# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Betahistine dihydrochloride 16mg tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Betahistine dihydrochloride 16 mg

Excipient(s) with known effect:
Each tablet contains 100 mg lactose monohydrate
For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Tablet
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.

## 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
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. 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.
There is no data available for patients with hepatic impairment.
There is no data available for patients with renal impairment.
There is limited data in the elderly, betahistine should be used with caution in this population.

Children and adolescents:

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

**4.3 Contraindications**

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.

Also contraindicated are the following:
- hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

**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.

Clinical intolerance to Betahistine may occur in bronchial asthma patients (see section 4.5 and 4.8) - These patients should therefore 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.

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 interactions**

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.

*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.

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.

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 insufficient data on the use of betahistine in pregnant women. Animal studies, though insufficient do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant therapeutic exposure. (see section 5.3). The potential risk for humans is unknown. As a precautionary measure, it is preferable to avoid the use of Betahistine during pregnancy.

Lactation
It is not known whether betahistine is excreted in breast milk in humans. Betahistine is excreted in rat milk. The effects post-partum seen in animal studies were limited to very high doses. The importance of taking the medicine by the mother must be weighed against the benefits of breastfeeding and the potential risk for the child.

Fertility
Animal studies show no influence on fertility in rats.

**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.
Betahistine is regarded to have no or negligible effects on the ability to drive and use machines as no effects potentially influencing this ability were found to be related to betahistine in clinical studies.

**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 (frequency cannot be estimated from the available data).

Immune system disorders:
*Not known*: hypersensitivity reactions, e.g. anaphylaxis.

Nervous system disorders:
*Common*: headache, occasional drowsiness

Cardiac disorders
*Not known*: palpitations

Respiratory disorders
*Not known*: Bronchospasms may occur in patients with bronchial asthma (see section 4.4)

Gastrointestinal disorders:
*Common*: dyspepsia [*], nausea

Skin and subcutaneous tissue disorders
*Not known*: cutaneous and subcutaneous hypersensitivity reactions, in particular angioneurotic oedema, urticarial, rash, and pruritus

[*]Mild gastric complaints (e.g. vomiting, gastrointestinal pain, abdominal distension and bloating) have been observed. These can normally be dealt with by taking the dose during meals or by lowering the dose."

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.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: antivertigo preparation, ATC code: N07C A01

The mechanism of action of betahistine is known partially. Betahistine has a very strong affinity as an antagonist for histamine $H_3$ receptors and a weak affinity as an agonist for histamine $H_1$ receptors. The active ingredient is a specific histamine agonist with virtually no $H_2$-activity.

Betahistine has two modes of action. Primarily, it has a direct stimulating (agonistic) effect on $H_1$ 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 $H_3$ receptors, and increases the levels of neurotransmitters released from the nerve endings. The increased amounts of histamine released from histaminergic nerve endings stimulates $H_1$ 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 explains 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 attach 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.

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 rapidly and completely absorbed after oral administration of the drug in tablets, and peak plasma concentrations of $^{14}$C-labelledbetahistine are attained after approximately one hour of oral administration for fasting subjects.

Distribution
Little or no binding occurs with human plasma proteins.

Metabolism and Elimination
Elimination of betahistine takes place mainly by metabolism and the metabolites are subsequently eliminated mainly by renal excretion
Following the absorption, the drug is metabolized rapidly in the metabolite and almost completely in metabolite 2-pyridylacetic acid.

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. The concentration of 2-pyridylacetic acid reaches its maximum at 1 hour after intake and declines with half approximately 3.5 hours. The 2-pyridylacetic acid is excreted almost quantitatively in urine within 24 hours after administration. In the dose range between 8 and 48 mg, about 85% of the original dose was recovered in the urine. No unchanged betahistine has been detected in urine.

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.

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**

Chronic toxicity
Adverse reactions affecting the central nervous system were seen in dogs and baboons after intravenous doses of 120 mg / kg and higher.

Studies on chronic oral toxicity over a period of 18 months in rats with a dose of 500 mg / kg and for 6 months in dogs with a dose of 25 mg / kg indicate that betahistine is well tolerated without definitive toxicity.

Mutagenic and carcinogenic potential Betahistine has no mutagenic potential.

In an 18-month chronic toxicity study in rats with a dose up to 500 mg / kg, there was no evidence of carcinogenic potential.

Reproductive toxicity
During reproductive toxicity studies, effects were only seen at exposures considered to be well above the maximum human exposure, indicating minimal relevance during clinical use.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Lactose monohydrate
Povidone K25,
Anhydrous citric acid
Maize starch,
Microcrystalline cellulose
Crospovidone
Hydrogenated vegetable oil

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

2 years

**6.4 Special precautions for storage**

Store below 30 ºC.
Store in the original package in order to protect from moisture.

**6.5 Nature and contents of container**

The tablets are packaged in blister strips (PVC/PVdC-aluminium).
Pack size of 14, 20, 30, 60, 84, 90 and 120 tablets.
Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

Any unused product or waste material should be disposed of in accordance with local requirements.

**7 MARKETING AUTHORISATION HOLDER**

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

**8 MARKETING AUTHORISATION NUMBER**

PA2315/078/002

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 7th October 2011
Date of last renewal: 30th August 2015

**10 DATE OF REVISION OF THE TEXT**

March 2019
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