ART WORK APPROVAL FORM

Product Name: VERTIBET	**Market:** Malaysia (Healol)	**Mfg. Location:** Unit-3

300 mm

1. Name of the Medicinal Product
VERTIBET
Betahistine Dihydrochloride Tablets 24 mg

2. Quality and Quantitative Composition
Qualitative declaration
Betahistine Dihydrochloride Ph. Eur.
Quantitative declaration
Each tablet contains:
Betahistine Dihydrochloride Ph. Eur. 24 mg
Excipients q.s.

3. Pharmaceutical Form
White to off white, round, biconvex tablets, debossed with "J4" on one side and scoreline on other side.
The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. Clinical Particulars
4.1 Therapeutic indications
Ménière's Syndrome as defined by the following triad of core symptoms:
- vertigo (with nausea/vomiting)
- hearing loss (hardness of hearing)
- tinnitus (ringing in the ears)
Symptomatic treatment of vestibular vertigo.

4.2 Posology and method of administration
The dosage for adults is 48mg divided over the day. 1 tablet - 2 times/day
Method of administration: Should be swallowed with water.
The dosage should be individually adapted according to the response. Improvement can sometimes only be observed after a couple of weeks of treatment. The best results are sometimes obtained after a few months. There are indications that treatment from the onset of the disease prevents the progression of the disease and/or the loss of hearing in later phases of the disease.
Paediatric population:
Betahistine Dihydrochloride Tablets is not recommended for use in children under the age of 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 post-marketing experience no dose adjustment appears to be necessary.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.
Phaeochromocytoma.

4.4 Special warnings and precautions for use
Patients with bronchial asthma and history of peptic ulcer need to be carefully monitored during the therapy.

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.
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. Betahistine should not be used during pregnancy unless clearly necessary.
Lactation
It is not known whether betahistine is excreted in human breast milk. Betahistine is excreted in rat milk. Effects seen post-partum in animal studies were limited to very high dose. 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
Betahistine is indicated for Mènière's syndrome defined by the triad of core symptoms vertigo hearing loss, tinnitus and for symptomatic treatment of vestibular vertigo. Both diseases can negatively affect the ability to drive and use machines.

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 [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 and 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.
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,

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INSERT/PIL/OUTSERT SPECIFICATION

Artwork Code 02 107 3564 00 **Open Size** 300 x 130 mm **Close Size** 38 x 130 mm **Folding Condition** Folded **Type of Paper** Maplitho
GSM of Paper 60 gsm **Colour of Paper** White **Colour of Matter** P P Black C **Pharmacode** 1948 **Any other special process** N.A.
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urticaria, rash, and pruritus.

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: 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 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, 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 benefits of betahistine in the vestibular system.

The efficacy of betahistine was shown in studies in patients with vestibular vertigo and with Meniere'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 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 protein 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 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 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

Not Applicable

6. Pharmaceutical Particulars:

6.1 List of excipients

Mannitol
Microcrystalline cellulose
Colloidal anhydrous silica
Povidone K-30
Citric acid anhydrous
Crospovidone
Purified talc
Stearic Acid

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store at a temperature not exceeding 30° C,
Store in original packaging in order to protect
from light.
Keep the medicine out of reach of children.

6.5 Nature and contents of container

Tablets are available in Alu-PVC/PVDC blister pack of 10 tablets.
Pack size: 5 x 10 Alu-PVC/PVDC

7. Marketing Authorization Holder

Healol Pharmaceuticals SDN BHD
74-3, Jalan Wangsa Delima 6,
KLSC Wangsa Maju, 53300,
Kuala Lumpur, Malaysia

8. Manufacturer Name

UNISON PHARMACEUTICALS PVT. LTD.
Unit-III, C-7,8,9, Steel Town, Opp. Nova Petrochemicals, Village Moraiya, Sanand, Ahmedabad, Gujarat 382213, INDIA

9. Date of revision of the text: July 2026

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