SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Betahistine dihydrochloride 8 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Betahistine 2HCl Accord 8 mg tablets

Each tablet contains
Betahistine dihydrochloride 8 mg

Excipient(s) with known effect:
Each tablet contains 50 mg lactose monohydrate

Betahistine 2HCl Accord 16 mg tablets

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, 6.5.mm tablets with bevelled edges with the inscription ‘BE’ on one side and a breakline on the other side.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

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 in bronchial asthma patients has been shown in relatively few patients. These patients 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.

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. 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 beta histine with salbutamol.

Beta histine 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 is a very limited amount of data from the use of betahistine in pregnant women. Animal studies, though insufficient do not indicate direct or indirect harmful effects with respect to reproductive toxicity (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
There is insufficient information on the excretion of betahistine in human milk. There are no animal studies on the excretion of betahistine in milk. Betahistine should not be used during breastfeeding.

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.
Beta histine 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
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 the national reporting system listed in below (To be completed nationally).

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 H3 receptors and a weak affinity as an agonist for histamine H1 receptors. The active ingredient is a specific histamine agonist with virtually no H2-activity.

Betahistine has two modes of action. Primarily, it has a direct stimulating (agonistic) effect on H1 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 H3 receptors, and increases the levels of neurotransmitters released from the nerve endings. The increased amounts of histamine released from histaminergic nerve endings stimulates H1 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 14C-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 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 bitahistine has been detected.

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

Repeated oral 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. However, specific carcinogenicity studies were not performed with Betahistine.

Limited studies conducted on pregnant rabbits showed no evidence of teratological effects.
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 °C.
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, 50, 60, 84, 90 and 120 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER
8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0314

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/05/2011

10 DATE OF REVISION OF THE TEXT

22/02/2016