NAME OF THE MEDICINAL PRODUCT
STUGERON

QUALITATIVE AND QUANTITATIVE COMPOSITION
25 mg cinnarizine per tablet.
For excipients, see List of Excipients.

PHARMACEUTICAL FORM
Tablets.

CLINICAL PARTICULARS
Therapeutic Indications
- Maintenance therapy for symptoms of labyrinthine disorders, including vertigo, dizziness, tinnitus, nystagmus, nausea and vomiting.
- Prophylaxis of motion sickness.
- Prophylaxis of migraine.
- Maintenance therapy for symptoms of cerebrovascular origin, including dizziness, ear buzzing (tinnitus), vascular headache, unsociability and irritability disorders, loss of memory and lack of concentration.
- Maintenance therapy for symptoms of peripheral circulatory disorders, including Raynaud's phenomenon, acrocyanosis, intermittent claudication, trophic disturbances, trophic and varicose ulcers, paraesthesia, nocturnal cramps, cold extremities.

Posology and Method of Administration
- Cerebral circulatory disorders: 1 tablet of 25 mg t.i.d.Peripheral circulatory disorders: 2 - 3 tablets of 25 mg t.i.d.Disorders of balance: 1 tablet of 25 mg t.i.d. Motion sickness: in adults: 1 tablet of 25 mg half an hour before travelling; to be repeated every 6 hours; in children: half of the adult dose is recommended.

STUGERON should preferably be taken after meals.
The suspension should be shaken before use.
The maximum recommended dosage should not exceed 225 mg daily. As the effect of STUGERON on vertigo is dose dependent, the dosage should be increased progressively.

Contraindications
STUGERON is contraindicated in patients with known hypersensivity to the drug.

Special Warnings and Special Precautions for Use
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 or CNS depressants are used concomitantly.

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.
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 Lactation

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.

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.

Undesirable Effects

Clinical Trial Data

Placebo-Controlled Double-Blind Data – Adverse Drug Reactions Reported at ≥1% Incidence

The safety of STUGERON (30 to 225 mg/day) was evaluated in 740 subjects (of which 372 were treated with STUGERON, 368 were given placebo) who participated in 7 placebo-controlled, double-blind clinical trials: three in the treatment of peripheral circulatory disorders, one in the treatment of cerebral circulatory disorders, two in vertigo, and one in seasickness.

ADRs reported by ≥1% of STUGERON-treated subjects noted in the double-blind clinical trials are shown in Table 1.

Table 1. Adverse Drug Reactions Reported by ≥1% of STUGERON-treated Subjects in 7 Double-Blind Placebo-Controlled Clinical Trials of STUGERON

System/Organ Class Preferred Term	**STUGERON (n=372) %**	**Placebo (n=368) %**
Nervous System Disorders		
Somnolence	8.3	4.6

Comparator and Open-Label Data – Adverse Drug Reactions Reported at ≥1% Incidence

Six comparator trials and thirteen open label trials were selected to determine the incidence of ADRs. In these 19 studies, 668 subjects were treated with doses ranging from 50 to 225 mg/day STUGERON, in the treatment of peripheral circulatory disorders, cerebral circulatory disorders, and vertigo.

ADRs reported by ≥1% of STUGERON-treated subjects noted in the comparator and open label clinical trials are shown in Table 2.

Table 2. Adverse Drug Reactions Reported by ≥1% of STUGERON-treated Subjects in 6 Comparator and 13 Open Clinical Trials of STUGERON

System/Organ Class Preferred Term	**STUGERON (n=668) %**
Gastrointestinal Disorders	
Nausea	1.5
Investigations	
Weight increased	2.1

Placebo, Comparator, and Open-Label Data – Adverse Drug Reactions Reported at <1% Incidence

Additional ADRs that occurred in <1% of STUGERON-treated subjects in the above 2 clinical datasets are listed below in Table 3.

Table 3. Adverse Drug Reactions Reported by <1% of STUGERON-treated Subjects in Either the Placebo- or Comparator-controlled or Open Clinical Trials.

Nervous System Disorders
Hypersomnia
Lethargy
Gastrointestinal Disorders
Stomach discomfort
Vomiting
Abdominal pain upper
Dyspepsia
Skin and Subcutaneous Tissue Disorders
Hyperhidrosis
General Disorders and Administration Site Conditions
Fatigue

Postmarketing Data

Adverse events first identified as ADRs during postmarketing experience with cinnarizine are included in Tables 4 and 5. The postmarketing review was based on review of all cases where there was a use of cinnarizine (STUGERON). In each table, the frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1000 to <1/100
Rare	≥1/10000 to <1/1000
Very rare	<1/10000 including isolated reports

In Table 4, ADRs are presented by frequency category based on spontaneous reporting rates.

Table 4: Adverse Drug Reactions Identified During Postmarketing Experience with cinnarizine (STUGERON) by Frequency Category Estimated From Spontaneous Reporting Rates

System/Organ Class Preferred Term	Frequency
Nervous System Disorders	
Dyskinesia	*Very rare*
Extrapyramidal disorder	*Very rare*
Parkinsonism	*Very rare*
Tremor	*Very rare*
Skin and Subcutaneous Tissue Disorders	
Lichenoid keratosis	*Very rare*
Lichen planus	*Very rare*
Subacute cutaneous lupus erythematosus	*Very rare*
Musculoskeletal, Connective Tissue and Bone Disorders	
Muscle rigidity	*Very rare*

Overdose

Symptoms

Acute cinnarizine overdoses have been reported with doses ranging from 90 to 2250 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. Within the first hour after ingestion, gastric lavage may be performed.
Activated charcoal may be given if considered appropriate.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Cinnarizine is a selective calcium entry blocker, belonging to group IV of the calcium antagonists (WHO-classification).
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 antivasoconstrictor 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 these metabolites occurs for about 1/3 in the urine and for 2/3 with the faeces.
Preclinical Safety Data
A comprehensive battery of nonclinical safety studies showed that effects were observed only after chronic exposures from approximately 5 to 72 times, on a mg/kg basis when compared to the maximum recommended human dose of 225 mg/day, calculated as 4.5 mg/kg as based on a 50 kg person.

PHARMACEUTICAL PARTICULARS
List of Excipients
25 mg tablets
Lactose, maize starch, sucrose, talc, hydrogenated vegetable oil, polyvidone (formulation F50).
Incompatibilities
None known.
Shelf Life
Observe expiry date on the outer pack.

Special Precautions for Storage
Tablets: store between 15° - 30°C.
Keep out of reach of children.
Nature and Contents of Container
Blister packs with 25 mg tablets.
Instructions for Use and Handling <and Disposal>
No special requirements.
MANUFACTURED BY
See outer carton.

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