Professional Information

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

ZYGOVERT 24 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 24 mg betahistine dihydrochloride.

Contains sugar alcohol: Each tablet contains 22,5 mg mannitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

Off-white to cream white, round, flat faced, bevelled edge, uncoated tablet with median line on one side and plain on the other side.

The median line is only to facilitate identification of the tablet and not to divide ZYGOVERT into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZYGOVERT is indicated for the symptomatic treatment of the vertigo associated with Ménière's syndrome.

4.2 Posology and method of administration

Posology

The usual daily dose is 24 mg to 48 mg of ZYGOVERT in divided doses.

One 24 mg tablet can be administered twice daily.

The dosage should be individually adapted according to the response.

Paediatric population:

ZYGOVERT is not recommended for use in children and adolescents below the age of 18 years due to a lack of data on safety and efficacy.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to betahistine dihydrochloride or to any of the excipients of ZYGOVERT listed in section 6.1.
- Patients with phaeochromocytoma. As betahistine is a synthetic analogue of histamine, it may induce the release of catecholamines from the tumour resulting in severe hypertension.

4.4 Special warnings and precautions for use

Caution is advised in the treatment of patients with a history of peptic ulceration, because of the occasional dyspepsia encountered in patients treated with ZYGOVERT.

Patients with bronchial asthma should be monitored carefully during treatment with ZYGOVERT.

Caution is advised in prescribing ZYGOVERT 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 and in patients with porphyria.

If ZYGOVERT is to be administered following treatment with an antihistamine and this treatment is discontinued abruptly, withdrawal symptoms such as sleep disorders and agitation may appear as a result of the sedative action of antihistamines.

Treatment with the antihistamine should be tapered over a period of six days.

4.5 Interaction with other medicines and other forms of interaction

No *in vivo* interaction studies have been performed. Based on *in vitro* data, no *in vivo* inhibition of cytochrome P450 enzymes is expected.

ZYGOVERT should not be concomitantly administered with antihistamines as interactions of betahistine with antihistamines may in theory affect the efficacy of one of these medicines.

In vitro data indicate an inhibition of betahistine metabolism by medicines that inhibit monoamine-oxidase (MAO), including MAO subtype B (e.g. selegiline). Caution is recommended when using ZYGOVERT and MAO inhibitors (including MAO-B selective) concomitantly.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of ZYGOVERT during pregnancy has not been established.
There is a very limited amount of data from the use of ZYGOVERT in pregnant women.
Animal studies, though insufficient, do not indicate direct or indirect harmful effects with respect to reproductive toxicity. The potential risk for humans is unknown. Avoid the use of ZYGOVERT during pregnancy.

Breastfeeding

The safety of ZYGOVERT during breastfeeding has not been established. ZYGOVERT should not be used during breastfeeding.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

ZYGOVERT may cause side effects, such as somnolence which may affect the ability to drive and use machines. Caution is advised before driving a vehicle or operating machinery until the effects

of ZYGOVERT are known.

4.8 Undesirable effects

Immune system disorders

Frequency unknown: hypersensitivity reactions, e.g. anaphylaxis

Nervous system disorders

Frequent: headache

Less frequent: head pressure

Frequency unknown: occasional drowsiness

Cardiac disorders

Less frequent: palpitations, chest discomfort

Respiratory, thoracic and mediastinal disorders

Less frequent: exacerbation of pre-existing bronchial asthma

Gastrointestinal disorders

Frequent: nausea, dyspepsia

Less frequent: vomiting*, gastrointestinal pain*, abdominal distension*, bloating*, retching*, flatulence*

Skin and subcutaneous tissue disorders

Frequency unknown: cutaneous and subcutaneous hypersensitivity reactions, angioneurotic oedema, urticaria, rash, pruritus.

* These effects are generally reduced by taking ZYGOVERT with food or by lowering the dose.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of ZYGOVERT is important. It allows continued monitoring of the benefit/risk balance of ZYGOVERT. Health care providers are asked to report any suspected adverse reactions via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

In case of overdose, the following symptoms, analogous to histamine overdose, might occur: headache, redness of the face, vertigo, tachycardia, hypotension, bronchial spasm, oedema, in particular oedema of the mucosa of the upper respiratory tract (Quincke's oedema). More serious complications (convulsions, pulmonary or cardiac complications) were observed in cases of intentional overdose of betahistine, especially in combination with other overdosed medicines.

Treatment

There is no specific antidote. Treatment of overdose should include standard supportive measures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 5.6 Histamine.

Pharmacotherapeutic group: Antivertigo preparations.

ATC code: N07CA01.

Mechanism of action

Betahistine is an analogue of histamine.

It improves the microcirculation of the labyrinth resulting in reduced endolymphatic pressure. 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.

In pharmacological studies, betahistine was found to have weak H_1 receptor agonistic and considerable H_3 antagonistic properties in the central nervous system and the autonomic nervous system.

Betahistine facilitates vestibular compensation

Betahistine 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, mediated via the H_3 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.

5.2 Pharmacokinetic properties

Absorption

Orally administered betahistine is readily and almost completely absorbed from all parts of the gastrointestinal tract. After absorption, betahistine is rapidly and almost completely metabolised into 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.

Under fed conditions C_{max} 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

Betahistine undergoes hepatic biotransformation. After absorption, betahistine is rapidly and almost completely metabolised 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

It is excreted in urine as the metabolite 2-pyridylacetic acid within 24 hours. No unchanged betahistine has been detected. Betahistine is excreted in breast milk at approximately the same level as found in plasma.

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. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid, anhydrous

Colloidal silica, anhydrous

Magnesium stearate (E572)

Mannitol

Microcrystalline cellulose (E460a)

Talc (E553b).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister strips in the outer carton until required for use.

6.5 Nature and contents of container

Aluminium/PVC/OPA and aluminium foil blister strips placed in an outer carton.

Pack size: 20 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

Southdowns Office Park

Building B, Ground Floor

22 Karee Street

Centurion, Pretoria

0157

8. REGISTRATION NUMBER

47/5.6/0329

9. DATE OF FIRST AUTHORISATION

30 August 2022

10. DATE OF REVISION OF THE TEXT

Not applicable.