PATIENT INFORMATION LEAFLET

METLOC 5 mg/5 mL Ampoule Containing Solution for IV Infusion
For intravenous use
Sterile

- **Active substance:** Each mL contains 1 mg metoprolol tartrate.
- **Excipients:** Sodium chloride, hydrochloric acid, sodium hydroxide and water for injection.

Before use this medicine, please read this PATIENT INFORMATION LEAFLET carefully, because it contains important information for you.

- *Keep this leaflet. You may need to read it again.*
- *If you have any further questions, consult your doctor or your pharmacist.*
- This medicine has been prescribed for you personally; you should not pass it on to others.
- *During use of this medicine please tell to your doctor that you use this medicine when you go to the doctor or hospital.*
- *Follow the information in the leaflet exactly. Do not use **lower or higher** dosages rather than recommended dosages regarding the medicine.*

In this patient information leaflet:

1. ***What METLOC is and what is it used for?***
2. ***What you need to know before you use METLOC?***
3. ***How to use METLOC?***
4. ***What are the possible side effects?***
5. ***How to store METLOC?***

Headings are included.

1. What is METLOC and what is it used for?

METLOC contains metoprolol tartrate. It is marketed as a 5 mL ampoule. Metoprolol belongs to a class called beta blockers and it is a beta-1-selective beta blocker. Treatment with metoprolol, reduces the effect of stress hormones on beta-1-receptors in the heart. It is used in the treatment and prevention of heart rhythm disorders, it slows down the heartbeat and reduces blood pressure.

METLOC is indicated for the following treatments:

- Treatment and prevention of heart rhythm disorders
- Treatment of heart attacks

2. What you need to know before you use METLOC?

DO NOT USE METLOC if,

- You are allergic to metoprolol tartrate or other beta-blockers,
- You have a slow heartbeat or your doctor has told you that you have a serious heart block,
- Your blood pressure is too low,
- You have severe vascular disease

Use METLOC CAREFULLY if,

Consult your doctor in the following cases:

- If you have asthma or other breathing problems (e.g: COPD),
- If you have severe kidney failure,
- If you suffer from heart failure/low blood pressure,
- If you suffer from heart rhythm disorder,
- If you suffer from Prinzmental's angina (a type of chest pain),
- If you suffer from pheochromocytoma (adrenal gland tumor),
- If you are receiving treatment for severe allergic reaction,
- If you are prone to low blood sugar (hypoglycemia),
- If you have a severe illness related to elevated levels of acid components in your body,
- If you have peripheral artery disease (intermittent claudication)

If these warnings are applicable to you even for any period of time in the past, please consult your doctor.

Use of METLOC with food and drinks

Food and drinks do not effect this drug, as it is administered as an injection.

Pregnancy

Consult your doctor or your pharmacist before using the drug.

If you are pregnant, you should use the METLOC only if absolutely necessary. METLOC may increase the heart rate of the fetus or the newborn baby.

If you are you are pregnant or planning to become pregnant, tell your doctor before using the medication.

If you find out about your pregnancy during your treatment, consult your physician or your pharmacist.

Breast-feeding

Consult your doctor or your pharmacist before using the drug.

If you are breastfeeding, you should use the METLOC only if absolutely necessary. METLOC is excreted into breast milk and side effects like slow heart rate in your baby.

Important information about some excipients present in METLOC
If you are not hypersensitive to the excipients of METLOC, you will not have an adverse effect due to these substances.

This medicinal product contains less than 1 mmol (23 mg) of sodium in each ampoule. No sodium related negative effect is expected at this dose.

Use with other medicines

Consult your doctor especially if you are using the following drugs.

- Drugs used in the treatment of the heart and blood vessels (e.g., amiodarone, quinidine, propafenone, diltiazem, verapamil, clonidine, disopramid, digitalis/digoxin, hydralazine)
- Epilepsy medication (barbituric acid derivatives)
- Anti-inflammatory and analgesic drugs (indomethacin, celecoxib),
- Drugs used in acute cases or severe allergic reactions (adrenaline)
- Drug used against the swelling of the mucous membranes in the nose (phenylpropanolamine)
- Allergy medication (diphenhydramine)
- Drugs used against fungal infections of the skin (terbinafine)
- Tuberculosis medication (rifampicin)
- Other beta-blockers (including eye drops),
- Drugs used in Parkinson's disease and depression (MAOIs)
- Inhalation anesthetics
- Diabetes medications in tablet form
- Drugs used in heartburn and acid reflux disease (cimetidine)
- Depression medication (e.g: paroxetine, fluoxetine and sertraline)

If you currently use or have recently used any prescribed or non-prescribed drug, please inform your doctor or your pharmacist on these drugs.

3. How to use METLOC?

Instructions for appropriate use and dose/administration frequency:
Your doctor will decide on your dose and duration of METLOC treatment based on your condition.

Route and method of administration:
METLOC is administered as a slow intravenous injection. METLOC must be administered by a doctor or a nurse.

Various age groups:

Use in children:
Experience in use of METLOC in children is limited.

Use in elderly:
Dose adjustment is not necessary in elderly patients.

Special conditions of use:

Renal impairment:
No dose adjustment is required in patients with kidney failure.

Hepatic impairment:
Metoprolol is usually given to patients with liver cirrhosis and patient with normal liver function at the same dose. Dose reduction should be considered in patients with severe liver dysfunction (e.g. shunt surgery patients).

Please talk to your doctor or pharmacist if you feel that the effect of METLOC is too strong or too weak.

If you have used more METLOC than you should

Your doctor has experience in the injection of MEDLOCK, receiving high doses is not likely.

If you have received an accidental high dose of METLOC, you may experience symptoms like, nausea, vomiting, cramps, sweating, weakness, extreme slow heart rate, possible heart attack and breathing problems.

Your doctor will know how to recognize if you get a high dose and how to treat it.

If you have used METLOC more than you should, talk to your doctor or pharmacist.

4. What are the possible side effects?

As with all medicines, there may be side effects in people who are sensitive to the ingredients of METLOC. The following side effects were reported in individuals treated with intravenous metoprolol (Metoprolol is the active substance of METLOC).

Side effects are listed as follows:

Very common	: may affect in less than 1 of 10.000 patients.
Common	: may affect less than 1 in 10 patients but more than 1 in 100 patients.
Uncommon	: may affect less than 1 in 100 patients, but more than 1 in 1000 patients.
Rare	: may affect less than 1 in 1000 patients, but more than 1 in 10.000 patients.
Very rare	: may affect in less than 1 of 10.000 patients.
Not known	: Cannot be estimated from the available data.

If you experience any of the following while using METLOC, inform your doctor

Very common:
Fatigue

Common:
Headache, dizziness, cold hands and feet, irregularities in heart rate, heart palpitation sensation in the chest, shortness of breath after exercise, stomach pain, nausea, vomiting, diarrhea, constipation.

Uncommon:
Chest pain, edema, weight gain, sleep disturbances, nightmares, depression, hypersensitivity of skin, tightness sensation of air passages, temporary worsening of symptoms of heart failure such as feeling fatigue or swelling of ankles, numbness (paresthesia), significant drop in blood pressure during a heart attack (cardiogenic shock).

Rare:
Tasting disorder, temporary decrease in libido (sexual desire), forgetfulness, confusion, anxiety, nervousness, hallucinations, worsening of psoriasis, hypersensitivity to sunlight, blood disorders (decrease in blood platelet count), heart rhythm disturbances, fainting, liver function test abnormalities, vision and hearing disorders, dryness, redness and/or irritation in the eyes, tinnitus, extension in AV-conduction time, excessive sweating, hair loss.

Not known:
Gangrene in the arms and legs of patients with severe circulatory disorders, chronic hepatitis (liver inflammation), pain in the joints, muscle cramps, runny nose, dry mouth, inflammation in the eyes (inflammation), lack of concentration.

If you experience any side effect not mentioned in this patient information leaflet, inform your doctor or your pharmacist.

Reporting of side effects:

If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store METLOC?

Keep METLOC out of the sight and reach of children, and in its packaging.

Store at room temperature below 25°C.

Use in compliance with the expiry date.

METLOC is normally stored by your doctor, or at the hospital.
The medical personnel is responsible for the appropriate storage, use, and disposal of METLOC.

Do not use METLOC after expiration date stated on the packaging.

Do not throw away drugs that have expired or are not used! Give them to the collection system determined by the Ministry of Environment and Urbanization.

Marketing Auth. Holder:

Haver Farma İlaç A.Ş.
Akbaba Mah. Maraş Cad. No:52/2/1
Beykoz/İSTANBUL

Phone: (0216) 324 38 38
Fax: (0216) 317 04 98
E-mail: info@haver.com.tr

Manufacturing Site:
Osel İlaç San. ve Tic. A.Ş.
Akbaba Mah. Maraş Cad. No:52
34820 Beykoz/İSTANBUL
Phone: (0216) 320 45 50
Fax: (0216) 320 41 45
E-mail: osel@osel.com.tr

This patient information leaflet was approved on 14/03/2017.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Metloc 5 mg/5 mL IV Ampoule Containing Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Drug substance: 1 ml solution for injection contains 1 mg of metoprolol tartrate. (Each 5 ml ampoule contains 5 mg metoprolol tartrate.)

Excipients:

Sodium chloride	45.0 mg
Sodium hydroxide	*
Hydrochloric acid	*

*sufficient amount to adjust the pH to 5.5-7.5

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Supraventricular tachyarrhythmias.

In the prophylaxis and treatment of pain tachyarrhythmia and myocardial ischemia in suspected or diagnosed myocardial infarction.

4.2. Posology and method of administration

Posology/administration frequency and duration:

Supraventricular tachyarrhythmia:

Initially, metoprolol up to 5 mg (= 5 mL) is administered intravenously at a rate of 1-2 mg per minute. This application can be repeated at intervals of 5 minutes until a satisfactory response is obtained. A total dose of 10 - 15 mg is usually sufficient (10 - 15 mL). The maximum recommended intravenous dose is 20 mg (= 20 mL).

In the prophylaxis and treatment of pain, tachyarrhythmia and myocardial ischemia in suspected or diagnosed myocardial infarction:

Acute: 5 mg (= 5 mL) is administered intravenously. The dose can be repeated every 2 minutes, the maximum dose is 15 mg (= 15 ml). A 50 mg metoprolol tartrate tablet is given orally every 6 hours 15 minutes after the last injection and continued for 48 hours. Treatment should be

continued orally with the metoprolol tartrate tablet.

See sections 4.3 and 4.4 for information on when not to start treatment.

Method of administration:

METLOC ampoule is administered intravenously.

Parenteral administration of METLOC ampoules should be carried out under the supervision of appropriate personnel in places where blood pressure and ECG measurements can be made and necessary procedures can be performed for resuscitation.

Additional information on special populations:

Hepatic impairment:

Since the elimination rate is not significantly affected by kidney functions, no dose adjustment is required in patients with kidney failure.

Renal impairment:

Metoprolol is usually given at the same dose to patients with liver cirrhosis and patients with normal liver function. Dose reduction should be considered in patients with symptoms of severe hepatic impairment (eg in patients who have undergone shunt surgery).

Pediatric population:

Experience with METLOC ampoule therapy in children is limited.

Geriatric population:

Dose adjustment is not required in elderly patients.

4.3. Contraindications

- Cardiogenic shock
- Sick sinus syndrome
- Second or third degree atrioventricular block
- Patients with unstable decompensated heart failure (pulmonary edema, hypoperfusion or hypotension) and patients on continuous or intermittent inotropic therapy with beta receptor agonists.
- Symptomatic bradycardia or hypotension. Metoprolol should not be used in patients with suspected acute myocardial infarction, as long as the heart rate is below 45 per minute and the P-Q interval is longer than 0.24 seconds or the systolic blood pressure is below 100 mm Hg.

▪ In the treatment of supraventricular tachyarrhythmias, METLOC ampoule should not be administered to patients with systolic blood pressure below 110 mm Hg.

• Serious peripheral vascular disease with gangrene threat

▪ In patients with known hypersensitivity to any substance in its composition or to other beta-blockers.

4.4. Special warnings and special precautions for use

Verapamil should not be administered intravenously to patients on beta-blocker therapy.

The haemodynamic status of patients who are initiated on metoprolol due to suspected or diagnosed heart failure should be closely monitored after each dose. In case of worsening of dyspnea or cold sweating, treatment should be discontinued.

Metoprolol may exacerbate symptoms of peripheral arterial circulatory disturbance (eg intermittent claudication). In severe renal failure, acute severe picture associated with metabolic acidosis, it should be careful in combination therapy with digitalis preparations.

METLOC ampoules should be used with necessary treatment in patients with occult or diagnosed heart failure.

In patients with Prinzmetal's angina, the number and severity of angina seizures may increase due to coronary spasm mediated by alpha receptors. Therefore, non-selective beta blockers should not be used in patients with Prinzmetal's angina, and selective beta-1 blockers should be used with caution.

In the treatment of hypertensive patients with bronchial asthma or other obstructive pulmonary disease, a bronchodilator therapy should additionally be administered. In this case $beta_2$; the agonist dose may need to be increased.

Metoprolol therapy has a lower risk of interfering with carbohydrate metabolism and masking signs of hypoglycemia than non-selective beta-blockers.

Very rarely it is possible to exacerbate a pre-existing moderate atrioventricular block (possibly leading to AV block).

Treatment with beta blockers makes it difficult to treat a possible anaphylactic reaction. A patient with pheochromocytoma should be given an alpha blocker along with METLOC

ampoule therapy.

If METLOC treatment needs to be discontinued, the treatment should be discontinued by gradually tapering the dose within 2 weeks. Otherwise, the symptoms of angina pectoris may get worse with the increased risk of myocardial infarction.

It should be noted to the anesthesiologist that the patient used metoprolol before surgery. It is not recommended to discontinue beta-blocker therapy in patients undergoing surgery. Initiating high doses of metoprolol should be avoided in patients undergoing surgery other than cardiac surgery, as it has been associated with bradycardia, hypotension and stroke, with fatal outcomes in patients with cardiovascular risk factors.

If the heart rate is below 40 per minute, systolic blood pressure is less than 90 mmHg and the P-Q interval is longer than 0.26 seconds, second or third doses should not be administered.

This medicinal product contains less than 1 mmol (23 mg) sodium in each ampoule. No adverse effects due to sodium are expected at this dose.

4.5. Interaction with other medicinal products and other forms of interaction

Metoprolol is a CYP2D6 substrate. Drugs that inhibit CYP2D6 (eg ritonavir, quinidine, terbinafine, paroxetine, fluoxetine, sertraline, celecoxib, propafenone, and diphenhydramine) may affect plasma concentrations of metoprolol. When starting treatment with these drugs, the dose amount in patients treated with METLOC ampoules may need to be reduced.

METLOC should not be used with the following drugs:

Barbituric acid derivatives: Barbiturates (work with pentobarbital) accelerate the metabolism of metoprolol by enzyme induction.

Propafenone: When Propafenone was given to 4 patients treated with metoprolol, the plasma concentration of metoprolol increased 2-5 times, and 2 patients experienced side effects specific to metoprolol. The interaction was confirmed by a study on 8 healthy volunteers. The interaction with propafenone can be explained by the fact that propafenone inhibits the metabolism of metoprolol, similar to quinidine, possibly mediated by cytochrome P450 2D6. This combination is difficult to apply because propafenone also has a beta-blocking effect.

Verapamil: Concomitant use of verapamil with beta-blocker drugs (atenolol, propranolol, and pindolol) causes bradycardia and low blood pressure. When verapamil and beta blockers are used together, they have an additive inhibitory effect on AV-conduction and sinus node function.

METLOC dosage may need to be adjusted in the following combinations:

Amiodarone:

One case report reported that patients treated with amiodarone may develop significant sinus bradycardia when metoprolol is given. Since the half-life of amiodarone is very long (50 days on average), the interaction continues for a long time after the drug is discontinued.

Antiarrhythmics, class I:

Concomitant use of class I antiarrhythmics and beta-blockers causes serious haemodynamic side effects in patients with left ventricular dysfunction, as their negative inotropic effect is additive. This combination should also not be used in "sick sinus syndrome" and pathological atrioventricular conduction disorder. This interaction has been documented in the study with disopyramide.

Nonsteroidal anti-inflammatory antirheumatic drugs (NSAIDs):

NSAID-antiphlogistic drugs have been shown to reduce the antihypertensive effects of beta blockers. The study was mainly done with indomethacin. This interaction is probably not seen with sulindac. A negative interaction study has been conducted with diclofenac.

Diphenhydramine:

Diphenhydramine reduces (2.5-times) clearance of metoprolol to alpha-hydroxymethoprolol via CYP 2D6 in individuals with rapid hydroxylation. Thus, the effect of metoprolol increases.

Digital glycosides:

Digital glycosides associated with beta blockers can increase atrioventricular conduction time or cause bradycardia.

Diltiazem:

Concomitant use of diltiazem and beta blockers has an additive inhibitory effect on AV-conduction and sinus node function.

Significant bradycardia has been observed when diltiazem was co-administered with metoprolol

(case reports).

Epinephrine:

In 10 case reports, patients on non-selective beta blockers (including pindolol and propranolol) developed severe hypertension and bradycardia when epinephrine (adrenaline) was given. These observations have been confirmed by studies conducted in healthy volunteers. It has also been reported that intravenous administration of local anesthetics containing epinephrine can have the same effects. The risk is less when cardioselective beta blockers are used.

Phenylpropanolamine:

When phenylpropanolamine (norepinephrine) is administered in a single dose of 50 mg in healthy volunteers, it may increase diastolic blood pressure to pathological values. Propranolol usually lowers blood pressure that rises with phenylpropanolamine. However, beta blockers may paradoxically exacerbate hypertensive reactions in patients receiving high doses of phenylpropanolamine. In a few cases, hypertensive crisis has been reported in patients using phenylpropanolamine alone.

Quinidine:

Quinidine inhibits the metabolism of metoprolol in those with rapid hydroxylation (more than 90% of the Swedish population), increasing the plasma level and thus the beta blocker effect. Similar interactions may be seen with other beta blockers metabolised by the same enzyme (CYP 2D6).

Clonidine:

Hypertensive reaction due to the sudden withdrawal of clonidine may be aggravated when used in combination with beta blockers. If discontinuation of clonidine therapy with beta-blockers is considered, beta-blocker therapy should be discontinued a few days before clonidine treatment.

Rifampicin:

Rifampicin increases the metabolism of metoprolol and decreases its plasma level.

Patients taking other beta-blocker medications (such as eye drops) or MAO inhibitors in combination with metoprolol should be closely monitored.

Inhalation anesthetics may potentiate the cardiodepressant effect in patients on beta-blocker therapy.

Doses of oral antidiabetics may need to be adjusted in patients taking beta-blockers. The plasma

concentration of metaprolol may increase when cimetidine or hydralazine is administered concomitantly.

Additional information on special populations

Pediatric population:

Insufficient studies have been performed to recommend the pediatric use of metoprolol.

4.6. Pregnancy and lactation

General advice

Pregnancy category: C

Women with childbearing potential/Contraception

Animal studies are insufficient with regard to effects on pregnancy/and/or/embryonal/fetal development/and/or/birth/and-or/postnatal development (see section 5.3) The potential risk to humans is unknown.

Pregnancy period

Metoprolol should not be used during pregnancy unless absolutely necessary. Beta-blockers may cause side effects such as bradycardia in the fetus and newborn babies. This issue should be taken into consideration when using it in the last three months of pregnancy and during delivery. METLOC treatment should be tapered 48-72 hours before the planned delivery time. If this is not possible, the newborn should be observed for 48-72 hours to detect symptoms of beta blockade (heart and lung complications).

Lactation period

Metoprolol should not be used during breastfeeding unless absolutely necessary. Metoprolol passes into breast milk in amounts corresponding to approximately 3 times the amount found in the mother's plasma. However, when administered in therapeutic doses, the risk of harmful reactions to the breastfed child is low.

Nevertheless, the baby fed with breast milk should be monitored for signs of beta blockade.

Reproductive ability/Fertility

There is no information on fertility.

4.7. Effects on ability to drive and use machines

Not applicable.

4.8. Undesirable effects

Side effects are usually dose-dependent and occur in about 10% of patients.

Undesirable effects due to the use of metoprolol are given below according to system organ class and frequency.

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).

Blood and lymphatic system disorders

Rare: Thrombocytopenia

Psychiatric disorders

Uncommon: Depression, nightmare, sleep disorders

Rare: Forgetfulness, confusion, nervousness, anxiety, hallucinations

Not known: Concentration impairment

Nervous system disorders

Common: Headache, dizziness

Uncommon: Paraesthesia

Eye disorders

Rare: Visual disturbances, dry eyes and/or redness

Not known: Conjunctivitis

Ear and labyrinth disorders

Rare: Tinnitus

Cardiac disorders

Common: Bradycardia, palpitation

Uncommon: Chest pain, transient worsening of heart failure symptoms, cardiogenic shock in patients with acute myocardial infarction

Rare: Prolonged AV-conduction time, cardiac arrhythmias

Vascular disorders

Common: Cold extremities

Rare: Syncope

Not known: Gangrene in patients with severe peripheral vascular impairment

Respiratory, thoracic and mediastinal disorders

Common: Shortness of breath after exercise

Uncommon: Bronchospasm in patients with bronchial asthma or asthmatic problems

Not known: Rhinitis

Gastrointestinal disorders

Common: Abdominal pain, nausea, vomiting, diarrhea and constipation

Rare: Taste disturbances

Not known: Dry mouth

Hepatobiliary disorders

Rare: Increased transaminases

Not known: Hepatitis

Skin and subcutaneous tissue disorders

Uncommon: Skin hypersensitivity reactions

Rare: Aggravation of psoriasis, photosensitivity reactions, hyperhidrosis, hair loss

Musculoskeletal, connective tissue and bone disorders

Not known: Muscle cramps, arthralgia

Reproductive system and breast disorders

Rare: Reversible libido dysfunction

General disorders and administration site conditions

Very common: Fatigue

Uncommon: Weight gain, edema

After intravenous administration of METLOC, a clinical decrease in blood pressure may occur in isolated cases.

Reporting of suspected adverse reactions

If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9. Overdose

Toxicity:

7.5 g caused lethal toxicity in an adult. 100 mg in a 5 year old boy showed no symptoms after gastric lavage. 1.4 g in an adult and 450 mg in a 12-year-old child caused moderate toxicity. 2.5 g severe toxicity was observed in an adult and very severe intoxication at 7.5 g.

Overdose Symptoms:

The most important are cardiovascular symptoms, but sometimes central nervous system symptoms and respiratory depression may come to the fore, especially in children and young adults. Bradycardia, AV-block I-III, QT-prolongation (extraordinary conditions), asystole, low blood pressure, poor peripheral circulation, heart failure, cardiogenic shock, respiratory depression, apnea.

Other Symptoms:

Fatigue, confusion, loss of consciousness, tremors, cramps, sweating, paresthesia, bronchospasm, nausea, vomiting, possibly esophageal spasm, hypoglycemia (especially in children) or hyperglycemia, hyperkalaemia, kidney impact, transient myasthenic syndrome may be seen. Taking alcohol, antihypertensives, quinidine or barbiturates together may worsen the patient's condition. The first signs of overdose are seen 20 minutes to 2 hours after taking the drug.

Treatment:

Activated charcoal or gastric lavage if needed. Atropine (intravenously; 0.25-0.50 mg for adults, 10-20 mcg/kg for children) should be given against the risk of vagal stimulation before gastric lavage. Intubation and artificial respiration are applied depending on the situation. Plasma volume is preserved with adequate fluid support. Glucose infusion is performed. ECG is monitored. Intravenously, 1.0-2.0 mg of atropine (to prevent vagal stimulation) is given, can be repeated if necessary.

In myocardial depression: Dobutamine or dopamine infusion and calcium glubionate (9 mg/mL 10-20 mL) are given. 50-150 mcg/kg glucagon is given intravenously for more than one minute, then administered as an infusion. Amrinone can also be given. Adding epinephrine has also been found to be beneficial in some cases. Sodium (in the form of chloride or bicarbonate) infusion is used for dilation and arrhythmias in the QRS complex. Pacemaker may be required. In case of cardiac arrest, prolonged resuscitation may be required. Terbutaline (by injection or inhalation) may be given when bronchospasm occurs. Symptomatic treatment is applied.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Selective beta-receptor blocker.
ATC code: C07A B02

Intravenous therapy with metoprolol in myocardial infarction reduces chest pain, reduces the incidence of atrial fibrillation and atrial flutter. Early administration (within 24 hours of onset of first symptoms) contributes to limiting the development of myocardial infarction. Early applications increase the benefit to be obtained from the treatment.

It decreases ventricular heart rate in patients with paroxysmal atrial tachycardia and atrial fibrillation/flutter.

Metoprolol is a $ß_1$-selective receptor blocker, blocking $beta_1$ receptors in the heart at doses lower than those required to block $beta_2$ receptors in the peripheral vessels and bronchi. With increasing doses, its selectivity for $ß_1$ adrenergic receptors may be reduced.

Metoprolol has no agonist effect on beta adrenergic receptors and has a very low membrane stimulation effect. Beta blockers have negative inotropic and chronotropic effects.

Metoprolol treatment reduces the increase in heart rate, cardiac output and blood pressure caused by the effect of catecholamines secreted during physical and mental stress. In stress situations associated with increased adrenaline secretion from the adrenal glands, metoprolol does not

prevent normal physiological vascular dilatation.

Metoprolol causes less contraction of the bronchial muscles at therapeutic doses than non-selective beta-blockers. This property of metoprolol enables treatment with $ß_2$-adrenergic receptor agonists in patients with bronchial asthma or advanced obstructive pulmonary disease.

Metoprolol affects insulin secretion and carbohydrate metabolism less than non-selective beta blockers. Therefore, it can be used in patients with diabetes mellitus.

Metoprolol affects less cardiovascular responses such as tachycardia in hypoglycemia than non-selective beta blockers, and blood sugar returns to normal levels faster.

5.2. Pharmacokinetic properties

Biotransformation:

Metoprolol is mainly metabolized in the liver by the CYP2D6 enzyme. Three major metabolites have been identified in plasma, none of which have clinically significant beta-blocker effects.

Distribution:

After intravenous injection, metoprolol is dispersed rapidly over 5-10 minutes. Plasma levels show a linear relationship with doses in the range of 5-20 mg. The plasma protein binding of metoprolol is low, approximately 5-10%.

Elimination:

Its half-life in plasma is 3-5 hours. Approximately 5% of the administered dose of metoprolol is excreted in the urine, unchanged, the remaining part as metabolites via the kidneys.

5.3. Preclinical safety data

Metoprolol has been extensively studied clinically. Relevant information can be found in other sections of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium chloride

Sodium hydroxide *

Hydrochloric acid *

Water for injection

* Sufficient amount to adjust pH to 5.5-7.5

pH of METLOC ampoule is approximately 6.

6.2. Incompatibilities

1 mg/mL METLOC ampoule equivalent to 40 mg of metoprolol can be added to 1000 mL of the following infusion solutions; Sodium chloride 9 mg/ml, Mannitol 150 mg/mL, Glucose 100 mg/ml, Glucose 50 mg/ml, Fructose 200 mg/ml, intravenous 100 mg/mL, Ringer's, Ringer's-Glucose, Ringer's Acetate

It is not suitable to add METLOC ampoule to Macodex.

6.3. Shelf life

24 months

METLOC ampoule diluted with infusion solution must be used within 12 hours.

6.4. Special precautions for storage

Store at room temperature below 25°C.

6.5. Nature and contents of container

The product, filled in amber colored Type I glass ampoules, is packaged in a carton box containing 1 ampoule of 5 mL.

6.6. Instructions for use and handling and disposal

Unused products or waste materials must be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulation".

7. MARKETING AUTHORISATION HOLDER

Name: HAVER FARMA İlaç A.Ş.

Address: Akbaba Mahallesi Maraş Cad. No: 52/2/1
Beykoz / İSTANBUL

Phone: 0 (216) 324 38 38

Fax: 0 (216) 317 04 98

E-mail: info@haver.com.tr

8. MARKETING AUTHORISATION NUMBER

2017/126

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation date: 14.03.2017

Renewal date of authorisation:-

10. DATE OF REVISION OF THE TEXT