Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Betahistine dihydrochloride 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, flat, bevel-edged tablet debossed '8' on one side and 'B' on other side with a diameter of 7 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Betahistine dihydrochloride 8 mg tablet is indicated for vertigo, tinnitus and hearing loss associated with Ménière's syndrome.

4.2 Posology and method of administration

Posology

Adults (including the elderly):
The usual dose is 8 to 16 mg, three times daily taken preferably with meals.
Maintenance doses are generally in the range 24-48 mg daily.

Paediatric population:
Betahistine should not be used in children aged below 18 years due to insufficient data on safety and efficacy.

Elderly:
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.

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.

Method of administration.
Oral use.
The tablets should be swallowed without being chewed with a glass of water during meals.

4.3 Contraindications

- Phaeochromocytoma.
- Hypersensitivity to the active substance 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 a history of peptic ulcer.

Clinical intolerance to betahistine dihydrochloride in bronchial asthma patients has been shown in a relatively few patients. These patients need to be carefully monitored during the therapy.

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 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 an analogue of histamine, 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 do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). 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.

Available pharmacological/ toxicological data in rats have shown excretion of betahistine in milk.

A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from betahistine therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility:

Animal studies did not show effects 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. 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
Common: nausea and dyspepsia

Nervous System disorders
Common: headache

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 have been reported.

Gastrointestinal disorders
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.

Skin and subcutaneous tissue disorders
Cutaneous and subcutaneous hypersensitivity reactions have been reported, 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, Website: www.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). More serious complications (e.g. convulsion, pulmonary or cardiac complications) were observed in cases of intentional overdose of betahistine especially in combination with other overdosed drugs. Treatment of overdose should include standard supportive measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-vertigo preparations. ATC-Code: N07CA01

The mechanism of action of betahistine is only partly 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 characterized 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. Plasma levels of betahistine are very low. 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 metabolized 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.

Excretion:
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

Non-clinical data reveal no special hazard for humans based on available data on genotoxicity.

Effects in non-clinical repeated dose and 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

Cellulose microcrystalline
Mannitol
Colloidal anhydrous silica
Anhydrous citric acid
Talc

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in the original pack in order to protect from moisture.

6.5 Nature and contents of container

Alu-PVC/PVdC blister packs of 84 and 120 tablets.

Alu-Alu blister packs of 84 and 120 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA22871/017/001

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Date of First Authorisation: 21st January 2022

10 DATE OF REVISION OF THE TEXT