SUMMARY OF PRODUCT CHARACTERISTICS

METPURE-XL

[S-Metoprolol Extended Release Tablets 12.5 / 25 / 50 mg]

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1. NAME OF THE MEDICINAL PRODUCT

METPURE-XL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Metpure-XL 12.5

Each extended release film-coated tablet contains:

S (-) Metoprolol Succinate ..... 11.875 mg equivalent to

S (-) Metoprolol Tartrate 12.5 mg

Metpure-XL 25

Each extended release film-coated tablet contains:

S (-) Metoprolol Succinate ..... 23.75 mg equivalent to

S (-) Metoprolol Tartrate 25 mg

Metpure-XL 50

Each extended release film-coated tablet contains:

S (-) Metoprolol Succinate ..... 47.50 mg equivalent to

S (-) Metoprolol Tartrate 50 mg

3. PHARMACEUTICAL FORM

Extended Release Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. Hypertension
2. Angina pectoris
3. Stable symptomatic chronic heart failure with impaired systolic left ventricular function as an adjunct to existing heart failure therapy
4. Prevention of cardiac death and re-infarction after the acute phase of myocardial infarction

4.2 Posology and method of administration

The product is intended for once daily treatment and is preferably taken in the morning.

Hypertension: The recommended dosage in patients with mild to moderate hypertension is 25 mg and can be increased to 50-100 mg once daily and/or combined with other antihypertensive agents.

Angina pectoris: The recommended dosage is 50-100 mg administered once daily. If needed, the product can be combined with other anti-anginal agents.

Stable heart failure, function class II: A recommended initial dosage for the first two weeks is 12.5 mg once daily. After two weeks, the dose can be increased to 25 mg once daily, and thereafter it can be doubled every second week. The target dose for long-term treatment is 100 mg once daily.

Stable heart failure, function classes III-IV: Recommended initial dose is 6.25 mg given once daily. After 1-2 weeks, the dose can be raised to 12.5 mg given once daily. Then, after further two weeks, the dosage can be increased to 25 mg given once daily. In those patients who tolerate a higher dose, the dosage can be doubled every second week up to a maximal dose of 100 mg daily.

Prophylactic treatment after myocardial infarction: Long-term oral treatment with S-Metoprolol in doses up to 100 mg given once daily.

4.3 Contraindications

Atrioventricular block of second or third degree, patients with unstable decompensated cardiac heart failure (pulmonary oedema, hypoperfusion or hypotension), and patients with continuous or intermittent inotropic therapy acting through beta-receptor agonism; marked clinically relevant sinus bradycardia, sick-sinus syndrome, cardiogenic shock, severe peripheral arterial circulatory disorder. Metoprolol should not be given to patients with suspected acute myocardial infarction as long as the heart rate is <45 beats/min, the P-Q interval is > 0.24 sec or the systolic blood pressure is <100 mm Hg. The product is contra-indicated in patients who have shown hypersensitivity to any component of the product or to other beta-blockers.

4.4 Special warnings and precautions for use

Intravenous administration of calcium antagonists of the verapamil-type should not be given to patients treated with β-blockers. Patients suffering from heart failure should have their decompensation treated both before and during treatment. Abrupt interruption of the medication is to be avoided. Sudden withdrawal of beta-blockade is hazardous, especially in high-risk patients, and may aggravate chronic heart failure as well as increase the risk of myocardial infarction and sudden death. Any withdrawal of the product should therefore, if possible, be made gradually over at least two weeks when the dose is reduced by half in each step, down to the final dose when a 25mg tablet is reduced to half a tablet. The final dose should be given for at least four days before discontinuation. If symptoms occur, a slower withdrawal rate is recommended.

4.5 Interaction with other medicinal products and other forms of Interaction

S-Metoprolol avoids accumulation of R-enantiomer due to drug-drug interaction.

4.6 Pregnancy and Lactation

Safety and efficacy has not been established.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable Effects

Bradycardia, postural disorders (very rarely with syncope), cold hands and feet, palpitations, fatigue, nausea, abdominal pain, diarrhoea and constipation have been reported with racemic Metoprolol. In clinical trial, S-Metoprolol has not shown adverse events.

4.9 Overdose

Reports of overdosage with S-Metoprolol have not been received.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

The cardiac β-blocking activity of Metoprolol resides with S(-) enantiomer with S:R activity ratio being 33:1. The β_1-receptor affinity of the S-Metoprolol is about 500 times greater than that of R-form.

Clinical experience

In a randomized double-blind double-dummy controlled trial (n=260) of S-Metoprolol 50 mg ER with racemic Metoprolol 100 mg ER, the responder rates in the S-Metoprolol group were higher by 10.8%, 13.6% ($P<0.05$) and 7.7% on days 14, 21 and 28 respectively. The absolute improvement of 13.6% on day 21 corresponds to a relative improvement of 23.3%. The NNT (number needed to treat), to avail of this additional response rate with S-Metoprolol, is only 7. The decrease in mean systolic and diastolic blood pressure was comparable in both the S-Metoprolol and racemic Metoprolol groups.

5.2 Pharmacokinetic properties

S-Metoprolol is well absorbed after oral administration, peak plasma concentrations of 55.98ng/ml in 6.83 ± 1.52 hours after dosing. The bioavailability of a single dose is approximately 94.54%. The bioavailability also increases if Metoprolol is given with food.

Very less amount of Metoprolol in plasma is protein bound. Metoprolol crosses the placenta, and is found in breast milk.

Metoprolol is extensively metabolized by enzymes of the cytochrome P450 system in the liver. Elimination is mainly by hepatic metabolism and the average elimination half-life is 6.83 ± 1.52 hours.

5.3 Preclinical safety data

An acute oral toxicity study was conducted to compare the acute oral toxicity profile of S-Metoprolol in Sprague Dawley rats. The study was designed to determine the oral LD50 of the test substance (upto 2000 mg/kg) or to establish a non-lethal dose level of 2000 mg of test substance per kilogram of body weight and to study the toxic effects of the test substance, their onset, severity, reversibility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient(s)

Metpure-XL 12.5

Hypromellose (USP)
Dibasic calcium phosphate (BP)
Lactose monohydrate BP
Povidone (Polyvinyl pyrrolidone K-30) (USP)
Macrogols (Polyethylene glycol 6000) (Ph.Eur.)
Stearic acid (USP)
Colloidal silicon dioxide (USP)
Talc (Ph.Eur.)
Sodium stearyl fumarate (USP)
Colour opadry white OY-IN-58910 (In house)
Isopropyl alcohol (BP)
Methylene chloride (USP)

Metpure-XL 25

Hypromellose (Methocel K4M) (USP)
Hypromellose (Methocel K 100M) (USP)
Dibasic calcium phosphate (BP)
Lactose monohydrate BP
Povidone (Polyvinyl pyrrolidone K-30) (USP)
Macrogols (Polyethylene glycol 6000) (Ph.Eur.)
Isopropyl alcohol (BP)
Methylene chloride (USP)

Stearic acid (USP)

Colloidal silicon dioxide (USP)

Talc (Ph.Eur.)

Sodium stearyl fumarate (USP)

Colour opadry white OY-IN-58910 (In house)

Metpure-XL 50

Hypromellose (Methocel K4M) (USP)

Hypromellose (Methocel K 100M) (USP)

Dibasic calcium phosphate (BP)

Lactose monohydrate BP

Povidone (Polyvinyl pyrrolidone K-30) (USP)

Macrogols (Polyethylene glycol 6000) (Ph.Eur.)

Isopropyl alcohol (BP)

Methylene chloride (USP)

Stearic acid (USP)

Colloidal silicon dioxide (USP)

Talc (Ph.Eur.)

Sodium stearyl fumarate (USP)

Colour opadry white OY-IN-58910 (In house)

6.2 Incompatibilities

None of the In-active ingredients of the formulation have been known to exhibit incompatibility with the Active Ingredients.

6.3 Shelf-life

24 months.

6.4 Special precautions for storage

Store in a dry and dark place below 25°C

6.5 Nature and contents of container

10 tablets are packed in Alu-alu strip (VMCH coated printed aluminium foil / Alu-alu foil) 10 such strips of 10 tablets each are packed in a superchromoboard carton along with a package insert.

6.6 Instructions for use and handling

Store in a dry and dark place below 25°C.

Keep away from the reach of children.

7. MARKETING AUTHORISATION HOLDER

Emcure Pharmaceuticals Ltd.

8. MARKETING AUTHORISATION NUMBER(S)

EMC/IND/5380

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26.10.2018

10. DATE OF REVISION OF THE TEXT

25.07.2023