Verticlear Orodispersible Film 24mg

1. NAME OF MEDICINAL
Verticlear Orodispersible Film 24mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each orodispersible film contains 24 mg betahistine dihydrochloride equivalent to 15.63mg betahistine.

3. PRODCT DESCRIPTION
Verticlear Orodispersible Film 24mg is off-white to yellow colour square shape film. Each film is approximately 32 x 32 mm

4. 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

5. POSOLOGY AND METHOD OF ADMINISTRATION

The dosage for adults is 48mg divided over the day.

24 mg orodispersible film
1 orodispersible film ; 2 times/day

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 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.

Method of administration
For oral use. Preferably with meals or after meals.
Prior to taking Betahistine dihydrochloride 24 mg orodispersible film on the tongue, patient should take approximately 20 mL of water to wet the mouth.

6. 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 tumour resulting in severe hypertension.

7. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In asthmatics, the administration of betahistine requires special monitoring (risk of bronchoconstriction).
In patients with a history of peptic ulcer, administration of betahistine requires special monitoring during the entire course of treatment.
Taking the drug in the middle of meals avoids gastralgia.
Betahistine is not the appropriate treatment for the following pathologies:

- Benign vertigo
- Dizziness related to a disorder of the central nervous system.

8. 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.

9. 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 at clinically relevant therapeutic exposure. As a precautionary measure, it is preferable to avoid the use of betahistine during pregnancy.

Breast-feeding
It is not known whether betahistine is excreted in human milk.
Betahistine is excreted in rat milk. Effects seen post-partum in animal studies were limited to very high doses. The importance of this medicine 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.

10. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

11. 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"

Blood and lymphatic system disorders
Thrombocytopenia.

Immune System disorders
Hypersensitivity reactions, e.g anaphylaxis.

Gastrointestinal disorders
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
Cutaneous and subcutaneous hypersensitivity reactions, in particular angioneurotic oedema, urticaria, rash and pruritus.

12. OVERDOSE

Symptoms

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 drugs.

Management
No specific antidote. Treatment of overdose should include gastric lavage, symptomatic treatment and standard supportive measures.

13. PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
Pharmacotherapeutic group: antivertigo preparations, ATC code: N07CA01

Mechanism of action
The mechanism of action of betahistine is only partly understood.

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 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.

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 metabolised 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.

Elimination
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 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.

14. PRECLINICAL SAFETY DATA

Chronic toxicity
Adverse effects in the nervous system were seen in dogs and baboons after intravenous doses at and above 120 mg/kg

Studies on the chronic oral toxicity of betahistine dihydrochloride were performed in rats over a period of 18 months and in dogs over 6 months. Doses of 500 mg/kg in rats and 25 mg/kg in dogs were tolerated without changes in the clinical chemical and hematological parameters. There were no histological findings related to treatment at these dosages. After increasing the dose to 300 mg/kg, the dogs showed vomiting. In an investigational study with betahistine in rats over 6 months at 39 mg/kg and above hyperemia in some tissues was reported in the literature. Data presented in the publication are limited. Therefore, the impact of this finding in this study is not clear.

Mutagenic and carcinogenic potential
Betahistine has no mutagenic potential.

Special carcinogenicity studies were not performed with betahistine dihydrochloride. However, in the 18 months chronic toxicity studies in rats there was no indication of any tumors, neoplasms or hyperplasia in the histopathological examination. Therefore, betahistine dihydrochloride up to a dose of 500 mg/kg did not show any evidence for carcinogenic potential in this limited 18 months study.

Reproductive toxicity

Betahistine has no effects on fertility in male and female rats and is not teratogenic in rats and rabbits up to and including 1000 mg/kg for rats and 75 mg/kg in rabbits. In a pre- and postnatal development study in rats, lower pup weight, smaller litter size and lower viability in F1 pups and increased post implantation loss in F1 generation were seen at maternally toxic doses of 1000 mg. Lower average force for startle response test was observed in F1 pups of 300 and 1000 mg/kg dose groups. At 100 mg/kg, no effects on pre- and postnatal development were noted. The relevance of changes noticed at higher doses to humans is unknown.

15. INCOMPATIBILITIES
Not applicable

16. PHARMACEUTICAL PARTICULARS

List of excipients

Hypromellose, Povidone, Masking flavor, Lemon flavour, Colloidal silicon doxide, Sucralose Maltodextrin, Titanium Dioxide, Glycerol, Peppermint flavour & Purified Water.

17. SHELF LIFE & STORAGE CONDITION
2 Years
Store below 30^{o}C.
Protect from light and moisture. Keep out of reach of children.
Jauhi dari kanak-kanak

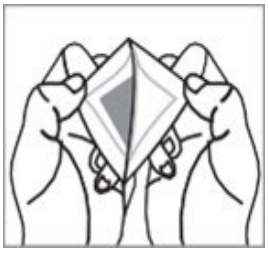
18. NATURE AND CONTENTS OF CONTAINER
Each orodispersible film is packed in 4 ply laminate pack (i.e paper/PET/Alu/PE- sachet)

19. PACK SIZE
30 orodispersible films per box

20. INSTRUCTION FOR USE

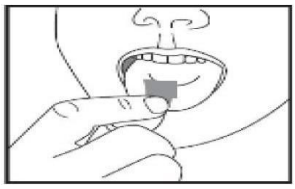
Important: Do not handle the Orodispersible film with wet hands!

A. Peel to open the pouch



B. Take the strip out

C. Place the strip on the tongue



21. PRODUCT REGISTRATION HOLDER
Duopharma Marketing Sdn.Bhd
Lot No. 2, 4, 6, 8 & 10, Jalan P/7, Seksyen 13, Kawasan Perusahaan Bandar Baru Bangi, 43650 Bandar Baru Bangi, Selangor Darul Ehsan, Malaysia

22. MANUFACTURER
Shilpa Medicare Limited
Avverhalli, Sompura Industrial Area,
Dabaspet, Bengaluru, 562111, India.

23. DATE OF REVISION OF THE TEXT
25 May 2026