PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Betahistine.2HCl 8, tablets 8 mg
Betahistine.2HCl 16, tablets 16 mg
Alternova A/S, Denmark

betahistine (as 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/742/01-02/MR
Registration number in the Netherlands: RVG 33325,33326

Date of first publication: 13 July 2009
Last revision: 30 May 2011

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: 31 January 2006
Concerned Member States: Mutual recognition procedure with AT, FI, and PL
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 Alternova A/S. 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 H1-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 H2-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.

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.

Manufacture
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 testing
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 betahistine 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.

Bioequivalence study
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.

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.

Results
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>$\text{AUC}_{0-t}$ ng.h/ml</th>
<th>$\text{AUC}_{0-\infty}$ ng.h/ml</th>
<th>$C_{\text{max}}$ ng/ml</th>
<th>$t_{\text{max}}$ 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 (0.33 – 2.0)</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 (0.33 – 1.5)</td>
<td>3.0 ± 0.4</td>
</tr>
</tbody>
</table>

*Ratio (90% CI)

|                     | --- | 1.01 (0.97 – 1.06) | 0.99 (0.91 – 1.08) |
|---|---|---|
| CV (%) | --- | 9.4 | 17.1 |

$\text{AUC}_{0-t}$ area under the plasma concentration-time curve from time zero to infinity
$\text{AUC}_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
$C_{\text{max}}$ maximum plasma concentration
$t_{\text{max}}$ time for maximum concentration
$t_{1/2}$ half-life

*In-transformed values

The 90% confidence intervals calculated for $\text{AUC}_{0-\infty}$ and $C_{\text{max}}$ 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.
Extrapolation of results
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 and 16 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 8 and 16 mg tablets were authorised in the Netherlands on 31 January 2006.

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 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

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

<table>
<thead>
<tr>
<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>
</tr>
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<td>Update DMF</td>
<td>NL/H/0742/001-002/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/0742/001-002/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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<td>Change in pack size of the finished product. Change in the number of units (e.g. tablets, ampoules etc.) in a pack. Change outside the range of the currently approved pack sizes.</td>
<td>NL/H/0742/002/IB/003</td>
<td>IB</td>
<td>6-11-2006</td>
<td>6-12-2006</td>
<td>Approval</td>
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<td>Change in the name and/or address of the marketing authorization holder.</td>
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<td>IA</td>
<td>13-2-2008</td>
<td>27-2-2008</td>
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<td>NL/H/0742/001-002/IA/005</td>
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<td>8-9-2008</td>
<td>22-9-2008</td>
<td>Approval</td>
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<td>Change in the name and/or address of the marketing authorization holder.</td>
<td>NL/H/0742/001-002/IA/006</td>
<td>IA</td>
<td>27-10-2008</td>
<td>10-11-2008</td>
<td>Approval</td>
<td>N</td>
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<td>Submission of a new or updated Ph. Eur. Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance. From a manufacturer currently approved.</td>
<td>NL/H/0742/001-002/IA/007</td>
<td>IA</td>
<td>30-11-2009</td>
<td>14-12-2009</td>
<td>Approval</td>
<td>N</td>
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<td>Renewal of the marketing authorisation.</td>
<td>NL/H/0742/001-002/R/001</td>
<td>Renewal</td>
<td>14-11-10</td>
<td>26-2-11</td>
<td>Approval</td>
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Annex I - Variation NL/H/0742/001-002/R/001- Renewal of the marketing authorisation

I RECOMMENDATION

Based on the review of the data submitted for this renewal application, the Reference Member State (RMS) is of the opinion that the benefit/risk balance of Betahistine 2HCL 8 and 16 mg (betahistine) NL/H/0742/001-002/R/001 is positive. The RMS therefore recommends the renewal of the marketing authorisation for Betahistine 2HCL 8 and 16 mg. Renewal can be granted with unlimited validity.

II SCIENTIFIC DISCUSSION

1 Introduction

Betahistine dihydrochloride is indicated for treatment of Meniere’s disease and vertigo, tinnitus, hearing loss, and nausea associated with Meniere’s disease.

As part of the renewal in January 2011 the MAH has submitted:
- A Periodic Safety Update Report (PSUR 2) covering the period 1 February 2009 – 31 May 2010, dated July 2010 and signed
- A Summary Bridging Report (SBR) covering the period 31 January 2006 – 31 May 2010, dated July 2010 and signed
- Clinical Expert Statement, signed
- The Summary of Product Characteristics (SPC), for which no changes have been proposed with respect to the (pre)clinical sections.

Betahistine dihydrochloride 8 and 16 mg tablets have been registered since 31 January 2006 through the mutual recognition procedure for which the Netherlands acts as RMS (NL/H/0742/001-002). The product was licensed in three other European Concerned Member States: Austria, Finland, and Poland. During this review period the product was withdrawn from the market in Austria (May 2009) and in Poland (September 2008). The MAH stated that this was not for safety reasons.

Assessor’s comment:
The clinical expert statement did not include relevant new safety or efficacy related information, thus as such this will not be summarized in this assessment report (AR).
For this product the Data Lock Point (DLP) within the EU PSUR harmonisation project is December 2008. Next PSUR should cover the period June 2010 up to up to 31 December 2011, to be submitted in February 2012.

2 Module 1/GMP compliance statements

GMP compliance
GMP certificates have been provided for all manufacturers of the finished product and responsible for batch release.

GMP active substance
Declarations by the QP of both manufacturing sites, have been submitted stating that the active substance manufacturers as referred to in the application forms operate in compliance with the detailed guidelines on GMP for starting materials.
In accordance with the CMD(h) Best Practice Guide on the processing of renewals in the mutual recognition and decentralised procedure (version November 2008) a quality expert statement has been submitted for Betahistine Alternova confirming that:

- the products are in compliance with the requirements of Directive 2001/83/EC which obliges the MAH “…. to take account of technical and scientific progress and introduce any changes….”.
- all changes relating to the quality of the products have been made following applications for variations and that the product conforms to the current CHMP quality guidelines.

The currently authorised specifications for the active substance and the finished products with the qualitative and quantitative composition have been provided.

There are no outstanding quality commitments

4 Clinical Efficacy and Safety

4.1 Clinical Efficacy
No new information was submitted.

4.2 Clinical Safety

4.2.1 Summary of Cumulative Experience 26 January 2006–31 May 2010 and Post Marketing Experience 31 January 2006 – 28 February 2010

The MAH has submitted a license renewal application through the MRP with the Netherlands acting as RMS.

World wide marketing authorisation status
The product has been approved in four countries: Austria, Finland, the Netherlands, and Poland. During this review period the product has been withdrawn in Poland and Austria for reasons not related to safety in respectively September 2008 and May 2009. The product has been marketed in one country: Finland.

Actions taken for safety reasons
No specific actions for safety reasons have been taken, either by the regulatory authorities or by the MAH.

Changes to the Reference safety information
For this PSUR, the MAH used the current SPC within this MRP as Reference Safety Information (RSI). During this review period there were no safety related changed in the SPC.

Patient exposure
Based on sales data (559,200 8 mg tablets and 272,300 16 mg tablets) and the defined daily dose (DDD) of 24 mg, patient exposure was estimated to amount 367,933 patient days during this review period (31 January 2006 – 31 May 2010).

However, in PSUR 2: the MAH states as follows:
The estimated patient exposure to Betahistin in the period covering this PSUR is calculated to 394 patients. The exposure since the product has been launched (1066 days) is calculated to 346 patients. The estimated patient exposure provides the number of patients all treated from product
launch date till data lock point with a DDD. However, some patients may have ceased, new patient may have entered into treatment and some patients may have been titrated from a lower initial dose to a higher dosage or vice versa. Consequently the calculation is a crude estimate of patient exposure.

Assessor’s comment: The RMS acknowledges the assumptions made to estimate patient exposure and that the figure is a crude estimate. However, the method to calculate the number of patients exposed is not understood. Based on the sales data and WHO DDD the number of patient days (367,933) equals 1,008 patient years. Moreover it is considered strange that the exposure since launch is lower (346 patients) than the number of patients exposed during the review period 1 February 2009 – 31 May 2010 (394 patients). Since it is not considered to affect the Benefit/Risk conclusions as drawn in this assessment report, it is considered sufficient that in future PSURs the MAH ensures to include the correct number of exposed patients as well as the underlying method of calculation.

There were no patients exposed in clinical trials sponsored by the MAH.

Adverse reactions
During the current review period the MAH did not receive adverse event reports from spontaneous sources.

Literature search by the MAH, covering the period 31 January 2006 - 31 May 2010 did not reveal new safety information or case reports.

Studies

Clinical studies
There were no newly analysed company-sponsored studies and no targeted new studies during the reporting period.

Published studies
In the PSUR the MAH stated that there were no new safety studies published containing relevant new safety findings on betahistine.

The search criteria were: “Betaistine/adverse reaction” or “Betahistine/safety” or “Betaistine/toxicity, ”01 February–05 March 2009”.

Assessor’s comment - The RMS does not agree on this. See below in this assessment report.

The MAH used the search criteria ‘betahistine/adverse reaction, betahistine/safety or betahistine/toxicity, 31 January 2006 – 31 January 2009’ during one PSUR period and 'betahistine AND 2010/06/01[PDAT]:201006/2[PDAT]' for the other PSUR period.

For future PSURs the MAH is requested to sort out for what reason the publications as presented below by the RMS were not revealed and adapt the search strategies in the literature accordingly.

From studies published during the current review period the RMS considers the following publications possibly relevant:

Jeck-Thole et al (2006) reviewed and analysed the safety profile of betahistine based on data obtained during >35 years of worldwide postmarketing surveillance. Until 31 December 2005, 554 adverse drug reaction (ADR) reports with 994 individual signs and symptoms were received by the marketing authorisation holder from worldwide sources and were reviewed and evaluated. Signs and symptoms of cutaneous hypersensitivity reactions during betahistine therapy were the most frequently reported complaints. They consisted of usually mild and self-limiting rash, pruritus and urticaria, and all symptoms were reversible after drug discontinuation. Betahistine was reported to be involved in one anaphylactoid reaction and one case of Stevens-Johnson syndrome. Anaphylactic reactions with fatal outcome were not reported. The reports that describe gastrointestinal complaints mostly concern nausea and vomiting or unspecific abdominal pain. These were typically non-serious complaints. Hepatobiliary involvement was reported 25 times, including increases in alkaline phosphatase, υ-glutamyltransferase, and alanine and aspartate aminotransferase levels. None of the patients concerned developed severe liver failure or died. ADRs related to the nervous system predominantly reveal heterogeneous events that are not suggestive of a specific adverse reaction profile for betahistine. A clinical intolerance to betahistine that gave rise to
asthma or bronchospasm was only reported in eight ADRs. A total of three cases of neoplasm have been reported. One case concerned a male patient of unknown age who experienced weight loss, insomnia, impatience and irritability soon after the start of betahistine therapy. An undiagnosed phaeochromocytoma was suspected. The remaining two cases were assessed as being unrelated to betahistine by the reporter. Finally, four deaths have been reported during the course of postmarketing surveillance for betahistine. The reporter assessed the causal relationship to betahistine in two as unrelated, in one as unlikely and the other as unassessable. In summary, clinical and postmarketing studies have revealed a good safety profile of betahistine that was confirmed by the safety surveillance data presented. (Jeck-Thole S, Wagner W. 2006. Betahistine: a retrospective synopsis of safety data. Drug Saf 29, 1049-1059)

Furthermore the following publication is relevant concerning the same safety issue but was published before current review period:
de Abajo et al (2004) performed a population-based case-control study about the absolute and relative risks of acute and clinically relevant drug-induced liver injury using the UK-based General Practice Research Database as source of information. One hundred and twenty-eight patients were considered as valid cases, being the crude incidence rate of 2.4 (95% confidence interval: 2.0, 2.8) per 100,000 person-years. A total of five thousand controls were randomly sampled from the person-time of study cohort. Associations were found for a variety of drugs, including betahistine (adjusted odds ratio; 95% CI = 15.3; 2.9, 80.7). Two cases were connected with 74,929 prescriptions of betahistine to 15,780 patients, leading to incident rates (including 95% CI) of 12.7 (1.5, 45.8) per 100,000 users and 2.7 (0.3, 9.6) per 100,000 prescriptions. The two cases associated with betahistine occurred after long exposure. (de Abajo FJ, Montero D, Madurga M, Garcia Rodriguez LA. 2004. Acute and clinically relevant drug-induced liver injury: A population case-control study. Brit J Clin Pharmacol 58, 71-80.)

Assessor’s comment - Taking into account the underlying data so far, the large patient exposure, and in line with the requests made to MAHs of other betahistines, the MAH should perform close monitoring of case reports involving hepatobiliary disorders and present a cumulative overview and discussion for further assessment in the next PSUR.

Another study published during this review period not presented by the MAH but considered relevant by the RMS:
Malavasi Gananca M et al (2008) published on their study proving that Betahistine at oral doses of 16 mg tid and 24 mg bid provides similar efficacy and tolerability in the treatment of vertigo in patients with Ménière’s disease. The objective of the study was to compare the efficacy and tolerability of Betahistine 16 mg tid and 24 mg bid in the treatment of vertigo in patients with Ménière’s disease. This was a randomized, open-label study of 120 consecutive patients with well-established Ménière’s disease treated with Betahistine 16 mg tid or 24 mg bid for 24 weeks. Treatment efficacy, assessed by clinical outcome level in terms of severity, frequency and duration of vertigo spells, was evaluated at baseline and at weeks 4, 12, and 24. Between-group comparisons of outcome data (Wilcoxon, Mann-Whitney U test) and adverse events (chi-squared test) were made. Betahistine 16 mg tid or 24 mg bid showed a significant improvement in clinical outcome level from baseline to week 24 (p<0.01). There was no significant difference between dosage groups regarding improvement in vertigo at any time point during the study. There was no significant difference between groups in the incidence of adverse events, which was low (maximum: headache, 16 mg tid, 16.7% of patients at week 4; 6.7% at week 24). The number of patients reporting adverse events diminished with time. The authors of the study report various adverse events without causality assessment: headache, epigastric disturbance, anxiety, insomnia, nausea, fatigue, lipothymia, weight gain, palpitation, and dyspepsia.

The RMS derived the following table on reported adverse events from this publication:

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Tid (16 mg)</th>
<th>Bid (24 mg)</th>
<th>0</th>
<th>0</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>2 (3.3)</td>
<td>1 (1.7)</td>
<td>1 (1.7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lipothymia</td>
<td>2 (3.3)</td>
<td>1 (1.7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Weight gain</td>
<td>1 (1.7)</td>
<td>1 (1.7)</td>
<td>0</td>
<td>0</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Palpitation</td>
<td>1 (1.7)</td>
<td>2 (3.3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1 (1.7)</td>
<td>2 (3.3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Assessor’s comment - Headache, epigastric disturbance, nausea and dyspepsia are sufficiently covered in current SPC.

From the unlabelled reported adverse events in this study the assessor only considers ‘anxiety’ to be clinically relevant, and possibly relevant for close monitoring taking into account the figures. This event might however also be due to the symptoms of Meniere’s disease, but this information could not be derived from this publication. Based on this published study the MAH is kindly requested to closely monitor case reports concerning anxiety and provide a cumulative overview plus discussion on this issue in next PSUR. This request is in line with the request made for other betahistines.

No other relevant new safety information was revealed in the submitted documents as part of this renewal.

Late breaking information, Drug interactions, Drug Abuse, Overdose, Pregnancy and Lactation, Medication errors, Special Patient Groups, Long term treatment

No new safety information has been identified with regard to the above mentioned topics.

Conclusion on Safety

Overall, the MAH did not receive adverse event reports during this review period.

Based on the publication of Jeck-Thole et al (2006) the MAH should perform close monitoring of case reports involving hepatobiliary disorders and present a cumulative overview for further assessment in the next PSUR.

Based on the publication of Malavasi Gananca et al (2008) the MAH is kindly requested to closely monitor case reports concerning anxiety and provide a cumulative overview plus discussion on this issue in next PSUR.

No other new safety issues were identified.

5 Product Information

5.1 Summary of Product Characteristics

The MAH considered the current SPC to be adequate. This is agreed upon.

5.2 Package leaflet and user testing

NO amendments have been proposed. This is agreed upon.

Package Leaflet

The PL has been harmonised for this product.

Assessment of User Testing

The PIL has already been usertested.

5.3 Labelling

Labelling texts are harmonised for this product. No changes are proposed. This is agreed upon.
6 Remaining post-approval commitments to be fulfilled by the MAH

The following post-approval commitments are still outstanding:

<table>
<thead>
<tr>
<th>Area</th>
<th>Description</th>
<th>Due date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacovigilance</td>
<td>Next PSUR should cover the period of 01 June 2010 up to 31 December 2011. The PSURs thereafter should be submitted each 3 years unless safety issues require earlier assessment</td>
<td>February 2012</td>
</tr>
<tr>
<td>Pharmacovigilance</td>
<td>Based on the publication of Jeck-Thole et al (2006) the MAH should perform close monitoring of case reports involving hepatobiliary disorders and present a cumulative overview and discussion for further assessment in the next PSUR.</td>
<td>February 2012</td>
</tr>
<tr>
<td>Pharmacovigilance</td>
<td>Based on the publication of Malavasi Gananca et al (2008) the MAH is kindly requested to closely monitor case reports concerning anxiety and provide a cumulative overview plus discussion on this issue in next PSUR.</td>
<td>February 2012</td>
</tr>
<tr>
<td>Pharmacovigilance</td>
<td>The MAH ensures to include the correct number of exposed patients as well as the underlying method of calculation</td>
<td>February 2012</td>
</tr>
<tr>
<td>Pharmacovigilance</td>
<td>For future PSURs the MAH is requested to sort out for what reason the publications as presented by the RMS were not revealed and adapt the search strategies in the literature accordingly.</td>
<td>February 2012</td>
</tr>
</tbody>
</table>

1Areas: Quality, Non-clinical, Clinical, Pharmacovigilance

2Due date for the follow-up measure or for the first interim report if a precise date cannot be committed to.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Based on the data accumulated during the review period, the benefit/risk ratio for the product remains favourable. There have been two new safety issues identified in the period under review: hepatobiliary disorders and anxiety. For both issues close monitoring and a cumulative overview in next PSUR is considered adequate.

The RMS is of the opinion that the renewal can be granted with unlimited validity. The next PSUR should be submitted within 60 days from the next data lock point (DLP) 31 December 2011. The common renewal date is 31 January 2011.