

AFT-Metoprolol CR

Metoprolol succinate (Ph. Eur.) 23.75 mg, 47.5 mg, 95 mg and 190 mg controlled-release tablets

Presentation

AFT-METOPROLOL CR tablets 23.75 mg are white, oval, biconvex, film-coated tablets scored on both sides. Size 9 mm x 5 mm.

AFT-METOPROLOL CR tablets 47.5 mg are white, oval, biconvex, film-coated tablets scored on both sides. Size 11 mm x 6 mm.

AFT-METOPROLOL CR tablets 95 mg are white, oval, biconvex, film-coated tablets scored on both sides. Size 16 mm x 8 mm.

AFT-METOPROLOL CR tablets 190 mg are white, oval, biconvex, film-coated tablets scored on both sides. Size 19 mm x 10 mm.

Uses

Actions

Metoprolol is a β_1 -selective β -blocker without significant-membrane stabilizing effect or partial agonist activity.

Metoprolol reduces or inhibits the agonistic effect of catecholamines on the heart (which are released during physical and mental stress). This means that the usual increase in heart rate, cardiac output, cardiac contractility and blood pressure, produced by the acute increase in catecholamines, is reduced by metoprolol. During high endogenous adrenaline levels metoprolol interferes much less with blood pressure control than non-selective β -blockers.

AFT-METOPROLOL CR gives a smoothed plasma concentration time and effect profile (β_1 -blockade) over 24 hours when compared to an immediate release β_1 -selective blocker tablet formulation.

AFT-METOPROLOL CR, when required to be used in combination with a β_2 -agonist, may be given to patients with symptoms of obstructive pulmonary disease. AFT-METOPROLOL CR when given together with a β_2 -agonist in therapeutic doses interferes less than non-selective β -blockers with the β_2 -mediated broncho-dilation.

AFT-METOPROLOL CR has less effect on insulin release, carbohydrate metabolism and cardiovascular response to hypoglycaemia than do non-selective β -blockers.

Metoprolol may cause a slight increase in blood triglycerides, a decrease in blood free fatty acids and sometimes a small decrease in the high density lipoproteins (HDL) fraction, although less than that observed following non-selective β -blockers. A long term study did show a significant reduction in total serum cholesterol levels.

Quality of life is maintained or improved during treatment with metoprolol including for patients with chronic heart failure or post myocardial infarction.

Effect in hypertension

AFT-METOPROLOL CR lowers elevated standing and supine blood pressure. A short duration (a few hours) and clinically insignificant increase in peripheral resistance may be observed after the institution of metoprolol treatment. During long-term treatment a reduction in total peripheral resistance, left ventricular hypertrophy may occur and improved left ventricular diastolic function and left ventricular filling.

A reduction in the risk of death from cardiovascular disease in men with mild to moderate hypertension metoprolol has been shown, mainly due to reduced risk for sudden cardiovascular death, to reduce the risk for fatal and non-fatal infarction and for stroke.

Effect on angina pectoris

Metoprolol has been shown to reduce the frequency, duration and severity of both angina attacks and silent ischemic episodes and to increase the physical working capacity in patients with angina pectoris.

Effect in chronic heart failure

In patients with symptoms of heart failure (New York Heart Association (NYHA) II-IV) and decreased ejection fraction (≤ 0.40) metoprolol, when added to standard therapy, has been shown to improve survival and to reduce the number of hospitalisations due to worsening heart failure. In addition, metoprolol therapy has increased ejection fraction, reduced left ventricular end systolic and end diastolic volumes, improved NYHA functional class and improved quality of life.

Effect on cardiac rhythm

AFT-METOPROLOL CR controls heart rate in supraventricular tachycardia or atrial fibrillation, and in the presence of ventricular extrasystoles inhibits the cardiac effects of increased sympathetic activity leading to decreased automaticity in the pacemaker cells and reduction of supraventricular conduction velocity.

Effect on myocardial infarction

Metoprolol reduces the risk of sudden death in patients with suspected or confirmed myocardial infarction. In high risk patients with diabetes mellitus or previous cardiovascular disease there is a reduction in mortality.

Metoprolol has also been shown to reduce the risk for non-fatal myocardial infarction and to reduce the incidence of recurrent myocardial infarction. There is a reduction in chest pain during the acute infarction phase due to the anti-ischemic effects of metoprolol.

Effect on hyperthyroidism

Metoprolol can reduce the clinical effects of hyperthyroidism.

Effect on heart disorders with palpitations

AFT-METOPROLOL CR is effective in reducing palpitations and improving the patient's general condition.

Effect on migraine

AFT-METOPROLOL CR is suitable for prophylactic treatment of migraine.

Pharmacokinetics

Absorption and distribution

Metoprolol is completely absorbed after oral administration. Due to extensive first-pass metabolism the systemic bioavailability of metoprolol from a single oral dose is approximately 50%. Bioavailability is reduced by about 20-30% for the controlled release preparation compared to the conventional tablets. The heart rate is the same as with conventional tablets.

Plasma protein binding of metoprolol is about 5-10%. Volume of distribution of 5.6 L/kg.

AFT-metoprolol CR consists of beads of metoprolol succinate coated with a polymer membrane controlling the drug release rate resulting in an even metoprolol plasma concentration over a 24 hour dose interval. There is consequently much less variation in metoprolol plasma concentrations and pharmacological effects compared with the conventional, immediate release tablet. Release rate is independent of physiological factors such as pH, food and peristalsis.

Metabolism and elimination

Metoprolol undergoes oxidative metabolism in the liver primarily by the CYP2D6 isoenzyme. Metabolites are inactive. The fraction excreted unchanged is usually about 5% and up to 30% in isolated cases.

Mean elimination half-life of metoprolol in plasma is 3.5 hours (range 1-9 hours). Clearance rate is approximately 1 litre/minute.

Pharmacokinetics of metoprolol are not effected by age.

Renal impairment does not effect the systemic bioavailability and elimination of metoprolol. However in patients with a glomerular filtration rate (GFR) of less than 5 mL/minute, significant accumulation of metabolites was observed.

Decreased liver function has little effect on metoprolol pharmacokinetics. Bioavailability increases and total clearance may be reduced in patients with severe liver cirrhosis and a portacaval shunt. Patients with a portacaval anastomosis had a total clearance of approximately 0.3 litres/minute and area under the plasma concentration-time curve (AUC) values of up to 6 times higher than in healthy subjects.

Indications

- Hypertension. To reduce blood pressure and to reduce the risk of cardiovascular and coronary mortality (including sudden death), and morbidity.
- Angina pectoris.
- Symptomatic mild to severe chronic heart failure as an adjunct to other heart failure therapy to: increase survival, reduce hospitalisation, improve left ventricular function, improve New York Heart Association (NYHA) functional class and improve Quality of Life.
- Cardiac arrhythmias, especially supraventricular tachycardia, reduction of ventricular rate in atrial fibrillation and ventricular extrasystoles.

- Maintenance treatment after myocardial infarction
- Hyperthyroidism.
- Functional heart disorder with palpitations.
- Migraine prophylaxis.

Dosage and Administration

Dosage should always be adjusted to the patient's individual requirements.

AFT-METOPROLOL CR is recommended for once daily treatment, should be taken at the same time of the day with regard to food and is preferably taken together with the morning meal. The tablets may be broken in half. AFT-METOPROLOL CR tablets should be swallowed with liquid and should not be chewed or crushed.

The following dosage recommendations may be taken as a guide:

Hypertension

The recommended dose in patients with mild to moderate hypertension is 47.5 mg metoprolol given once daily. In patients not responding to 47.5 mg the dose can be increased to 95-190 mg once daily or combined with other antihypertensive agents.

Long-term antihypertensive treatment with metoprolol in daily doses of 95-190 mg has been shown to reduce total mortality, including sudden cardiovascular death, stroke and coronary events in hypertensive patients.

Angina Pectoris

The recommended dose is 95-190 mg daily given as a single dose in the morning. AFT-METOPROLOL CR can be combined with other antianginal agents if needed.

Chronic Heart Failure

The dose of AFT-METOPROLOL CR should be adjusted in individual patients with chronic heart failure stabilised on other heart failure treatment. A recommended initial dose during the first two weeks is a 23.75 mg tablet once daily. It is recommended that patients with NYHA functional classes III-IV begin with half a 23.75 mg tablet once daily for the first week. It is recommended that the dose then be doubled every second week up to a maximum target dose of 190 mg AFT-METOPROLOL CR once daily (or to the highest tolerated dose). During long-term treatment the aim should be to reach 190 mg AFT-METOPROLOL CR once daily (or the highest tolerated dose).

Tolerability should be monitored carefully at each dose. A decrease in concomitant medication may be necessary in cases of hypotension. However initial hypotension does not necessarily mean that the dose cannot be tolerated in chronic treatment but the patient should be stabilized at the lower dose first.

Cardiac Arrhythmias

95-190 mg daily, given as a single dose once daily.

Myocardial Infarction

Treatment in the acute stage

After symptoms indicating myocardial infarction, treatment with metoprolol administered intravenously should be initiated as soon as possible. Such treatment should be initiated in a coronary care or similar unit immediately after the patient's haemodynamic condition has stabilised. Depending on the haemodynamic status of the patient (ECG, blood pressure, heart rate), three 5 mg bolus injections should be given, at 2 minute intervals.

In patients who tolerate the full intravenous dose (15 mg), AFT-METOPROLOL CR tablets 47.5 mg four times daily should be started 15 minutes after the last intravenous injection and be continued for 24 hours. Followed by AFT-METOPROLOL CR 95 mg twice daily for a further 24 hours.

Patients who do not tolerate the full intravenous (15 mg) dose should have their oral treatment initiated with caution starting with a lower dose.

Maintenance treatment after myocardial infarction

Long-term oral treatment with metoprolol-CR 190 mg once daily has been shown to reduce the risk of death (including sudden death) and reinfarction (also in patients with diabetes mellitus).

Functional heart disorder with palpitations

The recommended dosage is 95 mg once daily. If necessary, the dose may be increased to 190 mg.

Migraine prophylaxis

The recommended dosage is 95-190 mg once daily.

Hyperthyroidism

95-190 mg daily, given as a single dose in the morning. If necessary, the dose may be increased.

Impaired Renal Function

Dose adjustment is not required in patients with impaired renal function.

Impaired Hepatic Function

Dose adjustment is not normally needed in patients suffering from liver cirrhosis although a reduction in dose should be considered when there are signs of serious impairment of liver function (e.g. shunt-operated patients).

Elderly

Dose adjustment is not needed.

Children

There is limited experience with metoprolol treatment in children.

Contraindications

- Bronchial asthma or other obstructive lung disorders.
- Grade 2 and 3 A-V block and intranodal A-V block.
- Patients with unstable decompensated cardiac heart failure (pulmonary oedema, hypoperfusion or hypotension), and patients with continuous or intermittent inotropic therapy acting through β -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/minute, the P-Q interval is > 0.24 seconds or the systolic blood pressure is <100 mmHg.

AFT-METOPROLOL CR is contraindicated in patients who have shown hypersensitivity to other β -blockers or any of the tablet excipients.

Warnings and Precautions

Intravenous administration of calcium antagonists of the verapamil-type should not be given to patients treated with β -blockers.

The risk of AFT-METOPROLOL CR interfering with β_2 -receptors is less than with conventional tablet formulations of β_1 -selective blockers.

The risk of interfering with carbohydrate metabolism or masking hypoglycaemia is likely to be less with AFT-METOPROLOL CR than with conventional tablet formulations of β_1 -selective blockers and much less than with non-selective β -blockers.

Very rarely a pre-existing A-V conduction disorder of moderate degree may become aggravated (possibly leading to A-V block). If the patient develops increasing bradycardia, AFT-METOPROLOL CR should be given in lower doses or gradually withdrawn.

AFT-METOPROLOL CR may aggravate the symptoms of peripheral arterial circulatory disorders, mainly due to its blood pressure lowering effect.

Where AFT-METOPROLOL CR is prescribed for a patient known to be suffering from phaeochromocytoma, an alpha-blocker should be co-administered.

It is not recommended to stop β -blocker treatment in patients undergoing surgery but the anaesthetist should be informed

Abrupt withdrawal of β -blockade is hazardous especially in high risk patients, and should not be done. If discontinuation of AFT-METOPROLOL CR is required, this should preferably be done gradually over at least two weeks when the dose is halved in each step down to the final step when a whole 23.75 mg tablet is reduced to half a tablet. Slower withdrawal rate is recommended if symptoms occur. Sudden withdrawal of β -blockade may aggravate chronic heart failure and increases the risk for myocardial infarction and sudden death

In patients taking β -blockers anaphylactic shock assumes a more severe form.

Use in pregnancy [Category C]

AFT-METOPROLOL CR should not be given during pregnancy and lactation unless its use is considered essential. Beta-blockers may cause side effects (e.g. bradycardia) in the foetus, newborn and breast-fed infant.

Use in lactation

At normal therapeutic doses, the amount of metoprolol ingested from breast milk is in general minimal and insufficient to cause β -blockade in the infant.

Effects on ability to drive and use machines

Since occasional dizziness or fatigue may occur, patients should know how they react to AFT-METOPROLOL CR before driving or using machines.

Adverse Effects

Metoprolol is generally well tolerated. Most adverse reactions are generally mild and transient.

The following adverse events have been reported mostly with conventional metoprolol (metoprolol tartrate). In many cases a relationship to treatment with metoprolol has not been established.

Cardiovascular system

Common: Bradycardia, postural disorders (very rarely with syncope). Cold hands and feet, palpitations.

Uncommon: Deterioration of heart failure symptoms, cardiogenic shock in patients with acute myocardial infarction, first degree heart block, oedema, precordial pain.

Rare: Disturbances of cardiac conduction, cardiac arrhythmias.

Very rare: Gangrene in patients with pre-existing severe peripheral circulatory disorders.

Central Nervous System

Very common: Fatigue

Common: Dizziness, headache.

Uncommon: Paraesthesiae, muscle cramps.

Gastrointestinal

Common: Nausea, abdominal pain, diarrhoea, constipation.

Uncommon: Vomiting

Rare: Dry mouth

Haematologic

Very rare: Thrombocytopenia

Hepatic

Rare: Liver function test abnormalities

Very rare: Hepatitis

Metabolism

Uncommon: Weight gain

Musculoskeletal

Very rare: Arthralgia

Psychiatric

Uncommon: Depression, impaired concentration, somnolence or insomnia, nightmares

Rare: Nervousness, anxiety, impotence and/or sexual dysfunction.

Very rare: Amnesia and/or memory impairment, confusion, hallucinations.

Respiratory

Common: Dyspnoea on exertion.

Uncommon: Bronchospasm

Rare: Rhinitis

Sense organs

Rare: Disturbances of vision, dry and/or irritated eyes, conjunctivitis

Very rare: Tinnitus, taste disturbances

Skin

Uncommon: Rash (in the form of urticaria psoriasiform and dystrophic skin lesions), increased sweating.

Rare: Loss of hair

Very rare: Photosensitivity reactions, aggravated psoriasis.

Definition of frequencies:

very common: $\geq 10\%$

common: 1 - 9.9%,

uncommon: 0.1 - 0.9%

rare: 0.01 - 0.09%

very rare: $< 0.01\%$

Interactions

Metoprolol is a metabolic substrate for the cytochrome P450 isoenzyme CYP2D6. Potent inhibitors of the CYP2D6 enzyme such as antiarrhythmics, antihistamines, histamine-2-receptor antagonists, antidepressants, antipsychotics or COX-2 inhibitors may therefore increase the plasma concentration of metoprolol.

The plasma concentration of metoprolol is lowered by rifampicin and may be raised by alcohol and hydralazine.

Patients receiving concomitant treatment with sympathetic ganglion blocking agents, other β -blockers (i.e. eye drops) or monoamine oxidase inhibitors should be kept under close surveillance.

If a patient is treated with clonidine and metoprolol concurrently, and clonidine treatment is to be discontinued, metoprolol should be stopped several days before clonidine is withdrawn.

Rebound hypertension that can follow withdrawal of clonidine may be increased in patients receiving concurrent β -blocker treatment.

Increased negative inotropic and chronotropic effects may occur when metoprolol is given together with calcium antagonists of the verapamil and diltiazem type. Patients treated with β -blockers, should not be given calcium antagonists of the verapamil type parenterally.

Beta-blockers may enhance the negative inotropic and negative dromotropic effect of antiarrhythmic agents (of the quinidine type and amiodarone).

Both digitalis glycosides and β blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.

Some inhalation anaesthetics may enhance the cardiodepressant effect of β -blockers.

Concomitant treatment with indomethacin or other prostaglandin synthetase inhibiting agents may decrease the antihypertensive effect of β -blockers.

Under certain conditions, cardioselective β -blockers interfere much less with blood pressure control than non-selective β -blockers when adrenaline is administered to patients treated with β -blockers,.

The dosages of oral antidiabetics may have to be readjusted in patients receiving β -blockers.

Overdosage

Symptoms

Potential signs and symptoms associated with overdosage with metoprolol are: severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness and/or coma, nausea, vomiting and cyanosis.

Concomitant ingestion of alcohol, antihypertensives, quinidine or barbiturates may aggravate the patients condition.

The first symptoms of overdosage may be observed 20 minutes to 2 hours after ingestion.

Treatment

There is no specific antidote.

On the basis of the pharmacologic actions of metoprolol, the following general measures should be employed:

Elimination of the Drug: Induction of vomiting or gastric lavage should be performed.

Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

Hypotension: A vasopressor should be administered, e.g., levarterenol or dopamine.

Bronchospasm: A β_2 -stimulating agent and/or a theophylline derivative should be administered.

Cardiac Failure: A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

Pharmaceutical Precautions

Protect from light and moisture. Keep out of reach of children. Store below 25 °C.

Medicine Classification

Prescription Medicine.

Package Quantities

All strengths of AFT-METOPROLOL CR tablets are available in packs containing 30, 90, and 100 tablets.

Further Information

List of excipients: ethylcellulose, hydroxypropylmethyl cellulose, methylcellulose, microcrystalline cellulose, glycerol, maize starch, magnesium stearate, stearic acid and titanium dioxide (E 171).

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