SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Betahistine Sandoz 8 mg, tabletten
Betahistine Sandoz 16 mg, tabletten
Betahistine Sandoz 24 mg, tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<{[Nationally completed name] 8 mg tablets}>
Each tablet contains 8 mg of betahistine dihydrochloride.

<{[Nationally completed name] 16 mg tablets}>
Each tablet contains 16 mg of betahistine dihydrochloride.

<{[Nationally completed name] 24 mg tablets}>
Each tablet contains 24 mg of betahistine dihydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

<{[Nationally completed name] 8 mg tablets}>
White colour, round and flat uncoated tablet plain on both sides.
Diameter: approximately 7 mm

<{[Nationally completed name] 16 mg tablets}>
White colour, round and biconvex uncoated tablet scored on one side with embossing “I” on the either sides of the score and plain in the other side.
Diameter: approximately 8.7 mm
The tablet can be divided into equal doses.

<{[Nationally completed name] 24 mg tablets}>
White colour, round and biconvex uncoated tablet scored on one side with the embossing "II" on either sides of the score and plain on the other side.
Diameter: approximately 10 mm
The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Betahistine is indicated for the treatment of Menière's syndrome, symptoms of which may include vertigo (often associated with nausea and/or vomiting), tinnitus and hearing loss.

4.2 Posology and method of administration

Posology
Adults The dose should be individually adapted according to the response.

8 and 16 mg tablets
The usual daily dose is 24 - 48 mg betahistine dihydrochloride, divided into three equal doses.

24 mg tablets
The recommended initial daily dose is 24 mg betahistine dihydrochloride. In case this dose is not sufficient, the maximum daily dose can be increased to 48 mg betahistine dihydrochloride devided into two equal doses (24 mg in the morning and 24 mg in the evening).

Paediatric population
{Nationally completed name} is not recommended for use in children and adolescents below the age of 18 years due to a lack of sufficient data on safety and efficacy.

Elderly
Although data from clinical trials in this population are limited, it can be concluded from extensive post-marketing experience that dose adjustment is not necessary in elderly patients.

Renal impairment
There are no specific data available from clinical trials in this patient group but based on post-marketing experience it seems that dose adjustment is not necessary in these patients.

Hepatic impairment
There are no specific data available from clinical trials in this patient group but based on post-marketing experience it seems that dose adjustment is not necessary in these patients.
Duration of treatment
Treatment may be long-term. Improvement can sometimes only be observed after a couple of weeks. Best results are sometimes obtained after a few months.

Method of administration
The tablets are for oral use and are taken preferably with meals.

4.3 Contraindications
{Nationally completed name} is contraindicated in the cases of:
- 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

Caution is advised in the treatment of patients with peptic ulcer or a history of peptic ulceration, because of the occasional dyspepsia encountered in patients on betahistine.

Caution should be exercised in patients with bronchial asthma.

Caution is advised in prescribing betahistine to patients with either urticaria, rashes or allergic rhinitis, because of the possibility of aggravating these symptoms.

Caution is advised in the treatment of patients with severe hypotension.

{Nationally completed name} should not be used in patients under concomitant treatment with antihistamines (see section 4.5).

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 medicinal products.

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

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. However, betahistine may cause drowsiness which can affect the ability to drive and use machines.

4.8 Undesirable effects

The following undesirable effects have been reported. They are listed below by system organ class and frequency. .

Frequencies are defined as follows:
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)
Not known: (cannot be estimated from the available data)

MedDRA System Organ Class	Frequency	ADRs
Immune system disorders	**Not known**	Hypersensitivity reactions (e.g. anaphylaxis)
Nervous system disorders	**Common**	Headaches
	Not known	Drowsiness
Cardiac disorders	**Rare**	Palpitations, tightness of the chest
Respiratory, thoracic and mediastinal disorders	**Rare**	An existing bronchial asthma could be worsened
Gastrointestinal disorders	**Common**	Nausea, dyspepsia
	Rare	Retching, heartburn, gastric discomfort and pain, flatulence
	Not known	Emesis
Skin and subcutaneous tissue disorders	**Not known**	Cutaneous and subcutaneous hypersensitivity reactions, in particular angioneurotic oedema, rash, pruritus and urticaria

Note:
Gastric disorders can normally be avoided by taking {Nationally completed name} with or after a meal or by reducing the dosage.

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

Symptoms
Symptoms of betahistine overdose are dryness of the mouth, nausea, vomiting, dyspepsia, ataxia and - following intake of very high doses - convulsions may also occur.
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.

Management
There is no specific antidote. In addition to general measures aimed at toxin elimination (gastric lavage, administration of activated charcoal), treatment should include standard supportive measures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 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_1-receptor agonist and histamine H_3-receptor antagonist also in neuronal tissue, and has negligible H_2-receptor activity. Betahistine increases histamine turnover and release by blocking presynaptic H_3-receptors and inducing H_3-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_3-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

Pharmacokinetic/pharmacodynamic relationship(s)
Data on the pharmacokinetics of betahistine in humans are insufficient

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). 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.

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/non-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

Repeat oral dose toxicity studies in dogs and rats for 6 and 18 months respectively revealed no clinically relevant adverse effects.
Betahistine was not mutagenic in conventional *in vitro* and *in vivo* studies of genotoxicity.
Histopathological examination in the 18 months chronic toxicity study indicated no carcinogenic effects. However, specific carcinogenicity studies were not performed with Betahistine.
Limited studies of reproductive toxicity in rats and rabbits showed no teratogenic effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid anhydrous
Microcrystalline cellulose (PH-102)
Mannitol
Silica, Colloidal anhydrous
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

After first opening of the bottle: 70 days

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

- PVC/PVDC/Al foil blisters
- HDPE bottle with a PP screw closure with an induction seal liner

[NL/H/3705-3706]
Pack size
<Blister packs: 20, 30, 50, 90, 100 tablets>
<Bottle packs: 100, 120 tablets >

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

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

7. MARKETING AUTHORISATION HOLDER

Sandoz B.V.
Veluwezoom 22
1327 AH Almere
Nederland

8. MARKETING AUTHORISATION NUMBER(S)

Betahistine Sandoz 8 mg, tabletten is geregistreerd onder RVG 118846
Betahistine Sandoz 16 mg, tabletten is geregistreerd onder RVG 118847
Betahistine Sandoz 24 mg, tabletten is geregistreerd onder RVG 118848

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 28 mei 2018
Datum van laatste verlenging: 23 januari 2023

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft rubriek 9: 2 november 2022