HISTIDIZ Tablets

1. **Composition**

Betahistine 16mg

2. **Dosage form and strength**

Histidiz tablets are available in pack of 10. The tablet can be divided into two equal halves.

3. **Clinical particulars**

3.1 Therapeutic indication

In treatment of Meniere's syndrome including

- Vertigo
- Tinnitus
- Nausea
- Hearing loss

3.2 Posology and method of administration

Take one tablet thrice a day or as directed by doctor.

3.3 Contraindication

- Hypersensitivity
- Use with caution in asthma, ulcers, GERD and phaeochromocytoma

3.4 Special warnings and precautions for use

Following groups of patients should be monitored by a doctor during treatment:

- Stomach ulcer (peptic ulcer)
- asthma
- Nettle rash, skin rash or a cold in the nose caused by an allergy, since these complaints may be exacerbated.
- Low blood pressure

3.5 Drug interactions

Use with caution concurrently with other antihistamines.

3.6 Use in special population

- Pediatric: Not recommended for use in children and adolescents below age 18 due to lack of data on safety and efficacy.
- Geriatric: There is limited data in the elderly; Betahistine should be used with caution in this population.
- Liver impairment: There is no data available for patients with hepatic impairment.
- Renal failure: There is no data available for patients with renal impairment.
- Pregnancy and lactation: Consult doctor.

3.7 Effects on ability to drive and use machine

Histidiz Tablets are not likely to affect ability to drive or use tools or machinery. However, remember that diseases which are treated with Histidiz tablets (vertigo, tinnitus and hearing loss associated with Meniere's syndrome) can make patient feel dizzy or be sick, and can affect ability to drive or use machines.

3.8 Undesirable effects

Very few adverse effects have been reported with Betahistine. The following serious side effects may occur during treatment with Betahistine:

Allergic reactions:

- swelling of your face, lips, tongue or neck
- a drop in your blood pressure
- loss of consciousness difficulty breathing

If any of these side effects occur, stop treatment immediately and contact doctor.

Other side effects include:

Common (affects less than1 in 10 people):

- feeling sick (nausea)
- indigestion (dyspepsia)
- headache

Other side effects that have been reported with the use of Betahistine

Mild stomach problems such as being sick (vomiting), stomach pain, stomach swelling (abdominal distension) and bloating. Taking Betahistine with food can help reduce stomach problems.

3.9 Overdose

There is limited experience of overdose with Histidiz. Initiate general symptomatic and supportive measures in all cases of overdosages where necessary.

4. Pharmacological properties

4.1 Mechanism of action

The mechanism of action of betahistine dihydrochloride is only partly 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 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: 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 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.

4.2 Pharmacodynamic properties

In ten healthy male volunteers, single oral doses of 8, 16, and 32 mg of betahistine dihydrochloride given in a placebo-controlled, double-blind crossover study produced dose related effects on the vestibular system, as measured by electronystagmography (ENG). Maximal effects on the slow nystagmus phase were found 3 to 4 hours after drug intake. Nystagmus duration was reduced by a mean value of 35% (after 8 mg), 48% (16 mg), or 59% (32 mg); all reductions were statistically significant ($p<0.0005$).

Eleven patients with Ménière's disease were treated in a three month, open-label study of the pharmacological effects of betahistine dihydrochloride on hearing and ENG-recorded, rotation induced nystagmus. The study participants took one, 8 mg tablet three times a day (total daily dose, 24 mg). The speed of the quick phase of eye shift pre-treatment versus that achieved at the end of the three month treatment period was used as the parameter of effectiveness in this study.

Hearing was evaluated pre- and post-treatment using three pure tone hearing levels (250, 500, 1000 Hz). Hearing loss was less after treatment but the difference did not achieve statistical significance. At some rates of acceleration and at all rates of deceleration, there

was an increase in the mean eye shift per second; this increase reached statistical significance in six of the 12 tests.

4.3 Pharmacokinetic properties

Absorption

Betahistine is rapidly and completely absorbed after oral administration of the drug in tablets, and peak plasma concentrations of ^{14}C-labelled betahistine are attained after approximately one hour of oral administration for fasting subjects.

Distribution

Little or no binding occurs with human plasma proteins.

Metabolism and Elimination

Elimination of betahistine takes place mainly by metabolism and the metabolites are subsequently eliminated mainly by renal excretion

Following the absorption, the drug is metabolized rapidly in the metabolite and almost completely in metabolite 2-pyridylacetic acid.

After oral administration of betahistine, its plasma levels are very low. Therefore, the assessment of the pharmacokinetics of betahistine is based on the plasma concentration data of the only metabolite 2-pyridylacetic acid. The concentration of 2-pyridylacetic acid reaches its maximum at 1 hour after intake and declines with half approximately 3.5 hours. The 2-pyridylacetic acid is excreted almost quantitatively in urine within 24 hours after administration. In the dose range between 8 and 48 mg, about 85% of the original dose was recovered in the urine. No unchanged betahistine has been detected in urine.

85-90% of the radioactivity of an 8 mg dose appears in the urine over 56 hours, with maximum excretion rates reached within 2 hours of administration.

There is no evidence of presystemic metabolism and biliary excretion is not thought to be an important route of elimination for the drug or any of its metabolites. However betahistine is subject to metabolism in the liver.

5. Nonclinical properties

5.1 Animal Toxicology or Pharmacology

Not required.

6. Description

Already mentioned and covered in the above points.

7. Pharmaceutical particulars

7.1 Incompatibilities

There are no known incompatibilities.

7.2 Shelf-life

18 months.

7.3 Storage and handling instructions

Store at room temperature (15 to 30°C). Keep in a tightly closed container to protect from moisture. Keep out of reach and sight of children.