TRIMEZEN Modified-Release Tablets 35 mg

(Trimetazidine dihydrochloride)

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QUALITATIVE AND QUANTITATIVE COMPOSITION

Trimetazidine dihydrochloride……..35 mg
Excipients q.s. for one modified release film-coated tablet.
For a full list of excipients, see section 6.1.

PHARMACEUTICAL FORM

Modified release film-coated tablet

CLINICAL PARTICULARS

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 firstline antianginal therapies.

Posology and method of administration

Posology

Oral use.
The dose is one tablet of 35 mg of trimetazidine twice daily i.e. once in the morning and once in the evening during meals.
The benefit of the treatment should be assessed after three months and trimetazidine should be discontinued if there is no treatment response.

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 35 mg 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 35 mg 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.

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).

Special warnings and precautions for use:
This drug is not a curative treatment for angina attacks, nor is it indicated as an initial treatment for unstable angina, or myocardial infarction. It should not be used in the prehospital phase nor during the first days of hospitalisation.

In the event of an angina attack, the coronaropathy should be re-evaluated and an adaptation of the treatment considered (drug treatment and possibly revascularisation).

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)

Interaction with other medicinal products and other forms of interaction
No drug interaction has been reported.

Pregnancy and Breast-feeding

Pregnancy:
There are no data from the use of trimetazidine in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of TRIMEZEN during pregnancy.

Breast-feeding:
It is unknown whether trimetazidine/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. TRIMEZEN should not be used during breastfeeding.

Fertility:
Reproductive toxicity studies have shown no effect on fertility in female and male rats (see Section 5.3).

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.

Undesirable effects
Adverse reactions are listed below using 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):

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

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

Colour:
Black

Unit 3

MEDREICH LIMITED				Title: Art Work Approval Form			
Product	Trimezen Modified-Release Tablets 35 mg SL Eng - PIL			Specification:	Printed on 40-45 GSM News print Paper		
Customer	Pharmazen - Singapore						
Reason for Issue	PIF No.: New Product			Colours:	Single - Black		
				Dimensions:	175 x 220 mm (Open size),		
Related FG Codes	1301XXX	Pharmacode No.	XXXX	No. of Folds (only for PIL)	XX	Artwork made to	100%
Item Code	121XXXX-V1 (WA)	Layout No.:	NA				
Verified By				Approved By			
PDC:	PDC:			Regulatory:	QC:		CQA:

Overdose
Limited information is available on trimetazidine overdose. Treatment should be symptomatic.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties

OTHER CARDIOVASCULAR ANTIANGINAL DRUG
ATC Code: C01EB15
(C: cardiovascular system)

Mechanism of action
By preserving energy metabolism in cells exposed to hypoxia or ischaemia, trimetazidine prevents a decrease in intracellular ATP levels, thereby ensuring the proper functioning of ionic pumps and transmembrane sodium-potassium flow whilst maintaining cellular homeostasis

Trimetazidine inhibits β-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 β-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 (60 mg/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).

Pharmacokinetic properties
After oral administration, maximum concentration is found, on average, 5 hours after taking the tablet. Over 24 hours the plasma concentration remains at levels above or equal to 75% of the maximum concentration for 11 hours.

Steady state is reached by the 60th hour, at the latest.

The pharmacokinetic characteristics of trimetazidine MR are not influenced by meals. The apparent distribution volume is 4.8 l/kg; protein binding is low: in vitro measurements give value of 16%.

Trimetazidine is eliminated primarily in the urine, mainly in the unchanged form. The elimination half-life of trimetazidine MR is an average of 7 hours in healthy young volunteers and 12 hours in subjects aged more than 65 years.

Total clearance of trimetazidine is the result of major renal clearance which is directly correlated to creatinine clearance and, to a lesser extent, to liver clearance which is reduced with age.

Special populations
Elderly subjects
A specific clinical study carried out in an elderly population using a dosage of 2 tablets per day taken in 2 doses, analysed by a population pharmacokinetics approach, showed an increase in plasma exposure.

The elderly may have increased trimetazidine exposure due to age-related decrease in renal function.

A dedicated pharmacokinetic study performed in elderly 75-84 years or very elderly (≥ 85 years) participants showed that moderate renal impairment (creatinine clearance between 30 and 60 ml/min) increased respectively by 1.0 and 1.3 fold the trimetazidine exposure in comparison to younger participants (30-65 years) with moderate renal impairment.

Renal impairment
Trimetazidine exposure is increased on average by 1.7 in patients with moderate renal impairment (creatinine clearance between 30 and 60 ml/min) and on average by 3.1 fold in patients with severe renal impairment (creatinine clearance below 30 ml/min) as compared to healthy young volunteers, with normal renal function. No safety concerns were observed in this population as compared with the general population.

Paediatric population
The pharmacokinetics of trimetazidine has not been studied in the paediatric population (<18 years).

Preclinical safety data
Chronic toxicity studies conducted by the oral route in dogs and rats, showed a good safety profile. The genotoxic potential was assessed in in vitro studies, including evaluation of the mutagenic and clastogenic potential, and one in vivo study. All the tests were negative. Reproductive toxicity studies in mice, rabbits and rats showed no embryotoxicity or teratogenicity. In rats, fertility was not impaired and there was no effect on postnatal development.

PHARMACEUTICAL PARTICULARS
Description of the product
A pinkish brown coloured, round, biconvex, film coated tablets with "TZN 35" embossed on one side and plain on other side.

List of excipients
Tablet:
Anhydrous Calcium Hydrogen Phosphate
Colloidal Anhydrous Silica
Polyethylene Oxide
Povidone K-90
Xanthan Gum
Magnesium stearate

Film-coating:
Glycerol
Polyvinyl Alcohol, Talc, Macrogol/PEG, Titanium Dioxide,
Lecithin (soya), Iron oxide Red.
Magnesium stearate

Incompatibilities
Not applicable

Shelf-life
3 years

Special precautions for storage
Store below 30°C

Nature and contents of container
10 tablets are packed in one PVC/PE/PVDC- Aluminium blister
Such 10 blisters are placed in a carton along with a package insert.

DATE OF REVISION OF THE TEXT
XX-XX-XXXX

Manufacturer:

MEDREICH LIMITED (Unit 3)
4/3, Avalahalli, Anjanapura Post,
Kanakapura Road, Bengaluru - 560062, India.

Imported/Distributed by:
Pharmazen Medicals Pte Ltd
8 Kaki Bukit Ave 1 #02-04
Singapore 417941

Colour:
Black

Unit 3

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Verified By				Approved By			
PDC:	**PDC:**	**Regulatory:**		**QC:**		**CQA:**	