

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Betahistine 2 HCl Accord 8 and 16 mg tabletten,
Accord Healthcare Ltd., United Kingdom**

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/2045/001- 002/MR
Registration number in the Netherlands: RVG 24028-9**

12 September 2011

Pharmacotherapeutic group:	antivertigo preparations
ATC code:	N07C A01
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:	16 February 1999
Concerned Member States:	Mutual recognition procedure with BE, CZ, ES, FR, HU, IE, IT, PL, PT, RO, and UK
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 2 HCl Accord 8 and 16 mg tabletten, from Accord Healthcare Ltd. The date of authorisation was on 16 February 1999 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.

The mechanism of action of betahistine is partially known. Betahistine has a very strong affinity as an antagonist for histamine H₃ receptors and a weak affinity as an agonist for histamine H₁ receptors.

Betahistine has two modes of action. Primarily, it has a direct stimulating (agonistic) effect on H₁ receptors located on blood vessels in the inner ear. It appears to act on the precapillary sphincter in the stria vascularis of the inner ear, thus reducing the pressure in the endolymphatic space.

In addition, betahistine has a powerful antagonistic effects at H₃ receptors, and increases the levels of neurotransmitters released from the nerve endings. The increased amounts of histamine released from histaminergic nerve endings stimulates H₁ receptors, thus augmenting the direct agonistic effects of betahistine on these receptors. This explains the potent vasodilatory effects of betahistine in the inner ear. This may explain the efficacy of betahistine in the treatment of vertigo.

Taken together these properties contribute to its therapeutic benefits in Ménière's syndrome. Ménière's syndrome is characterised by attack of vertigo, tinnitus, nausea, headache, hearing loss. The efficacy of betahistine 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 product Betaserc 8 mg and 16 mg tablets (NL license RVG 05852 and 13612) which has been registered in the Netherlands since 1970 by Solvay Pharmaceuticals. 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 one bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Serc 16 mg tablets, registered in the UK. 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

General information

The active substance is betahistine (di)hydrochloride, a well-known active substance described in the European Pharmacopoeia (Ph. Eur.*). The substance is freely soluble in water, soluble in methanol and ethanol and practically insoluble in carbon tetrachloride, chloroform and ether. Polymorphism is not reported.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Manufacture

The assessment of the manufacturing process was part of granting a CEP by the EDQM.

Quality control of drug substance

The drug substance specification is in line with the Ph.Eur. and CEP, with additional requirements for residual solvents. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for one full-scaled batch.

Stability of drug substance

The re-test of the substance is 5 years if stored under the proposed conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

* *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

Betahistine 2HCl Accord 8 mg – are white, round, flat, 6.5.mm tablets with bevelled edges with the inscription 'BE' on one side and a breakline on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Betahistine 2HCl Accord 16 mg – are white, round, flat, 9.0. mm tablets with bevelled edges with the inscription 'BF' on one side and a breakline on the other side. The tablet can be divided into two equal halves.

The excipients are:

Lactose monohydrate, povidone K25, anhydrous citric acid, maize starch, microcrystalline cellulose, crospovidone, and hydrogenated vegetable oil.

The tablets are packaged in blister strips (PVC/PVdC-aluminium).

The excipients and packaging are usual for this type of dosage form. The tablets are dose-proportional.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The drug product was developed in order to be similar to the originator products Serc-8 and Serc-16 of Solvay Pharmaceuticals. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process has been clearly described. The drug substance is dissolved and the solvent is used for granulation. The granules are dried, sieved, mixed with extragranular excipients and compressed into tablets. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two full-scale batches of each strength. Batch analysis results for one additional production scale batch (third full scale batch) of each strength of Betahistine Dihydrochloride Tablets will be made available to the agency as and when available.

Excipients

The excipients comply with Ph.Eur. or BP* requirements. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for description, average weight, identification, resistance to crushing, uniformity of dosage units, dissolution, loss on drying, related substances, assay, microbial limit test and subdivision of tablets. Shelf-life limits for related substances are different from release limits, which is acceptable. The analytical methods have been adequately described and validated.

Batch analytical data from the proposed production site have been provided on two full-scale batches of each strength, demonstrating compliance with the release specification. Results of a third batch will be provided post authorisation.

Stability tests on the finished product

Stability data on the product has been provided for two full-scale batches of each strength stored at 25 °C/60% RH (up to 18 months), 30 °C/65% RH (up to 12 months) and 40 °C/75% RH (up to 6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PVDC-Alu blisters. The shelf-life of 24 months when stored below 30 °C can be granted based on the provided data. Additional data should be provided to fully support the claimed shelf-life.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

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

II.2 Non clinical aspects

This product is a generic formulation of Betaserc tablets, which are 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 is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Betahistine 2 HCl Accord 16 mg tabletten (Accord Healthcare Ltd., United Kingdom) is compared with the pharmacokinetic profile of the reference product Serc 16 mg tablets (Solvay Pharmaceuticals BV, The Netherlands).

The choice of the reference product

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products (if applicable) in different member states.

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

Bioequivalence study

A open label, balanced, randomised, two-treatment, two-period, two-sequence, single dose, two-way crossover, oral bioequivalence study was carried out under fasted conditions in 26 healthy adult male subjects. Each subject received a single dose (16 mg) of one of the 2 betahistine formulations. After an overnight fast of at least 10 hours, the subjects were orally administered the single dose sitting posture with 240 mL of water at an ambient temperature.

A washout period of 6 days was maintained between the successive dosing days.

A total of 22 venous blood samples were collected in each period at pre-dose and 0.167, 0.333, 0.50, 0.667, 0.833, 1.00, 1.167, 1.333, 1.50, 1.75, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00 and 24.00 hours post dose administration.

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.

After absorption, betahistine is almost completely metabolised into the inactive metabolite 2-pyridyl acetic acid (2-PAA). Plasma samples were therefore analysed for the inactive metabolite 2-PAA content. Measuring the metabolite instead of the parent drug is justified because no unchanged betahistine has been detected in human plasma or urine.

According to the SPC, the tablets should be taken with food. This advice is based on improvement of gastric tolerability. According to the literature food does not interact with absorption. 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.

Results

Twenty-four subjects were dosed. Twenty-three subjects completed the clinical phase of the study and the plasma samples of all the 23 subjects were analysed. One subject was excluded from the study in period II because of protocol violation (subject was found positive during breath test for alcohol consumption on the day of check-in for period-II).

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

Treatment N=23	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Reference	2337.97 \pm 474.30	2407.55 \pm 486.72	456.12 \pm 63.44	0.67	4.32 \pm 0.86
Test	2336.43 \pm 471.10	2402.37 \pm 485.34	453.98 \pm 73.71	0.83	4.17 \pm 0.93
*Ratio (90% CI)	1.00 (0.97 – 1.03)	1.00 (0.97 – 1.03)	1.00 (0.97 – 1.02)	---	---
CV (%)	5.7	5.8	5.3	---	---
AUC_{0-∞} 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					

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} 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 inactive metabolite 2-PAA under fasted conditions, it can be concluded that Betahistine 2 HCl Accord 16 mg tabletten, tablets and the Serc 16 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Extrapolation of results

A biowaiver of the results of this study with the 16 mg tablet to the 8 mg tablet is acceptable, as the two tablets are produced by the same manufacturer at the same site, have the same qualitative composition, are dose proportional and show a comparable and fast *in vitro* dissolution profile.

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

In view of requests towards the MAHs of other generics or innovator of betahistine dihydrochloride, the MAH has committed to perform close monitoring of case reports involving hepatobiliary disorders or anxiety and present a cumulative overview of both topics for further assessment in the next PSUR. Furthermore the applicant also committed to present a cumulative overview of both topics for further assessment in the next PSUR.

Product information

SPC

The SmPC has been brought in line with the recently approved SPC of a betahistine containing product during a type II variation after a mutual recognition procedure NL/H/1044/001-002/II/009; June 2009. The proposed SmPC is considered to be acceptable.

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 MAH has submitted a readability test which has already been submitted during the national procedure. It concerned a patient information leaflet for Betahistine 2 HCL Accord 8 mg and 16 mg tablets. The test was performed with 20 participants in two testing rounds. The PIL has not been amended in between rounds.

The success criteria were defined as that a minimum of 18 out of 20 subjects should be able to find the information in the PIL and that a minimum of 16 out of 20 subjects should be able to show that they can understand the information and act appropriately. Even so, all questions must achieve this success criteria and it is not appropriate to sum the data. Although these criteria are not completely in line with the criteria defined in the Readability guideline ('A satisfactory test outcome for the method outlined above is when 90% of literate adults are able to find the information requested within the PL, of whom 90% can show they understand it, i.e. each and every question must be answered correctly by at least 81% of the participants'), the overall definition is comparable. Furthermore, all questions comply with above mentioned criteria and therefore this definition is acceptable.

The results have shown that the key messages for safe use can be found and understood by the subjects. Furthermore, no recommendations were suggested to the structure and presentation of the PIL. The conclusions of the readability test suggest a good readability and traceability of the PIL. The readability test can be regarded as acceptable.

Bridging report

The MAH also provided a bridging report between the user tested national PL and the PL after being brought in line with the already approved PL after finalisation of procedure NL/H/1044/01-02/II/009. The MAH bridges both PL based upon identical messages for safe use and a similar design and lay-out. This is acceptable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

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

The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. Betahistine 2 HCl Accord 8 16 mg tabletten is authorised in the Netherlands on 16 February 1999.

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 2 HCl Accord 8 16 mg tabletten with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 1 May 2011.

A European harmonised birth date has been allocated 16 May 1968, and subsequently the first data lock point for betahistine is December 2012. As the MAH wishes to adapt the PSUR cycle to the harmonised DLP, the next PSUR submission shall take place in February 2012. A PSUR cycle of three years will be followed.

The date for the first renewal will be: 30 August 2015

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

Quality - medicinal product

- The MAH has committed to provide batch analysis results for one additional production scale batch (third full scale batch) of each strength of betahistine dihydrochloride tablets when available.
- The stability data of the ongoing stability studies up to 24 months of three batches of each strength should be provided when these become available, in order to fully establish the shelf-life.

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

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached