Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vertigon 16 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 16 mg of betahistine dihydrochloride
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White, 8.5 mm, round, flat bevel edged tablet marked “BH 16” on one side and “G” on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Betahistine is indicated for the treatment of vertigo, tinnitus, hearing loss and nausea associated with Ménière's syndrome.

4.2 Posology and method of administration

Posology

Adults (including the elderly)

Initial oral treatment is 8 mg to 16 mg three times daily, taken with food. Maintenance doses are generally in the range 24 - 48 mg daily. Dosage can be adjusted to suit individual patient needs.

Paediatric population
Betahistine tablets are not recommended for use in children below 18 years due to insufficient data on safety and efficacy.

Geriatric population
Although there are limited data from clinical studies in this patient group, extensive post marketing experience suggests that no dose adjustment is necessary in this patient population.

*Patients with renal impairmen*t
There are no specific clinical trials available in this patient group, but according to post-marketing experience no dose adjustment appears to be necessary.

Patients with hepatic impairment
There are no specific clinical trials available in this patient group, but according to post-marketing experience no dose adjustment appears to be necessary.

Method of administration
For oral use.

4.3 Contraindications

Phaeochromocytoma. As betahistine is a synthetic analogue of histamine it may induce the release of catecholamines from the tumour resulting in severe hypertension.

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Concurrent use with antihistamines (see section 4.5).

4.4 Special warnings and precautions for use

Caution is advised in the treatment of patients with peptic ulcer or a history of peptic ulceration, because of the occasional dyspepsia encountered in patients on betahistine.

Caution should be exercised in patients with bronchial asthma.

Patients with bronchial asthma (as clinical intolerance has been seen in a relatively few patients) and history of peptic ulcer need to be carefully monitored during the therapy.

Caution is advised in prescribing betahistine to patients with urticaria, rashes or allergic rhinitis, because of the possibility of aggravating these symptoms.

Betahistine is not indicated for treatment of the following diseases: benign paroxysmal vertigo and vertigos in relation with a central nervous system disease.

4.5 Interaction with other medicinal products and other forms of interaction

No *in vivo* interaction studies have been performed. Based on *in vitro* data, no *in vivo* inhibition on Cytochrome P 450 enzymes is expected.

In vitro data indicate an inhibition of betahistine metabolism by drugs that inhibit monoamino-oxidase (MAO) including MAO subtype B (e.g. selegiline). Caution is recommended when using betahistine and MAO inhibitors (including MAO-B selective) concomitantly.

As betahistine is an analogue of histamine, interaction of betahistine with antihistamines may in theory affect the efficacy of one of these drugs.

There is a case report of an interaction with ethanol and a compound containing pyrimethamine with dapsone and another potentiation of betahistine with salbutamol.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of betahistine in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition and postnatal development. The potential risk for humans is unknown. Betahistine should not be used during pregnancy unless clearly necessary (see also section 5.3).

Breast-feeding
It is not known whether betahistine is excreted in human milk. There are no animal studies on the excretion of betahistine in milk. The importance of the drug to the mother should be weighed against the benefits of nursing and the potential risks for the child.

4.7 Effects on ability to drive and use machines

Vertigo, tinnitus and hearing loss associated with Ménière's syndrome can negatively affect the ability to drive and use machines. In clinical studies specifically designed to investigate the ability to drive and use machines betahistine had no or negligible effects.

However, rare reports of drowsiness associated with betahistine have been made. Patients should be advised that if they are affected in this way they should avoid activities requiring concentration, such as driving and operating machinery.

4.8 Undesirable effects

Betahistine is generally well tolerated and relatively few side effects have been reported.

The frequency categories assigned to the adverse reactions below are estimates, as for most reactions suitable data for calculating incidence are not available. In addition the incidence of adverse reactions associated with betahistine dihydrochloride may vary according to the indication.

Data from clinical trials were used to determine the frequency of very common to rare undesirable effects. The frequencies assigned to all other undesirable effects (i.e., those occurring at <1/1,000) were mainly determined using post-marketing data, and refer to a reporting rate rather than a true frequency.

The following convention has been used for the classification of frequency:
very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data; reported spontaneously during post-marketing use and in scientific literature)

MedDRA system organ class	**Very common**	**Common**	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system disorders				thrombocytopenia	
Immune system disorders					hypersensitivity reactions, e.g. anaphylaxis
Nervous system disorders		headache	somnolence		drowsiness
Gastrointestinal disorders	dry mouth, diarrhoea	nausea dyspepsia			mild gastric complaints (e.g. vomiting, gastrointestinal pain, abdominal distension and bloating). These can normally be dealt with by taking the dose during meals or by lowering the dose.

Skin and subcutaneous tissue disorders					Skin rashes, cutaneous and subcutaneous hypersensitivity reactions, in particular angioneurotic oedema, urticaria, rash, and pruritus.
General disorder and administrative site conditions			asthenia		
Investigations				increase of transaminases	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms
The symptoms of betahistine overdose are nausea, vomiting, dyspepsia, ataxia and seizures at higher doses.

A few overdose cases have been reported. Some patients experienced mild to moderate symptoms with doses up to 640 mg (e.g. nausea, somnolence, abdominal pain). More serious complications (e.g. convulsion, pulmonary or cardiac complications) were observed in cases of intentional overdose of betahistine, especially in combination with other drugs.

Management
No specific antidote. Treatment of overdose should include gastric lavage, symptomatic treatment and standard supportive measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivertigo preparations, ATC code: N07C A01

The mechanism of action of betahistine is only partly understood. Single oral doses of betahistine of up to 32 mg in normal subjects produced maximal suppression of induced vestibular nystagmus 3-4 hours post-dose, with larger doses being more effective in reducing the nystagmus duration.
There are several plausible hypotheses that are supported by animal studies and human data:

- Betahistine affects the histaminergic system

Betahistine acts both as a partial histamine H_1-receptor agonist and histamine H_3-receptor antagonist also in neuronal tissue, and has negligible H_2-receptor activity. Betahistine increases histamine

turnover and release by blocking presynaptic H_3-receptors and inducing H_3-receptor downregulation.

Pulmonary epithelial permeability in man is increased by betahistine. This is derived from a reduction in the time of clearance from the lung to blood of a radioactive marker. This action is prevented by oral pre-treatment with terfenadine, a known H_1 receptor blocker.

Whilst histamine has positive inotropic effects on the heart, betahistine is not known to increase cardiac output and its vasodilator effect may produce a small fall in blood pressure in some patients.

- Betahistine may increase blood flow to the cochlear region as well as to the whole brain

Pharmacological testing in animals has shown that the blood circulation in the striae vascularis of the inner ear improves, probably by means of a relaxation of the precapillary sphincters of the microcirculation of the inner ear. Betahistine was also shown to increase cerebral blood flow in humans.

- Betahistine facilitates vestibular compensation

Betahistine accelerates the vestibular recovery after unilateral neurectomy in animals, by promoting and facilitating central vestibular compensation; this effect characterised by an up-regulation of histamine turnover and release, is mediated via the H_3-receptor antagonism. In human subjects, recovery time after vestibular neurectomy was also reduced when treated with betahistine.

- Betahistine alters neuronal firing in the vestibular nuclei

Betahistine was also found to have a dose dependent inhibiting effect on spike generation of neurons in lateral and medial vestibular nuclei.

The pharmacodynamic properties as demonstrated in animals may contribute to the therapeutic benefit of betahistine in the vestibular system.

The efficacy of betahistine was shown in studies in patients with vestibular vertigo and with Ménière's disease as was demonstrated by improvements in severity and frequency of vertigo attacks.

5.2 Pharmacokinetic properties

Absorption
Orally administered betahistine is readily and almost completely absorbed from all parts of the gastro-intestinal tract. After absorption, the drug is rapidly and almost completely metabolised into 2-pyridylacetic acid. Plasma levels of betahistine are very low. Pharmacokinetic analyses are therefore based on 2-PAA measurements in plasma and urine.

Under fed conditions C_{max} is lower compared to fasted conditions. However, total absorption of betahistine is similar under both conditions, indicating that food intake only slows down the absorption of betahistine.

Distribution
The percentage of betahistine that is bound by blood plasma proteins is less than 5 %.

Biotransformation
After absorption, betahistine is rapidly and almost completely metabolised into 2-PAA (which has no pharmacological activity).

After oral administration of betahistine the plasma (and urinary) concentration of 2-PAA reaches its maximum 1 hour after intake and declines with a half-life of about 3.5 hours.

Elimination
2-PAA is readily excreted in the urine. In the dose range between 8 and 48 mg, about 85% of the original dose is recovered in the urine. Renal or faecal excretion of betahistine itself is of minor importance.

Linearity
Recovery rates are constant over the oral dose range of 8 – 48 mg indicating that the pharmacokinetics of betahistine are linear, and suggesting that the involved metabolic pathway is not saturated.

5.3 Preclinical safety data

Repeated oral dose toxicity studies in dogs and rats for 6 and 18 months respectively revealed no clinically relevant adverse effects.

Betahistine was not mutagenic in conventional *in vitro* and *in vivo* studies of genotoxicity. Histopathological examination in the 18 months chronic toxicity study indicated no carcinogenic effects. However, specific carcinogenicity studies were not performed with betahistine.

Limited studies of reproductive toxicity in rats and rabbits showed no teratogenic effects.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline
Mannitol (E421)
Citric acid monohydrate (E330)
Silica, colloidal anhydrous Talc (E553b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original container in order to protect from light and moisture.

6.5 Nature and contents of container

PVdC (285 mm)/Aluminium (20 mm) blister strips. Available in packs of 20, 28, 30, 56, 84, 90, 100, 112, 120, 168 and 180 tablets.

Polypropylene tablet containers sealed with polyethylene caps with optional polyethylene ullage filler. Available in packs of 5, 7, 10, 15, 20, 21, 25, 28, 30, 50, 56, 60, 84, 90, 100, 112, 120, 168, 250, 500 and 1000 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Aurobindo Pharma (Malta) Limited
Vault 14, Level 2, Valletta Waterfront
Floriana FRN 1913
Malta

8 MARKETING AUTHORISATION NUMBER

PA1445/013/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 April 2000
Date of last renewal: 9 December 2007

10 DATE OF REVISION OF THE TEXT

January 2016