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.

Each tablet contains 50 mg lactose monohydrate.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.

White, flat, round tablets with bevelled edges, score line on one side, diameter 6.5 mm.

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

For the treatment of Meniére's syndrome, symptoms of which may include vertigo, nausea, tinnitus and hearing loss.

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.

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.

4.3 Contraindications

Betahistine is contraindicated in case of:

- Hypersensitivity to the active substance(s) 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 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.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose – galactose malabsorption should not take this medicinal product.

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 monoaminooxidase (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 at clinically relevant therapeutic exposure. 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 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 risks for the child.

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 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).]

Gastrointestinal disorders:

Common: nausea & 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, 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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard Or search for MHRA Yellow Card in the Google Play or Apple App Store.

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: antivertigo 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

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 does not have mutagenic potential.

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.

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

Lactose monohydrate

Maize starch

Cellulose microcrystalline, E 460

Citric acid, anhydrous, E 330

Povidone K 25, E 1201

Crospovidone type A, E 1202

Hydrogenated vegetable oil

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blisters of PVC / PE / PVDC – aluminium.

Packs of 14, 20, 24, 28, 30, 48, 50, 60, 84, 90, 96, and 100 tablets are available. 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

Morningside Healthcare Ltd

Unit C, Harcourt Way

Leicester, LE19 1WP, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 20117/0236

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/06/2015

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19/02/2020