Summary Product Characteristics

1. Name of the medicinal product

product Trimetazidine

Dihydrochloride Tablets 35mg

Strength

35mg

Pharmaceutical form

Oral solid dosage form - Tablets

2. Qualitative and quantitative composition

Each film coated modified release tablet contains;

Trimetazidine Dihydrochloride 35mg

For full list of excipients, see section 6.1

3. Pharmaceutical form

Film coated modified release tablet.

A yellow coloured circular shape biconvexed film coated modified release tablet plain on both the sides.

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

Posology:

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

Elderly

Elderly patients may have increased trimetazidine exposure due to age-related decrease in renal function. 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.

Renal impairment

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.

Paediatric population

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

Method of administration:

Oral use

VASOCARE can be administered with a meal.

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

This product should be used with caution in patients who are predisposed to closed-angle glaucoma. This medicine is not a curative treatment for angina attacks, nor is indicated as an initial treatment for unstable

angina, or myocardial infraction, nor in the pre-hospital phase or 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 (medicinal treatment and possible 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.

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

- moderate renal impairment,
- elderly patients older than 75

years old Athletes:

This medicine contains an active substance which may give a positive reaction in doping tests.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interactions have been identified.

4.6 Fertility, pregnancy and lactation

Fertility:

Reproductive toxicity studies have shown no effect on fertility in female and male rates.

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. As a precautionary measure, it is preferable to avoid the use of Vasocare during pregnancy.

Lactation:

It is unknown whether trimetazidine/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Vasocare 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, which may affect ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile

Trimetazidine has been treated as a drug with a high safety and tolerability profile.

Information is scarce about trimetazidine's effect on mortality, cardiovascular events, or quality of life. Long-term, randomized, controlled trials comparing trimetazidine against standard antianginal agents, using clinically important outcomes would be justifiable. Recently, an international multicentre retrospective cohort study has indeed shown that in patients with heart failure of different etiologies, the addition of trimetazidine on conventional optimal therapy can improve mortality and morbidity.

The EMA recommends that doctors should no longer prescribe trimetazidine for the treatment of patients with tinnitus, vertigo, or disturbances in vision.The recent EMA evaluation also revealed rare cases (3.6/1 000 000 patient years) of parkinsonian (or extrapyramidal) symptoms (such as tremor, rigidity, akinesia, hypertonia), gait instability, restless leg syndrome, and other related movement disorders; most patients recovered within 4 months after treatment discontinuation, so doctors are advised not to prescribe the medicine either to patients with Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome, or other related movement disorders, or to patients with severe renal impairment.

b. Tabulated summary of adverse reactions

Trimetazidine may cause the following undesirable effects ranked under the following frequency:

Very common (≥1/10); common (≥1/100 to<1/10); Uncommon (≥1/1000 to <1/100); rare (≥1/10000 to

<1/1000); Very rare (<1/10000), not known (cannot be estimated from the available data).

System Organ Class	Frequency	Preferred Term
Nervous system diorders	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	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

C. Description of selected adverse reactions

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extrapyramidal) symptoms (such as tremor, rigidity, akinesia, hypertonia), gait instability, restless leg syndrome, and other related movement disorders; most patients recovered within 4 months after treatment discontinuation, so doctors are advised not to prescribe the medicine either to patients with Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome, or other related movement disorders, or to patients with severe renal impairment.

d. Paediatric population

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

e. Other special population(s) Hepatic impairment

Trimetazidine pretreatment reduced the liver injury. Indeed, it lowered the increase in ALAT and ASAT activities observed immediately after reperfusion and maintained higher concentrations of hepatic ATP.

Simultaneously, bile flow was increased.

Renal impairment

In patients with moderate renal impairment (creatinine clearance [30-60] ml/min), the recommended dose is 1 tablet of 20mg or 3ml (60 drops) of oral drop solution twice daily, i.e., one in the morning and one in the evening during meals.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

Limited information is available on Trimetazidine overdose. Treatment should be symptomatic**.** Symptoms of overdose

- Loss of consciousness
- shakiness and unsteady walk

- unsteadiness, trembling, or other problems with muscle control or coordination

Some side effects may occur that usually do not need medical attention. These side effects may go away during treatment as your body adjusts to the medicine. Also, your health care professional may be able to tell you about ways to prevent or reduce some of these side effects.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group and ATC Code: Other cardiovascular antianginal drug. ATC code: C01EB15.

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 (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

a. General introduction

Trimetazidine Dihydrochloride is a active metabolite used to treat heart-related conditions like angina. It helps metabolize fatty acids, which helps your body use oxygen. The drug allows for more blood flow to your heart and limits quick changes in your blood pressure. This can help lessen chest pain from blocked blood vessels.The trimetazidine Dihydrochloride solubility is lowest in toluene and highest in methanol. The solubility values in these monosolvents rank as methanol > ethyl acetate > ethanol > DMF > n-propanol > n-butanol > isopropyl alcohol >1,4-dioxane > acetonitrile > acetone >2-butanone > toluene.

b. General

Characteristics

Absorption

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 VASOCARE 35mg Modified-Release Tablets are not influenced by meals.

Distribution

The apparent distribution volume is 4.8 l/kg; protein binding is low: in vitro measurements give value of 16%.

Biotransformation

Trimetazidine works by inhibiting a specific enzyme called long-chain 3-ketoacyl-CoA thiolase, which is involved in the beta-oxidation process of fatty acids. By blocking this enzyme, trimetazidine reduces the oxidation of fatty acids and promotes the oxidation of glucose instead.

Elimination

Trimetazidine is eliminated primarily in the urine, mainly in the unchanged form. The elimination half-life of VASOCARE 35mg Modified-Release Tablets 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.

Linearity/Non-Linearity

Trimetazidine pharmacokinetics are linear following single dose administration up to 100mg. Repeated doses showed a time-linear pharmacokinetic response.

c. Characteristics in specific groups of subjects or patients

Elderly

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.

A specific clinical study carried out in an elderly population (older than 75 years old) using a dosage of 2 tablets of trimetazidine MR 35mg per day taken in 2 doses, analysed by a kinetic population method, showed on average a 2-fold increase in plasma exposure in patients with severe renal impairment (creatinine clearance below 30ml/min) as compared to those with a creatinine clearance above 60 ml/min. No safety concern was observed in the elderly population as compared to the general population.

Renal impairment

Trimetazidine exposure is increased on average by 1.7-fold 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 30ml/min) as compared to healthy volunteers, with normal renal function (see sections 4.2 and 4.3). No safety concern was observed in this population as compared to the general population**.**

d.Pharmacokinetic / pharmacodynamics relationship

Trimetazidine is indicated for the symptomatic treatment of stable angina pectoris in patients inadequately controlled or intolerant to first line therapies. Patients should be counselled regarding the risk of use with reduced renal or hepatic function, worsening of extrapyramidal symptoms or other movement disorders, and risk of falls.Trimetazidine works by inhibiting a specific enzyme called long-chain 3-ketoacyl-CoA thiolase, which is involved in the beta-oxidation process of fatty acids. By blocking this enzyme, trimetazidine reduces the oxidation of fatty acids and promotes the oxidation of glucose instead.In young, healthy subjects, the half life of trimetazidine is 7.81 hours. In patients over 65, the half life increases to

11.7 hours. Trimetazidine clearance is strongly correlated with creatinine clearance. In eldery patients with a creatinine clearance of 72 ± 8 mL/min, trimetazidine clearance was 15.69 L/h.

5.3 Preclinical safety data

Chronic toxicity studies conducted by the oral route in dogs (5 to 40 mg.kg-1.d-1) and rats (5 to 200 mg.kg-1.d-1), showed a good safety profile. Neither embryo-foetotoxic effects nor teratogenicity were detected in mice and in rabbits. The general study on reproduction and embryogenesis in 3 generations of rats showed no anomalies. The genotoxic potential was thoroughly assessed with three in vitro studies including the evaluation of the mutagenic and clastogenic potential and one in vivo study. All tests were negative.

6. Pharmaceutical particulars

6.1 List of excipients

Hypromellose K4M
Hpromellose K100M
Microcrystalline Cellulose
Povidone K30
Colloidal Anhydrous
Silica Magnesium
Stearate
Hypromellose E15
Purified Talc
Titanium
Dioxide
Quinoline
Yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store below 30°C. Protect from light & moisture.

6.5 Nature and contents of the container

Commercial Presentation: 4's, 10's, 20's, 30's & 100's
3 x 10's (10 tablets are packed in one Alu-Alu blister and 3Alu-Alu blister is kept in one carton along with package insert).

6.6 Special precautions for disposal

No special requirements

7. Marketing authorization holder and manufacturing site address Marketing authorization holder:

Company name: INNOCIA LIFESCIENCES PVT. LTD.,
Address: Block A, No 12, Balaji Nagar, Ambattur,
Chennai-600053 Country: INDIA
Telephone: 044 26585811 &
26585855 E-Mail: ah@innocialife.com

Manufacturing Site address:
Company name: ATOZ Pharmaceuticals
Pvt.Ltd., Address: No.12, Balaji Nagar,
Ambattur, Chennai-600053, Country: INDIA.
Telephone: +91 44 2658 5811/2658 5855
E-Mail: sundar@atozlabs.com

8. Marketing authorization number

H2014/CTD1608/453/R1

9. Date of first registration / renewal of the registration

Date of first authorization: 07 August 2014 Date of latest renewal

10. Date of revision of the text

25 December 2023, 18th August 2026