

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Serc 16 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 16 mg betahistine dihydrochloride.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet:
Product imported from the UK
Round, biconvex, scored, white to almost white tablets imprinted '267' on one side and plain on the other.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

Initially 16 mg three times daily taken preferably with meals. Maintenance doses are generally in the range 24 - 48 mg daily.

Paediatric population:

Serc is not recommended for use in children below 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.
Use in 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 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.

Lactation:

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.

4.7 Effects on ability to drive and use machines

Betahistine is indicated for vertigo, tinnitus and hearing loss associated with Ménière's syndrome which 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 ($< 1/10,000$)]

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, rash, pruritus and urticaria.

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 in animals, by promoting and facilitating central vestibular compensation; this effect is characterised 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.

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 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:

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.

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 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 fetuses, 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 fetuses, 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.

6 PHARMACEUTICAL PARTICULARS**6.1 List of excipients**

Microcrystalline cellulose
Mannitol
Citric acid monohydrate
Colloidal anhydrous silica
Talc.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The shelf life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package.

6.5 Nature and contents of container

Cardboard outer containing blister strips. Pack size 84.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

Imbat Limited
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Santry
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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1151/079/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 26th September 2008

10 DATE OF REVISION OF THE TEXT

May 2014