CINNARIZINE TABLETS 25MG / 75MG TAJ PHARMA

1. NAME OF THE MEDICINAL PRODUCT

Cinnarizine Tablets 25mg Taj Pharma

Cinnarizine Tablets 75mg Taj Pharma

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

a) Each uncoated modified-release tablet contains:

Cinnarizine USP	25mg
Excipients	q.s.

b) Each uncoated modified-release tablet contains:

Cinnarizine USP	75mg
Excipients	q.s.

3. PHARMACEUTICAL FORM

Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cinnarizine is used for the control of vestibular disorders such as vertigo, tinnitus, nausea and vomiting such as that seen in Meniere's disease.

Cinnarizine is also effective in the control of motion sickness.

4.2 Posology and method of administration

Posology

Vestibular symptoms:

Adults, elderly and children over 12 years:

Two tablets three times a day.

Children 5-12 years:

One tablet three times a day.

The stated doses should not be exceeded.

Motion sickness:

Adults, elderly and children over 12 years:

Two tablets two hours before travel and one tablet every eight hours during journey if necessary.

Children 5-12 years:

One tablet two hours before travel and half a tablet every eight hours during journey if necessary.

Method of administration

For oral use.

Cinnarizine should preferably be taken after meals. The tablets may be sucked, chewed or swallowed whole with water.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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. Cinnarizine should only be given to patients with Parkinson's disease 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 Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 these drugs or of cinnarizine.

Cinnarizine may prevent an otherwise positive reaction to dermal reactivity indicators if used within 4 days prior to skin testing as it is an antihistamine.

4.6 Fertility, pregnancy and lactation

Pregnancy

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.

Breast-feeding

There are no data on the excretion of cinnarizine in human breast milk. Taking cinnarizine whilst breast-feeding is not recommended.

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.

4.8 Undesirable effects

The safety of cinnarizine was evaluated in 372 cinnarizine-treated subjects who participated in 7 placebo-controlled trials for the indications peripheral circulatory disorders, cerebral circulatory disorders, vertigo and seasickness; and in 668 cinnarizine treated subjects who participated in six comparator and thirteen open label clinical trials for the indications peripheral circulatory disorders, cerebral circulatory disorders and vertigo. Based on pooled safety data from these clinical trials, the most commonly reported (>2% incidence) adverse drug reactions (ADRs) were: somnolence (8.3) and weight increased (2.1).

Including the above mentioned ADRs, the following ADRs have been observed from clinical trials and 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) and not known (cannot be estimated from the available data).

System organ class	**Adverse drug reactions**		
	Frequency category		
	Common	**Uncommon**	**Not known**
Nervous system disorders	Somnolence	Lethargy	Dyskinesia, extrapyramidal disorder (sometimes associated with depressive feelings), Parkinsonism, tremor

Gastrointestinal disorders	Nausea, dyspepsia	Vomiting, upper abdominal pain	
Hepatobiliary disorders			Cholestatic jaundice
Skin and subcutaneous tissue disorders		Hyperhidrolysis, Lichenoid keratosis including lichen planus	Subacute cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders			Muscle rigidity
General disorders and administrative site conditions		Fatigue	
Investigations	Weight increased		

Cases of hypersensitivity, headache and dry mouth have also been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

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. Vomiting, alterations in consciousness ranging from somnolence to stupor and coma, extrapyramidal symptoms and hypotonia are the most commonly reported signs and symptoms associated with a cinnarizine overdose. 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 to cinnarizine and in the event of overdosage, treatment is symptomatic and supportive care. The administration of activated charcoal should only be considered in patients presenting within one hour of taking a potentially toxic overdose (*i.e.* more than 25mg/75mg/kg).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivertigo preparations,

Mechanism of action

Cinnarizine is a piperazine derivative with the actions and uses of the antihistamines.

Cinnarizine has been shown to be a non-competitive antagonist of the smooth muscle contractions caused by various vasoactive agents including histamine. It acts on smooth muscle by selectively inhibiting the transport of calcium ions across cell membranes into depolarised cells, therefore reducing the availability of free Ca^{+} ions for the induction and maintenance of contraction.

Pharmacodynamic effects

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.

5.2 Pharmacokinetic properties

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

In animals, cinnarizine is extensively metabolised, N-dealkylation being the major pathway.

Cinnarizine undergoes extensive metabolism mainly via CYP2D6 but there is considerable interindividual variation in the extent of metabolism.

Elimination

Approximately two thirds of the metabolites are excreted with the faeces, the rest in the urine (unchanged as metabolites and glucuronide conjugates), mainly during the first five days after a single dose.

The reported elimination half-life for cinnarizine ranges from 4 to 24 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 foetal 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 List of excipients

Starch, maize, Lactose anhydrous, Mannitol, Magnesium stearate, Talc.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/Al blisters.

Pack sizes:

Blisters: 7, 14, 28, 30, 50, 90, 100 and 500mg modified-release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special requirements

7. MANUFACTURED IN INDIA BY:

TAJ PHARMACEUTICALS LTD.
Mumbai, India
Unit No. 214.Old Bake House,
Maharashtra chambers of Commerce Lane,
Fort, Mumbai - 400001
at:Gujarat, INDIA.
Customer Service and Product Inquiries:
1-800-TRY-FIRST (1-800-222-434 & 1-800-222-825)
Monday through Saturday 9:00 a.m. to 7:00 p.m. EST
E-mail: tajgroup@tajpharma.com