SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Brand Name: METOMAP

Generic Name: METOPROLOL INJECTION BP

2. Qualitative and quantitative composition

Each ml contains:

Metoprolol Tartrate BP 1mg

Water for Injection BP ..... q.s

3. Pharmaceutical form

Liquid Injection

4. Clinical particulars

4.1 Therapeutic indications

Metoprolol Injection is used:

- To treat uneven heart beats (arrhythmias).
- In the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality

4.2 Posology and method of administration

Posology

The dose must always be adjusted to the individual requirements of the patient. The following are guidelines:

Cardiac arrhythmias: Initially up to 5 mg injected intravenously at a rate of 1-2 mg per minute. The injection can be repeated at 5 minute intervals until a satisfactory response has been obtained. A total dose of 10-15 mg generally proves sufficient.

Because of the risk of a pronounced drop of blood pressure, the i.v. administration of METOMAP to patients with a systolic blood pressure below 100 mmHg should only be given with special care.

During anaesthesia: 2-4 mg injected slowly i.v. at induction is usually sufficient to prevent the development of arrhythmias during anaesthesia. The same dosage can also be used to control arrhythmias developing during anaesthesia. Further injections of 2 mg may be given as required to a maximum overall dose of 10 mg.

Myocardial infarction: Early intervention. To achieve optimal benefits from intravenous METOMAP, suitable patients should present within 12 hours of the onset of chest pain.

Intravenous METOMAP Injection should be initiated in a coronary care or similar unit when the patient's haemodynamic condition has stabilised.

Therapy should commence with 5 mg i.v. every 2 minutes to a maximum of 15 mg total as determined by blood pressure and heart rate. The second or third dose should not be given if the systolic blood pressure is < 90 mmHg, the heart rate is <40 beats/min and the P-Q time is >0.26 seconds, or if there is any aggravation of dyspnoea or cold sweating.

Renal impairment: Dose adjustment is generally not needed in patients with impaired renal function.

Hepatic impairment: Dose adjustment is normally not needed in patients suffering from liver cirrhosis because metoprolol has a low protein binding (5-10%). However, in patients with severe hepatic dysfunction a reduction in dosage may be necessary.

Elderly: Several studies indicate that age-related physiological changes have negligible effects on the pharmacokinetics of metoprolol. Dose adjustment is not needed in the elderly, but careful dose titration is important in all patients.

Paediatric population: The safety and efficacy of metoprolol in children has not been established.

4.3 Contraindications

METOMAP (Metoprolol Injection BP) should not be used in the presence of:
Known hypersensitivity to Metoprolol and related derivatives
Sinus bradycardia
Sick sinus syndrome
Second and third degree A-V block
Right ventricular failure secondary to pulmonary hypertension
Overt heart failure
Cardiogenic shock
Severe peripheral arterial circulatory disorders
Anesthesia with agents that produce myocardial depression, e.g. ether
The intravenous form also contraindicated in the presence of asthma and other obstructive respiratory diseases

Myocardial Infarction Patients- Additional Contraindications

METOMAP is contraindicated in patients with a heart rate< 45 beats/min; significant heart block greater than first degree (PR interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg; or moderate to severe cardiac failure.

4.4 Special warnings and precautions for use

When treating patients with suspected or definite myocardial infarction the Haemodynamic status of the patient should be carefully monitored after each of the three 5 mg intravenous doses. The second or third dose should not be given if the heart rate is <40 beats/min, the systolic blood pressure is <90 mmHg and the P-Q time is >0.26 sec, or if there is any aggravation of dyspnoea or cold sweating.
Metoprolol injection, as with other beta-blockers:

- Should not be withdrawn abruptly during oral treatment. When possible, Metoprolol Injection should be withdrawn gradually over a period of 10 - 14 days, in diminishing doses to 25 mg daily for the last 6 days. During its withdrawal patients should be kept under close surveillance, especially those with known ischaemic heart disease. The risk for coronary events, including sudden death, may increase during the withdrawal of beta-blockade.
- Must be reported to the anaesthetist prior to general anaesthesia. It is not generally recommended to stop Metoprolol Injection treatment in patients undergoing surgery. If withdrawal of metoprolol is considered desirable, this should, if possible, be completed at least 48 hours before general anaesthesia. Routine initiation of high-dose metoprolol to patients undergoing non-cardiac

surgery should be avoided, since it has been associated with bradycardia, hypotension, stroke and increased mortality in patients with cardiovascular risk factors. However, in some patients it may be desirable to employ a beta-blocker as premedication. In such cases an anaesthetic with little negative inotropic activity should be selected to minimise the risk of myocardial depression.

- Although contra-indicated in severe peripheral arterial circulatory disturbances, may also aggravate less severe peripheral arterial circulatory disorders.
- May be administered when heart failure has been controlled. Digitalisation and/or diuretic therapy should also be considered for patients with a history of heart failure, or patients known to have a poor cardiac reserve. Metoprolol Injection should be used with caution in patients where cardiac reserve is poor.
- May cause patients to develop increasing bradycardia, in such cases the Metoprolol Injection dosage should be reduced or gradually withdrawn.
- Due to the negative effect on conduction time, should only be given with caution to patients with first-degree heart block.
- May increase the number and duration of angina attacks in patients with Prinzmetal's angina, due to unopposed alpha-receptor mediated coronary artery vasoconstriction. Metoprolol Injection is a beta1-selective beta-blocker; consequently, its use may be considered although utmost caution must be exercised.
- May mask the early signs of acute hypoglycaemia, in particular tachycardia. During treatment with Metoprolol Injection, the risk of interfering with carbohydrate metabolism or masking hypoglycaemia is less than with non-selective beta-blockers.
- May mask the symptoms of thyrotoxicosis.
- May increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions.
- Although cardioselective beta-blockers may have less effect on lung function than non-selective beta-blockers, as with all beta-blockers these should be avoided in patients with reversible obstructive airways disease unless there are compelling clinical reasons for their use. When administration is necessary, these patients should be kept under close surveillance. The use of a $beta_2$-bronchodilator e.g. (terbutaline) may be advisable in some patients. The dosage of the $beta_2$-agonist may require an increase when treatment with Metoprolol Injection is commenced.
- The label shall state: “Use with caution in patients who have a history of wheezing, asthma or any other breathing difficulties, see enclosed user leaflet.”
- Like all beta-blockers, careful consideration should be given to patients with psoriasis before Metoprolol Injection is administered.
- In patients with a phaeochromocytoma, an alpha-blocker should be given concomitantly.
- In labile and insulin-dependent diabetes it may be necessary to adjust the hypoglycaemic therapy.
- Intravenous administration of calcium antagonists of the verapamil type should not be given to patients treated with beta-blockers.

- The initial treatment of severe malignant hypertension should be so designed as to avoid sudden reduction in diastolic blood pressure with impairment of autoregulatory mechanisms.

This medicinal product contains less than 1 mmol sodium (23mg) per ampoule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Antihypertensives

Metoprolol Injection Dosage should be adjusted according to the individual requirenments of the patient especially when used concominantely with other antihypertensive agents.

MAO Inhibitors and Adrenergic Neuron Blockers

Patients receiving MAO inhibitors or catecholamine-depleting drugs (such as reserpine or guanethidine) should be closely monitored because the added ß-adrenergic blocking action of Metoprolol Injection may produce an excessive reduction of sympathetic activity. Metoprolol Injection should not be combined with other ß-blockers. Similarly, patients taking selective serotonin Reuptake Inhibitors (SSRI's), such as paroxetine, fluoxetine and setaraline, in combination with Metoprolol Injection, should be aware that the plasma concentration of Metoprolol may be raised. This occurs as Metoprolol is metabolised via cytochrome P450 2D6, which is inhibited by SSRI's.

Calcium Entry Blockers

As with other β-blockers, Metoprolol Injection should not be given to patients receiving calcium antagonists of the verapamil type. However, in exceptional cases, when in the opinion of the physician concomitant use is considered essential, such use should be instituted gradually in a hospital setting under careful supervision. Negative inotropic, dromotropic, and chronotropic effects may occur when Metoprolol Injection is given together with calcium antagonists. Verapamil and diltiazem may reduce the clearance of metoprolol.

Antiarrhythmic Agents

β-blockers may enhance the negative inotropic and negative dromotropic effect of anti arrhythmic agents such as quinidine and amiodarone. Coadministration of these and other antiarrythmics (e.g. propaferone) may raise plasma levels of metoprolol.

Digitalis Glycosides

Digitalis glycosides, in association with β-blockers, may increase atrioventricular conduction time and may induce bradycardia.

Clonidine Withdrawal Syndrome

The hypertensive crisis which may follow the withdrawal of clonidine may be accentuated in the presence of β-blockade. It has been proposed that withdrawal of the β-blocker several days before the clonidine may reduce the danger of rebound effects.

Oral Anti-Diabetics

The dosage of oral anti-diabetics may have to be readjusted in patients receiving β-blockers.

Indomethacin

Concurrent treatment with indomethacin may decrease the antihypertensive effect of β-blockers.

Cytochrome P450 Inducers and Inhibitors

Metoprolol is a metabolic substrate for the cytochrome P450 isoenzyme CYP2D6. Drugs that act as enzyme-inducing and enzyme-inhibiting substances may exert an influence on the plasma level of metoprolol. Plasma levels of metoprolol may be raised by co-administration - 12 - of compounds metabolised by CYP2D6, such as antihistamines, histamine-2-receptor antagonists (e.g. cimetidine, ranitidine), antidepressants, antipsychotics and COX-2-inhibitors. The plasma concentration of metoprolol is lowered by rifampicin and may be raised by alcohol and hydralazine.

Lidocaine

Metoprolol may reduce the clearance of lidocaine.

Inhalation Anesthetics

In patients receiving β-blocker therapy, inhalation anesthetics enhance the cardiodepressant effect.

4.6 Fertility, pregnancy and lactation

Pregnancy

Metoprolol Injection should not be used in pregnancy or nursing mothers unless the physician considers that the benefit outweighs the possible hazard to the foetus/infant. In general, beta-blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion and early labour. It is therefore suggested that appropriate maternofoetal monitoring be performed in pregnant women treated with Metoprolol Injection.

As with all beta-blockers, Metoprolol Injection may cause side effects especially bradycardia and hypoglycaemia in the foetus, and in the newborn and breast-fed infant. There is an increased risk of cardiac and pulmonary complications in the neonate.

Metoprolol Injection has, however, been used in pregnancy-associated hypertension under close supervision, after 20 weeks gestation. Although Metoprolol Injection crosses the placental barrier and is present in the cord blood, as yet no evidence of foetal abnormalities has been reported.

Breast-feeding

Breast-feeding is not recommended. The amount of Metoprolol ingested via breast milk should not produce significant beta-blocking effects in the neonate if the mother is treated with normal therapeutic doses.

4.7 Effects on ability to drive and use machines

Metoprolol Injection has a minor influence on the ability to drive and use machines. It should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

Metoprolol is well tolerated and adverse reactions have generally been mild and reversible.
The following events have been reported as adverse events in clinical trials or reported from routine use.
The following definitions of frequencies are used:

Psychiatric disorders
Uncommon: Depression, Insomnia, nightmares

Nervous system disorders
Common: Dizziness, headache
Uncommon: Concentration impairment, somnolence, paraesthesiae

Cardiac disorders
Common: Bradycardia, palpitations
Uncommon: Deterioration of heart failure systems, Cardiogenic shock in patients with acute myocardial infarction, first degree heart block

Vascular disorders
Common: Posturaldisorders(very rarely with syncope)

Respiratory, thoracic and mediasthinal disorders
Common: Dyspnoea on exertion
Uncommon: Bronchospasm

Gastrointestinal disorders
Common: Nausea, abdominal pain, diarrhoea, constipatiton
Uncommon: Vomiting

Skin and subcutaneous tissue disorders
Uncommon: Rash, increased sweating

Musculoskeletal and connective tissue disorders
Uncommon: Muscle cramps

General disorders and administration site disorders
Very common: fatigue
Common: cold hands and feet
Uncommon: Precordial pain, oedema

4.9 Overdose

Symptoms

Symptoms of overdose may include hypotension, cardiac insufficiency, bradycardia and bradyarrhythmia, cardiac conduction disturbances and bronchospasm.

Management

Care should be provided at a facility that can provide appropriate supporting measures, monitoring and supervision.
Atropine, adrenostimulating drugs or pacemaker to treat bradycardia and conduction disorders.
Hypotension, acute cardiac failure, and shock to be treated with suitable volume expansion, injection of glucagon (if necessary, followed by an intravenous infusion of glucagon), intravenous administration of adrenostimulating drugs such as dobutamine, with α_1 receptor agonistic drugs added in presence of vasodilation. Intravenous use of Ca^{2+} can also be considered.
Bronchospasm can usually be reversed by bronchodilators.

5. Pharmacological properties

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: ß-Adrenoceptor Antagonist
ATC code: C07AB02

Metoprolol is a competitive beta-adrenoceptor antagonist. It acts preferentially to inhibit beta-adrenoceptors (conferring some cardioselectivity), is devoid of intrinsic sympathomimetic activity (partial agonist activity) and possesses beta-Adrenoceptor blocking activity comparable in potency with propranolol.

Pharmacodynamic effects

A negative chronotrophic effect on the heart is a consistent feature of metoprolol administration. Thus, cardiac output and systolic blood pressure rapidly decrease following acute administration.

5.2. Pharmacokinetic properties

Absorption

Absorption is complete after intravenous administration.

Distribution

The plasma protein binding of Metoprolol is low, approximately 5-10%. Metoprolol crosses the blood brain barrier and placenta, maternal and foetal concentrations are equal.

Biotransformation

Metoprolol undergoes oxidative metabolism in the liver primarily by the CYP2D6 isoenzyme.

Elimination

Metoprolol is eliminated mainly by hepatic metabolism. Plasma half-life is 3.5 hours (range 1-9 hours). Rates of metabolism vary between individuals, with poor metabolisers (approximately 10%) showing higher plasma concentrations and slower elimination than extensive metabolisers. Within individuals, however, plasma concentrations are stable and reproducible.
As a rule, over 95% of an oral dose can be recovered in the urine. About 5% of the given oral dose and 10% of an i.v. dose is excreted in the urine in unchanged form, this figure rising up to 30% in isolated cases.

5.3. Preclinical safety data

Pre-clinical information has not been included because the safety profile of Metoprolol Tartrate has been established after many years of clinical use.

6. Pharmaceutical particulars

6.1. List of excipients

Sodium Chloride
Water for injection

6.2. Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3. Shelf life

36 months from the date of manufacturing.

6.4. Special precautions for storage

Do not store above 30°C. Protect from light.

6.5. Nature and contents of container

A clear colourless solution filled in 5ml USP Type-1 clear glass ampoule and 5Nos. of ampoules packed in a Tray Pack in a carton with pack insert.

6.6. Special precautions for disposal and other handling

For single use only
Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7. Marketing authorisation holder

Manufactured By:

Skymap Healthcare Pvt. Ltd.
Address: B-2, Dev Bhoomi Industrial Estate,
Puhana Iqbalpur Road, Roorkee-247667
Distt. Haridwar, Uttarakhand, India

8. Marketing authorisation number(s):

09095/09622/NMR/2022

9. Date of first authorisation/renewal of the authorization:

Nov 12, 2023

10. Date of revision of the text: NA