Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vertigon 8 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 8 mg Betahistine dihydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White to off-white round (diameter 7.0 mm), flat uncoated tablets debossed with 'X' on one side and '87' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Dosage

Adults:
Initial oral treatment is 8 to 16 mg three times daily, taken preferably with meals.
Maintenance doses are generally in the range 24 - 48 mg daily. . The daily dose should be given in 2 or 3 divided doses throughout the day. Daily dose should not exceed 48 mg. Dosage can be adjusted to suit individual patient needs. Sometimes improvement could be observed only after a couple of weeks of treatment. The best results are sometimes obtained after a few months. There are indications that treatment from the onset of the disease prevents the progression of the disease and/or the loss of hearing in later phases of the disease.

Vertigon 8 mg/16 mg:

8 mg tablets	16 mg tablets
1 - 2 tablets 3 times/day	½ - 1 tablet 3 times/day

Vertigon 24mg:
The recommended starting dose is 24 mg betahistine

If the maximum daily dose of 48 mg is indicated adults take one 24 mg tablet twice daily (in the morning and in the evening)

24 mg tablets
1 tablet 2 times/day

Renal 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.

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.

Elderly 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 population.

Paediatric population:
Betahistine tablets are not recommended for use in children and adolescents below age 18 due to lack of data on safety and efficacy.

Method of administration
Take the tablets preferably with meals or after meals with a glass of water. Betahistine may cause mild indigestion (listed in section 4.8). Taking betahistine with food may help to relieve indigestion.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1

Betahistine is contraindicated in patients with phaeochromocytoma. As betahistine is a synthetic analogue of histamine it may induce the release of catecholamines from the tumor resulting in severe hypertension.

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.

Patients with bronchial asthma and peptic ulcer should be monitored carefully during the treatment with betahistine.

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

Caution is advised in patients with severe hypotension.

Betahistine is not the appropriate treatment for the following pathologies:

• Benign paroxysmal vertigo,
• Dizziness related to central nervous system disease.

<u>Precautions for use</u>
Taking the drug in the middle of meals helps avoid gastralgia.

4.5 Interaction with other medicinal products and other forms of interaction

There are no proven cases of hazardous interactions. No in-vivo interaction studies have been performed. Based on in-vitro data no in-vivo inhibition on Cytochrome P450 enzymes is expected.

Although an antagonism between Betahistine and antihistamines could be expected on a theoretical basis, no such interactions have been reported.

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

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.

Betahistine is a histamine analogue, concurrent administration of H1 antagonists may cause a mutual attenuation of effect of the active agents.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of betahistine in pregnant women. Animal studies, do not indicate direct or indirect harmful effects with respect to reproductive toxicity, embryonal/foetal development, parturition and postnatal development. at clinically relevant therapeutic exposure. As a precautionary measure, it is preferable to avoid the use of betahistine during pregnancy.

Breast-feeding

It is not known whether betahistine is excreted in human milk. Betahistine is excreted in rat milk. Effects seen post-partum in animal studies were limited to very high doses. The importance of the drug to the mother should be weighed against the benefits of nursing and the potential risk for the child. There are no animal studies on the excretion of betahistine in milk.

Fertility
Animal studies did not show effects on fertility in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Betahistine is indicated for vertigo, tinnitus and hearing loss associated with Ménière's syndrome which 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.

4.8 Undesirable effects

The following undesirable effects have been experienced with the below indicated frequencies in betahistine-treated patients in placebo-controlled clinical trials and in post-marketing reports: 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); and not known (cannot be estimated from the available data).

Nervous system disorders:
Common: headache

Gastrointestinal disorders:
Common: nausea & dyspepsia

In addition to those events reported during clinical trials, the following undesirable effects have been reported spontaneously during post-marketing use and in scientific literature. A frequency cannot be estimated from the available data and is therefore classified as "not known".
Blood and lymphatic system disorders
Not known: Thrombocytopenia.

Immune system disorders:
Not known: hypersensitivity reactions, e.g. anaphylaxis.
Gastrointestinal disorders:
Gastro-intestinal upset has rarely been reported.
Not known: Mild gastric complaints (e.g. vomiting, gastrointestinal pain, dry mouth, diarrhea, 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
Not known: cutaneous and subcutaneous hypersensitivity reactions, in particular angioneurotic oedema, urticarial, rash, and pruritus

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

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).Other symptoms of betahistine overdose are vomiting, dyspepsia, ataxia and seizures. More serious complications (convulsion, pulmonary or cardiac complications) were observed in cases of intentional overdose of betahistine especially in combination with other overdosed drugs. No specific antidote. Gastric lavage and symptomatic treatment are recommended within one hour after intake. Treatment of overdose should include general supportive measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 2.7 Central Nervous System. Antiemetic and anti-vertigo ATC code: N07C A01

The mechanism of action of betahistine is only partially understood.
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 H1-receptor agonist and histamine H3-receptor antagonist also in neuronal tissue, and has negligible H2-receptor activity.
Betahistine increases histamine turnover and release by blocking presynaptic H3-receptors and inducing H3-receptor downregulation.
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 is characterised by an up-regulation of histamine turnover and release, is mediated via the H3 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 metabolized into 2-pyridylacetic acid (pharmacologically inactive). Plasma levels of betahistine are very low (eg below the detection limit of 100 pg / mL). Pharmacokinetic analyses are therefore based on 2-PAA measurements in plasma and urine.
Under fed conditions Cmax 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 fecal 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 dose toxicity studies of six months duration in dogs and 18 months duration in albino rats revealed no clinically relevant harmful effects at dose levels in the range 2.5 to 120 mg. kg^{-1}.

Chronic toxicity:
Adverse effects in the nervous system were seen in dogs and baboons after intravenous doses at and above 120 mg/kg.
Chronic oral toxicity testing for 18 months in rats at a dose of 500 mg/kg and 6 months in dogs at a dose of 25 mg/kg showed betahistine to be well tolerated with no definitive toxicities.

Mutagenic and carcinogenic potential:
Betahistine is devoid of mutagenic potential and there was no evidence of carcinogenicity in rats. In an 18 months chronic toxicity study in rats betahistine up to a dose of 500 mg/kg did not show any evidence for carcinogenic potential. Tests conducted on pregnant rabbits showed no evidence of teratological effects.

Reproduction toxicity
Effects in reproductive toxicity studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Mannitol
Povidone
Crospovidone
Citric acid
Colloidal anhydrous silica
Talc
Stearic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage condition.

6.5 Nature and contents of container

Blisters of Polyamide/ Aluminium/ PVC/ Aluminium:
8 mg: 10, 20, 30, 50, 60, 84, 90, 100 & 120 tablets.

White opaque round HDPE bottle with polypropylene closure containing cotton coil: 30 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

PA1445/023/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd October 2014
Date of last renewal: 10th July 2019

10 DATE OF REVISION OF THE TEXT

June 2023