Betaserc® OD (Betahistine dihydrochloride 48mg) Modified Release Film-Coated Tablet

1. Name of Medicinal
Betaserc® OD (Betahistine dihydrochloride 48mg) Modified Release Film-Coated Tablet

2. Qualitative and Quantitative Composition
Betaserc® OD contains betahistine dihydrochloride corresponding to 31.26 mg betahistine.

Excipients (non-medicinal ingredients): Microcrystalline cellulose, mannitol (E421), citric acid monohydrate, citric acid monohydrate, co-processed polyvinyl acetate and povidone polymer, talc, opadry 03F180011 White and opadry II 85F220031 Yellow

3. Pharmaceutical Description
Betaserc® OD is round biconvex tablet, yellow, coated and smooth on both sides.

4.1 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 Dosage and administration
The dosage for adults is

48mg tablets
1 tablet
Once Daily

Method of administration:
Betaserc® OD: Should be swallowed whole with water.

Due to the properties of the modified release tablets, the tablet may not dissolve completely and the remainder of the tablet shell may appear in the stool.

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.

Pediatric population:
Betaserc® OD 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 Warning and precautions
Patients with bronchial asthma and history of peptic ulcer need to be carefully monitored during the therapy.

4.5 Interactions with other medications
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 (see section Preclinical safety data). Betahistine should not be used during pregnancy unless clearly necessary.

Lactation:
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 (see section Preclinical Safety Data).The importance of the drug to the mother should be weighed against the benefit 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 of drive and use machines
Betahistine is indicated for Ménière'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.

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: 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) 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.

4.9 Overdose
A few overdose cases have been reported. Some patients experienced mild to moderate symptoms with doses up to 640mg (nausea, somnolence and abdominal pain).
More serious complications (e.g. convulsions, pulmonary and 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.

5.1 Pharmacodynamics
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 in animals, by promoting and facilitating central vestibular compensation; this effect, characterized by an upregulation of histamine turnover and release, is mediated through 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.

5.2 Pharmacokinetics

Absorption:

Orally administered betahistine is readily and almost completely absorbed from all parts of the gastrointestinal 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 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.

Excretion:

2-PAA is readily excreted in the urine. In the dose range of 8 to 48 mg, about 85% of the original dose is excreted 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.

5.3 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 does not have 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.

Reproduction 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.

6.1 Incompatibilities
Not applicable

6.2 Shelf life and storage conditions
Please refer to the expiry date and storage condition stated on the carton.
Store in the original package in order to protect from light.

Do not use the medicine after the expiry date stated on carton.
Keep this medicine out of the reach and sight of children.

6.3 Pack sizes
Betaserc® OD are supplied in packages containing 30, 60 or 90 film-coated tablets per pack (not all pack sizes may be marketed).

The blisters are cold form blister Alu-Alu

6.4 Further information
Any unused product or waste material should be disposed of in accordance with local requirements.

The information in this leaflet is limited. For further information, please contact your doctor or pharmacist.

7.0 Manufacturer and importer:
Abbott Laboratories de Mèxico, S.A de C.V.
Calzada de Tlalpan
No.3092, Col. Ex-Hacienda Coapa, C.P. 04980,
Coyoácan, Ciudad de Mèxico

8. Revision Date
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