Public Assessment Report

UK National Procedure

Betahistine dihydrochloride 8 mg tablets
Betahistine dihydrochloride 16 mg tablets
Betahistine dihydrochloride 24 mg tablets

PL 20117/0236
PL 20117/0237
PL 20117/0238

Morningside Healthcare Ltd
LAY SUMMARY

This is a summary of the public assessment report (PAR) for Betahistine dihydrochloride 8 mg, 16 mg and 24 mg tablets. These medicinal products will be collectively referred to as Betahistine tablets in the remainder of this summary.

This summary explains how Betahistine tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Betahistine tablets.

For practical information about using Betahistine tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Betahistine tablets and what are they used for?
Betahistine tablets are generic medicines. This means that Betahistine tablets are similar to reference medicines already authorised in the European Union (EU) called Serc-8, Serc-16 and Betaserc 24.

Betahistine tablets are used for the treatment of Menière’s syndrome, symptoms of which may include dizziness (often associated with feeling sick and/or being sick), ringing in the ear (tinnitus) and hearing loss.

How do Betahistine tablets work?
Betahistine is similar to histamine, a substance which is found naturally in the human body. Betahistine works by reducing signals in the balance centre of the brain which lead to dizziness.

How are Betahistine tablets used?
The usual dose is 24 mg–48 mg betahistine daily, divided into three equal doses. The daily dose should not exceed 48 mg.

The tablets are usually taken over several months as it may take a while before they start to work.

The tablets should be taken with a glass of water during or after meals.

Betahistine tablets should not be used by children and adolescents below the age of 18 years.

Betahistine tablets can only be obtained with a prescription.

What benefits of Betahistine tablets have been shown in studies?
Because Betahistine tablets are generic medicines, studies in patients have been limited to tests to determine that these medicines are bioequivalent to their respective reference medicines, Serc-8, Serc-16 and Betaserc 24. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.
What are the possible side effects of Betahistine tablets?
Because Betahistine tablets are generic medicines possible side effects are taken as being the same as those of the reference medicines, Serc-8, Serc-16 and Betaserc 24.

For the full list of all side effects reported with Betahistine tablets see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why are Betahistine tablets approved?
It was considered that the benefits of using Betahistine tablets to treat Menière’s syndrome outweigh the risks and the grant of Marketing Authorisations was recommended.

What measures are being taken to ensure the safe and effective use of Betahistine tablets?
Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Betahistine tablets
The MHRA agreed to grant Marketing Authorisations for Betahistine tablets on 29 June 2015.

For more information about treatment with Betahistine tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in August 2015.

The full PAR for Betahistine tablets follows this summary.
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I Introduction

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Betahistine dihydrochloride 8 mg, 16 mg and 24 mg tablets could be approved. These prescription only medicines (POM) are used for the treatment of Menière’s syndrome in adults.

The applications for Betahistine dihydrochloride 8 mg, 16 mg and 24 mg tablets were made under Article 10(1) of Directive 2001/83/EC, as amended, as so-called generic applications. The reference medicinal products for these applications are Serc-8 (PL 43900/0052) and Serc-16 (PL 43900/0051), which were first authorised in the UK on 5 February 1986 and 10 May 1990, respectively, and are currently authorised to BGP Products Ltd, and Betaserc 24, which is authorised to Solvay Pharma, France and has been authorised in the EU for more than 10 years.

Betahistine is a member of the group of beta–2 pyridylalkylamines. Betahistine is a structural analogue of the endogenous histamine. The exact biochemical mode of action of betahistine, and its receptor specificity and affinity, has not been elucidated to date. Betahistine pharmacodynamic studies in animals showed predominantly H1 – receptor agonist activity of betahistine. On the basis of the animal studies, various hypotheses for the mode of action of betahistine on the vestibular function have been postulated.

A bioequivalence study comparing Betahistine dihydrochloride 24 mg tablets to Betaserc 24 mg tablets (Solvay Pharma, France) was submitted with the applications. Assurance has been provided that the study has been conducted according to the principles of Good Clinical Practice (GCP).

No new non-clinical data were submitted, which is acceptable given that the applications are for generic versions of originator products that have been in clinical use for over 10 years.

It has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products. For manufacturing sites within the Community, the MHRA has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The pharmacovigilance system, as described by the MA holder, fulfils the requirements and provides adequate evidence that the MA holder has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The MA holder has provided a Risk Management Plan (RMP).

Since Betahistine dihydrochloride 8 mg, 16 mg and 24 mg tablets are intended for generic substitution, their use will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

The MHRA considered that the applications could be approved and Marketing Authorisations were granted on 29 June 2015.
II Quality aspects

II.1 Introduction
Betahistine dihydrochloride 8 mg, 16 mg and 24 mg tablets contain 8 mg, 16 mg and 24 mg betahistine dihydrochloride, respectively, and the excipients lactose monohydrate, maize starch, cellulose microcrystalline (E 460), citric acid anhydrous (E 330), povidone K 25 (E 1201), crospovidone type A (E 1202) and hydrogenated vegetable oil.

The 8 mg tablets are white, flat and round with bevelled edges and a score line on one side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

The 16 mg tablets are white, flat and round with bevelled edges and a break-line. These tablets have the inscription “BH” on one side of the score and “16 mg” on the other side of the score. These tablets can be divided into equal halves.

The 24 mg tablets are white, flat and round with bevelled edges and a break-line. These tablets have inscription “BH” on one side of the score and “24 mg” on the other side of the score. These tablets can be divided into equal halves.

The tablets are presented in PVC/PE/PVDC – aluminium blisters. Packs sizes of 14, 20, 24, 28, 30, 48, 50, 60, 84, 90, 96, and 100 tablets have been authorised. Not all pack sizes may be marketed.

II.2 Drug Substance
INN: Betahistine hydrochloride
Chemical name: • N-methyl-2-(pyridin-2-yl)ethanamine dihydrochloride
• 2-[2-(methylamino)ethyl]pyridine, dihydrochloride

Structure:

Molecular formula: C₈H₁₄Cl₂N₂
Molecular weight: 209.1

All aspects of the manufacture and control of the active substance, betahistine dihydrochloride, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

II.3 Medicinal Product
Pharmaceutical development
The aim of the pharmaceutical development of Betahistine dihydrochloride 8 mg, 16 mg and 24 mg tablets was to develop generic version of the innovator products, Serc-8, Serc-16 and Betaserc 24.

The proposed and the reference products were tested for a number of parameters to support the claim that the products were comparable.
All excipients comply with their European Pharmacopoeia monographs, with the exception of hydrogenated vegetable oil, which is controlled in line with the British Pharmacopoeia. In the absence of a European Pharmacopoeia monograph for this excipient this is satisfactory. Satisfactory certificates of analysis have been provided for all excipients showing compliance with their proposed specifications.

The supplier of lactose monohydrate has confirmed that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material other than calf rennet is used during the production of lactose monohydrate. None of the other excipients are of animal or human origin.

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated using commercial-scale batches and has shown satisfactory results.

Finished Product Specification
The finished product specifications proposed for the products are acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided that complies with the release specification. Certificates of analysis have been provided for any working standards used.

Stability of the product
Stability studies were performed in accordance with current guidelines, on batches of the finished product stored in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years. These medicinal products do not require any special storage conditions.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of marketing authorisations is recommended.

II.5 SmPCs, PILs and labelling
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted marketing authorisations at a national level are available on the MHRA website.

The following product labelling was approved for use in the UK:

Blister:
III  Non-clinical aspects

III.1  Introduction
No new non-clinical data have been submitted and none are required for applications of this type. The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory.

III.2  Pharmacology
No new pharmacology data are required for these applications and none have been submitted.

III.3  Pharmacokinetics
No new pharmacokinetic data are required for these applications and none have been submitted.

III.4  Toxicology
No new toxicology data are required for these applications and none have been submitted.
III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Betahistine dihydrochloride 8 mg, 16 mg and 24 mg tablets are intended for generic substitution, they will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
The grant of marketing authorisations is recommended.

IV Clinical aspects

IV.1 Introduction
The applicant has submitted a report of a bioequivalence study in support of these applications. The applicant’s clinical overview has been written by an appropriately qualified expert and is considered acceptable.

IV.2 Pharmacokinetics

Bioequivalence study
A single-dose, randomised, crossover study was conducted to compare the rate and extent of absorption of betahistine following administration of Betahistine dihydrochloride 24 mg tablets and Betaserc 24mg tablets in healthy male and female volunteers.

Thirty-seven subjects were recruited into the study. Subjects took a single dose of either the test or the reference product with 240 mL of drinking water. There was a wash out period of 72 hours between study treatment administrations.

Blood samples were collected at pre-dose and at intervals up to 24 hours after administration of each dose. One subject dropped out of the trial, therefore results from 36 subjects were analysed using a validated method.

The main pharmacokinetic parameters are summarised below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Log-transformed test/reference ratio with 90% Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$  (ng/mL)</td>
<td>92.95% (89.90%-99.43%)</td>
</tr>
<tr>
<td>$AUC_{t}$ (ng.h/mL)</td>
<td>100.46% (94.08%-107.26%)</td>
</tr>
<tr>
<td>$AUC_{\infty}$ (ng.h/mL)</td>
<td>100.21% (64.08%-106.74%)</td>
</tr>
</tbody>
</table>

The 90% confidence intervals for $AUC$ and $C_{\text{max}}$ were within the acceptance range of 80.00 to 125.00%. Bioequivalence between the test product and the reference product has been adequately demonstrated. Biowaiver to the 8mg and 16mg strengths is justified as the criteria for biowaiver are met.

Assessor’s Comment/Conclusion
Based on the results, it was concluded that the proposed product, Betahistine dihydrochloride 24 mg tablets, and the reference product, Betaserc 24mg tablets, are bioequivalent. The results of this study may be extrapolated to Betahistine dihydrochloride 8 mg and 16 mg tablets.
IV.3 Pharmacodynamics
No new pharmacodynamic data are required for these applications and none have been submitted.

IV.4 Clinical efficacy
No new clinical efficacy data are required for these applications and none have been submitted.

IV.5 Clinical safety
With the exception of the data generated during the bioequivalence study, no new safety data are presented for these applications and none are required. No new or unexpected safety issues arose during the bioequivalence study.

IV.6 Risk Management Plan
The applicant has submitted an RMP, 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 dihydrochloride 8 mg, 16 mg and 24 mg tablets. Routine pharmacovigilance activities and risk minimisation measures should be adequate for this product, which contains a widely used active substance with a well-established safety profile.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Important identified risks</strong></td>
<td></td>
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<tr>
<td>Off-label use (including pheochromocytoma)</td>
<td>The risk associated with the use of this drug product in patients with pheochromocytoma is described in the SPC, and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
<tr>
<td><strong>Important potential risks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peptic ulcers</td>
<td>The risk of peptic ulcers associated with the use of the drug product is described in the SPC, and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>No</td>
</tr>
<tr>
<td><strong>Important missing information</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use in children and adolescents less than 18 years of age</td>
<td>The SPC states that no information is available regarding the use of the drug product in children and adolescents below the age of 18 years.</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Use in pregnancy and breast-feeding</td>
<td>The SPC states that no information is available regarding the use of the drug product during pregnancy and breast-feeding and suggests that administration of the drug product should be weighed against the benefits and the potential risks.</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
IV.7 Discussion on the clinical aspects
The grant of marketing authorisations is recommended for these applications.

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 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

The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with betahistine dihydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.

VII Steps taken for assessment

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<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation Applications on 4 January 2013.</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 12 February 2013.</td>
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<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the quality dossier on 23 May 2013.</td>
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<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s request, providing further information on the quality dossier on 15 November 2013.</td>
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<tr>
<td>5</td>
<td>Following assessment of the response the MHRA requested further information relating to the clinical dossier on 16 December 2013, 23 May 2014 and 10 November 2014.</td>
</tr>
<tr>
<td>6</td>
<td>The applicant responded to the MHRA’s request, providing further information on the clinical dossier on 22 April 2014, 12 August 2014 and 31 January 2015.</td>
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<td>7</td>
<td>The applications were granted on 29 June 2015.</td>
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</table>

VIII Steps taken after initial authorisation

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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