COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Betahistine Amarox 8 mg, 16 mg and 24 mg, tablets
(betahistine dihydrochloride)

NL/H/5212/001-003/DC

Date: 24 March 2023

This module reflects the scientific discussion for the approval of Betahistine Amarox 8 mg, 16 mg and 24 mg, tablets. The procedure was finalised on 7 January 2022. 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
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ERP	European Reference Product
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
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 Amarox 8 mg, 16 mg and 24 mg, tablets, from Amarox Pharma B.V.

The product is indicated for the treatment of vertigo, tinnitus and hearing loss associated with Ménière's syndrome.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the European Reference Products (ERP) Betaserc 8, tablet, 8 mg (RVG 05852) and Betaserc 16, tablets, 16 mg (RVG 13612), registered in The Netherlands by Mylan Healthcare B.V. since 8 July 1970 and 1 February 1989, respectively. For the 24 mg strength, the ERP is Betaserc 24, tablets, 24 mg, registered in France since 28 December 2000 by Mylan Medical SAS (CIS 62972963).

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

II. QUALITY ASPECTS

II.1 Introduction

Betahistine Amarox is produced in three strengths:
The 8 mg strength are white to off-white, round, flat, bevel-edge tablets debossed with '8' on one side and 'B' on other side. Each tablet contains 8 mg betahistine dihydrochloride equivalent to 5.21 mg betahistine.
The 16 mg strength are white to off-white, round, biconvex, scored tablets debossed with '16/B' on one side and plain on other side, which can be divided into equal doses. Each tablet contains 16 mg betahistine dihydrochloride equivalent to 10.42 mg betahistine.
The 24 mg strength are white to off-white, round, biconvex, scored tablets debossed with '24/B' on one side and plain on other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses. Each tablet contains 24 mg betahistine dihydrochloride equivalent to 15.63 mg betahistine.

The three tablet strengths are dose proportional.

The excipients are: microcrystalline cellulose (E460), mannitol (E421), colloidal anhydrous silica (E551), citric acid (E330) and talc (E553b).

The tablets are packed in Alu (aluminium)-PVC/PVdC blister packs or Alu-Alu blister packs.

II.2 Drug Substance

The active substance is betahistine dihydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white powder and is very soluble in water. It has no chiral centres and shows no polymorphism.

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 of the CEP. An adequate justification is provided for not including particle size distribution testing in the drug substance specification. An additional test for microbiological quality of the drug substance is included. Batch analytical data demonstrating compliance with this specification have been provided for three full scale batches.

Stability of drug substance

The active substance is stable for 4 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.

Dissolution was compared between the test and reference products. The development and the discriminatory power of the quality control (QC) dissolution test method are adequately discussed. Comparative dissolution profiles between the reference product and the final formulation of the test product have been performed at three pH levels for all strengths. The dissolution was very fast (>85% in 15 minutes) for both reference and test products, of all strengths at all tested pH levels. Similarity is confirmed and the biobatch (24 mg) is considered acceptable from a pharmaceutical point of view. A bioequivalence study has been performed with the highest strength (24 mg). A biowaiver of strengths was requested for the 8 mg and 16 mg tablets. In view of composition of the three strengths (quantitatively proportional) and

the provided dissolution profiles, showing that all strengths have very fast dissolution, the biowaiver of strengths is acceptable from a pharmaceutical point of view.

A risk assessment on elemental impurities is adequately performed. No additional control for elemental impurities at release of drug product is necessary.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three batches of common blend in accordance with the relevant European guidelines. Storage conditions and packaging for holding of intermediates are sufficiently described. The product is manufactured using conventional manufacturing techniques. Breakability of the 16 mg tablets into two equal halves was confirmed in the process validation studies.

Control of excipients

All excipients are reported in a Ph. Eur. monograph. For their specification, analytical methods and validation, reference is made to the Ph. Eur. Several functionality related characteristics are included in the specifications of the excipients and are sufficiently justified. For purified water in-house specifications and methods are established, which cover for all parameters mentioned in the Ph. Eur. monograph of purified water with equal or more stringent limits. All 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, identity, average mass, dose uniformity, dissolution, assay, related substances, microbiological purity, loss on drying, subdivision of tablets (only for the 16 mg strength). Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Release and shelf-life specifications are identical except for the limits for total impurities and Loss on drying.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been submitted. The risk evaluation is adequately performed and it was agreed by the member states that no risk is identified and no further control on nitrosamines is necessary.

Two kinds of blisters are used: PVC/PVdC-Alu blisters and Alu/Alu blisters. Sufficient information is provided about both commercial packaging systems and the packaging for bulk tablets.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three validation batches of each strength, 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 batches stored at 25°C/ 60% RH (24 months) and 40°C/75% RH (6 months). The batches were stored in both proposed blister

packs. The stability was tested in accordance with the ICH stability guideline, demonstrating the stability of the product for 36 months without special storage conditions.

Photostability studies according to Guideline ICH Q1B have been performed and show that the product is not sensitive to light. Based on this and the accelerated conditions studies results, a shelf life of 3 years was granted with storage condition 'This medicinal product does not require any special storage conditions'.

Specific measures concerning 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 Amarox 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 Amarox is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was 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 was made to the preclinical data obtained with the ERP. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 member states agreed that no further clinical studies are required, besides the 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 Amarox 24 mg, tablets (Amarox Pharma B.V., the Netherlands) was compared with the pharmacokinetic profile of the reference product Betaserc 24, tablets, 24 mg, (Mylan Medical SAS, France).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

The following general requirements must be met where a waiver for additional strength is claimed, according to the EMA Bioequivalence guideline:

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 strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The additional strengths are manufactured by the same process, and they are qualitatively similar and quantitatively proportional. The dissolution was investigated according to the EMA Bioequivalence guideline. The calculated f_2 similarity factor values were within criteria (>50%). An f_2 value between 50 and 100% suggests that the dissolution profiles are similar.

Bioequivalence studies

Design

A open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study was carried out under fasting conditions in 36 healthy male subjects, aged 21-43 years. Each subject received a single dose (24 mg) of one of the two betahistine formulations. The tablet was orally administered with 240 mL water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 9 days.

Blood samples were collected pre-dose and at 0.167, 0.333, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 14 and 16 hours after administration of the products.

The design of the study is acceptable.

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
All 36 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of betahistine dihydrochloride, 24 mg under fasted conditions.

Treatment N=36	**AUC_{0-t}** (ng.h/mL)	**$AUC_{0-\infty}$** (ng.h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)
Test	3805.456 ± 721.644	4107.903 ± 885.413	736.353 ± 123.051	0.75 (0.33 - 1.25)
Reference	3849.039 ± 665.462	4162.778 ± 834.636	715.250 ± 108.382	0.75 (0.50 - 2.00)
***Ratio (90% CI)**	0.99 (0.96 - 1.01)	--	1.03 (0.99 – 1.07)	--

$AUC_{0-\infty}$	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 the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study
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 study Betahistine Amarox 24 mg, tablets is considered bioequivalent with Betaserc 24, tablets (24 mg).

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).

The results of the bioequivalence study with the 24 mg formulation can be extrapolated to the 8 mg and 16 mg strengths, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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 Amarox.

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

Important identified risks	• Hypersensitivity reactions (including anaphylaxis)
Important potential risks	None
Missing information	• Use in pediatric 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 European reference product Betaserc. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the highest strength product is similar to the pharmacokinetic profile of the reference product. A biowaiver was granted for the additional two strengths. Risk management is adequately addressed. These generic medicinal products can be used instead of the reference products.

V. USER CONSULTATION

The package leaflet (PL) 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 language used for the purpose of user testing the PL was English. The test consisted of a pilot test with two participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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 Amarox 8 mg, 16 mg and 24 mg, tablets have a proven chemical-pharmaceutical quality and are generic forms of Betaserc 8, 16 and 24, tablets (8 mg, 16 mg and 24 mg).

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 Amarox with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 7 January 2022.

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/5212/1-3/IA/001	Change in pack size of the finished product (within the range of the currently approved pack sizes)	Yes	25-8-2022	Non approval	Submitted under incorrect classification
NL/H/5212/1-3/IB/002/G	Change in pack size of the finished product (within and outside the range of the currently approved pack sizes)	Yes	02-11-2022	Approval	N/A