions; anaphylaxis and angioneurotic oedema
Important potential risks	None
Missing information	- Use in children below 18 years of age - Use in pregnancy and breastfeeding

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 No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Betaserc 24 mg tablets (for content) and Solifenacin succinate 5 and 10 mg film-coated tablets (for layout). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Betahistine 2Hcl Accord 24 mg, tablets has a proven chemical-pharmaceutical quality and is a generic form of Betaserc 24 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 2Hcl Accord with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 November 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
NL/H/4000/IA/001/G	- Replacement or addition of a manufacturer responsible for importation and/or batch release - Updated certificate from an already approved manufacturer	yes	09-04-2020	Approved	-
NL/H/4000/IA/002/G	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product	yes	12-03-2020	Approved	-
NL/H/4000/001/IB/003	To revise the In-process limit of thickness & as a consequential change to the In-process limit of Resistance to crushing (Hardness) for Betahistine dihydrochloride 24 mg tablets.	No	25-06-2020	Approved	-