STUNARONE TABLETS

Composition
Active substances
Cinnarizine.
Excipients:
lactose monohydrate, maize starch, sucrose, talc, cottonseed oil hydrogenated, polyvidone K 90.

Pharmaceutical form and active substance quantity per unit

Stunarone tablets 25 mg.

White, circular, biconvex, halfscored tablet with the inscription “JANSSEN” on one side and “S/25” on the other side.

Therapeutic indications

Symptomatic treatment of nausea and vertigo due to Meniere's disease and other labyrinthine disturbances and for travel sickness.

Dosage/Administration
Disorders of balance:
In adults: 1 tablet of 25 mg t.i.d.

Motion sickness:
in adults: 1 tablet of 25 mg half an hour before traveling; to be repeated every 6 hours.
in children (5-12): half of the adult dose is recommended.

Stunarone tablets should preferably be taken after meals with some liquid.
Stunarone tablet may be divided at the score line only for easier administration, but not for administering a partial dose. Please use a tablet divider to achieve half a dosage.

Contraindications

Stunarone tablets is contraindicated in patients with a history of extrapyramidal symptoms, Parkinsonism or depression.
Insufficient clinical data are as yet available for use of Stunarone tablets in children aged under 5 years.
Stunarone tablets should not be used in cases of recent myocardial infarction or hypersensitivity to the active substance or any other ingredient listed in the excipient section.

Warnings and precautions

Elderly patients in particular must be investigated during treatment for the occurrence of extrapyramidal symptoms and depression. If these occur,, the product must be discontinued.
Caution is required in cases of pronounced arterial hypertension. Stunarone tablets can cause somnolence, especially at the start of treatment. Therefore, special caution is required when alcohol, CNS depressants or Tricyclic antidepressants are used concomitantly with Stunarone tablets.
Like other antihistamines, Stunarone tablets can cause epigastric pain, taking it after meals may reduce this.

Stunarone tablets contain sucrose and lactose.Patients with rare hereditary fructose/galactose intolerance, complete lactase deficiency, glucose-galactose malabsorption or sucrase-isomaltase failure, should not use this medicinal product.

Interactions

The sedative effect of Stunarone tablets may be potentiated when they are used concomitantly: alcohol, CNS depressants and tricyclic antidepressants.
If the product is co-administered with vasodilators, potentiation of their effect is possible

Pregnancy, lactation

Pregnancy

No clinical data are available from use in pregnant women. No teratogenic effect was observed in animal studies. See “Preclinical data.” The potential risk to humans is not known. Caution is required in use in pregnancy.

Lactation

The evidence is insufficient with regard to whether cinnarizine is excreted in the breast milk. Breast-feeding during the treatment should therefore definitely be discouraged.

Effects on ability to drive and use machines

Somnolence may occur, especially at the start of treatment, and thus impair reactions. Attention in road traffic and when using machines, etc. can therefore be reduced.

Undesirable effects

The safety of Stunarone tablets was evaluated in 303 cinnarizine-treated subjects who participated in 6 placebo-controlled trials for the indications peripheral circulatory disorders, cerebral circulatory disorders, vertigo and prevention of motion sickness; and in 937 cinnarizine-treated subjects who participated in six reference and 13 open label clinical trials for the indications peripheral circulatory disorders, cerebral circulatory disorders and vertigo. Based on pooled safety data from these clinical trials, the most commonly reported (>1% incidence) Adverse Drug Reactions (ADRs) were: somnolence (9.9%), nausea (3.0%) and weight increased (1.5%).

Including the above mentioned ADRs, the following ADRs have been observed from clinical trials and post-marketing experiences reported with the use of Stunarone tablets. Frequencies displayed use the following convention:
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).

Nervous system disorders

Common: Somnolence.
Uncommon: Hypersomnia.
Very rare: Dyskinesia, extrapyramidal disorders, parkinsonism, tremor.

Gastrointestinal disorders
Common: Nausea.
Uncommon: Vomiting.
Rare: Upper abdominal pain, dyspepsia.

Hepatobiliary disorders
Very rare: Jaundice cholestatic.

Skin and subcutaneous tissue disorders
Uncommon: Hyperhidrosis. Lichenoid keratosis
Very rare: Lichen planus, subacute cutaneous lupus erythematosus.

Musculoskeletal and connective tissue and bone disorders
Very rare: Muscle rigidity.

General disorders and administration site conditions
Uncommon*:* Fatigue

Investigations
Common*:* Weight increased.

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/

Overdose

Signs and symptoms

Acute overdoses have been reported with cinnarizine doses ranging from 90 to 2,250 mg. The most commonly observed symptoms associated with overdose of cinnarizine are: alterations in consciousness ranging from somnolence to stupor and coma, vomiting, extrapyramidal symptoms and hypotension. A small number of young children displayed seizures. The clinical consequences were not serious in most cases, but deaths have been reported after overdoses with a single drug or multiple drugs involving cinnarizine.

Treatment
There is no specific antidote. The treatment is symptomatic and supportive. It is advisable to contact a poison control center to obtain the latest recommendations for the management of an overdose.

Properties /effects

ATC code N07CA02

Mechanism of action

Cinnarizine is a selective calcium channel blocker. According to the WHO classification, Stunarone tablets is a class IV calcium antagonist. Cinnarizine also has an antihistaminergic (H_1) action. Cinnarizine inhibits the contraction of the muscle cells of the vessel walls (anti-vasoconstrictor effect) by blocking calcium channels. In addition to this direct calcium antagonism, cinnarizine decreases the contractile activity of vasoactive substances such as norepinephrine and serotonin, by receptor-operated calcium channel blockade. Blockade of the

cellular influx of calcium is tissue-selective and results in an anti-vasoconstrictor effect without influence on blood pressure, heart rate, cardiac contractility and conduction.
Stunarone's tablets sphere of action also extends to the brain.
Cinnarizine is further able to improve deficient microcirculation by decreasing erythrocyte deformation and blood viscosity. Cellular resistance to hypoxia is increased. Cinnarizine inhibits stimulation of the vestibular system, which results in suppression of nystagmus and other autonomic disturbances. Acute episodes of vertigo can be prevented or reduced by cinnarizine.

Pharmacodynamics

See mechanism of action.

Clinical efficacy

No data available.

Pharmacokinetics

Absorption

After a single oral dose of 75 mg cinnarizine, a peak plasma level between 200 and 400 ng/mL, depending on interindividual variations, is reached after 1 - 4 hours.The relative bioavailability of Stunarone tablets is over 75%.

Distribution
In animal studies, cinnarizine is distributed rapidly after absorption in blood, liver, fat tissue, lungs and kidneys . Lower concentrations appear in the brain, heart, spleen and, somewhat later, in the gonads. The highest concentrations are measured in liver, kidneys and fat tissue. There is no evidence of accumulation.
The plasma protein binding of cinnarizine is 91%.
Metabolism

Cinnarizine is extensively metabolized via the metabolic path CYP2D6.

Elimination

The observed plasma half-life of cinnarizine is between 4 and 24 hours. A small proportion of cinnarizine appears unchanged in the urine (renal dose fraction < 1%), most of it is excreted in the form of metabolites (about 1/3 in the urine, about 2/3 in the feces).

***Kinetics in specific* patient groups**

Hepatic impairment / Renal impairment

Metabolism, excretion and plasma concentrations are not influenced by kidney dysfunction. In the case of liver damage, delayed elimination of cinnarizine can be expected. The dose should therefore be adjusted accordingly..

Preclinical data

A comprehensive battery of nonclinical safety studies showed that effects were observed only after chronic exposures that were 5 to 26 times (on a mg/m^2 basis) those at the maximum recommended human dose of 100 mg/day, calculated as 2 mg/kg as based on a 50 kg person.
Mutagenicity and carcinogenicity

An *in vitro* mutagenicity study with *Salmonella typhirmurium* indicated that cinnarizine showed no mutagenic potential. The carcinogenicity has not been specifically evaluated.
Reproductive toxicity
In reproductive studies in the rat, rabbit and dog, there were no effects on fertility and no teratogenicity. At maternally toxic doses in the rat, that were 3 times (on a mg/m2 basis) those at the maximum recommended human dose, cinnarizine resulted in decreased litter size, an increase in the percentage of of resorbed fetuses and a decrease in fetal birth weight.

Other information

Incompatibilities

None known

Effects on diagnostic methods

Due to the antihistaminergic effect, Stunarone tablets can influence skin tests for the diagnosis of allergies for up to 4 days after the last dose.

Shelf life
The expiry date of the product is indicated on the packaging materials
Special precautions for storage
Keep out of the reach and sight of children!
Store under 25° C.

Packs
Packs of 25 mg tablets (score line) (B)

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Importer and registration Holder: J-C Health Care Ltd, Kibbutz Shefayim, 6099000, Israel