

PRODUCT MONOGRAPH

PrSERC[®]

(Betahistine Dihydrochloride)

16 mg and 24 mg tablets

Anti-vertigo Agent

Abbott Laboratories, Limited
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Saint-Laurent, Quebec
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PrSERC®

(Betahistine Dihydrochloride)

16 mg and 24 mg tablets

THERAPEUTIC CLASSIFICATION

Anti-vertigo Agent

CLINICAL PHARMACOLOGY

Betahistine is a histamine H₁-agonist with an intrinsic activity equal to that of histamine and an H₁-agonistic activity of about 0.07 times that of histamine. This H₁-agonist activity has been confirmed in *in vivo* studies where, like histamine, the hypotensive response produced by betahistine could be blocked by H₁-receptor antagonists.^{5,6,7} Betahistine also induces bronchoconstriction and increased vasopermeability after parenteral administration, further confirming its H₁-agonistic properties.^{2,5,7} In contrast to histamine, betahistine is virtually inactive at the H₂-receptor. Only marginal increases in gastric acid secretion are produced following very high parenteral doses of betahistine.⁹ The compound did not produce relaxation in the rat uterus,⁵ and no H₂-agonist activity was noted in heart muscle.² Receptor binding studies have shown that betahistine is a potent H₃-receptor antagonist.^{14,15}

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; which has no pharmacological activity). Plasma levels of betahistine are very low. Pharmacokinetic analyses are therefore based on 2-PAA measurements in plasma and urine. The plasma concentration of 2-PAA reaches its maximum 1 hour after intake and declines with a half-life of about 3.5 hours. 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. 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. 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.

INDICATIONS AND CLINICAL USE

SERC (betahistine dihydrochloride) tablets are indicated for reducing the episodes of recurrent vertigo associated with Ménière's disease.

CONTRAINDICATIONS

The use of SERC (betahistine dihydrochloride) tablets is contraindicated in patients with known hypersensitivity to betahistine or to any of the tablet constituents.

Several patients with a history of peptic ulcer have experienced an exacerbation of symptoms while using SERC. Although experiments in animals and in humans have shown that the gastrointestinal side effects associated with betahistine dihydrochloride are not related to gastric acid production, SERC is contraindicated in the presence of peptic ulcer and in patients with a history of this condition. SERC is also contraindicated in patients with pheochromocytoma.

PRECAUTIONS

General:

Although clinical intolerance to SERC (betahistine dihydrochloride) tablets has not been demonstrated in patients with bronchial asthma, caution should be exercised when giving the product to asthmatic patients.

Use in Children:

SERC is not recommended for use in children.

Use in Pregnancy and Lactation:

Pregnancy:

The safety of SERC in human pregnancy has not been established. 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.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

The following undesirable effects have been experienced with the below indicated frequencies in betahistine-treated patients in placebo-controlled clinical trials.

Gastrointestinal disorders

Common ($\geq 1/100$ to $< 1/10$): nausea and dyspepsia.

Nervous system disorders

Common ($\geq 1/100$ to $< 1/10$): headache*.

*The incidence of headache in placebo-treated patients (5.9% in a pool of 457 patients) was similar in comparison to betahistine-treated patients (5.1% in a pool of 468 patients).

Post-Market Adverse Drug Reactions

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 have been reported.

Nervous system disorders

Somnolence occurred during treatment with betahistine dihydrochloride, but a causal relationship has not been established.

Cardiac disorders

Ventricular extrasystoles occurred during treatment with betahistine dihydrochloride, but a causal relationship has not been established.

Gastrointestinal disorders

Mild gastric complaints (e.g. vomiting, gastrointestinal pain, abdominal distension and bloating) have been observed. These can normally be minimized or eliminated by taking the dose during meals or by lowering the dose.

Skin and subcutaneous tissue disorders

Cutaneous and subcutaneous hypersensitivity reactions have been reported, in particular angioneurotic oedema, urticaria, skin rashes of various types, and pruritus.

DRUG INTERACTIONS

No *in vivo* interaction studies have been performed. *In vitro* data revealed no inhibition of Cytochrome P450 enzymes.

As betahistine is an analogue of histamine, interaction of betahistine with antihistamines may in theory affect the efficacy of one of these drugs.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

A few overdose cases (up to 640 mg), with mild to moderate symptoms of nausea, dry mouth, dyspepsia, abdominal pain and somnolence have been reported. Presumably, more serious complications (e.g. convulsion, pulmonary or cardiac complications) may occur in cases of intentional overdose of betahistine above 640 mg, especially in combination with other overdosed drugs. Standard overdose protocol/ supportive measures should be followed.

DOSAGE AND ADMINISTRATION

The usual daily dosage range is 24-48 mg administered orally in divided doses.

BID Dosing:

24 mg tablets: 1 tablet twice daily.

TID Dosing:

16 mg tablets: ½ to 1 tablet three times daily.

As SERC (betahistine dihydrochloride) can cause gastrointestinal upset in some patients, it is recommended that doses be taken with a meal.

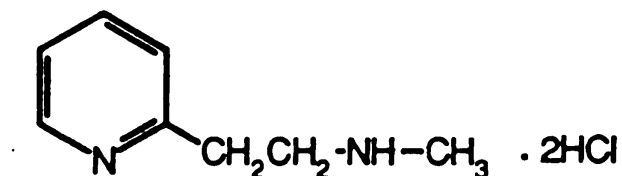
PHARMACEUTICAL INFORMATION

Drug Substance:

Proper Name: Betahistine dihydrochloride

Chemical Name: 2-[2-(methylamino)ethyl]pyridine dihydrochloride

Structural Formula:



Molecular Weight: 209.1

Molecular Formula: C₈H₁₂N₂.2HCl

Description:

Betahistine dihydrochloride is a white to almost white crystalline product which is very hygroscopic. The product is very soluble in water, freely soluble in methanol and 96% methanol, and slightly soluble in isopropanol. The pKa values are 3.5 and 9.7. The substance melts at about 152 °C.

Composition:

The 16 mg and 24 mg tablets contain 16 mg and 24 mg of betahistine dihydrochloride respectively. Non-medicinal ingredients include: citric acid, colloidal anhydrous silica, mannitol, microcrystalline cellulose, and talc.

Storage Recommendations:

Store tablets at controlled room temperature (15-30°C) and protect from exposure to moisture.

AVAILABILITY OF DOSAGE FORMS

SERC (betahistine dihydrochloride) tablets are available as follows:

16 mg tablets: Round, biconvex, scored, white to almost white tablet with bevelled edges, one side inscribed with “ S ”, the other side with “267” on either side of the score. The diameter of the tablet is 8.5 mm. The tablet can be divided into equal halves. The tablets are individually blister packaged and are provided in boxes of 100.

24 mg tablets: Round, biconvex, scored, white to almost white tablet with bevelled edges, one side inscribed with “ S ”, the other side with “289” on either side of the score. The diameter of the tablet is 10 mm. The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses. The tablets are individually blister packaged and are provided in boxes of 100.

INFORMATION FOR THE PATIENT:

PrSERC® (betahistine dihydrochloride) Tablets

Please read the following information carefully.

This (booklet/leaflet/sheet) contains general information about SERC. If you need more specific information, ask your doctor or pharmacist. It is important for you to carefully follow your doctor's instructions regarding how and when to take SERC.

What is SERC® and what is it used for?

SERC is the brand name for a drug called "betahistine dihydrochloride".

SERC is used for reducing the episodes of recurrent vertigo associated with Meniere's disease.

What should I tell my doctor before taking SERC®?

There are a few things your doctor should know about your health before you take SERC. This will help your doctor decide if SERC is the best medicine for you at this time.

Be sure to tell your doctor:

- if you have a peptic ulcer or have a history of this condition;
- if you have an adrenal tumour that produces excessive amounts of adrenalin (pheochromocytoma);
- if you suffer from bronchial asthma, since asthmatic patients should use SERC with caution;
- about all health problems you have now, or have had in the past;
- about all other medications you take, including ones you can take without a doctor's prescription including, for example, "natural" or "herbal" remedies;
- if you are pregnant, plan to become pregnant, or are breastfeeding;
- if you are allergic to any of the components that are present in SERC tablets (see "What is in SERC").

How do I take SERC® properly?

It is very important to take SERC exactly as your doctor has instructed. If you're not sure when or how many tablets to take each day, check with your doctor or pharmacist. SERC is not recommended for use in children.

It is recommended that SERC tablets be taken with meals.

If you forget to take one dose of SERC, take a tablet (s) as soon as you remember, unless it is almost time for your next dose. If it is almost time for your next dose, do not take the missed tablet (s) at all. Never double-up on a dose to make up for the one you have missed; just go back to your regular schedule.

Are there any side effects?

Like any medication, SERC may cause side effects in some people. Most people have few or no side effects from SERC. Side effects that do occur tend to be generally mild and do not last a long time. The few side effects that have been reported are allergic skin reactions (such as rashes of various types, hives and itching), stomach-ache, nausea, vomiting, bloating, indigestion, drowsiness and headache. If any of these become troublesome, consult your doctor. If in the rare event you experience a severe allergic reaction (which might include but is not limited to breathing or swallowing difficulties, or swelling in the face or skin) consult your doctor immediately. If you experience any unusual or unexpected symptoms while using SERC consult your doctor.

What should I do in case of overdose?


In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.


What is in SERC®?

Each SERC 16 mg and 24 mg tablet contains either 16 mg or 24 mg of betahistine dihydrochloride, respectively, and the following non-medicinal ingredients: citric acid, colloidal anhydrous silica, mannitol, microcrystalline cellulose, and talc.

Check with your doctor whether you might be allergic to any of the above ingredients.

What does SERC[®] look like?

The 16 mg tablets are round, biconvex, scored, white to almost white tablet with bevelled edges, one side inscribed with “”, the other side with “267” on either side of the score. The tablet can be divided into equal halves.

The 24 mg tablets are round, biconvex, scored, white to almost white tablet with bevelled edges, one side inscribed with “” the other side with “289” on either side of the score. The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Where should I keep SERC[®]?

Keep your tablets at room temperature (15 to 30°C), protect from exposure to moisture, and where children cannot reach them.

Important Note:

This information is intended to alert you to some of the times when you should call your doctor or pharmacist. Other situations which cannot be predicted may arise while you are taking medicines. Nothing should stop you from calling your doctor or pharmacist with any questions or concerns you have about using SERC.

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PHARMACOLOGY

Animal:

Pharmacodynamics

In vitro:

In studies on a variety of isolated organs and isolated tissues, betahistine dihydrochloride produced responses similar to those induced by histamine. Betahistine had little or no affinity for histamine H₂-receptors as confirmed by its activity in tests using rat uterine muscle,⁵ rabbit and guinea pig hearts and atrial pairs,² and isolated guinea pig ileum.⁵

In vivo:

In evaluations of its effects on the circulation of the inner ear, betahistine dihydrochloride was found to produce greater effects than histamine. Betahistine increased blood flow in the labyrinthine arteries of dogs by 60.9% following a dose of 100 µg. Circulation in the stria vascularis and spiral ligament of guinea pigs and chinchillas was increased by a mean of 50% when betahistine was administered at doses as low as 0.1 mg/animal.¹ In guinea pigs, cochlear blood flow was increased for 30 minutes following a dose of 0.2 mg/kg.^{2,3,4}

In cats, betahistine was also found to have a dose dependent inhibiting effect on spike generation of neurons in lateral and medial vestibular nuclei. Betahistine at 60 and 120 times the normal human dose accelerates the vestibular recovery after unilateral neurectomy. Taken together these properties may contribute to its beneficial therapeutic effects in Ménière's disease and vestibular vertigo.

Betahistine increases histamine turnover and release likely by blocking presynaptic H₃-receptors and inducing H₃-receptor downregulation. This effect on the histaminergic system could provide an explanation for the efficacy of betahistine in the treatment of vertigo and vestibular diseases.

Studies of the effects on the cardiovascular system, the pulmonary system, the renal system, the gastrointestinal system, and the central nervous system all indicated that betahistine produced effects similar to, but less potent than, those of histamine.

Following rapid intravenous administration of betahistine dihydrochloride, a brief fall in blood pressure was evoked in rats, guinea pigs, dogs, and cats.^{5,6} This effect could be blocked by the administration of histamine H₁-antagonists, but not by histamine H₂-antagonists. When betahistine was injected slowly into anaesthetized dogs, general blood pressure decreased while basilar blood flow increased by up to 200%.⁷ Pronounced increases in blood flow were found in the coronary (225%), labyrinthine (161%), and communicating hepatic arteries (156%).

Intravenous doses of 0.2 to 0.4 mg/kg given to anaesthetized guinea pigs produced an increase in pulmonary resistance.² Administration of an intraperitoneal doses of 40 mg/kg caused death by respiratory failure.⁵

In the perfused baboon kidney, the addition of betahistine to the perfusate produced increases in urine flow, osmotic clearance, urea and creatinine clearance.⁸

Betahistine doses of 80 to 1600 µg/kg/min administered as a continuous infusion to dogs with Heidenhain pouches produced a slight increase in the rate of acid secretion corresponding to 8.8% to 17.6% of the maximum response to histamine.⁹ In dogs with gastric fistulae, an increase in acid secretion was obtained with a subcutaneous dose of 20 mg/kg betahistine. This increase corresponded with that produced by 30 µg/kg of histamine.

The effect of betahistine on continuous avoidance behaviour in rats was compared with that of histamine.¹⁰ Betahistine injected intraventricularly at a dose of 0.32 mg/animal and histamine at a dose of 0.08 mg/animal produced a significant increase in the avoidance rate; an increase was also observed after an intraperitoneal dose of 4.0 mg/kg betahistine, but this did not achieve statistical significance.¹⁰ Betahistine did not affect the righting reflex when given to newborn chicks at a dose of 100 mg/kg, while a dose of 50 mg/kg histamine produced sleep characterized by loss of the righting reflex.¹¹

Pharmacokinetics

The absorption, distribution, metabolism, and excretion of betahistine dihydrochloride were studied in female rats. Following the oral or intravenous administration of 0.5 mg radio-labelled

compound, total excretion of the radioactive label was 80 to 90%, about 67% of which was in the urine. Of the total excretion which took place, 98.5% appeared in the urine within 24 hours. The metabolite pattern in rat urine showed only one main metabolite – 2-pyridylacetic acid.

The distribution of radio-labelled betahistine was evaluated at 0.5, 1, 3, 6, 24 or 48 hours after the oral or intravenous administration of a 1 mg dose. Following intravenous administration, radioactivity was distributed rapidly throughout the body, with immediate and intensive secretion into the stomach and intestines. There was a transient accumulation of radioactivity in the liver and the portal vein. After oral administration, radioactivity was distributed throughout the body, with high accumulation in the stomach and intestines. Levels of radioactivity in excess of blood levels were observed in the bronchial epithelium, the eye, and the preputial gland. At 24 hours, only the preputial gland and the alimentary system still showed evidence of accumulated radioactivity. By 48 hours, there was no remaining activity.

Human Studies:

Pharmacodynamics

In ten healthy male volunteers, single oral doses of 8, 16, and 32 mg of betahistine given in a placebo-controlled, double-blind cross-over study produced dose-related effects on the vestibular system, as measured by electronystagmography (ENG).¹² Maximal effects on the slow nystagmus phase were found 3 to 4 hours after drug intake. Nystagmus duration was reduced by a mean value of 35% (after 8 mg), 48% (16 mg), or 59% (32 mg); all reductions were statistically significant ($p < 0.0005$).

Eleven patients with Meniere's disease were treated in a three month, open-label study of the pharmacological effects of betahistine on hearing and ENG-recorded, rotation-induced nystagmus.¹³ The study participants took one, 8 mg tablet three times a day (total daily dose, 24 mg). The speed of the quick phase of eye shift pre-treatment versus that achieved at the end of the three month treatment period was used as the parameter of effectiveness in this study. Hearing was evaluated pre- and post-treatment using three pure tone hearing levels (250, 500, 1000 Hz).

Hearing loss was less after treatment but the difference did not achieve statistical significance. At some rates of acceleration and at all rates of deceleration, there was an increase in the mean eye shift per second; this increase reached statistical significance in six of the 12 tests.

Pharmacokinetics

The pharmacokinetic profile of betahistine was studied in six healthy male volunteers. Tablets containing 8 mg of radio-labelled betahistine were administered to the subjects following an overnight fast, 30 minutes before a standard breakfast. Urine was collected for at least 56 hours after dosing, and five blood samples were drawn from each volunteer at 1, 2, 3, 8, and 25 hours for the first two volunteers, and at 1, 2, 3, 5.5, and 8 hours for the next four subjects.

Total urinary excretion of the radio-label was 90.7%, and the urinary half life was 3.5 hours. More than 85% of the administered dose was excreted in the urine within 24 hours. Only one primary urinary metabolite was identified - 2-pyridylacetic acid. Maximum plasma levels of radioactivity were attained by the 1 hour sampling time; the plasma half life of the radio-label was 3.4 hours.

TOXICOLOGY

Acute Toxicity:

The oral LD₅₀ for betahistine dihydrochloride is 3040 mg/kg in the albino rat. The intravenous LD₅₀ is 5.1 mg/kg in the rabbit. Side effects in the nervous system were seen in dogs and baboons after intravenous doses at and above 120 mg/kg. Signs of toxicity included ataxia, salivation, inactivity, hyperpnoea, tremors, and cyanosis. Severe gastroenteritis was noted during pathology.

Chronic Toxicity:

In a six month study, dogs were given of up to 25 mg/kg/day. There were no significant abnormalities noted in any of the parameters assessed. In rats given doses of up to 120 mg/kg/day for 18 months, there were no significant abnormalities noted in any of the parameters assessed. Oral dosing up to and above 250 mg/kg in dogs and in rats respectively, of Betahistine dihydrochloride administered during 3 months did not result in adverse effects.

Emesis was observed at 300 mg/kg and 120 mg/kg following oral and iv dosing respectively in dogs and sporadically in baboons.

Reproduction and Teratology:

A reproductive study which examined two generations of rats revealed no adverse effects on any of the parameters which were assessed. Betahistine has not shown any mutagenic effect.

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