Trimetazidine Hydrochloride Modified Release Tablets 35mg

1. Name of the medicinal product

Trimetazidine Hydrochloride Modified Release Tablets 35mg Taj Pharma

2. Qualitative and quantitative composition

Each film coated modified-release tablet contains:
Trimetazidine hydrochloride BP 35mg
Excipients q.s.
Colour: Tartrazine

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Modified-release tablet.

4. Clinical particulars

4.1 Therapeutic indications

–Trimetazidine is indicated in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line antianginal therapies.

4.2 Posology and method of administration

The dose is one tablet of 35mg of trimetazidine twice daily during meals.

Special populations

Patients with renal impairment

In patients with moderate renal impairment (creatinine clearance [30-60] ml/min) (see sections 4.4 and 5.2), the recommended dose is 1 tablet of 35mg in the morning during breakfast.

Elderly patients

Elderly patients may have increased trimetazidine exposure due to age-related decrease in renal function (see section 5.2). In patients with moderate renal impairment (creatinine clearance [30-60] ml/min), the recommended dose is 1 tablet of 35mg in the morning during breakfast.

Dose titration in elderly patients should be exercised with caution (see section 4.4).

Paediatric population:

The safety and efficacy of trimetazidine in children aged below 18 years have not been established. No data are available.

4.3 Contraindications

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

– Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders

– Severe renal impairment (creatinine clearance < 30ml/min)

4.4 Special warnings and precautions for use

Trimetazidine can cause or worsen parkinsonian symptoms (tremor, akinesia, hypertonia), which should be regularly investigated, especially in elderly patients. In doubtful cases, patients should be referred to a neurologist for appropriate investigations.

The occurrence of movement disorders such as parkinsonian symptoms, restless leg syndrome, tremors, gait instability should lead to definitive withdrawal of trimetazidine.

These cases have a low incidence and are usually reversible after treatment discontinuation. The majority of the patients

recovered within 4 months after trimetazidine withdrawal. If parkinsonian symptoms persist more than 4 months after drug discontinuation, a neurologist opinion should be sought.

Falls may occur, related to gait instability or hypotension, in particular in patients taking antihypertensive treatment (see section 4.8).

Caution should be exercised when prescribing trimetazidine to patients in whom an increased exposure is expected:

- moderate renal impairment (see sections 4.2 and 5.2),
- elderly patients older than 75 years old (see section 4.2)

4.5 Interaction with other medicinal products and other forms of interaction

Occurrence of interactions with other medicinal products or foodstuffs has not been found.

Trimetazidine can be used with heparin, calciparine, oral anticoagulants, medicinal products used in disturbances of lipid metabolism, salicylic acid, β-adrenolytic medicinal products, calcium channel blocking medicinal products, digitalis glycosides.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of Trimetazidine in pregnant women. Animal studies are insufficient (see section 5.3). The potential risk for humans is unknown. Trimetazidine should not be taken during pregnancy unless clearly necessary.

Lactation

It is unknown whether trimetazidine is excreted in human or animal breast milk. Since excretion in breast milk and a risk to the suckling child cannot be excluded, trimetazidine should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Trimetazidine does not have haemodynamic effects in clinical studies, however cases of dizziness and drowsiness have been observed in post-marketing experience (see section 4.8), which may affect ability to drive and use machines.

4.8 Undesirable effects

Classification of expected frequencies:

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).

System Organ Class	**Frequency**	**Preferred Term**
Nervous system disorders	Common	Dizziness, headache
	Not known	Parkinsonian symptoms (tremor, akinesia, hypertonia), gait instability, restlessleg syndrome, other related movement disorders, usually reversible after treatment discontinuation
	Not known	Sleep disorders (insomnia, drowsiness)
Cardiac	Rare	Palpitations, extrasystoles,

disorders		tachycardia
Vascular disorders	Rare	Arterial Hypotension, Orthostatic hypotension that may be associated with malaise, dizziness or fall, in particular in
		patients taking antihypertensive
		treatment, flushing
Gastrointestinal disorders	Common	Abdominal pain, diarrhoea, dyspepsia, nausea and vomiting
	Not known	Constipation
Skin and subcutaneous tissue disorders	Common	Rash, pruritus, urticaria.
	Not known	Acute generalized exanthematuspustulosis (AGEP), angioedema
General disorders and administration conditions	Common	Asthenia
Blood and lymphatic system disorders	Not known	Agranulocytosis Thrombocytopenia Thrombocytopenic purpura
Hepatobiliary disorders	Not known	Hepatitis

4.9 Overdose

No cases of occurrence of poisoning by trimetazidine owing to its overdose have been reported.

5. Pharmacological properties

5. 1 Pharmacodynamic properties

Pharmacotherapeutic group: Other cardiac preparation

Trimetazidine inhibits □-oxidation of fatty acids by blocking long-chain 3-ketoacyl-CoA thiolase, which enhances glucose oxidation. In an ischaemic cell, energy obtained during glucose oxidation requires less oxygen consumption than in the □-oxidation process. Potentiation of glucose oxidation optimizes cellular energy processes, thereby maintaining proper energy metabolism during ischaemia.

Pharmacodynamic effects

In patients with ischaemic heart disease, trimetazidine acts as a metabolic agent, preserving the myocardial high-energy phosphate intracellular levels. Anti-ischemic effects are achieved without concomitant haemodynamic effects.

Clinical efficacy and safety

Clinical studies have demonstrated the efficacy and safety of trimetazidine in the treatment of patients with chronic angina, either alone or when the benefit from other antianginal medicinal products was insufficient.

In a 426-patients randomized, double blind, placebo-controlled study (TRIMPOL-II), trimetazidine (60mg/day) added to metoprolol 100mg daily (50 mg b.i.d) for 12 weeks significantly improved statistically exercise tests parameters and clinical symptoms as compared

to placebo: total exercise duration +20.1s, p= 0.023, total workload +0.54 METs, p=0.001, time to 1-mm ST-segment depression +33.4s, p=0.003, time to onset of angina +33.9s, p<0.001, angina attacks/week -0.73, p=0.014 and short acting nitrates consumption/week, -0.63, p=0.032, without hemodynamic changes.

In a 223 patients randomized, double blind, placebo-controlled study (Sellier), one 35 mg trimetazidine modified release tablet (b.i.d.) added to 50 mg atenolol (o.d.) for 8 weeks produced a significant increase (+34.4s, p=0.03) in the time to 1-mm ST-segment depression in exercise tests, in a sub-group of patients (n=173), when compared to placebo, 12 hours after taking the drug. A significant difference was also evidenced for the time to onset of angina pectoris (p=0.049). No significant difference between groups could be found for the other secondary endpoints (total exercise duration, total workload and clinical endpoints).

In a 1962 patients three-month randomised, double-blinded study (Vasco study) on top of atenolol 50 mg/d, two dosages of trimetazidine (70 mg/d and 140 mg/d) were tested versus placebo. In the overall population, including both asymptomatic and symptomatic patients, trimetazidine failed to demonstrate a benefit on both ergometric (total exercise duration, time to onset of 1mm ST and time to onset angina) and clinical endpoints. However, in the subgroup of symptomatic patients (n= 1574) defined in a post-hoc analysis, trimetazidine (140 mg) significantly improved total exercise duration (+23.8 s versus +13.1 s placebo; p=0.001) and time to onset of angina (+46.3 s versus +32.5 s placebo; p=0.005).

5.2 Pharmacokinetic properties

Absorption

Trimetazidine after oral administration and absorption from the digestive tract reaches the maximum concentration in the serum after about 5 hours from administration of the drug.

The steady concentration of the drug in the serum is reached after 60 hours and is stable throughout the period of treatment. No interactions with foodstuffs have been found.

Distribution

The drug binds to plasma proteins at about 16%. The volume of distribution is 4.8 l/kg, which means good penetration of the drug into the tissues.

Elimination

Trimetazidine is eliminated mainly in the urine, in unchanged form. The average half-life is 7 hours, in patients over age 65 years it increases to 12 hours.

Pharmacokinetics in special populations

No pharmacokinetic data are available for the use of trimetazidine in hepatically impaired patients.

5.3 Preclinical safety data

The acute toxicity of trimetazidine in mice, rats and guinea pigs is low. Repeated- dose toxicity studies with trimetazidine have been performed in rats and in dogs and no toxicological target organ was identified in these studies. Trimetazidine was not genotoxic in a standard battery of in vitro and in vivo tests. Reproductive toxicity studies were performed with trimetazidine in rats, mice and rabbits, and no adverse effects of trimetazidine on reproductive function (especially no teratogenic effects) were observed.

In embryotoxicity studies in rats and rabbits, trimetazidine did not show any teratogenic effects. No modifications of reproductive functions were observed in a three generation study performed in rats. No conventional studies on fertility or pre/postnatal development were performed.

6. Pharmaceutical particulars

6.1 List of excipients

Hydroxypropyl methylcellulose, Calcium Hydrogen phosphate, Magnesium stearate, Colloidal anhydrous silica, Stearic acid, Macrogol, Glycerine, Titanium dioxide, Iron oxide red.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 Years

6.4 Special precautions for storage

Do not store above 30 °C.

6.5 Nature and contents of container

Blisters (PVC/aluminium) in packs of 7, 14, 28, 30, 50, 100 and 500 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:
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