Package Insert
Stugil – D®

Product Summary

1. Name of the medicinal product
Stugil – D®

2. Qualitative and quantitative composition
Each tablet contains
Cinnarizine 20 mg
Dimenhydrinate 40 mg

3. Pharmaceutical form
Tablet

4. Clinical particulars
4.1 Therapeutic indications
Cinnarizine is effective in the control of motion sickness. Dimenhydrinate is used mainly as an anti-emetic in the prevention and treatment of motion sickness; irradiation sickness, postoperative vomiting, drug-induced nausea and vomiting, and the symptomatic treatment of nausea and vertigo due to Meniere’s disease and other labyrinthine disturbances.

4.2 Posology and method of administration
Posology
Cinnarizine should preferably be taken after meals.

Adults, elderly and children over 12 years:
As prescribed by the physician.

Children 5 to 12 years:
One half the adult dose.

Dimenhydrinate
**Adults**: For motion sickness it is usually given in doses of 50 mg three times daily, the first dose for preventing motion sickness being taken about 30 minutes before the journey.

For other treatment, 4-hourly administration may be required. Doses of 100 mg may be required but a daily total of 300 mg should not usually be exceeded.

**Children**: 2 to 6 years - 12.5 to 25 mg two to three times daily. Not more than 75 mg should be given in any 24 hours. Do not exceed the stated dose.

7 to 12 years - 25 to 50 mg two to three times daily. Not more than 150 mg should be given in any 24 hours. Do not exceed the stated dose.

**Elderly**: Same as adult dose.

Route of administration: Oral.

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**4.3 Contraindications**

Known hypersensitivity to any of the active constituents.

In patients with porphyria. Children under 2 years old.

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**4.4 Special warnings and precautions for use**

As with other antihistamines, cinnarizine may cause epigastric discomfort; taking it after meals may diminish gastric irritation.

In patients with Parkinson's disease, cinnarizine should only be given if the advantages outweigh the possible risk of aggravating this disease.

Use of cinnarizine should be avoided in porphyria.

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

Cinnarizine 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. Please also refer to section 4.5 Interactions with Other Medicinal Products and Other Forms of Interaction.

**Diagnostic Interference**

Because of its antihistamine effect, cinnarizine may prevent an otherwise positive reaction to dermal reactivity indicators if used within 4 days prior to testing.

Dimenhydrinate should be used with caution in patients with

- Epilepsy
• prostatic hypertrophy or urinary retention
• glaucoma
• hepatic diseases
• pyloroduodenal obstruction

In patients with renal impairment, a reduction in the dose of any antihistamine (e.g. dimenhydrinate) may be necessary.

Use in children under 6 years old should only be under professional advise. Diphenhydramine should not be taken with cough and cold medicines in children aged 2-6 years old.

Children and the elderly are more susceptible to the side effects.

It has been suggested that Dimenhydrinate could mask warning symptoms of damage caused by ototoxic drugs such as the amino-glycoside antibiotics.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent use of alcohol, CNS depressants or tricyclic antidepressants may potentiate the sedative effects of either of these drugs or of cinnarizine.

Diagnostic interference

Because of its antihistamine effect, cinnarizine may prevent otherwise positive reactions to dermal reactivity indicators if used up to 4 days prior to skin testing. Also refer to section 4.4 Special Warnings and Precautions for Use.

Dimenhydrinate will interact with anticholinergic, anti-depressant (tricyclic and MAOIs) and anti-parkinsonian drugs such as Trihexyphenidyl, increasing the anticholinergic side effects, dry mouth, urine retention, confusion, etc.

The effects of Betahistine may be antagonized.

Sedating antihistamines may enhance the sedative effects of CNS depressants including alcohol, other sedating antihistamines, barbiturates, hypnotics, opioids, anxiolytic sedatives and antipsychotics.

It is important that the dose of Neperidine, Morphine or other narcotic analgesics and of barbiturates be reduced by ¼ or ½ when used concomitantly.

4.6 Fertility, Pregnancy and lactation

The safety of cinnarizine 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 cinnarizine in pregnancy. There are no data on the excretion of cinnarizine in human breast milk. Use of cinnarizine is not recommended in nursing mothers. Dimenhydrinate should not be used in pregnancy unless the physician considers it is essential. There was a significant incidence of cleft palate and clefts with other defects in children whose mothers have taken diphenhydramine (a component of Dimenhydrinate). Dimenhydrinate is excreted in breast milk to such an extent that effects on the suckling child are likely if therapeutic doses of Dimenhydrinate are administered to breast-feeding women.

4.7 Effects on ability to drive and use machines
Cinnarizine may cause drowsiness, especially at the start of treatment; patients affected in this way should not drive or operate machinery. Patients undergoing treatment with Dimenhydrinate should not take charge of vehicles, other means of transport or machinery where loss of attention may lead to accidents because Dimenhydrinate may cause drowsiness and dulling of mental alertness.

4.8 Undesirable effects
The safety of cinnarizine was evaluated in 167 cinnarizine-treated subjects who participated in 1 placebo-controlled trial (166 placebo-treated subjects) in the prophylaxis of seasickness. In this trial, only Somnolence has been included as an ADR with an incidence of 8.4% in the cinnarizine group compared to 4.8% in the placebo group. Including the above mentioned ADR, the following ADRs have been observed from post-marketing experiences reported with the use of cinnarizine. 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), not known (cannot be estimated from the available data).

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<th>System Organ Class</th>
<th>Adverse Drug Reactions</th>
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Adverse effects with Dimenhydrinate may vary in incidence and severity from patient to patient. The most common effect is sedation which may vary from slight drowsiness to deep sleep. The drug may be associated with inability to concentrate, lassitude, dizziness, hypotension, muscular weakness and incoordination. When they do occur the sedative effects may diminish after a few days.

Rare with Dimenhydrinate are gastro-intestinal side effects.

Dimenhydrinate may very rarely produce headache, blurred vision, tinnitus, elation or depression, irritability, nightmares, anorexia, difficulty in micturition, dryness in the mouth, tightness in the chest, tingling, heaviness and weakness of the hands.

Although cardio-vascular side effects are rare, minor increases in blood pressure and occasional mild hypotension have been reported. Leucopenia and rarely agranulocytosis, jaundice and extra-pyramidal reactions have also been reported. Occasionally hypersensitivity reactions have followed its uses by both mouth or topical application. These include bronchospasm, angioedema, rashes and photosensitivity.

### 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 2,250mg. 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.
Management
There is no specific antidote. For any overdose, the treatment is symptomatic and supportive care. Activated charcoal may be given if considered appropriate.

In the case of severe overdosage of Dimenhydrinate, the stomach should be emptied by gastric lavage. Emetics should not be used. The patient should be kept quiet, particularly in the case of children, to minimise the excitation which occurs. Convulsions may be controlled with Diazepam preferably given intravenously. Since Dimenhydrinate is rapidly metabolised with only traces being recoverable in the urine, diuresis is of little, if any, value.

5. Pharmacological properties
5.1 Pharmacodynamic properties
Cinnarizine has been shown to be a non competitive antagonist of the smooth muscle contractions caused by various vasoactive agents including histamine.
Cinnarizine also acts on vascular smooth muscle by selectively inhibiting the calcium influx into depolarized cells, thereby reducing the availability of free Ca2+ ions for the induction and maintenance of contraction.
Vestibular eye reflexes induced by caloric stimulation of the labyrinth in guinea pigs are markedly depressed by cinnarizine.
Cinnarizine has been shown to inhibit nystagmus.

Dimenhydrinate is the salt produced by interaction of the antihistimanic base diphenhydramine with the acidic compound 8-chiorotheophylline. Dimenhydrmnate markedly depresses labyrinthine function.
Because of the receptors with which it interacts, Dimenhydrinate is described as an H1-antagonist or the blocker of histamine and belongs to the Theanolamine group.
The mode of action is a result of the binding with high affinity to ‘in the brain. It is not, however, clear whether the anti-motion sickness activity of Dimenhydrinate is related to its ability to block muscarinic receptors.

5.2 Pharmacokinetic properties
In animals, cinnarizine is extensively metabolised, N-dealkylation being the major pathway. Approximately two thirds of the metabolites are excreted with the faeces, the
rest in the urine, mainly during the first five days after a single dose.

**Absorption**
In man, after oral administration, absorption is relatively slow, peak serum concentrations occurring after 2.5 to 4 hours.

**Distribution**
The plasma protein binding of cinnarizine is 91%.

**Biotransformation**
Cinnarizine is extensively metabolised mainly via CYP2D6, but there is considerable interindividual variation in the extent of metabolism.

**Elimination**
The reported elimination half-life for cinnarizine ranges from 4 to 24 hours. The elimination of metabolites occurs as follows: one third in the urine (unchanged as metabolites and glucuronide conjugates) and two-thirds in the faeces.

Dimenhydrinate is well absorbed from the gastro-intestinal tract after oral dosing with extensive first-pass effect. The drug is metabolised in the liver and excreted usually as metabolites in the urine. The drug is highly bound to plasma proteins and is widely distributed in the body. Following oral administration, the effects develop in about 30 minutes and are maximal within 1-2 hours and last for 3-6 hours.

**5.3 Preclinical safety data**
Nonclinical safety studies showed that effects were observed only after chronic exposures from approximately 7 to 35 times the recommended maximum daily human dose of 90 mg/day calculated on a body surface area basis. Cinnarizine blocked the cardiac hERG channel in vitro, however in isolated cardiac tissue and following intravenous application in guinea-pigs, no QTc prolongation or proarrhythmic effects were observed at substantially higher exposures than those expected clinically. In reproductive studies in the rat, rabbit, and dog, there was no evidence of adverse effects on fertility and no teratogenicity. At high doses associated with maternal toxicity in the rat there was a decreased litter size, an increase in resorptions and a decrease in fetal birth weight.

In vitro mutagenicity studies indicated that the parent compound is not mutagenic however, after reacting with nitrite and forming the nitrosation product, a weak mutagenic activity was observed. Carcinogenicity studies have not been conducted.
however, no pre-neoplastic changes were evident during chronic 18-month oral administration in rats up to approximately 35 times the maximum human dose level.

6. Pharmaceutical particulars
6.1 Incompatibilities
None supplied.

6.3 Shelf life
As mentioned on the package material.

6.4 Special precautions for storage
As mentioned on the package material.

Administrative data
7. Marketing authorisation holder
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8. Toll free number for reporting
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9. Date of text
29th November 2016