Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

By-Vertin 16 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 16 mg betahistine dihydrochloride.

Each tablet contains 140 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
Cylindrical, biplane white tablet with bevel-edges on both sides, diameter 9 mm.
Embossed 'B16' on one side, scored reverse.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Betahistine 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 (including the elderly):
Initial oral treatment is 8 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.

4.3 Contraindications

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

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 history of peptic ulcer need to be carefully monitored during therapy.
Caution is advised in prescribing betahistine to patients with either urticaria, rashes of allergic rhinitis, because of the possibility of aggravating these symptoms.

Caution is advised in patients with severe hypotension.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

There are no proven cases of hazardous interactions.

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.

No in vivo interaction studies have been performed. Based on in vitro data no in vivo inhibition on Cytochrome P450 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 a histamine analogue, interaction of betahistine with antihistamines may in theory affect the efficacy of one of these drugs.

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.

Lactation

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

Betahistine is indicated for Morbus Meniere and symptomatic vertigo. Both diseases 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 [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)]

Gastrointestinal disorders:
Rare: gastro-intestinal upset, nausea, dyspepsia

Nervous system disorders:
Not known (cannot be estimated from the available data): headaches, and occasional drowsiness

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”.

Immune system disorders:
Hypersensitivity reactions, e.g. anaphylaxis

Gastrointestinal disorders:
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:
Cutaneous and subcutaneous hypersensitivity reactions, in particular angioneurotic oedema, urticaria, 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 moderate symptoms with doses up to 640 mg (e.g. nausea, somnolence, abdominal pain). More serious complication (e.g. convulsion, pulmonary or cardiac complications) were observed in cases of intentional overdose of betahistine especially in combinations with other overdosed drugs. Treatment of overdose should include standard supportive measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The ATC code of betahistine is N07CA01. Betahistine is an antivertigo preparation, which belongs to the group of miscellaneous drugs that act on the nervous system.

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).

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.

Single oral doses of betahistine of up to 32 mg in normal subjects produced maximal suppression of induced vestibular nystagmus 3 to 4 hours post-dose, with larger doses being more effective in reducing the nystagmus duration.

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 H1- 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.
In man, betahistine has little effect on exocrine glands.

5.2 Pharmacokinetic properties

Absorption
Betahistine is completely absorbed after oral administration, and peak plasma concentrations of ^{14}C-labelled betahistine are attained after approximately one hour of oral administration for fasting subjects.

Distribution
Little or no binding occurs with human plasma proteins.

Metabolism & elimination
Elimination of betahistine takes place mainly by metabolism and the metabolites are subsequently eliminated mainly by renal excretion. 85-90% of the radioactivity of an 8 mg dose appears in the urine over 56 hours, with maximum excretion rates reached within 2 hours of administration. After oral *administration* of betahistine, its plasma levels are very low. Therefore, the assessment of the pharmacokinetics of betahistine is based on the plasma concentration data of the only metabolite 2-pyridylacetic acid. There is no evidence of presystemic metabolism and biliary excretion is not thought to be an important route of elimination for the drug or any of its metabolites, however betahistine is subject to metabolism in the liver.

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 $mg.kg^{-1}$. Betahistine is devoid of mutagenic potential and there was no evidence of carcinogenicity in rats. Tests conducted on pregnant rabbits showed no evidence of teratological effects.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone
Microcrystalline cellulose
Lactose monohydrate
Colloidal anhydrous silica
Crospovidone
Stearic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

Alu/PVC/PVDC blister strips.
Available in packs of 14, 20, 42, 50, 60 and 84 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Fannin Limited
Fannin House
South County Business Park
Leopardstown
Dublin 18

8 MARKETING AUTHORISATION NUMBER

PA1457/011/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 January 2001

Date of last renewal: 23 October 2010

10 DATE OF REVISION OF THE TEXT

February 2017