CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Betabare 24 mg tablets
Egis Pharmaceuticals Plc, Hungary

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/1639/001/MR
Registration number in the Netherlands: RVG 103403

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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 first authorisation in NL:	5 November 2008
Concerned Member States:	Mutual recognition procedure with CZ, HU, PL, and SK.
Application type/legal basis:	Directive 2001/83/EC, Article 10(1), 10(3) in the Netherlands

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SmPC), 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 Betabare 24 mg tablets, from Egis Pharmaceuticals Plc. The date of authorisation was on 5 November 2008 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 SmPC.

Betahistine´s H1-agonist activity at histamine receptors in peripheral blood vessels has been demonstrated in man by the abrogation of betahistine-induced vasodilation with the histamine antagonist diphenhydramine. Betahistine has minimal effects on gastric acid secretion (an H2-receptor mediated response). Mechanism of action of betahisitine 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 product Betaserc 24 mg tablets, which has been registered in France by Solvay. In addition, reference is made to Betaserc authorisations in the individual member states (reference product).

For the Netherlands (RMS), the legal basis is article 10(3) hybrid application. The MAH already has authorisations for a 8 mg and 16 mg strength. Now the MAH wants to register in addition a 24 mg tablet, with proportionally the same constitution as the 8 and 16 mg tablets.
In the CMSs the marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC. As the dosing schedule for the 24 mg tablets is slightly different (BID, two times a day) as for the 8 and 16 mg tablets (as approved in NL= TID, three times a day), the MAH has submitted supportive data to justify this dosing scheme = 12-24 mg twice a day. These data are presented in paragraph II.3 Clinical aspects.

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 24 mg, registered in France. 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 pre-clinical 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, as this is not required for generic medicinal products.

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
Betahistine diHCl is described in the Ph.Eur.*. The drug substance is a white to yellowish, crystalline, very hygroscopic powder. It is very soluble in water and soluble in ethanol. Betahistine diHCl does not possess asymmetric carbon atoms. No polymorphs are known.

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/EMA 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
Betahistine diHCl sodium is prepared from two starting materials via a one-step synthesis and subsequent salt forming and purification processes. Adequate specifications for the starting materials and reagents have been provided. The drug substance has been adequately characterised.

Specification
The drug substance specification is in compliance with the Ph.Eur. monograph Substances for pharmaceutical use and with the Ph.Eur. monograph, with additional requirements for residual solvents. The specification is acceptable in view of the route of synthesis and the various ICH guidelines. Batch analytical data have been provided for 3 production scaled batches showing compliance with the specification.

Stability
Stability data have been obtained during storage for a maximum of 60 months at 25°C/60% RH and during storage for 6 months at 40°C/75% RH. The drug substance was adequately packaged. The substance is stable at both conditions. Based on the stability data provided, the claimed retest period of 2 years without storage conditions can be granted.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
The product is formulated as uncoated, direct-release tablets. The tablets are packaged into PVC/PVdC-Al blisters. Each tablet contains the active ingredient Betahistine dihydrochloride, 24 mg per tablet.
The tablets are packed in PVC/PVdC-Al blisters.
The excipients are: povidone K90, microcrystalline cellulose, lactose monohydrate, colloidal anhydrous silica, crospovidone, and stearic acid.

Pharmaceutical development
The development of the product is satisfactorily performed and explained. The excipients used are common in the manufacture of tablets and some are also present in the innovator product. The packaging materials are usual and suitable for the product at issue.

Dissolution data at different conditions show that for the test tablet after 10 minutes more than 80% was dissolved, and after 15 minutes 90% or more. Dissolution data of the 24 mg test tablet were similar to the registered 16 mg tablet strength (by the same manufacturer), which is dose proportional with the 24 mg formulation.
No polymorphism has been observed. The active substance is known to be hygroscopic, but the MAH states that no or almost no degradation is observed during stress testing.

Manufacturing process
The tablets are prepared from a common granulate, using conventional manufacturing techniques. The granulate is compressed. The manufacturing process has sufficiently been described. Process validation data on three batches have been provided. The process is shown to be consistent and yield a product complying with the specifications and showing good homogeneity.

Product specification
The product specification for the tablets includes tests for appearance, identification, disintegration, friability, hardness, assay, loss on drying, degradation, dissolution rate, related substances, mass, microbiological requirements and uniformity of dosage units. The proposed tests and requirements are acceptable. Batch analysis data have been provided on three product scaled batches. Compliance with the release requirements has been demonstrated.

Stability tests on the finished product
The tablets have been stored for 24 months at 25°C/60% RH, 3 months at 30°C/65% RH and 3 months at 40°C/75% RH. Three consecutive batches have been included in stability studies. Out of specification results are observed at accelerated conditions. At long-term conditions the same trends are observed but less pronounced. The claimed shelf-life of 2 years when stored below 25°C in Alu-PVC/PVDC blister packaging could be granted.

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 product is a generic formulation of Betaserc, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

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 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 Betabare 24 mg tablets (Egis Pharmaceuticals Plc, Hungary) is compared with the pharmacokinetic profile of the reference product Betaserc 24 mg tablets (Solvay, France).

The MAH has performed a comparative dissolution test with the test product (biobatch) versus the reference product from the Polish market. Since 85% of the drug is dissolved in less than 15 minutes, conform the Note for Guidance on the investigation of bioavailability and bioequivalence ((CPMP/EWP/QWP/1401/98) the dissolution profiles are considered to be similar.

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

Study design
An open randomized, two treatment (R = reference and T = test), two period, two sequence crossover bioequivalence study was carried out under fasted conditions in 24 healthy volunteers, aged 18-44 years. Smoking < 10 cigarettes daily was allowed. Each subject received a single dose (24 mg) of one of the 2 betahistine formulations. The tablet was orally administered with 200 ml water. The tablets were taken under fasted conditions, and fasting continued till 4 hours after administration. There were 2 dosing periods, separated by a washout period of one week. Blood samples were collected predose and at 1, 1.5, 2, 3, 4, 6, 8, 10, 13 and 16 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.

According to the SmPC, the tablets should be taken with food. This advice is based on improvement of gastric tolerability. For immediate release tablets, fasting is the most sensitive condition to measure bioequivalence. It is therefore accepted that the study was performed under fasted conditions

There seems to exist no direct relationship between plasma concentration and clinical effect of betahistine. Betahistine is almost completely absorbed, but subsequently rapidly and almost completely metabolized into 2-pyridyl acetic acid (2-PAA), with extremely low concentrations of betahistine itself. In a study by Schmidt & Huizing (1992, Acta Oto-Laryngol, suppl 497, pp.1-19) no betahistine could be detected after a single intake of 32 mg plain tablet using GC-MS with detection limit of 100 pg/ml. It is therefore accepted that the metabolite is measured instead of the parent drug.

Results
One female subject withdrew informed consent after period 1, because of an upper respiratory tract infection. Twenty-three subjects were eligible for pharmacokinetic analysis.

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

Treatment N= 23	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	3281 ± 643	3385 ± 664	751 ± 157	0.5 (0.25-2)	---
Reference	3153 ± 591	3261 ± 624	715 ± 179	0.6 (0.25-1.5)	---
***Ratio (90% CI)**	1.03 (0.98-1.08)	1.03 (0.98-1.08)	1.05 (0.99-1.10)	---	---
CV (%)	9.3	9.7	10.0	---	---

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

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ 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 2-PAA under fasted conditions, it can be concluded that Betabare 24 mg tablets and Betaserc 24 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 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).

Supportive data to justify BID (twice a day) dosing
For the RMS, the Netherlands, the 24 mg tablet is a line extension. The 24 mg tablet has to be administered BID, whereas in the NL a TID (three times a day) regimen is common. During the DCP for Betahistine 24 mg (NL/H/1037-1041/001/DC) questions were raised at D70/100 regarding the safety (high C_{max}) and efficacy (lower C_{trough}) of the BID regimen compared to the TID regimen. A higher C_{max} seems not of concern, as toxicity was moderate in doses more than 10-fold higher (see also SmPC originator). A low C_{trough} may neither be a problem, as efficacy only settles in at long term after treatment for weeks, when patients are at steady state. The 24 mg tablets/dosing schedule is therefore considered acceptable by the RMS.
Of note, several EU countries have already the 24 mg Betaserc tablet. The 24 mg Betaserc tablet was withdrawn of the market in the NL for commercial reasons in 1998.

Risk management plan
Betahistine was first approved in 1968, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of betahistine 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 SmPC. 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

SmPC
The SmPC is identical to the SmPC for procedures NL/H/1037-1041/001/DC.

Readability test
A readability testing for the PIL, was performed for the PIL as submitted (and approved) for MRP [NL/H/709+710+742+808/01-02]. As the PIL for the 24 mg tablets is more or less the same as for these 8 and 16 mg tablets, no new RMS assessment of the PIL-readability test was performed. The user testing of these procedures can be used for the 24 mg tablets.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Betabare 24 mg tablets have a proven chemical-pharmaceutical quality and are a generic form of Betaserc 24 mg tablets. Betaserc is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided sufficient supporting literature to justify the BID dosing posology with the 24 mg strength. It may be safely concluded that there are no clinical consequences of the BID regimen compared to the TID regimen regarding safety and efficacy.

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

The SmPC, package leaflet and labelling are in the agreed templates and are in agreement with other betahistine dihydrochloride containing products. Braille conditions are met by the MAH.

The Board followed the advice of the assessors. Betabare 24 mg tablets were authorised in the Netherlands on 5 November 2008.

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 Betabare 24 mg tablets with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 13 July 2009.

A European harmonised birth date has been allocated (16 May 1968) and subsequently the first data lock point for betahistine is December 2008. However, as these products will then not be marketed yet in the CMSs, there is no need to submit a PSUR in February 2009. The first PSUR will cover the period from August 2008 until December 2011. After which, the PSUR submission cycle is 3 years.

The date for the first renewal will be: 31 August 2013.

The following post-approval commitments have been made during the procedure:

<u>Quality – active substance</u>

- The MAH has committed to submit a variation to introduce the latest version of the CEP after finalization of these procedures. This commitment has been fulfilled by submission of variation NL/H/1639/001/IA/001. See '*steps taken after finalisation of the initial procedure*' table on page 10.

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
SmPC	Summary of Product Characteristics
$t_{½}$	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

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
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 apporved. Replacement DMF by CEP.	NL/H/1639/ 001/IA/001	IA	14-12-2009	28-12-2009	Approval	N
Addition of a manufacturer responsible for packaging and batch release, not including batch.	NL/H/1639/ 001/IA/002	IA	14-12-2009	28-12-2009	Approval	N
Repeat-use procedure with Bulgaria and Romania.	NL/H/1639/ 001/E/001	E	2-11-2010	31-1-2011	Approval	N
Change of site responsible for batch release and packaging of the product.	NL/H/1639/ 001/IA/003/ G	IA/G	15-3-2012	14-4-2012	Approval	N
Renewal of the marketing authorisation.	NL/H/1639/ 001/R/001	R	16-7-2012	29-12-2012	Approval	Y, Annex I
Addition of a new manufacturing site. A minor change in manufac-turing is introduced.	NL/H/1639/ 001/IB/004/ G	IB/G	12-5-2014	11-6-2014	Approval	N
Changes in Hungary: • change in the name of the marketing authorisation holder • change in the name of the manufacturer of the finished product.	NL/H/1639/ 001/IA/005/ G	IA/G	8-5-2015	7-6-2015	Approval	N

Annex I – Renewal of the marketing authorisation (NL/H/1639/001/R/001)

I RECOMMENDATION

Based on the review of the data submitted for the renewal application, the member states consider that the benefit/risk balance of Betabare 24 mg tablets is positive. A renewal with unlimited validity was granted.

II SCIENTIFIC DISCUSSION

II.1 Introduction

Betahistine is indicated for the treatment of Ménière's syndrome, symptoms of which may include vertigo, tinnitus, hearing loss and nausea.

Betabare (betahistine) 24 mg tablets was first approved by the Netherlands on 5 November 2008, and subsequently registered through an MRP in a number of other countries.

The reference product is Betaserc, with an EU harmonised birth date of 16 May 1968. Betahistine takes part in the EU Worksharing procedure with Latvia as p-RMS.

As part of this renewal the MAH submitted:
- PSUR covering the period 13 July 2009 – 31 December 2011 (period of 29.5 months)
- Clinical Expert Statement, dated 10 February 2012
- The current SmPC
- The proposed SmPC with track-changes, amended to align with the innovator SmPC.

II.2 GMP compliance statements

The following documents have been submitted:
- GMP compliance statements for all manufacturers beside the manufacturers of the active substance
- Declaration of the qualified person as regards the manufacturer of the active substance
- Contact person for pharmacovigilance
- Contact person with the overall responsibility for product defects and recalls
- Contact person for scientific service in charge of information about the medicinal product

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS 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.

<u>GMP active substance</u>
Regarding GMP for the active substance a statement is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

II.3 Quality

In accordance with the CMD(h) Best Practice Guide on the processing of renewals in the mutual recognition and decentralised procedure a quality expert statement has been submitted for Betabare 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.

- That 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.

II.4 Clinical aspects

II.4.1 Clinical efficacy

No new clinical data on efficacy have become available during this review period.

II.4.1 Clinical safety

II.4.1.1 Summary of Cumulative Experience 13 July 2009 – 31 December 2011

During the period covered by this review there have been no new licence application rejections for safety reasons, drug suspensions, withdrawals, clinical trial suspensions, dosage modifications, changes in target population or indication, or formulation, or restrictions to distribution.
The actually valid core SmPC based on the SmPC approved in the MRP procedure has been updated with the with the approved core safety profile (CSP).
During the period of this safety report there have been no changes to reference safety information.

Betabare (betahistine) is approved in eight countries and marketed in five countries. Based on the WHO defined daily dose (DDD) and the sales data, the patient exposure is 7,616,860 patient/days for the covered period. During the period covered by this safety report the MAH has not conducted any trials with the products.

During the period covered by this PSUR no spontaneous or regulatory authority report was sent to the MAH in connection with betahistine preparations.

From the literature the MAH derived the following case, which was not from a country were the MAH's product was approved:

- One literature case (De Riu 2010) was found concerning oromandibular dystonia with positive de- and rechallenge: A 62-year-old elderly woman reported at the dental department for involuntary stereotypic contractions of the lower facial muscles and tongue, which severely hindered her speech and swallowing. She developed the oromandibular dystonia following long-term use of betahistine for the treatment of vertigo. According to the authors "an elevated plasma betahistine level attributable to long-term use may have enabled the drug to cross the blood-brain barrier and accumulate in the brain."

Oromandibular dystonia is not listed as adverse reaction to betahistine in the SmPC. In the PSUR of the innovator, three additional cases concerning dystonia were presented, but the MAH concluded that even with this fourth report of a dystonia event, there is insufficient evidence of a causal association in view of the low doses used and low penetration of betahistine across the blood-brain barrier and the extensive use of betahistine. This conclusion is accepted and it is considered that no action is required at the moment.

Studies
No targeted sponsored studies have been done during the period of this safety report. No targeted new safety studies have been done during the period of this safety report. During the period of this PSUR one safety related study has been found in the literature:

Lezius et al 2011: High-dosage betahistine dihydrochloride between 288 and 480 mg/day in patients with severe Ménière's disease: a case series.
The authors stated that despite the considerable limitations of an observational study – in particular in Ménière's disease – high dosages of betahistine between 288 and 480 mg/day seem to be effective in patients who did not sufficiently respond to lower dosages. Moreover, such dosages are well tolerated. The MAH commented that nevertheless the extremely high dose the patients experienced only mild side effects including gastrointestinal complaints, fatigue and altered taste were reported.

Overall, it is noted that betahistine is well tolerated, apparently even at 10 times the approved dose. No new safety issues were identified in this study.

Overall safety information
There was no information regarding efficacy modification for the product under review. No late-breaking information was received. No new safety issues were identified with regard to drug interaction, overdose, drug abuse/misuse, pregnancy or lactation, special patient groups, long-term treatment, or prescription and medication errors.

II.4.1.2 Report of Post Marketing Experience 13 July 2009 – 31 December 2011

The clinical expert statement concludes that considering the following aspects:

"The present betahistine dihydrochloride 24 mg tablet product is a generic version of the widely marketed product Betaserc, which has been available for clinical use since more than 25 years.

Although there remains considerable doubt as to the clinical effectiveness of oral betahistine in Ménière's disease and related complaints, there seems to be still some consensus on the possible positive subjective effects of treatment in these patients. Schmidt et al (1992) concluded from their extensive study on both published literature as well as their own investigation, that the improvement that is reported in the majority of studies lies within the range of 60-80%, regardless of type of therapy. As long as a more effective treatment has not been found, one should choose the least noxious therapy available. Not a single study on betahistine treatment has been traced by these authors in whom the results were reported in accordance with the proposed criteria.

Supportive value has been obtained from clinical experience with betahistine in audiovestibular disorders, like tinnitus and vertigo, other than with Ménière's disease.

The MAH's own periodic safety update reports on pharmacovigilance support label claim for product safety, while its Summary of Product Characteristics (SmPC) provides sufficient information regarding proper administration of betahistine tablets. During the period of this statement a core SmPC has been prepared that based on the SmPCs approved in the MRP procedures.

The clinical findings published in the literature and the post-marketing experiences in connection with the product support its efficacy and safety. Overall the evidence indicates that the benefits of treatment outweigh its low toxicity. There are no new clinical and non-clinical data available, which change the benefit-risk evaluation of the product, or result in a new one. The marketing authorisation for the product can be renewed for an unlimited period when the 5-year period expires. The authorities have been kept informed of any additional data significant to the assessment of the benefit/risk ratio of the product concerned. On the basis of this fact the lengthening of marketing authorisation of betahistine tablets is strongly supported from medical point of view."

This conclusion of the MAH is agreed.

II.4.1.3 Conclusion on Safety

In the period covered by the PSUR there were no new relevant data, modifying the previous cumulative experience regarding safety for betahistine.

II.5 Product information

The SmPC has been updated to include the changes agreed in the CSP.

II.6 Outstanding commitments

Regarding PSUR submission, the MAH committed to fulfil all requirements as set out in new pharmacovigilance legislation.

There are no post-approval commitments outstanding.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

No new clinical data have become available that changed the benefit risk assessment. The product is still in compliance with the requirements regarding quality. The assessment of the submitted data did not reveal new safety concerns. The member states consider that the renewal can be granted with unlimited validity. The renewal procedure ended positively on 29 December 2012. The common renewal date was set on 31 August 2012.