Summary of Product Characteristics

1. Name of the medicinal product
ANATAX (Betahistine Dihydrochloride 16mg Tablets)

2. Qualitative and quantitative composition
Each tablet contains Betahistine dihydrochloride 16 mg

Excipient(s) with known effect: NN

For a full list of excipients, see section 6.1.

3. Pharmaceutical form
Tablets for oral administration

White round scored tablet embossed with T7 on one side, plain on the other.

4. Clinical particulars
4.1 Therapeutic indications

Betahistine is indicated for the treatment of vertigo, tinnitus and hearing loss associated with Meniere's syndrome.

4.2 Posology and method of administration

Posology:
Adults (including the elderly):
Initially 16mg 3 times daily, taken preferably with meals.

Maintenance doses are generally in the range 24-48mg daily.

Paediatric population:
Not recommended for use in children below 18 years due to insufficient data on safety and efficacy.

Elderly 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.

Method of Administration:
Oral use.

4.3 Contraindications

Betahistine is contraindicated in patients with a phaeochromocytoma and hypersensitivity to betahistine dihydrochloride or 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 betahistine dihydrochloride in bronchial asthma patients has been shown in a relatively few patients. These patients need to be carefully monitored during the therapy.

Lactose
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption 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 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 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 Meniere'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 (≥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)].

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 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. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system (see details below).

Paper based reporting: TMDA yellow card

Online reporting: https://sqrt.tmda.go.tz/

*USSD reporting: send a simple short text message to report any suspected Adverse Drug Reaction by dialing *152*00# and follow the instructions*

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 preparation.
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 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 Meniere'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 Cmax 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-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 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 dose 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

NNN
6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 30°C. Store in the original package.

6.5 Nature and contents of container

Betahistine Dihydrochloride 16mg Tablets are packed in ALU/PVC/PVDC blister of 6 X 10'S

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. Marketing authorisation holder
UNITED PHARMACEUTICALS MANUFACTURING LIMITED COMPANY
NUZHAT SAHAB, AL-RAQEEM- NEAR PUBLIC SECURITY
HOUSING
REG. NO. 2161, P.O. BOX 69, AMMAN 11591 NA
JORDAN

8. Marketing authorisation number(s)
TZ 19 H 0192

9. Date of first authorisation/renewal of the authorisation
August 02, 2019

10. Date of revision of the text
October 10, 2023