

## **SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Betaserc 24 mg orodispersible tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Betaserc 24 mg orodispersible tablets contain 24 mg betahistine dihydrochloride corresponding to 15.63mg betahistine.

### Excipients with known effect:

Betaserc 24 mg orodispersible tablets contain 3.4 mg Aspartame (E951) per tablet.

Betaserc 24 mg orodispersible tablets contain 0.15 mg sucrose per tablet.

For the full list of excipients see section 6.1.

## 3. PHARMACEUTICAL FORM

Orodispersible tablet.

A round, flat, unscored, white to yellowish uncoated orodispersible tablet with bevelled edges and without inscriptions. The diameter is about 9 mm; the tablet weight is about 200 mg.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Betaserc 24 mg orodispersible tablet is indicated in adults for symptomatic treatment of Ménière's syndrome and vestibular vertigo.

### 4.2 Posology and method of administration

#### Posology

Betaserc 24 mg orodispersible tablets
1 tablet
2 times/day

Betahistine dosage for adults is generally in the range of 24–48 mg daily divided into two or three doses and it should be individually adapted according to the response. Other formulations are available to obtain dosage lower than 48 mg daily.

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.

#### *Elderly*

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.

#### *Paediatric population*

The safety and efficacy of Betaserc 24 mg orodispersible tablets in children below 18 years have not been established. No data are available.

### Method of administration

Oral use.

Tablets should be placed on the tongue and allowed to disintegrate before swallowing with or without water.

## **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Phaeochromocytoma.

## **4.4 Special warnings and precautions for use**

Patients with bronchial asthma or history of peptic ulcer need to be carefully monitored during the therapy.

This medicinal product contains aspartame E951, a source of phenylalanine. May be harmful for people with phenylketonuria.

This medicinal product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

## **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 monoamine 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 are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition and postnatal development. The potential risk for humans is unknown. Betahistine should not be used during pregnancy unless clearly necessary.

### Breast-feeding

It is not known whether betahistine is excreted in human milk.

There are no animal studies on the excretion of betahistine in milk. The importance of the drug to the mother should be weighed against the benefits of nursing and the potential risks for the child.

### Fertility

There are no adequate fertility data for betahistine

## 4.7 Effects on ability to 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 ( $\geq 1/10$ ); Common ( $\geq 1/100$  to  $< 1/10$ ); Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); Very rare ( $< 1/10,000$ )].

In addition to those events reported during clinical trials, 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

Not known: Hypersensitivity reactions, *e.g.* anaphylaxis

#### Nervous system disorders

Common: Headache

#### Gastrointestinal disorders

Common: Nausea and dyspepsia

Not known: 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

Not known: Cutaneous and subcutaneous hypersensitivity reactions, in particular angioneurotic oedema, urticaria, rash, and pruritus.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the **national reporting system** listed in [Appendix V](#).

## **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: Other nervous system drugs, anti-vertigo preparations. ATC code: N07CA01.

#### Mechanism of action

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 H<sub>1</sub>-receptor agonist and histamine H<sub>3</sub>-receptor antagonist also in neuronal tissue, and has negligible H<sub>2</sub>-receptor activity. Betahistine increases histamine turnover and release by blocking presynaptic H<sub>3</sub>-receptors and inducing H<sub>3</sub>-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 H<sub>3</sub> 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.

### Clinical efficacy and safety

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 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 (2-PAA). The absolute bioavailability of betahistine, dosed as the immediate release tablet or the orodispersible tablet, is estimated to be around 1% due to its very high first pass metabolism. Plasma levels of betahistine are very low. The majority of pharmacokinetic analyses are therefore based on 2-PAA measurements in plasma and urine. In a study utilizing a sensitive bioanalytical method it was demonstrated that plasma concentrations of the parent betahistine reach the maximum within one hour post-administration.

Under fed conditions, using a modified-release formulation, C<sub>max</sub> 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) by MAO enzymes.

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.

### **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

Limited data are available for betahistine on reproduction. In a one-generation study in rats, an oral dose of 250 mg/kg/day betahistine had no adverse effect on male and female fertility, implantation of foetuses, parturition and viability of pups during lactation. No abnormalities were noted in weaned rats. In pregnant rabbits treated orally with 10 or 100 mg/kg betahistine, no adverse effects were noted on implantations, vitality or weight of foetuses, and no foetal skeletal or soft tissue abnormalities were noted. From these studies it can be concluded that betahistine has no detectable effects on relevant reproduction parameters in rat and rabbits in the described studies. Betahistine is not teratogenic. However, due to the investigational character of the studies a risk could not fully be excluded.

### Local tolerance

The orodispersible tablet did not show irritation or abnormalities in the oral cavity in a 14 day local tolerance test in hamster.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

cellulose, microcrystalline  
crospovidone (type A)  
citric acid anhydrous  
silica, colloidal anhydrous  
talc  
peppermint flavour

#### masking flavour

sucrose  
aspartame (E951)  
acesulfame potassium (E950)

### **6.2 Incompatibilities**

Not applicable

### **6.3 Shelf life**

3 years

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.



## **6.5 Nature and contents of container**

Betaserc 24 mg orodispersible tablets are supplied in packs of 20, 30, 50, 60 or 100 tablets, packaged in blister strips of polyamide/aluminium/PVC and aluminium lidding foil.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal**

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

## **7. MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

## **8. MARKETING AUTHORISATION NUMBER**

[To be completed nationally]

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

[To be completed nationally]

## **10. DATE OF REVISION OF THE TEXT**

DD/MM/YYYY