1. TRADE NAME OF THE MEDICINAL PRODUCT
STUNARONE TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
25 mg cinnarizine per tablet.

3. PHARMACEUTICAL FORM
White, circular, biconvex, half-scored tablet with the inscription “JANSSEN” on one side and “S/25” on the other side.

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
Symptomatic treatment of nausea and vertigo due to Meniere’s disease and other labyrinthine disturbances and for travel sickness.

4.2. Posology and method of administration

Diseases 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 should preferably be taken after meals.

4.3. Contraindications
STUNARONE is contraindicated in patients with known hypersensitivity to the drug.

4.4. Special warnings and special precautions for use
As with other antihistamines STUNARONE may cause epigastric distress; taking it after meals may diminish gastric irritation.
In patients with Parkinson's disease STUNARONE should only be given if the advantages outweigh the possible risk of aggravating this disease.

STUNARONE may cause somnolence, especially at the start of treatment. Therefore caution should be taken when alcohol or CNS depressants are used concomitantly.

Use of cinnarizine should be avoided in porphyria.

There have been no specific studies in hepatic or renal dysfunction. Stugeron should be used with care in patients with hepatic or renal insufficiency.

Patients with rare hereditary problems of fructose or galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or sucrase-isomaltase insufficiency, should not take this medicine because it contains lactose and sucrose.

4.5. Interaction with other medicaments and other forms of interaction

*Alcohol, CNS depressants and Tricyclic Antidepressants:* Concurrent use of alcohol, CNS depressants or tricyclic antidepressants may potentiate the sedative effects of either of these medications or of STUNARONE.

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

4.6. Pregnancy and lactation

4.6.1 Use during pregnancy

The safety of Stugeron in human pregnancy has not been established although studies in animals have not demonstrated teratogenic effects. As with other drugs it is not advisable to administer Stugeron in pregnancy.

4.6.2 Use during lactation

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

4.7. Effects on ability to drive and use machines

Since somnolence may occur, especially at the start of treatment. Patients affected in this way should not drive or operate machinery.
4.8. Undesirable effects

Clinical Trial Data

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

The safety of STUNARONE (30 to 225 mg/day) was evaluated in 740 subjects (of which 372 were treated with STUNARONE, 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 STUNARONE-treated subjects noted in the double-blind clinical trials are shown in Table 1.

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>STUNARONE (n=372) %</th>
<th>Placebo (n=368) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous System Disorders</td>
<td>8.3</td>
<td>4.6</td>
</tr>
<tr>
<td>Somnolence</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>System/Organ Class</th>
<th>STUGERON (n=668) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1.5</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
</tr>
<tr>
<td>Weight increased</td>
<td>2.1</td>
</tr>
</tbody>
</table>
**Placebo, Comparator, and Open-Label Data – Adverse Drug Reactions Reported at <1% Incidence**

Additional ADRs that occurred in <1% of STUNARONE-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.

<table>
<thead>
<tr>
<th>Nervous System Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersonnia</td>
</tr>
<tr>
<td>Lethargy</td>
</tr>
</tbody>
</table>

**Gastrointestinal Disorders**

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach discomfort</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
</tr>
<tr>
<td>Dyspepsia</td>
</tr>
</tbody>
</table>

**Skin and Subcutaneous Tissue Disorders**

<table>
<thead>
<tr>
<th>Hyperhidrosis</th>
</tr>
</thead>
</table>

**General Disorders and Administration Site Conditions**

<table>
<thead>
<tr>
<th>Fatigue</th>
</tr>
</thead>
</table>

**Postmarketing Data**

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

- **Very common**: \( \geq 1/10 \)
- **Common**: \( \geq 1/100 \) to \(<1/10\)
- **Uncommon**: \( \geq 1/1,000 \) to \(<1/100\)
- **Rare**: \( \geq 1/10,000 \) to \(<1/1,000\)
- **Very rare**: \(<1/10,000\) including isolated reports
Table 4: Adverse Drug Reactions Identified During Postmarketing Experience with cinnarizine (STUGERON) by Frequency Category Estimated From Spontaneous Reporting Rates

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>Preferred Term</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td>Extrapyramidal disorder</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lichenoid keratosis</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td>Lichen planus</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td>Subacute cutaneous lupus erythematosus</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td>Hyperhydrosis</td>
<td>uncommon</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal, Connective Tissue and Bone Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle rigidity</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholestatic jaundice</td>
<td>Not known</td>
<td></td>
</tr>
</tbody>
</table>

4.9. Overdose

**Symptoms**

The signs and symptoms are mainly due to the anticholinergic (atropine-like) activity of cinnarizine.

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.

Activated charcoal should only be considered in patients presenting within one hour of taking a potentially toxic overdose (ie more than 15mg/kg).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: antivertigo preparations ,ATC Code N07CA02

**Mechanism of action**
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.

5.2. 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.

5.3. NON-CLINICAL INFORMATION

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.

[Single dose LD50 values in various animal models show a large margin of safety on a mg/kg basis when compared to the maximum recommended human dose (MRHD) of 225 mg/day or 4.5 mg/kg as based on a 50 kg person. LD50 values
were >1000 mg/kg in the mouse following oral, subcutaneous and intraperitoneal administrations. Similarly, the LD50 values in the rat and dog were >640 mg/kg and >160 mg/kg, respectively, for all three routes of administration. The LD50 following intravenous administration in the mouse and rat were 22 mg/kg and 24 mg/kg, respectively. The LD50 in the guinea pig was >40 mg/kg following oral and subcutaneous administrations. Results from acute oral subcutaneous and intraperitoneal toxicity in the mouse rat with dihydrochloride salt were similar to the results of the parent compound.

Repeat dose oral (administered in the diet) toxicity studies in the rat showed some decrease in food consumption and changes in serum chemistry (decrease in inorganic phosphorus, increase in calcium/phosphor ratio), organ weight (decrease in spleen and heart, increase in liver, kidney and brain) and histopathology (chronic centrilobular degeneration and pancreatic modifications). These observations were generally in the high dose group (320 mg/kg or about 72 x MRHD) and were more pronounced after 18-months of treatment. After 3- or 12-months oral dosing in the dog, all observations were similar to controls except for some decreased body weight (after 3 months at 80 mg/kg or about 18 x MRHD) or some limited histopathological findings (focal nuclear vacuolation and satellitosis in the CNS, hydropic aspect in the liver, pancreatic modifications, lymphoid depletion, inhibition of spermatogenesis and atrophy of female genital tract) after 12 months at the high dose of 20 mg/kg (~5 x MRHD).

In reproductive studies in the rat, rabbit, and dog, there were no effects on fertility and no teratogenicity. At very high doses (80 to 320 mg/kg, about 18-72 x MRHD) in the rat, maternal toxicity resulted in decreased litter size, an increase in the percent of resorptions and a decrease in fetal birth weight.

In vitro mutagenicity study with Salmonella typhimurium indicated that the parent compound is not mutagenic up to 10 umol/plate. However, after reacting with nitrite and forming the nitrosation product, a weak mutagenic activity was observed. Carcinogenicity has not been specifically evaluated. However, no pre-neoplastic changes were evident during chronic 18-month oral administration in rats up to a dose of approximately 72 times the maximum human dose level.

6. PHARMACEUTICAL PARTICULARS
6.1. List of excipients

25 mg tablets
Lactose monohydrate, maize starch, sucrose, talc, cottonseed oil hydrogenated, polyvidone K90.

6.2. Incompatibilities

None known.
6.3 Special precautions for storage

Store between 15 and 30°C.
Keep out of reach of children.

6.4 Nature and contents of container

Blister packs with 25 mg tablets

Manufacturer: Janssen Cilag S.p.A, Via C. Janssen 04010, Borgo S.Michele, Latina, Italy

License Holder: J-C Health Care Ltd, Kibbutz Shefayim, 60990, Israel