Rx

Cinnarizine and Dimenhydrinate Tablets

Stugeron®Plus

Composition:

Each uncoated tablet contains:
Cinnarizine I.P. ……..... 20 mg
Dimenhydrinate B.P. … 40 mg
Excipients……..q.s.
For a full list of excipients, see section List of excipients.

Description

Stugeron Plus consists of 20 mg cinnarizine and 40 mg dimenhydrinate as a fixed dose combination.
Dimenhydrinate, the chlorotheophylline salt of diphenhydramine, acts as antihistamine with anticholinergic (antimuscarinic) properties, exerting parasympatholytic and centrally depressant effects.
Cinnarizine is a selective calcium entry blocker belonging to group IV of the calcium antagonists (WHO-classification) and also have an anti-histamine (H1)-effect.
Stugeron Plus is available as oral tablets.

Therapeutic indication

For the treatment of vertigo

Properties

Pharmacodynamic

Cinnarizine inhibits contractions of vascular smooth muscle cells 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 blocking receptor-operated calcium channels. Blockade of the cellular influx of calcium is tissue-selective, and results in anti- vasoconstrictor properties without effect on blood pressure and heart rate.

Cinnarizine may further improve deficient microcirculation by increasing erythrocyte deformability and decreasing 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.

Dimenhydrinate, the chlorotheophylline salt of diphenhydramine, acts as antihistamine with anticholinergic (antimuscarinic) properties, exerting parasympatholytic and centrally depressant effects. The substance exhibits anti-emetic and antivertiginous effects through influencing the chemoreceptor trigger zone in the region of the 4th ventricle.

Both cinnarizine and dimenhydrinate are known to be effective in the treatment of vertigo.
The combination product is more effective than the individual compounds in the population studied.
The product has not been evaluated in motion sickness.

Pharmacokinetics

Absorption and Distribution

Dimenhydrinate rapidly releases its diphenhydramine moiety after oral administration. Diphenhydramine and cinnarizine are rapidly absorbed from the gastro-intestinal tract. Cmax of cinnarizine and diphenhydramine are reached in humans within 2 - 4 hours. The plasma protein binding of cinnarizine is 91%. The plasma elimination half-lives of both substances range from 4 to 5 hours, when given either alone or as the combination product.

Metabolism

Cinnarizine and diphenhydramine are extensively metabolised in the liver. Studies of diphenhydramine in human liver microsomes in vitro indicate the involvement of various CYP-enzymes, including CYP2D6. Cinnarizine is also partly metabolized by CYP2D6.

Elimination

Cinnarizine is mainly eliminated via the faeces (40-60%) and to a lower extent also in urine, mainly in the form of metabolites conjugated with glucuronic acid. The major route of elimination of diphenhydramine is in the urine, mainly in the form of metabolites, with the deaminated compound, diphenylmethoxy acetic acid, being the predominant metabolite (40- 60%).

Contraindications

Severe renal impairment (creatinine clearance of ≤ 25 ml/min) Severe hepatic impairment.
Stugeron Plus is contra-indicated in patients with known hypersensitivity to the active substances, diphenhydramine or other antihistamines of similar structure or to any of the excipients.

Special warnings and special precautions for use

Stugeron Plus does not reduce blood pressure significantly; however, it should be used with caution in hypotensive patients.

Stugeron Plus should be taken after meals to minimise any gastric irritation. Stugeron Plus should be used with caution in patients with conditions that might be aggravated by anticholinergic therapy, e.g. raised intra-ocular pressure, pyloro-duodenal obstruction, prostatic hypertrophy, hypertension, hyperthyroidism or severe coronary heart disease.
Caution should be exercised when administering Stugeron Plus to patients with Parkinson's disease.

Interactions with other medicinal products and other forms of interaction
Alcohol/CNS depressants/Tricyclic Antidepressants: Concurrent use may potentiate the sedative effects of either of these medications or of Stugeron Plus.

Amino glycosidic antibiotics: Stugeron Plus may mask ototoxic symptoms associated with amino glycosidic antibiotics and mask the response of the skin to allergic skin tests.

Anti-arrhythmics: The concomitant administration of medicines that prolong the QT interval of the ECG (such as Class Ia and Class III anti-arrhythmics) should be avoided.

Diagnostic Interference: Because of its antihistamine effect, Stugeron Plus may prevent otherwise positive reactions to dermal reactivity indicators if used up to 4 days prior to skin testing.

Pregnancy and Lactation
Use during pregnancy
The safety of Stugeron Plus in human pregnancy has not been established. The teratogenic risk of the single active substance; dimenhydrinate/ diphenhydramine and cinnarizine is low. No teratogenic effects were observed in animal studies.
Dimenhydrinate may have an oxytocic effect and may shorten labour. Stugeron Plus should not be used during pregnancy.

Use during lactation
Dimenhydrinate is excreted in human breast milk.
There are no data on the excretion of cinnarizine in human breast milk: nursing should therefore be discouraged in women using Stugeron Plus.

Effects on Ability to Drive and Use Machines
Stugeron Plus may cause drowsiness, especially at the start of treatment. Patients affected in this way should not drive or operate machinery.
Posology and Method of Administration
Adults: 1 tablet three times daily, to be taken unchewed with some liquid after meals.

Children and adolescents under the age of 18 years: Stugeron Plus is not recommended; as no data available on the use of Stugeron Plus in this age group.

Elderly: Dosage as for adults.

Renal impairment:

Stugeron Plus should be used with caution in patients with mild to moderate renal impairment.

Stugeron Plus should not be used by patients with a creatinine clearance of < 25mL/min (severe renal impairment).

Hepatic impairment:

No studies in patients with hepatic impairment are available. Stugeron Plus should not be used by patients with severe hepatic impairment.

Undesirable Effects

The most frequently occurring ADRs are somnolence (including drowsiness, tiredness, fatigue) occurring in about 8% of patients and dry mouth occurring in about 5% of patients in clinical trials. These reactions are usually mild and disappear within a few days even if treatment is continued.

In addition the following adverse reactions are associated with dimenhydrinate and cinnarizine:

Dimenhydrinate: paradoxical excitability (especially in children), worsening of an existing angle-closure glaucoma, reversible agranulocytosis.

Cinnarizine: constipation, weight gain, tightness of the chest, cholestatic jaundice, extrapyramidal symptoms, lupus-like skin reactions, lichen planus.

Overdose

Symptoms

Symptoms of overdosage with Stugeron Plus include drowsiness, dizziness and ataxia with anticholinergic effects such as dry mouth, flushing of the face, dilated pupils, tachycardia, pyrexia, headache and urinary retention. Convulsions, hallucinations, excitement, respiratory depression, hypertension, tremor and coma may occur, particularly in cases of massive overdosage.

Treatment

General supportive measures should be used to treat respiratory insufficiency or circulatory failure. Gastric lavage with isotonic sodium chloride solution is recommended. Body temperature should be closely monitored, since pyrexia may occur as a consequence of antihistamine intoxication, especially in children.

Cramp-like symptoms may be controlled by careful application of a short-acting barbiturate.

In cases of marked central-anticholinergic effects, physostigmine (after physostigmine test) should be administered slowly intravenously (or, if necessary, intramuscularly): 0.03 mg/kg body weight (adults max. 2 mg, children max. 0.5 mg).

Dimenhydrinate is dialyzable, however treatment of overdosage by this measure is considered as unsatisfactory. Sufficient elimination can be achieved by means of haemoperfusion using activated charcoal. No data are available concerning the dialysability of cinnarizine.

PHARMACEUTICAL PARTICULARS

List of excipients

Starch IP,
Microcrystalline Cellulose IP,
Hypromellose IP,
Magnesium Stearate IP,
Crosscarmellose Sodium IP,
Colloidal Silicon Dioxide IP,
Purified water** IP
** → Does not appear in the final product

Shelf life

Please refer to the outer carton.

Storage Conditions

Do not store above 30^0C.
Keep out of the sight and reach of children.

Nature and Contents of Pack

Mono carton containing 1 Blister of 10 tablets each.

Made in India by:

Johnson & Johnson Pvt. Ltd.,
Gala No. 3, BULDG No. B-2 Citylink Warehousing Complex,
S.No. 120-121, Mumbai Nashik Highway, Village Vadpe,
Taluka – Bhiwandi -421302, Maharashtra.

Manufactured at:
Encore Healthcare Pvt. Ltd.,
Plot No. D-5, M.I.D.C., Industrial Area,
Paithan, Aurangabad – 431 148.
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DATE OF REVISION OF THE TEXT

22 Dec 2023

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