

Summary of Product Characteristics

1. Name of the medicinal product

Agiserc 16

2. Qualitative and quantitative composition

Each tablet contains 16 mg of Betahistine dihydrochloride
For the full list of excipients see section 6.1

3. Pharmaceutical form

Tablets.

White, round, scored on one side and printed with "Agiserc" on the other side.

4. Clinical particulars

4.1 Therapeutic indications

Meniere's syndrome.

Symptomatic treatment of peripheral vertigo.

4.2 Posology and method of administration

Adults :

The usual optimal dose for adults (including the elderly) is 16 mg 3 times daily.

An initial dose of 8 mg 3 times daily is possible if required. If a dose of 8mg is required, other products registered in Israel containing 16mg beta-histine dihydrochloride, which can be equally divided to receive an 8 mg dose, should be used.

The daily dose varies from 24 to 48 mg, and it should be divided into three doses in order to achieve less variable plasma concentrations.

It is recommended that the tablets/divided tablets are swallowed whole.

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.

Paediatric population:

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

Phaeochromocytoma.

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

4.4 Special Warnings and precautions for use

Caution is advised in the treatment of patients with a history of peptic ulcer. Clinical intolerance to Agiserac in bronchial asthma patients has been shown in a relatively few patients. These patients 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 of 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 at clinically relevant therapeutic exposure. As a precautionary measure, it is preferable to avoid the use of betahistine during pregnancy.

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. The importance of the drug to the mother should be weighed against the benefits 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 to drive and use machines.

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

Gastrointestinal disorders Mild gastric complaints (e.g. vomiting, gastrointestinal pain, abdominal distension and bloating) have been observed. 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, have been reported, 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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il>

Additionally, you can also report to www.padagis-pharma.co.il.

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. convulsions, pulmonary or cardiac complications) were observed in cases of intentional overdose of betahistine especially in combination with other overdose 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 characterized 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 inhibitory effect on neuronal activation 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 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 PPA 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 faecal 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.

Chronic oral toxicity testing for 18 months in rats At a doses of 500 mg/kg and 6 months in dogs at a dose of 25 mg/kg. showed betahistine to be well tolerated with no definitive toxicities.

Mutagenic and carcinogenic potential

Betahistine does not have mutagenic potential.

In an 18 months chronic toxicity study in rats betahistine up to a dose of 500 mg/kg did not show any evidence for carcinogenic potential.

Reproduction toxicity

Effects in reproductive toxicity studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline cellulose, Mannitol, Talc, Citric acid monohydrate, Silica, Colloidal Anhydrous .

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store in a cool place below 25°C.

Protect from light and moisture.

6.5 Nature and contents of container

Aluminium foil, PVC/PVDC

Quantity in container: 30 tablets

6.6 Special precautions for disposal and other handling

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

7. Manufacturer and marketing authorization holder

PADAGIS ISRAEL PHARMACEUTICALS LTD, Rakefet 1st, Shoham

8. Registration NUMBER

056-87-27365

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