SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Betahistine Dihydrochloride 16mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 16mg betahistine dihydrochloride.

Excipient(s) with known effect: lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Betahistine Dihydrochloride 16mg Tablets are white, circular, flat, bevelled edged tablets marked B16 on one side with a break line on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Vertigo, tinnitus and hearing loss associated with Ménière's syndrome.

4.2 Posology and method of administration

Adults, including the elderly: Initially 16 mg (two tablets) three times daily, taken preferably with meals. Maintenance doses are generally in the range 24 to 48 mg daily. Dosage should be altered according to clinical response.

Paediatric population: not recommended for use in children below 18 years due to insufficient data on safety and efficacy.

Geriatric 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 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 postmarketing experience no dose adjustment appears to be necessary.

4.3 Contraindications

Use in patients with hypersensitivity to betahistine dihydrochloride or any component of the tablet. Use in patients with phaeochromocytoma.

4.4 Special warnings and precautions for use

Betahistine dihydrochloride is considered to be unsafe in patients with porphyria

Betahistine dihydrochloride should be administered with caution to patients with bronchial asthma (due to clinical intolerance) or a history of peptic ulcer.

Betahistine dihydrochloride is not recommended for use in children.

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

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.

Betahistine dihydrochloride should not be used concurrently with antihistamines (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 are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition and postnatal development. 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 human milk. Betahistine is excreted in rat milk. Effects 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 dihydrochloride-treated patients in placebo-controlled clinical trials (very common (≥ 1/10); very common (_1/10); common (_1/100 to <1/10); uncommon (≥ /1,000 to < 1/100); rare (≥ /10,000 to < 1/1,000); very rare (<1/10,000))

Gastrointestinal disorders
Common: nausea and dyspepsia

Nervous systems 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 systems 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 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.

There is no specific antidote to betahistine dihydrochloride. Gastric lavage and symptomatic treatment is recommended. Treatment of overdose should include standard supportive measures.

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 dihydrochloride is a histamine-like drug in which pharmacological activity can be attributed to a specific effects and/or more direct influences on recovery mechanisms the vestibular nuclei. It has weak agonist activity at histamine H_1 receptors and moderate antagonist activity at H_3; receptors. The antagonist action of betahistine dihydrochloride at the H_3: receptor can be expected to potentiate the release of presynaptic histamine in vivo by blocking the auto-inhibitory feedback at histaminergic terminals, its action on medial vestibular nucleus cells is to significantly reduce their responsiveness to histamine. This action of betahistine dihydrochloride occurs at post-synaptic H_1 receptors, since betahistine dihydrochloride lacks any effect at H_2 receptors. The effects of betahistine dihydrochloride are thus consistent with a partial agonist action at these receptors, with betahistine dihydrochloride having little excitatory action on its own but reducing the excitatory responses to histamine by occupying H_1 receptor sites.

The reduced response of the medial vestibular nucleus cells to histamine in the presence of betahistine dihydrochloride may be the result of the activation of H_2 receptor-coupled second-messenger pathways alone rather than the normal activation of both H_1 and H_2 second-messenger systems together. Thus, simultaneous stimulation of the H_1 and H_2 receptor pathways is known to cause a large amplification of the cellular cAMP response, above that caused by stimulation of the H_2 receptor pathway alone. The reduction in the amplitude and total duration of the histamine-induced excitation in medial vestibular nucleus cells in the presence of betahistine dihydrochloride is suggestive of such a mechanism. This partial agonist action of betahistine dihydrochloride at H_1 receptor may be an important part of its mechanism of action.

• 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:
Betahistine dihydrochloride is readily and almost completely absorbed after oral administration from all parts of the gastro-intestinal tract, and peak plasma concentrations of ^{14}C-labelled betahistine dihydrochloride are attained one hour after oral administration to fasting subjects. 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.
Betahistine dihydrochloride is eliminated by the kidney with 85 - 90% of the radioactivity of an 8 mg dose appearing in the urine over 56 hours. Maximum excretion rates are reached within 2 hours of administration. Plasma levels of the parent drug are below the limits of detection of the assay.

Bioavailability has therefore been assessed from urinary excretion of its main metabolite, 2-pyridylacetic acid.

There is no evidence for presystemic metabolism. Biliary excretion is not important as a route of elimination of either the drug or its metabolites in the rat and is unlikely to be so in man.

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

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 25mg/kg showed Betahistine to be well tolerated with no definitive toxicities
Betahistine was not mutagenic in conventional in vitro and in vivo studies of genotoxicity.

Histopathological examination in the 18 months chronic toxicity study indicated no carcinogenic effects. However, specific carcinogenicity studies were not performed with Betahistine.

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.

6.1 List of excipients

Povidone K90
Microcrystalline cellulose
Lactose monohydrate
Colloidal anhydrous silica
Crospovidone
Stearic acid

6.2 Incompatibilities

None known

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package. Keep container in the outer carton.

6.5 Nature and contents of container

Blister strips consisting of 250 µm transparent PVC, a 60 g/m2 PVDC layer and 20 µm hard temper aluminium foil, contained in a carton.

Pack sizes: 60, 84, 90, 100 and 120 tablets.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Athlone Pharmaceuticals Limited
Ballymurray
Roscommon
County Roscommon
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 30464/0020

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23rd March 2000

10 DATE OF REVISION OF THE TEXT

07/06/2018