For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

TORHISGO

1. Generic Name

Betahistine Tablets I.P.

2. Qualitative and quantitative Composition:

TORHISGO 8

Each uncoated tablet contains:

Betahistine

Hydrochloride I.P. ……. 8 mg

TORHISGO 16

Each uncoated tablet contains:

Betahistine

Hydrochloride I.P. ……... 16 mg

The list of excipients used are Colloidal Silicon Dioxide, Polyvinyl Pyrrolidone, Microcrystalline Cellulose, Starch, Crospovidone and Magnesium Stearate.

3. Dosage form and strength

Dosage form: Uncoated Tablet

Strength: 8 mg and 16 mg

4. Clinical particulars

4.1. Therapeutic indication

Betahistine is indicated in the treatment of Menier's syndrome, characterized by unilateral or bilateral tinnitus, vertigo, sensorineural hearing loss.

4.2. Posology and method of administration

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.

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.

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.

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.

Paediatric population

Betahistine tablets are not recommended in children and adolescents below age 18. The safety and efficacy of betahistine tablets in children and adolescents below 18 years have not been established.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- 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 peptic ulcer or a history of peptic ulceration, because of the occasional dyspepsia encountered in patients on betahistine.

Clinical intolerance to Betahistine may occur in bronchial asthma patients. These patients should therefore be monitored carefully during the treatment with betahistine.

Caution is advised in patients with severe hypotension.

4.5. Drugs 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.

As betahistine is a histamine analogue, interaction of betahistine with antihistamines may in theory affect the efficacy of one of these drugs.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

There are insufficient data on 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 breast milk. Betahistine is excreted in rat milk. The effects seen post-partum in animal studies were limited to very high doses. The importance of taking the medicine by the mother must be weighed against the benefits of breastfeeding and the potential risk for the child.

Fertility

Animal studies show no influence 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 with frequency listed below: 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); and very rare (<1/10,000).

Nervous system disorders:

Common: headache.

Gastrointestinal disorders:

Common: dyspepsia, nausea.

In addition to these adverse reactions reported during clinical trials, the following unexpected adverse reactions have been reported spontaneously in the scientific literature during post-marketing use. A frequency cannot be estimated from the available data and therefore these side effects are 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 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. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com or at email: pv@torrentpharma.com or call on 1800-120-3001.

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 (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. Mechanism of Action

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:

In biochemical studies, betahistine showed weak H1 receptor agonist and strong H3 antagonistic properties in the central nervous system and autonomic nervous system. The H2 receptor activity appeared to be negligible (e.g. stimulation of gastric acid secretion).

Betahistine increases the turnover and release of histamine most likely by blocking presynaptic H3 receptors and inducing the downregulation of H3 receptors.

Betahistine may increase blood flow to the inner ear:

It has been shown in pharmacological animal experiments that betahistine improves the flow in the stria vascularis of the inner ear, probably by relaxing the precapillary sphincters of the microcirculation in the inner ear.

Betahistine facilitates vestibular compensation:

Betahistine accelerates vestibular healing after unilateral neurectomy in animals by stimulating and facilitating vestibular compensation; this effect, characterized by increases in histamine turnover and release, is mediated via H3 receptor antagonism. The recovery period after vestibular neurectomy was also reduced by betahistine in humans.

Betahistine alters the release of neuron action potentials in the vestibular nuclei:

Betahistine also has a dose-dependent inhibitory effect on the release of action potentials of neurons in the lateral and medial vestibular nuclei.

Ménière's syndrome is characterized by attacks of dizziness, tinnitus, headache, nausea. Over time, hearing loss can occur. Clinical studies show that betahistine can prevent an attack and reduce the severity of attacks.

5.2. Pharmacodynamic properties

The mechanism of action of betahistine is known partially. Betahistine has a very strong affinity as an antagonist for histamine H_3 receptors and a weak affinity as an agonist for histamine H_1 receptors. The active ingredient is a specific histamine agonist with virtually no H_2-activity.

Betahistine has two modes of action. Primarily, it has a direct stimulating (agonistic) effect on H_1 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 effect at H_3 receptors, and increases the levels of neurotransmitters released from the nerve endings. The increased amounts of histamine released from histaminergic nerve endings stimulates H1receptors, 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.

5.3. Pharmacokinetic properties

Absorption

Betahistine is rapidly and completely absorbed from all parts of the gastrointestinal tract after oral administration. After absorption, it is rapidly and almost completely metabolized to 2-

pyridylacetic acid (2-PAA). Plasma levels of betahistine are very low. Pharmacokinetic analyses are therefore based on 2-PAA measurements in plasma and urine. After oral administration of betahistine, the plasma concentration of 2-PAA reaches its maximum after 1 hour.

During food intake the Cmax is lower than during fasting. However, the total absorption of betahistine is similar under both conditions, indicating that food alone delays the absorption of betahistine.

Distribution

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

Metabolism

Following the absorption, the drug is rapidly and almost completely metabolized to 2- PPA (2-pyridylacetic acid). 2-PAA has a half-life of approximately 3.5 hours.

Elimination

The 2-pyridylacetic acid is rapidly excreted in the urine. In the dose range between 8 and 48 mg, about 85% of the original dose was recovered in the urine. Renal or fecal 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.

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

Chronic toxicity

Adverse reactions affecting the central nervous system were seen in dogs and baboons after intravenous doses of 120 mg / kg and higher.

Studies on chronic oral toxicity over a period of 18 months in rats at a dose of 500 mg / kg and for 6 months in dogs at a dose of 25 mg / kg indicate that betahistine is well tolerated without definitive toxicity.

Mutagenic and carcinogenic potential

Betahistine has no mutagenic potential.

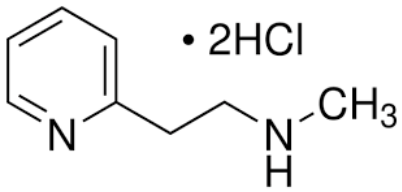
In an 18-month chronic toxicity study in rats at doses up to 500 mg / kg, there was no evidence of carcinogenic potential.

Reproductive toxicity

During reproductive toxicity studies, effects were only seen at exposures considered to be well above the maximum human exposure, indicating minimal relevance during clinical use.

7. Description

Betahistine Hydrochloride is N-methyl-2-(2-pyridyl) ethylamine dihydrochloride. The empirical formula is $C_8H_{12}N_2HCL$, and its molecular weight is 209.1 g/mol. The chemical structure of Betahistine Hydrochloride is:



Torhisgo 8 &16

Torhisgo 8 is white to off white, round, biconvex, both side plain & uncoated tablets. The list of excipients used are Colloidal Silicon Dioxide, Polyvinyl Pyrrolidone, Microcrystalline Cellulose, Starch, Crospovidone and Magnesium Stearate.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than the date of expiry.

8.3. Packaging information

TORHISGO 8 &16 is available in Pack of 10.

8.4. Storage and handing instructions.

Store protected from light & moisture, at a temperature not exceeding 30°C.

Keep all medicines out of reach of children

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies.
- Have kidney or liver problems.
- Are pregnant or plan to become pregnant.
- Are breastfeeding or plan to breastfeed.
- Have any serious illness.
- Are taking any medicines (prescription, over the counter, vitamins, or herbal products)

10. Details of manufacturer

Pure & Cure Healthcare Pvt. Ltd.

(A subsidiary of Akums Drugs & Pharmaceuticals Ltd.)

Plot No. 26A, 27-30, Sector-8A, II.E.,

SIDCUL, Ranipur, Haridwar-249 403, Uttarakhand.

11. Details of permission or licence number with date

Mfg. Lic. No is 31/UA/2013, issue on 23.06.2014.

12. Date of revision

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/TORHISGO 8 mg and 16 mg/MAR 2026 /01/PI