**Metoprolol tartrate solution for injection 1 mg/ml**

**Metoprolol tartrate**

**Clinical Particulars**

**Therapeutic indications**

* Early intervention (within 12 hours) in suspected acute myocardial infarction.
* Cardiac arrhythmias (especially supraventricular tachyarrhythmias).
* Can be tried in tachyarrhythmias caused by digitalis intoxication and in supraventricular and ventricular tachyarrhythmias of other origin.

**Dosage and method of administration**

**Dosage**The dosage is individual. The following recommendations can be used as a guideline.

**Cardiac arrhythmias**Initiate with a slow intravenous injection of up to 5 mg (= 5 ml) at a rate of no more than 1-2 mg per minute. This dose can be repeated after 5 minutes until a sufficient level of effect is achieved. It has been demonstrated that a total dose of 10-15 mg is generally sufficient. Doses exceeding 20 mg are unlikely to provide a better therapeutic effect.

**Myocardial infarction
Acute treatment**Intravenous administration of Metoprolol takes place immediately after the patient's admission to the hospital. Treatment should be initiated in the cardiology department or a similar department when the patient is hemodynamically stable. A total of 3 injections of 5 ml each should be administered, with a 2-minute interval, guided by the electrocardiogram and blood pressure (see sections 4.3 and 4.4).

In patients receiving the full intravenous dose (15 mg), oral treatment with conventional metoprolol tablets should be started 15 minutes after the last intravenous injection, at a dose of 50 mg, 2 to 4 times daily, or a corresponding dose of metoprolol ZOC, depending on the patient's response, for 2 to 3 days.

Maintenance dose of metoprolol tartrate 100 mg is twice daily (morning and evening) or metoprolol ZOC 200 mg once daily.

Oral treatment should be initiated with caution in patients receiving a lower intravenous metoprolol dose (less than 15 mg). A lower dose should be started.

**Impaired kidney function**Dose adjustment is not necessary in patients with impaired kidney function.

**Impaired liver function:** In patients with severe liver dysfunction, it may be necessary to reduce the dose of Metoprolol.

**Elderly:** Dose adjustment is not necessary in the elderly.

**Pediatric patients:** Experience in children is limited.

**Method of administration:** Intravenous injection

**Contraindications**

* Hypersensitivity to the active substance or any of the excipients listed in section 6.1.
* Hypersensitivity to other beta-blockers.
* 2nd and 3rd degree AV block.
* Patients with unstable or acutely decompensated heart failure (pulmonary edema, hypoperfusion, or hypotension) requiring intravenous inotropic therapy.
* Patients continuously or intermittently treated with inotropic β-receptor agonist therapy.
* Severe sinus bradycardia.
* Sick sinus syndrome (unless a permanent pacemaker is in place).
* Cardiogenic shock.
* Severe peripheral arterial circulatory disorders.
* Concurrent use of intravenous verapamil, due to the risk of hypotension, AV conduction disturbances, and left ventricular failure.

Metoprolol is not indicated for patients with a myocardial infarction and a heart rate < 45 beats/min, a PQ interval > 0.24 sec, or a systolic blood pressure < 100 mm Hg and/or severe decompensation of the heart.

**Special warnings and precautions for use**

**Intravenous administration**Intravenous administration of Metoprolol for acute treatment in an intensive care unit should only be done under the supervision of an electrocardiogram and blood pressure monitoring. As with other beta-blockers, in some patients, a clinically significant decrease in blood pressure has been observed after intravenous administration of Metoprolol. Intravenous administration of Metoprolol in patients with a systolic blood pressure below 100 mm Hg (13.3 kPa) should be done cautiously, as further significant blood pressure drop may occur. When treating patients with suspected or confirmed myocardial infarction, the electrocardiogram and blood pressure should be monitored after each of the 3 intravenous doses of 5 mg.

the 2nd or 3rd dose should not be administered if the heart rate is lower than 40 beats per minute, the systolic blood pressure is lower than 90 mm Hg, or if there is a P-Q interval greater than or equal to 0.26 seconds, or any increase in dyspnea or cold sweats.

Metoprolol contains 3.6 mg (0.157 mmol) of sodium per ml. Caution is advised in patients with a controlled sodium diet.

Although metoprolol, at usual doses, has a less negative impact on bronchial musculature than non-selective beta-blockers, caution is still necessary. In patients with bronchial asthma being treated with Metoprolol, bronchodilators that selectively stimulate beta2 receptors, such as terbutaline, may be prescribed if needed. If the patient is already using a beta2 receptor-stimulating agent, it may sometimes be necessary to adjust its dosage.

As beta-blockers can affect glucose metabolism, caution is necessary in patients with diabetes mellitus. The impact on glucose metabolism and the masking effect on hypoglycemic symptoms are smaller with metoprolol treatment compared to non-selective beta-blockers.

Metoprolol should not be administered to patients with untreated decompensation of heart failure. Decompensation should be controlled first.

The use of a beta-blocking agent can lead to severe, sometimes life-threatening deterioration of heart function, especially in patients whose heart function depends on sympathetic support. This is not so much due to an excessive beta-blocking effect but because patients with marginal heart function tolerate even a slight reduction in sympathetic activity poorly. This can result in decreased inotropy, reduced heart rate, and slowed AV conduction. The consequence can be pulmonary edema, AV block, and shock. In rare cases, exacerbation of an existing AV conduction disorder can occur, potentially leading to AV block.

If concurrent treatment with digitalis is used, it should be noted that both drugs slow AV conduction, potentially leading to AV dissociation. Mild cardiovascular complications may also occur, including dizziness, bradycardia, and a tendency to faint. If bradycardia increases, the dosage should be reduced or gradually discontinued.

In patients with peripheral circulatory disorders such as Raynaud's disease or intermittent claudication, worsening of the condition may occur mainly due to the blood pressure-lowering effect. Beta-blockers should be used with great caution if the condition worsens.

If Metoprolol is prescribed to a patient with pheochromocytoma, an alpha-blocker should also be given.

Abrupt discontinuation of oral beta-blockade can be dangerous and should be avoided. When it is necessary to discontinue Metoprolol treatment, it should typically be done gradually over at least 2 weeks by tapering the dose until finally taking half of a 25 mg tablet (half of a 50 mg tablet). This lowest dose should be taken for at least 4 days before stopping treatment. During this period, especially patients with ischemic heart disease should be closely monitored because the risk of coronary events, including sudden death, is increased when discontinuing beta-blockade. Hypertension and arrhythmias may also occur.

Prior to surgery, the anesthesiologist should be informed that the patient is using metoprolol. In every patient, the benefit of continuing treatment with a beta-blocking agent should be weighed against the risk of discontinuing this treatment. If necessary, metoprolol administration should be discontinued 48 hours prior to anesthesia. It may be desirable to use a beta-blocking agent as pre-medication in some patients undergoing surgery. By protecting the heart from the effects of stress, the beta-blocking agent can reduce excessive sympathetic stimulation.

timulation, thereby preventing disturbances such as arrhythmias or acute coronary insufficiency. In patients using beta-blockers, anesthesia should be used that has the least negative inotropic effect.

It should also be avoided to initiate patients who require non-cardiac surgery on a high dose of metoprolol as this has been associated with bradycardia, hypotension, and stroke, including fatal outcomes in patients with cardiovascular risk factors. The occurrence of anaphylactic shock may be more severe in patients using beta-blockers.

**Metoprolol contains sodium.**This medicine contains less than 1 mmol of sodium (23 mg) per ampoule, which means it is essentially "sodium-free."

**Interactions with other medicines and other forms of interaction**

Metoprolol is a metabolic substrate for the Cytochrome P450 enzyme CYP2D6. Medications that have enzyme-inducing and enzyme-inhibiting effects can influence the plasma levels of metoprolol. Metoprolol plasma levels increase with concomitant use of agents metabolized by CYP2D6, such as antiarrhythmics, antihistamines, histamine-2 receptor antagonists, antidepressants, antipsychotics, and COX-2 inhibitors. Rifampicin lowers the plasma levels of metoprolol. Alcohol and hydralazine increase the plasma levels of metoprolol.

**Calcium antagonists**When used concurrently with calcium antagonists of the verapamil and diltiazem types, there may be an increase in negative inotropic and chronotropic effects. Calcium antagonists of the verapamil type should not be administered intravenously to patients treated with beta-blockers due to the risk of hypotension, AV conduction disorders, and left ventricular failure (see section 4.3). The combination is contraindicated in patients with impaired heart function. When used concomitantly with dihydropyridine derivatives such as nifedipine, one should be less concerned about this, although the blood pressure-lowering effect can be enhanced.

**Sympathetic ganglion blockers, MAO inhibitors, or other beta-blockers**Patients receiving sympathetic ganglion blockers, MAO inhibitors, or other beta-blockers (including eye drops) concurrently should be monitored.

**Clonidine**Concomitant use of clonidine with a non-selective beta-blocker, and possibly with a selective beta-blocker, increases the risk of 'rebound' hypertension. If clonidine is administered concurrently, clonidine therapy should be continued for some time after discontinuation.

**Anti-arrhythmics**Caution is advised when using some antiarrhythmics, such as those of the quinidine or amiodarone type, concurrently because beta-blockers can potentiate their negative inotropic and negative dromotropic effects.

Digitalis glycosides, when used with beta-blockers, can prolong atrioventricular conduction time and cause bradycardia.

**Inhalation anesthetics**An increase in the cardiodepressive effect due to simultaneous administration of inhalation anesthetics is possible. However, because beta-blockade can prevent excessive fluctuations in blood pressure,

Intubation during intubation can occur and can be quickly antagonized with beta-sympathomimetics, simultaneous use is not contraindicated.

**Prostaglandin Synthetase Inhibitors**Concomitant use of beta-blockers with indomethacin or other prostaglandin synthetase inhibitors can reduce the blood pressure-lowering effect.

In patients treated with adrenaline and a beta-blocker, a selective beta-blocker has less effect on blood pressure than a non-selective beta-blocker.

**Insulin and oral anti-diabetic agents**The blood sugar-lowering effect of insulin and oral blood sugar-lowering agents can be enhanced by beta-blockers, especially non-selective beta-blockers. In such cases, the dose of the oral blood sugar-lowering agent should be adjusted.

**Lidocaine:** Metoprolol may reduce the clearance of some drugs, such as lidocaine.

**Fertility, Pregnancy, and Lactation**

**Pregnancy:** A limited number of data on the use of metoprolol during pregnancy in humans so far do not indicate an increased risk of congenital abnormalities in humans.

Animal studies have shown no harmful effects on reproduction at clinically relevant doses. Based on pharmacological activity, possible adverse effects on the fetus and neonate (especially hypoglycemia, hypotension, bradycardia, and respiratory problems) should be considered when used later in pregnancy. Beta-blockers may decrease placental blood flow.

Metoprolol can be used during pregnancy if the benefits to the mother outweigh the risks to the embryo or fetus. The newborn should be monitored for symptoms of beta-blockade for 24-48 hours after birth if treatment is continued up to delivery.

**Lactation:** Metoprolol should not be used during breastfeeding unless deemed necessary.

Metoprolol is excreted in breast milk. Although the concentration of metoprolol is very low, infants receiving breast milk from a patient treated with metoprolol should be carefully monitored for symptoms of beta-blockade.

**Fertility:** Fertility data do not indicate any particular concerns.

**Influence on the Ability to Drive and Use Machines**No research has been conducted regarding the effects on driving and the ability to operate machinery. When driving vehicles and operating machinery, the possibility of side effects such as fatigue or dizziness, which may occur in some patients, should be considered.

**Side Effects**Metoprolol is well tolerated, and side effects are generally mild and transient. The following side effects have been reported during clinical trials or after routine use. In many cases, a definitive relationship with the use of metoprolol tartrate has not been established.

Within each frequency group, side effects are ranked in decreasing order of severity.

**Overdose**

**Symptoms:** The most common effects in case of severe overdose are hypotension, heart rhythm and conduction disturbances (bradycardia, AV block, widened QRS complex), decreased cardiac output, decreased consciousness to coma, generalized seizures, respiratory failure, and bronchospasms.

**General treatment:** Strict observation, treatment in an intensive care unit, intubation and ventilation if necessary.

**In case of moderate poisoning**: Treatment of bradycardia with atropine (1-2 mg), administration of saline solution in case of hypotension.

**In case of severe poisoning: The above plus:** Administration of glucagon (3-5 mg IV, up to a maximum of 10 mg as an intravenous bolus injection), then if necessary, 2-5 mg/hour up to a maximum of 10 mg/hour. Administration of catecholamines: beta-adrenoceptor stimulant such as dobutamine 2.5 to 10 micrograms/kg/minute / norepinephrine.

Consideration of calcium administration.

Consideration of insulin/glucose administration.

Consideration of phosphodiesterase inhibitors administration.

In case of persistent hypotension: intra-aortic balloon pump or extracorporeal circulation.

Bronchospasms can usually be counteracted with bronchodilators.

Note: The expected effect of pacemaker implantation is usually very limited because, of the effects induced by the beta-blocker, negative inotropy is of greater importance than heart rate, and the pacemaker impulse is less well followed due to intoxication. Even with an increase in heart rate with a pacemaker in place, blood pressure and cardiac output may remain low.

**The following frequency definitions are used:** Very common (> 1/10), common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100), rare (> 1/10,000, < 1/1,000), and very rare (< 1/10,000), including reports of isolated cases.

**Cardiovascular disorders
Common:** Bradycardia; orthostatic abnormalities (very rare with syncope); cold hands and feet; palpitations.
**Uncommon:** Worsening of heart failure symptoms; cardiogenic shock in patients with acute myocardial infarction; first-degree heart block; edema; precordial pain.
**Rare:** Cardiac conduction disorders; cardiac arrhythmias.
**Very rare:** Gangrene in patients with (pre-existing) severe peripheral circulatory disorders.

**Nervous system disorders
Very common:** Fatigue.
**Common:** Dizziness; headache.
**Uncommon**: Paresthesias; muscle cramps.

**Gastrointestinal disorders
Common:** Nausea; abdominal pain; diarrhea; constipation.
**Uncommon:** Vomiting.
**Rare:** Dry mouth.
**Very rare:** Taste disturbances.

**Blood and lymphatic system disorders
Very rare:** Thrombocytopenia.
Liver and gallbladder disorders
**Rare:** Liver function abnormalities, abnormal liver function tests.
**Very rare:** Hepatitis.

**Metabolism and nutrition disorders
Uncommon:** Weight gain.
Musculoskeletal and connective tissue disorders
**Very rare:** Arthralgia.

**Psychiatric disorders
Uncommon:** Depression; decreased alertness; drowsiness or insomnia; nightmares.
**Rare:** Nervousness; anxiety; impotence/sexual dysfunction.
**Very rare:** Amnesia/memory loss; confusion; hallucinations; depersonalization.

**Respiratory, thoracic, and mediastinal disorders
Common:** Dyspnea on exertion.
**Uncommon:** Bronchospasms, even in patients without obstructive lung abnormalities.
**Rare:** Rhinitis.

**Eye disorders
Rare:** Visual disturbances; dry and/or irritated eyes; conjunctivitis.

**Ear and labyrinth disorders
Very rare:** Tinnitus.

**Skin and subcutaneous tissue disorders
Uncommon:** Transient skin rash (urticaria, psoriasis-like or dystrophic skin lesions); increased sweating.
Rare: Hair loss.

**Special precautions for storage**Store below 25 ºC. Do not store in the refrigerator or freezer. Store in the original packaging to protect from light.