ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, APPLICANTS / MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State EU/EEA	Marketing Authorisation Holder	Applicant	(Invented) Name	Strength	Pharmaceutical Form	Route of administration
Austria		HENNIG ARZNEIMITTEL GmbH & Co. KG Liebigstraße 1 – 2 65439 Flörsheim/Main Germany	Vertimen 8 mg Tabletten	8 mg	tablet	oral use
Austria		HENNIG ARZNEIMITTEL GmbH & Co. KG Liebigstraße 1 – 2 65439 Flörsheim/Main Germany	Vertimen 16 mg Tabletten	16 mg	tablet	oral use
Bulgaria		HENNIG ARZNEIMITTEL GmbH & Co. KG Liebigstraße 1 – 2 65439 Flörsheim/Main Germany	Vertisan 8 mg Таблетка	8 mg	tablet	oral use
Bulgaria		HENNIG ARZNEIMITTEL GmbH & Co. KG Liebigstraße 1 – 2 65439 Flörsheim/Main Germany	Vertisan 16 mg Таблетка	16 mg	tablet	oral use
Czech Republic		HENNIG ARZNEIMITTEL GmbH & Co. KG Liebigstraße 1 – 2 65439 Flörsheim/Main Germany	Vertisan® 8 mg Tableta	8 mg	tablet	oral use
Czech Republic		HENNIG ARZNEIMITTEL GmbH & Co. KG Liebigstraße 1 – 2 65439 Flörsheim/Main Germany	Vertisan® 16 mg Tableta	16 mg	tablet	oral use
Germany	HENNIG ARZNEIMITTEL GmbH & Co. KG		Betavert® N 8 mg Tabletten	8 mg	tablet	oral use

Member State EU/EEA	Marketing Authorisation Holder	Applicant	(Invented) Name	Strength	Pharmaceutical Form	Route of administration
	Liebigstraße 1 – 2 65439 Flörsheim/Main Germany					
Germany	HENNIG ARZNEIMITTEL GmbH & Co. KG Liebigstraße 1 – 2 65439 Flörsheim/Main Germany		Betavert® N 16 mg Tabletten	16 mg	tablet	oral use
Hungary		HENNIG ARZNEIMITTEL GmbH & Co. KG Liebigstraße 1 – 2 65439 Flörsheim/Main Germany	Vertisan® N 8 mg Tabletta	8 mg	tablet	oral use
Hungary		HENNIG ARZNEIMITTEL GmbH & Co. KG Liebigstraße 1 – 2 65439 Flörsheim/Main Germany	Vertisan® N 16 mg Tabletta	16 mg	tablet	oral use
Poland		HENNIG ARZNEIMITTEL GmbH & Co. KG Liebigstraße 1 – 2 65439 Flörsheim/Main Germany	Vertisan 8	8 mg	tablet	oral use
Poland		HENNIG ARZNEIMITTEL GmbH & Co. KG Liebigstraße 1 – 2 65439 Flörsheim/Main Germany	Vertisan 16	16 mg	tablet	oral use
Romania		HENNIG ARZNEIMITTEL GmbH & Co. KG Liebigstraße 1 – 2 65439 Flörsheim/Main Germany	Vertisan® 8 mg Comprimate	8 mg	tablet	oral use
Romania		HENNIG ARZNEIMITTEL	Vertisan® 16 mg	16 mg	tablet	oral use

Member State EU/EEA	Marketing Authorisation Holder	Applicant	(Invented) Name	Strength	Pharmaceutical Form	Route of administration
		GmbH & Co. KG Liebigstraße 1 – 2 65439 Flörsheim/Main Germany	Comprimate			
Slovak Republic		HENNIG ARZNEIMITTEL GmbH & Co. KG Liebigstraße 1 – 2 65439 Flörsheim/Main Germany	Vertisan® 8 mg Tablety	8 mg	tablet	oral use
Slovak Republic		HENNIG ARZNEIMITTEL GmbH & Co. KG Liebigstraße 1 – 2 65439 Flörsheim/Main Germany	Vertisan® 16 mg Tablety	16 mg	tablet	oral use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR POSITIVE OPINION

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF BETAVERT N AND ASSOCIATED NAMES (SEE ANNEX I)

Betahistine is an analogue of histamine, which is indicated in the treatment of vertigo associated with functional disorders of the vestibular apparatus in the context of Menière's symptom complex.
The originator product is Betaserc® 8 available in 8 mg tablets. The Marketing Authorisation Holder of the originator is Solvay Pharma B.V. settled in Netherlands.
This procedure concerns Betavert N, a generic version of betahistine dihydrochloride tablets.
Betavert N was approved in EU, on 18 April 2007, during a Mutual Recognition Procedure (MRP) with Germany as Reference Member State (RMS) plus 7 Concerned Member States (CMS): AT, BG, CZ, HU, PL, RO and SK. The Marketing Authorisation Holder of Betavert N is Hennig Arzneimittel GmbH & Co.KG

The MAH has demonstrated that Betavert N (Hennig Arzneimittel GmbH, Germany) and the originator, Betaserc® 8 (Duphar, UK), are bioequivalent after single administration. This was done by a bioequivalence study investigating urine levels of the main metabolite and by supportive in vitro studies, performed in the course of the national authorisation procedure, leading to the conclusion that it is justified to waive for further bioequivalence studies in human volunteers.

The Czech Republic came to the conclusion that the bioequivalence has not been properly demonstrated in vivo because of the choice of the analytical method. The issue was referred to the CMD(h) and an assessment was carried out by the RMS. Because no agreement was reached at the Day 60, the procedure was referred to the CHMP. The CHMP assessed the dossier and the available data, including the issue raised by the objecting CMS.

Critical evaluation
The CHMP asked the MAH to clearly prove the bioequivalence between Betavert N and the originator.
The MAH demonstrated the bioequivalence with two types of data: an in vivo BE-study (bioequivalence study) with urine measurement and in vitro studies on BA/BE based on Biopharmaceutics Classification System (BCS).
The solubility of the drug substance and the fast dissolution rate of the drug product were already unquestionably proven.
The determination of 2-Pyridylacetic acid (PAA), the active metabolite of betahistine, from urine samples was not considered as up-to-date method, the measurement of PAA in human plasmas would have considered more appropriate.

Quality aspects

Drug substance
The active substance Betahistine hydrochloride is described in Ph.Eur. The CHMP considered the chemical-pharmaceutical documentation and Expert Report, of Betahistine, of sufficient quality in view of the present European regulatory requirements.
The control tests and specifications for drug substance product were adequately drawn up.
No significant changes were observed in 6 months accelerated stability study (40°C/ 75% RH) and up to 5 years controlled room temperature stability study. Based on these, the CHMP proposed a re-test period of 5 years for betahistine hydrochloride.

Drug Product
The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Analytical data were submitted and the choice of excipients was justified and their functions explained.

The analysis results show that the finished products meet the specifications proposed.
The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.

Non clinical aspects

Betahistine is a structural analogue of the endogenous histamine. Its exact biochemical mode of action as well as its receptor specificity and affinity has not been clarified until now.
Pharmacodynamic, pharmacokinetic and toxicological properties of betahistine are well known. As betathistine is a widely used, well-known active substance, no further studies are required and the MAH provides none. The CHMP agreed that there were no objections to approval of Betavert N 8 mg and Betavert N 16 mg from a nonclinical point of view.

Clinical aspects

Pharmacokinetics

The pure betahistine dihydrochloride could not reliably quantify in the human body.
Absorption: following oral administration, betahistine dihydrochloride is rapidly and completely absorbed. Peak plasma concentrations of C14-labelled betahistine dihydrochloride are reached approximately 1 hour after oral administration in fasting volunteers. The absolute bioavailability of betahistine dihydrochloride is not known.
Distribution: The human volume of distribution of betahistine dihydrochloride is not known. Betahistine is excreted in breast milk in concentrations similar to those found in plasma.
The binding of Betahistine to human plasma proteins has been measured by equilibrium dialysis. Human plasma protein binding is under 5%.
Metabolism: Betahistine dihydrochloride is rapidly metabolised in the liver to the inactive major metabolite, 2-pyridylacetic acid and to demethyl-betahistine [2-(2 aminoethylpyridine)].
Elimination: Excretion of Betahistine is almost entirely (85 % – 90 %) in the urine within 24 hours Betahistin is excreted almost completely as the major metabolite in the urine. Only traces of desmethyl-betahistine dihydrochloride are recovered in the urine. Biliary elimination is not a significant route of elimination for the active agent or any of its metabolites.

Bioequivalence

The bioequivalence between Betavert N and the originator is based on Biopharmaceutics Classification System (BCS) approach (biowaiver). The conditions for the suitability of this biowaiver have been discussed taking into account: solubility, dissolution, and absorption/permeability.
The results of solubility study showed a high solubility of the active substance about a broad pH range. Considering the dissolution test, both strengths of the test product can be classified as “very rapid dissolving tablets”. The drug substance is completely and fast dissolved independent of the applied medium.
The evaluation of the permeability and the absorption of the active substance was derived from a bioequivalence and a mass balance study in vivo.
The BCS-studies of betahistine substance and formulations presented herein along with the properties of the drug substance (therapeutic index, safety and complete absorption) and the formulations (composition) provided robust support for waiving *in vivo* BE studies for Betavert N. Moreover, betahistine fulfils the regulatory requirements for granting a biowaver, being assigned to the group of compounds with high solubility and complete absorption - accordant with Class I of BCS.
The CHMP, considered these data, concluded that betahistine dihydrochloride can be assigned to the highly soluble class according to Biopharmaceutics Classification System, Class I.

Clinical efficacy/ safety

Efficacy and safety of betahistine dihydrochloride in the treatment of symptoms associated with Menière’s disease have been demonstrated in preclinical-and clinical trials. No new safety data are provided or needed. PK study, also, revealed no safety issues.

Pharmacovigilance system
The MAH has provided documents that set out a detailed description of the system of pharmacovigilance. A statement signed by the MAH and the qualified person for pharmacovigilance, indicating that the MAH has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

The RMS considers that the Pharmacovigilance system as described by the MAH fulfils the requirements as described in Volume 9A of the Rules Governing Medicinal Products in the European Union and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Benefit Risk Assessment
The Benefit-Risk-Assessment is positive.
The mechanism of action of betahistine dihydrochloride is not compleately clear but the product has been on the EU market for a long time, therefore could be concluded that its use is well established and its efficacy is proven.
The preparation of Betahistine is not recommended for use in children and adolescents due to lack of data on safety and efficacy. Non-clinical pharmacodynamic, pharmacokinetic and toxicological properties of betahistine dihydrochloride are also well known.
The solubility of the drug substance and the fast dissolution rate of the drug product have been proven.
In conclusuion, considering the absorption correlated with high permeability, the allocation of betahistine dihydrochloride to BCS Class I is considered justified by the CHMP. Consequently the drug product is eligible for BCS based biowaiver approach.

GROUNDS FOR POSITIVE OPINION

The CHMP concluded that betahistine dihydrochloride can be classified as Class I according to Biopharmaceutics Classification System. The product is considered as bioequivalent to the originator, and the benefit-risk balance is considered positive.

The CHMP has recommended the granting of the Marketing Authorisation(s) for Betavert N and associated names (see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

The valid Summary of Product Characteristics, labelling and package leaflet are the final versions achieved during the Coordination group procedure.