PUBLIC ASSESSMENT REPORT  
of the Medicines Evaluation Board  
in the Netherlands  

Betahistine.2HCl 8, tablets 8 mg  
Betahistine.2HCl 16, tablets 16 mg  
Disphar International B.V., the Netherlands  

betahistine dihydrochloride  

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states. 
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation. 
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand. 

This assessment report shall be updated by a following addendum whenever new information becomes available. 

General information on the Public Assessment Reports can be found on the website of the MEB. 

To the best of the MEB’s knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information. 

EU-procedure number: NL/H/709/01-02/MR  
Registration number in the Netherlands: RVG 32005, 32006  
13 July 2009  

Pharmacotherapeutic group: antivertigo preparations  
ATC code: N07CA01  
Route of administration: oral  
Therapeutic indication: Ménière’s syndrome, symptoms of which may include vertigo, tinnitus, hearing loss and nausea  

Prescription status: prescription only  
Date of authorisation in NL: 15 February 2005  
Date of withdrawal in NL: 20 November 2007  
Concerned Member States: Mutual recognition procedure with IT  
Application type/legal basis: Directive 2001/83/EC, Article 10(1)  

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.
I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Betahistine.2HCl 8, tablets 8 mg, and Betahistine.2HCl 16, tablets 16 mg, from Disphar International B.V. The date of authorisation was on 15 February 2005 in the Netherlands. The product is indicated for treatment of Ménière’s syndrome, symptoms of which may include vertigo, tinnitus, hearing loss and nausea.

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

Betahistine’s H<sub>1</sub>-agonist activity at histamine receptors in peripheral blood vessels has been demonstrated in man by the abrogation of betahistine-induced vasodilatation with histamine antagonist diphenhydramine. Betahistine has minimal effects on gastric acid secretion (an H<sub>2</sub>-receptor mediated response). Mechanism of action of betahistine in Ménière’s syndrome is unclear. The efficacy of betahistine in the treatment of vertigo may be due to its ability to modify the circulation of the inner ear or due to a direct effect on neurons of the vestibular nucleus.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Betaserc 8 and 16 mg tablets (NL License RVG 05852 and 13612, respectively), which have been registered in the Netherlands by Solvay Pharma B.V. since 1970 and 1989, respectively (original product). In addition, reference is made to Betaserc authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Betaserc 16 mg tablets, registered in the Netherlands. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new preclinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted.
II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is betahistine dihydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Betahistine hydrochloride is a white to yellowish, very hygroscopic, crystalline powder.

Manufacture
The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

A detailed description of the synthesis has been provided by the MAH.

Specification
The active substance specification is considered adequate to control the quality. The limits are in line with the EP monograph and ICH requirements. Batch analytical data demonstrating compliance with this specification have been provided for 3 production scale batches.

Stability
Stability data on the active substance have been provided for 3 batches stored at 25ºC/60%RH. Two batches were stored up to 36 months and one batch was stored up to 48 months. Based on the data submitted, a retest period could be granted of 2 years without specific storage conditions.

* Ph.Eur., USP, BP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively.

Medicinal Product

Composition
Betahistine.2HCl 8 & 16, tablets contain as active substance 8 and 16 mg of betahistine dihydrochloride, respectively. The tablets of both strengths are white or almost white, round, embossed B8 (8 mg tablets) or B16 (16 mg tablets) on one side, scored reverse. In addition, the 16 mg tablet can be divided into equal halves. Both tablet formulation are fully dose proportional.

The tablets are packed in Alu/PVC/PVDC blister strips heat seal lacquered to aluminium. The blister foil is transparent. Information on the plastics has been provided. A declaration that the primary packaging materials comply with the EP and Directive 72/2002 has been provided.

The excipients are: povidone K90, microcrystalline cellulose, lactose monohydrate, colloidal anhydrous silica, crospovidone and stearic acid.
Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The used excipients are well known and safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph.Eur. monographs. Uniformity of content was shown for 3 batches of each strength.

Dissolution tests
Dissolution tests were performed of the brand leader products in the Netherlands, Italy and UK/Ireland. The following can be derived from the dissolution data presented:
• The dissolution of both proposed products is fast (over 90% in 25 minutes)
• The dissolution of the innovator batches is fast (over 90% in 15-20 minutes)
• Both strengths show similar profiles.
Furthermore, bioequivalence with the reference product has been proven by a bioequivalence study. Comparative analysis results of the reference products, including impurities, are presented.

Manufacturing process
The manufacturing process is adequately and sufficiently detailed described. Sieve measures and mixing times are stated. No overages are used. Water is used as granulation solvent. The manufacturing process has been validated according to relevant European/ICH guidelines. The critical processes are defined and validation reports are enclosed for both manufacturers with production scale batches. The process is shown to be consistent and yield a product complying with the specifications and showing good homogeneity.

Product specification
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, colour, diameter, height, resistance to crushing, friability, disintegration, average mass, uniformity of mass, loss on drying, identification, content, by–and degradation products, content uniformity, uniformity of mass, and microbial contamination. 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 3 production scale batches of each strength have been provided from the proposed production site(s), demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided for 3 batches of each strength, stored at 25°C/60%RH and 40°C/75% RH, in accordance with applicable European guidelines demonstrating the stability of the product over 36 months. On basis of the data submitted, a shelf life was granted of 3 years. The labelled storage conditions are: “Store below 25°C in the original packaging”.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies TSE statements are enclosed for lactose and stearic acid (vegetable source). There is no risk of TSE.

II.2 Non clinical aspects
This active substance has been available on the Dutch market for 39 years. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of beta-histidine hydrochloride released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.
II.3 Clinical aspects

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

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Betahistine.2HCl 16 mg tablet is compared with the pharmacokinetic profile of the Dutch reference product Betaserc 16 mg tablet. After absorption, betahistine is almost completely metabolised into the inactive metabolite 2-pyridyl acetic acid (2-PAA). As the parent drug is almost not detectable in plasma, bioequivalence based on the metabolite PAA is considered acceptable.

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

A single-dose, open randomised, two-way crossover bioequivalence study was carried out under fasted conditions in 24 healthy male volunteers, aged 20 to 31 years. Each subject received a single dose (16 mg) of one of the 2 betahistine dihydrochloride formulations. The tablet was orally administered with 200 ml water after 10 hours of fasting. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 10 and 14 hours after administration of the products. All subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t\text{max} (median, range)) of 2-PAA under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-\infty} ng.h/ml</th>
<th>AUC_{0-t} ng.h/ml</th>
<th>C_{max} ng/ml</th>
<th>t_{max} h</th>
<th>t_{1/2} h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>1475 ± 238</td>
<td>1560 ± 237</td>
<td>344 ± 107</td>
<td>0.67</td>
<td>3.1 ± 0.5</td>
</tr>
<tr>
<td>Reference</td>
<td>1471 ± 273</td>
<td>1551 ± 278</td>
<td>347 ± 117</td>
<td>0.67</td>
<td>3.0 ± 0.4</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>---</td>
<td>1.01 (0.97 – 1.06)</td>
<td>0.99 (0.91 – 1.08)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>CV (%)</td>
<td>---</td>
<td>9.4</td>
<td>17.1</td>
<td>---</td>
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</tr>
</tbody>
</table>

AUC\text{0-\infty} area under the plasma concentration-time curve from time zero to infinity
AUC\text{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

The 90\% confidence intervals calculated for AUC\text{0-\infty} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of the inactive metabolite 2-PAA under fasted conditions, it can be concluded that Betahistine.2HCl 16 and the Betaserc 16 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The 16 mg tablets are dose proportional with the 8 mg tablets. The results of the bioequivalence study performed with the 16 mg tablets therefore apply to the 8 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).
Risk management plan
Betahistine hydrochloride was first approved in 1970, and there is now more than 10 years postauthorisation experience with the active substance. The safety profile of betahistine dihydrochloride can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation, which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The SPC assessment was based on the innovator product Betaserc in the Netherlands. The chemical-pharmaceutical sections of the Dutch SPC are an adequate reflection of these product characteristics, otherwise the Dutch SmPC is in line with the innovator SPC. The contents is also in agreement with the MRP-SPC of procedure NL/H/225/01-02 (Betahistine.2HCL Disphar 8 and16 mg tablets).

Readability test
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 first round with 10 participants. Based on the conclusions and recommendations from this first test round, the MAH made some amendments to the package leaflet.

A second test, this time with the adapted text, was performed with 10 participants. Amendments made in several sections of the package leaflet led to a notable improvement in the scores on the questions in the amended sections. In total, the number of respondents who gave a correct answer increased from 68% in the first round to 82% in the second round.

There were sufficient questions about the critical sections. The conclusions are clear, concise and clearly presented. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The patient leaflet has been adapted sufficiently taking into account the results of the test.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Betahistine.2HCl 8&16, tablets 8 and 16 mg have a proven chemical-pharmaceutical quality and are generic forms of Betaserc 8 and 16 mg tablets. Betaserc tablets are 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC assessment was based on the innovator product Betaserc in the Netherlands. The chemical-pharmaceutical sections of the Dutch SPC are an adequate reflection of these product characteristics, otherwise the Dutch SmPC is in line with the innovator SPC. The contents is also in agreement with the MRP-SPC of procedure NL/H/225/01-02 (Betahistine.2HCL Disphar 8 and 16 mg tablets). Braille conditions are met by the MAH.

The Board followed the advice of the assessors. Betahistine.2HCl Disphar 8 and 16 mg tablets were authorised in the Netherlands on 15 February 2005.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Betahistine.2HCl Disphar tablets with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 20 July 2006.

The first PSUR will cover the period from July 2006 to July 2009. The second PSUR will cover the period from July 2009 to July 2011 to coincide with the renewal. Thereafter, the PSUR submission cycle will be 3 years.

The date for the first renewal will be: 20 July 2011.

There were no post-approval commitments made during the procedure.
List of abbreviations

<table>
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
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<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification</td>
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<td>AUC</td>
<td>Area Under the Curve</td>
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<tr>
<td>BP</td>
<td>British Pharmacopoeia</td>
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<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximum plasma concentration</td>
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<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
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<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
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<td>EDMF</td>
<td>European Drug Master File</td>
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<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<td>EU</td>
<td>European Union</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>GLP</td>
<td>Good Laboratory Practice</td>
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<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<tr>
<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<td>MEB</td>
<td>Medicines Evaluation Board in the Netherlands</td>
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<tr>
<td>OTC</td>
<td>Over The Counter (to be supplied without prescription)</td>
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<td>PAR</td>
<td>Public Assessment Report</td>
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<tr>
<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<tr>
<td>PIL</td>
<td>Package Leaflet</td>
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<tr>
<td>PSUR</td>
<td>Periodic Safety Update Report</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>Half-life</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Time for maximum concentration</td>
</tr>
<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
</tr>
<tr>
<td>USP</td>
<td>Pharmacopoeia in the United States</td>
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## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
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<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
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<tr>
<td>Update DMF</td>
<td>NL/H/0709/001-002/II/001</td>
<td>II</td>
<td>21-10-2006</td>
<td>20-12-2006</td>
<td>Approval</td>
<td>N</td>
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<td>Update of the finished product manufacturing process description</td>
<td>NL/H/0709/001-002/II/002</td>
<td>II</td>
<td>21-10-2006</td>
<td>20-12-2006</td>
<td>Approval</td>
<td>N</td>
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<tr>
<td>Betahistine.2HCl 8&amp;16, tablets 8 and 16 mg were withdrawn at 20 November 2007</td>
<td>NL/H/0709/01-02/MR</td>
<td>Withdrawal</td>
<td>20-11-07</td>
<td></td>
<td>Approval</td>
<td>N</td>
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