

PRODUCT NAME

STUGERON[®] (cinnarizine)

DOSAGE FORMS AND STRENGTH

Tablets.

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

For excipients, see List of Excipients.

CLINICAL INFORMATION**Indications**

- Disorders of balance - maintenance therapy for symptoms of labyrinthine disorders, including vertigo, dizziness, tinnitus, nystagmus, nausea and vomiting.
- Prophylaxis of motion sickness.

Dosage and Administration***Dosage***

Disorders of balance - Adult

- 1 tablet of 25 mg three times a day

Prophylaxis of motion sickness:

- Adults and adolescents aged 13 years and above: 1 tablet of 25 mg at least half an hour before travelling; to be repeated every 6 hours;
- Children aged 6 to 12 years: half of the adult dose is recommended.

Administration

STUGERON[®] should preferably be taken after meals. It is for oral administration.

Contraindications

STUGERON[®] is contraindicated in patients with known hypersensitivity to the drug.

Warnings and Precautions

As with other antihistamines STUGERON[®] may cause epigastric distress; taking it after meals may diminish gastric irritation.

In patients with Parkinson's disease STUGERON[®] should only be given if the advantages outweigh the possible risk of aggravating this disease.

STUGERON[®] may cause somnolence, especially at the start of treatment. Therefore caution should be taken when alcohol, central nervous system (CNS) depressants or tricyclic antidepressants are used concomitantly.

Interactions

Alcohol/CNS Depressants and tricyclic antidepressants

The sedative effects of STUGERON[®] and of any of the following may be potentiated when used concomitantly: alcohol, CNS depressants, or tricyclic antidepressants.

Diagnostic interference

Because of its antihistamine effect, STUGERON® may prevent otherwise positive reactions to dermal reactivity indicators if used up to 4 days prior to skin testing.

Pregnancy and Breast-feeding

Pregnancy

Although in animal studies, STUGERON® has shown no teratogenic effects, as with all drugs, STUGERON® should be used during pregnancy only if the therapeutic benefits justify the potential risks for the fetus.

Breast-feeding

There are no data on the excretion of STUGERON® in human breast milk: nursing should therefore be discouraged in women using STUGERON®.

Effects on Ability to Drive and Use Machines

Since somnolence may occur, especially at the start of treatment, caution should be taken during activities such as driving or operating machinery.

Adverse reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of cinnarizine based on the comprehensive assessment of the available adverse event information. A causal relationship with cinnarizine cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical trial data

Placebo-controlled double-blind data – adverse reactions reported at $\geq 1\%$ incidence

The safety of STUGERON® (30 to 225 mg/day) was evaluated in 601 subjects (of which 303 were treated with STUGERON®, 298 were given placebo) who participated in 6 placebo-controlled, double-blind clinical trials: 2 in the treatment of peripheral circulatory disorders, 1 in the treatment of cerebral circulatory disorders, 1 in the treatment of vertigo, 1 in the prevention of motion sickness, and 1 in the treatment of both vertigo and cerebral circulatory disorders.

Adverse reactions reported by $\geq 1\%$ of STUGERON®-treated subjects noted in the double-blind clinical trials are shown in Table 1.

Table 1. Adverse Reactions Reported by $\geq 1\%$ of STUGERON[®]-treated Subjects in 6 Double-Blind Placebo-Controlled Clinical Trials of STUGERON[®]

System/Organ Class Preferred Term	STUGERON [®] (n = 303) %	Placebo (n = 298) %
Nervous System Disorders		
Somnolence	9.9	5.4
Gastrointestinal Disorders		
Nausea	3.0	1.7

Comparator and open-label data – adverse reactions reported at $\geq 1\%$ incidence

Six comparator trials and 13 open label trials were selected to determine the incidence of adverse reactions. In these 19 studies, 937 subjects were treated with doses ranging from 25 to 450 mg/day STUGERON[®], in the treatment of peripheral circulatory disorders, cerebral circulatory disorders, and vertigo.

Adverse reactions reported by $\geq 1\%$ of STUGERON[®]-treated subjects noted in the comparator and open label clinical trials are shown in Table 2.

Table 2. Adverse Reactions Reported by $\geq 1\%$ of STUGERON[®]-treated Subjects in 6 Comparator and 13 Open-Label Clinical Trials of STUGERON[®]

System/Organ Class Preferred Term	STUGERON [®] (n = 937) %
Investigations	
Weight increased	1.5

Placebo, comparator, and open-label data – adverse reactions reported at $< 1\%$ incidence

Additional adverse reactions that occurred in $< 1\%$ of STUGERON[®]-treated subjects in the above 2 clinical datasets (25 studies with a total of 1240 subjects treated with doses ranging from 25 to 450 mg/day) are listed below in Table 3.

Table 3. Adverse Reactions Reported by < 1% of STUGERON®-treated Subjects in Placebo-controlled, Comparator-controlled, and Open-label Clinical Trials of STUGERON®.

System/Organ Class Preferred Term	STUGERON® (n=1240) %
Nervous System Disorders	
Hypersomnia	0.16
Gastrointestinal Disorders	
Vomiting	0.24
Abdominal pain upper	0.08
Dyspepsia	0.08
Skin and Subcutaneous Tissue Disorders	
Hyperhidrosis	0.32
General Disorders and Administration Site Conditions	
Fatigue	0.40

Postmarketing data

Adverse events first identified as adverse reactions during postmarketing experience with cinnarizine are included in Table 4. The postmarketing review was based on review of all cases where there was a use of cinnarizine. In Table 4, adverse reactions are presented by frequency category based on spontaneous reporting rates, with frequencies provided according to the following convention:

Very common	≥ 1/10 (≥10%)
Common	≥ 1/100 and < 1/10 (≥1% and < 10%)
Uncommon	≥ 1/1000 and < 1/100 (≥ 0.1% and < 1%)
Rare	≥ 1/10000 and < 1/1000 (≥0.01 and < 0.1%)
Very rare	< 1/10000 including isolated reports (< 0.01%)
Not known	Cannot be estimated from the available data

Table 4: Adverse Reactions Identified During Postmarketing Experience with cinnarizine (STUGERON®) by Frequency Category

System/Organ Class Preferred Term	Frequency Estimated from Spontaneous Reporting Rates
Nervous System Disorders	
Dyskinesia	<i>Very rare</i>
Extrapyramidal disorder	<i>Very rare</i>
Parkinsonism	<i>Very rare</i>
Tremor	<i>Very rare</i>
Hepatobiliary Disorders	
Jaundice cholestatic	<i>Very rare</i>
Skin and Subcutaneous Tissue Disorders	
Lichenoid keratosis	<i>Very rare</i>
Lichen planus	<i>Very rare</i>
Subacute cutaneous lupus erythematosus	<i>Very rare</i>
Musculoskeletal, Connective Tissue and Bone Disorders	
Muscle rigidity	<i>Very rare</i>

Overdose

Symptoms and signs

Acute cinnarizine overdoses have been reported with doses ranging from 90 to 2,250 mg. The most commonly reported signs and symptoms associated with overdose of cinnarizine include: alterations in consciousness ranging from somnolence to stupor and coma, vomiting, extrapyramidal symptoms, and hypotonia. In a small number of young children, seizures developed. Clinical consequences were not severe in most cases, but deaths have been reported after single and polydrug overdoses involving cinnarizine.

Treatment

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: antivertigo preparations, ATC code N07CA02

Cinnarizine has an anti-histamine (H₁)-effect. 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.

Pharmacokinetic Properties

Absorption

The peak plasma levels of cinnarizine are obtained 1 to 3 hours after intake.

Distribution

The plasma protein binding of cinnarizine is 91%.

Metabolism

Cinnarizine is extensively metabolized mainly via CYP2D6.

Elimination

The reported elimination half-life for cinnarizine ranges from 4 to 24 hours. The elimination of metabolites is about 1/3 in the urine and 2/3 in the feces.

NON-CLINICAL INFORMATION

A comprehensive battery of nonclinical safety studies showed that effects were observed only after chronic exposures that were 10 to 160 times (on a mg/kg basis) those at the maximum recommended human dose of 100 mg/day, calculated as 2 mg/kg as based on a 50 kg person.

PHARMACEUTICAL INFORMATION

List of Excipients

25mg tablets:

Cotton seed oil hydrogenated, lactose monohydrate, maize starch, polyvidone, sucrose, talc.

Incompatibilities

None known.

Shelf Life

3 years.

Storage conditions

Store below 30°C.

Protect from light.

Keep out of sight and reach of children.

Nature and Contents of Container

Blister packs with 2 x 25 tablets. One box contains 50 tablets.

Instructions for Disposal

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

MANUFACTURED BY

Janssen-Cilag S.p.A
Via C. Janssen,
Borgo San Michele,
Latina, Italy.

PRODUCT REGISTRATION HOLDER

Johnson & Johnson Sdn Bhd (3718-D)
Level 8, The Pinnacle,
Persiaran Lagoon, Bandar Sunway,
46150, Petaling Jaya, Selangor, Malaysia

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