BETAHISTINE DIHYDROCHLORIDE TABLETS 8MG/ 16MG/ 24MG TAJ PHARMA

1. NAME OF THE MEDICINAL PRODUCT

Betahistine Dihydrochloride Tablets 8mg Taj Pharma

Betahistine Dihydrochloride Tablets 16mg Taj Pharma

Betahistine Dihydrochloride Tablets 24mg Taj Pharma

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

a) Each uncoated tablet contains:

Betahistine Dihydrochloride	8mg
Excipients	q.s.

b) Each uncoated tablet contains:

Betahistine Dihydrochloride	16mg
Excipients	q.s.

c) Each uncoated tablet contains:

Betahistine Dihydrochloride	24mg
Excipients	q.s.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Betahistine Dihydrochloride 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 8mg/16mg/24mg 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 Dihydrochloride 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

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1

Betahistine Dihydrochloride is contraindicated in patients with phaeochromocytoma. As Betahistine Dihydrochloride 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 peptic ulcer or a history of peptic ulceration, because of the occasional dyspepsia encountered in patients on Betahistine Dihydrochloride.

Patients with bronchial asthma should be monitored carefully during the treatment with Betahistine Dihydrochloride.

Caution is advised in prescribing Betahistine Dihydrochloride 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.

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.

Although an antagonism between Betahistine Dihydrochloride 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 Dihydrochloride with salbutamol.

In vitro data indicate an inhibition of Betahistine Dihydrochloride metabolism by drugs that inhibit monoamino-oxidase (MAO) including MAO subtype B (e.g. selegiline). Caution is recommended when using Betahistine Dihydrochloride and MAO inhibitors (including MAO-B selective) concomitantly.

Betahistine Dihydrochloride 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 Dihydrochloride in pregnant women. Animal studies, though insuffcient 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 Dihydrochloride during pregnancy.

Lactation

There is insufficient information on the excretion of Betahistine Dihydrochloride in human milk. There are no animal studies on the excretion of Betahistine Dihydrochloride in milk. Betahistine Dihydrochloride should not be used during breastfeeding.

4.7 Effects on ability to drive and use machines

Betahistine Dihydrochloride is indicated for vertigo, tinnitus and hearing loss associated with Ménière's syndrome which 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 Dihydrochloride 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 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).

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:

Not known: hypersensitivity reactions, e.g. anaphylaxis.

Gastrointestinal disorders:

Not known: Mild gastric complaints (e.g. vomiting, gastrointestinal pain, abdominal distension and bloating). These can normally be dealt with by taking the dose during meals or by lowering the dose.

Skin and subcutaneous tissue disorders

Not known: cutaneous and subcutaneous hypersensitivity reactions, 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.

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 Dihydrochloride overdose are vomiting, dyspepsia, ataxia and seizures. More serious complications (convulsion, pulmonary or cardiac complications) were observed in cases of intentional overdose of Betahistine Dihydrochloride 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: 2.7 Central Nervous System. Antiemetic and anti-vertigo

The mechanism of action of Betahistine Dihydrochloride is only partially understood.

There are several plausible hypotheses that are supported by animal studies and human data:

Betahistine Dihydrochloride affects the histaminergic system:

Betahistine Dihydrochloride 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 Dihydrochloride increases histamine turnover and release by blocking presynaptic H3-receptors and inducing H3-receptor downregulation.

Betahistine Dihydrochloride 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 Dihydrochloride was also shown to increase cerebral blood flow in humans.

Betahistine Dihydrochloride facilitates vestibular compensation:

Betahistine Dihydrochloride accelerates the vestibular recovery after unilateral neurectomy in animals, by promoting and facilitating central vestibular compensation; this effect is characterised 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 Dihydrochloride.

Betahistine Dihydrochloride alters neuronal firing in the vestibular nuclei:

Betahistine Dihydrochloride 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 Dihydrochloride in the vestibular system.

The efficacy of Betahistine Dihydrochloride 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 Dihydrochloride 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 Dihydrochloride 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 Dihydrochloride is similar under both conditions, indicating that food intake only slows down the absorption of Betahistine Dihydrochloride.

Distribution

The percentage of Betahistine Dihydrochloride that is bound by blood plasma proteins is less than 5 %.

Biotransformation

After absorption, Betahistine Dihydrochloride is rapidly and almost completely metabolised into 2-PAA (which has no pharmacological activity).

After oral administration of Betahistine Dihydrochloride 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 fecal excretion of Betahistine Dihydrochloride 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 Dihydrochloride are linear, and suggesting that the involved metabolic pathway is not saturated.

5.3 Preclinical safety data
Repeated 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 Dihydrochloride is devoid of mutagenic potential and there was no evidence of carcinogenicity in rats. Tests conducted on pregnant rabbits showed no evidence of teratological effects.

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6.1 List of excipients
Microcrystalline cellulose, Mannitol, Povidone, Crospovidone, Citric acid anhydrous, Colloidal anhydrous silica, Talc, Stearic acid

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
PVC/PVDC/Al blisters.

Pack sizes: Blisters: 7, 14, 28, 30, 50, 90, 100 and 500mg modified-release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special requirements.

7. MANUFACTURED IN INDIA BY:

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