

IPAR



**Public Assessment Report for a
Medicinal Product for Human Use**

Scientific Discussion

Betahistine dihydrochloride 8 mg Tablets
Betahistine dihydrochloride
PA22871/017/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Betahistine dihydrochloride 8 mg, 16 mg and 24 mg tablets, from Azure Pharmaceuticals Ltd on for the treatment of vertigo, tinnitus and hearing loss associated with Meniere's syndrome.

HPRA acted as RMS in this decentralised (DCP) procedure, and Malta was the CMS.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Betahistine dihydrochloride 8 mg 16 mg 24 mg Tablets
Name(s) of the active substance(s) (INN)	Betahistine dihydrochloride
Pharmacotherapeutic classification (ATC code)	N07CA01
Pharmaceutical form and strength(s)	8mg 16mg 24mg Tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA22871/017/001-003
Marketing Authorisation Holder	Azure Pharmaceuticals Ltd
MRP/DCP No.	IE/H/1107/001-003/DC
Reference Member State	IE
Concerned Member State	MT

II. QUALITY ASPECTS**II.1. Introduction**

This application is for Betahistine dihydrochloride 8 mg, 16 mg and 24 mg Tablets.

II.2 Drug substance

The active substance is betahistine dihydrochloride, an established active substance described in the European Pharmacopoeia, which is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product**P.1 Composition**

Each tablet contains 8 mg, 16 mg, or 24 mg of the active substance betahistine dihydrochloride. The excipients in the medicinal products are listed in section 6.1 of the SmPC. A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur. / EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Betahistine dihydrochloride 8 mg, 16 mg and 24 mg Tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Betaserc 8mg, 16mg and 24mg on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Ecotoxicity/environmental risk assessment

Betahistine 8mg, 16mg and 24 mg tablets is intended for generic substitution. An increased exposure to the environment is not anticipated and the justification provided for the absence of specific studies in the environmental risk assessment is acceptable.

III.3 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of Betahistine dihydrochloride are well known. As Betahistine dihydrochloride is a widely used, well-known active substance, the applicant has not provided additional nonclinical studies and further studies are not required. An overview based on literature review of the pre-clinical pharmacology, pharmacokinetics and toxicology was provided and is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

Betahistine is a well known active substance with established efficacy and tolerability.

The content of the SmPCs approved during the decentralised procedure is in accordance with that accepted for the reference products, Serc 8mg, Serc16mg and Betaserc 24mg Tablets by Mylan IRE Healthcare Limited.

For this generic application, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test Betahistine dihydrochloride 24mg tablet is compared with the pharmacokinetic profile of the reference product Betaserc 24mg tablets by Mylan IRE Healthcare Limited. The study was an open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study in healthy, adult, human subjects under fasting conditions to compare and evaluate the oral bioavailability and to assess the bioequivalence of test formulation and reference formulation. Based on the pharmacokinetic parameters of the 2-pyridyl acetic acid metabolite of betahistine the reference tablet Betaserc 24mg tablets and the test Betahistine dihydrochloride 24mg tablet are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The 8mg and 16mg betahistine dihydrochloride tablets are dose proportional with the 24 mg strength. The pharmacokinetics of betahistine and of the metabolite 2-PAA are linear in the therapeutic range. Therefore, the results of the bioequivalence study performed with the 24mg tablet apply also to the 8mg and 16mg tablets, and there is no requirement for studies in the two lower strengths.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the study conducted.

IV.2 Pharmacokinetics

As this is a generic application, only a bioequivalence study has been submitted. The known pharmacokinetics of betahistine is outlined below and are also described in the SmPC.

Absorption:

Orally administered betahistine is readily and almost completely absorbed from all parts of the gastro-intestinal tract. After absorption, the drug is rapidly and almost completely metabolized into 2-pyridylacetic acid. Plasma levels of betahistine are very low. Pharmacokinetic analyses are therefore based on 2-PAA measurements in plasma and urine.

Under fed conditions C_{max} is lower compared to fasted conditions. However, total absorption of betahistine is similar under both conditions, indicating that food intake only slows down the absorption of betahistine.

Distribution:

The percentage of betahistine that is bound by blood plasma proteins is less than 5 %.

Biotransformation:

After absorption, betahistine is rapidly and almost completely metabolized into 2-PAA (which has no pharmacological activity). After oral administration of betahistine the plasma (and urinary) concentration of 2-PAA reaches its maximum 1 hour after intake and declines with a half-life of about 3.5 hours.

Excretion:

2-PAA is readily excreted in the urine. In the dose range between 8 and 48 mg, about 85% of the original dose is recovered in the urine. Renal or faecal excretion of betahistine itself is of minor importance.

Linearity:

Recovery rates are constant over the oral dose range of 8–48 mg indicating that the pharmacokinetics of betahistine are linear, and suggesting that the involved metabolic pathway is not saturated.

IV.3 Pharmacodynamics

As this is a generic application no new pharmacodynamic data were required, and the known pharmacodynamic behaviour of betahistine is outlined the SmPC.

IV.4 Clinical Efficacy

Not applicable as this is a generic application.

IV.5 Clinical Safety

Safety review of the bioequivalence study provided did not raise any new or significant safety concerns.

Risk Management Plan

The Applicant 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 8 mg, 16 mg and 24 mg Tablets.

Summary of safety concerns

Important identified risks	Hypersensitivity reactions (including anaphylaxis)
Important potential risks	None
Missing information	Use in paediatric population (<18 years of age) Use in pregnancy and lactation

Routine pharmacovigilance activities and routine risk minimisation measures are considered sufficient to identify, characterise and minimise the risks of the product in the proposed indication.

PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

IV.6 Discussion on the clinical aspects

As this approval concerns a generic application, there are no new efficacy or safety studies required as the applicant can refer to the data of the reference medical products. Instead, the demonstration of bioequivalence is pivotal to the assessment and has already been described.

V. OVERALL CONCLUSIONS

Betahistine (8mg, 16mg and 24mg) is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile. From a quality perspective the overall assessment of Betahistine Dihydrochloride tablets is favourable. Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPCs are consistent with those of the reference products.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Betahistine Dihydrochloride 8mg 16mg 24mg Tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

06.10.2026