METOHEXAL 50 TABLET / METOHEXAL 100 TABLET

Product Description
METOHEXAL 50 TABLET: Each tablet contains metoprolol tartrate 50.0 mg
METOHEXAL 100 TABLET: Each tablet contains metoprolol tartrate 100.0 mg.

Pharmacodynamics
Metoprolol is a $beta_1$-selective beta-blocker, i.e. it blocks $beta_1$-receptors in the heart at doses considerably lower than required for blocking $beta_2$-receptors.
Metoprolol has only an insignificant membrane stabilizing effect, and it does not possess an agonist effect. Metoprolol reduces or blocks the stimulating effect of catecholamines (released especially in association with physical and mental stress) on the heart. Metoprolol reduces the tachycardia, increased cardiac output and increased contractility of the heart usually caused by the sudden increase of catecholamines, as well as lowers blood pressure. It is classified as cardioselective lacking intrinsic sympathomimetic and membrane stabilising activity.
The plasma concentration and efficacy ($beta_1$-blockade) of metoprolol prolonged-release tablets are more even over a given 24-hour period than those achieved with conventional tablet forms of $beta_1$-selective beta-blockers.
Since the plasma concentrations are stable, the clinical $beta_1$-selectivity is better than that achieved with conventional tablet forms of $beta_1$-selective beta-blockers. Moreover, the risk of adverse effects associated with concentration peaks (e.g. bradycardia and weakness of the limbs) is minimal.
If necessary, metoprolol may be administered concomitantly with a $beta_2$-agonist to patients with symptoms of obstructive pulmonary disease.

Pharmacokinetics
Absorption and distribution
Metoprolol is absorbed totally after an oral dose. Because of the extensive first-pass metabolism of metoprolol the bioavailability of a single oral dose is approximately 50%. The bioavailability of prolonged-release tablets is approximately 20-30% lower than that of conventional tablets which, however, does not have a significant clinical effect since the AUC values (pulse) will remain the same as when using conventional tablets. Only a small proportion of metoprolol, approximately 5-10%, is bound to plasma proteins.
Each metoprolol prolonged-release tablet contains a large number of controlled-release metoprolol pellets. Each pellet is coated with a polymer film which controls the release rate of metoprolol.
A prolonged-release tablet dissolves rapidly and the prolonged-release granules spread into the gastrointestinal tract, releasing metoprolol continously over a period of 20 hours. The elimination half-life of metoprolol averages 3.5 hours (see Metabolism and elimination). After once daily administration maximal plasma concentrations of metoprolol in the plasma will reach about twice the minimal levels.
Metabolism and elimination
Metoprolol is metabolised by oxidation in the liver. The three known main metabolites have not been shown to possess a clinically significant beta-blocking effect.
Metoprolol is metabolized predominantly but not exclusively by the liver enzyme cytochrome (CYP) 2D6. Due to polymorphism of the CYP 2D6 gene, rates of metabolism vary between individuals, with poor metabolisers (approximately 7-8%) showing higher plasma concentrations and slower elimination than extensive metabolisers. Within individuals, however, plasma concentrations are stable and reproducible. Over 95% of an oral dose is excreted in the urine. Approximately 5% of the dose is excreted unchanged, in isolated cases up to 30%. The plasma elimination half-life of metoprolol averages 3.5 hours (range 1-9 hours). Total clearance is approximately 1 litre/min. The pharmacokinetics of metoprolol in the elderly does not differ significantly from that seen in the younger population. The systemic bioavailability and the elimination of metoprolol are normal in patients with renal insufficiency. However, the elimination of the metabolites is slower than normal. Significant accumulation of metabolites has been observed in patients with a glomerular filtration rate (GFR) less than 5 ml/min. However, the accumulation of metabolites does not potentiate the beta-blocking effect of metoprolol.
In patients with liver cirrhosis, the bioavailability of metoprolol may increase and the total clearance decrease. The increase in exposure is, however, considered clinically relevant only in patients with severe impairment or a portocaval shunt. The total clearance in patients with a portocaval shunt is approximately 0.3litres/min and the AUC values approximately six times larger than those in healthy subjects.

Indication
Metoprolol tartrate is given in the treatment of hypertension, coronary heart disease and arrhythmias.
For the emergency treatment of cardiac arrhythmias, metoprolol tartrate may be given intravenously in an initial dose of up to 5 mg administered at a rate of 1 to 2 mg per minute.
Metoprolol is also used as an adjunct in the early management of acute myocardial infarction to limit progression and myocardial damage and reduce morbidity.

Recommanded Dose
Metoprolol tartrate is given in treatment of hypertension in an initial dose of 100 mg daily, increased weekly according to the response of the patient to 400 mg daily or 200 mg twice daily. Better control may be obtained with the more frequent dosage regimens.
The usual dose for angina pectoris is 50 mg to 100 mg twice or three times daily.
In the treatment of cardiac arrhythmias, metoprolol tartrate may be given intravenously in an initial dose of up to 5 mg administered at a rate of 1 to 2 mg per minute; this may be repeated, if necessary, at intervals of 5 minutes to a total dose of 10 to 15 mg. When acute arrhythmias have been controlled, maintenance therapy with doses not exceeding 50 mg three times daily by mouth is recommended and should be started 4 to 6 hours after intravenous therapy.
Metoprolol used as an adjunctive medication in the early management of acute myocardial infarction should be given within 12 hours of the onset of chest pain; metoprolol 5 mg should be given intravenously at 2-minute intervals to a total of 15 mg where tolerated. This should be followed, after 15 minutes, by the commencement of oral treatment in patients who have received the full intravenous dose, with 50 mg every 6 hours for 2 days. In patients who have failed to tolerate the full intravenous dose a reduced oral dose should be given as and when their condition permits. Subsequent maintenance dosage is 100 mg given twice daily by mouth.

Mode Of Administration
Oral

Contraindication
Metoprolol should not be given to the following patients :
- Known hypersensitivity to metoprolol and related derivatives, or to any of the excipients; hypersensitivity to other beta-blockers (cross-sensitivity between beta-blockers can occur)
- Atrioventricular block of second or third degree
- Decompensated heart failure
- Clinically relevant sinus bradycardia (heart rate less than 45 to 50 beats/min)
- Sick-sinus syndrome
- Severe peripheral arterial circulatory disorders
- Cardiogenic shock
- Untreated pheochromocytoma (see A10. Warnings and Precautions)
- Hypotension
- Severe bronchial asthma or history of severe bronchospasm
- Patients with myocardial infarction who have a heart rate of less than 45 to 50 beats/min, P-R interval of greater than 0.24 sec, a systolic blood pressure of less than 100 mmHg, and/or severe heart failure

Warning and Precautions
Bronchospastic diseases
In general, patients with bronchospastic diseases should not be given beta-blockers, including metoprolol. However, because of its relative cardioselectivity, oral metoprolol may be administered with caution to patients with mild or moderate bronchospastic diseases who do not respond to, or cannot tolerate, other suitable treatments. Since $beta_1$-selectivity is not

absolute, a $beta_2$-agonist should be administered concomitantly, and the lowest possible dose of metoprolol should be used.

Diabetic patients

Metoprolol should be used with caution in patients with diabetes mellitus, especially those who are receiving insulin or oral hypoglycemic agents (see A11. Interactions With Other Medicaments). Diabetic patients should be warned that beta-blockers, including metoprolol, may mask the tachycardia occurring with hypoglycemia; however, other manifestations of hypoglycemia such as dizziness and sweating may not be significantly suppressed, and sweating may be increased.

Cardiovascular system

Beta-blockers, including metoprolol, should not be used in patients with untreated congestive heart failure (see A9. Contraindication). This condition should first be stabilized. Because of their negative effect on atrioventricular conduction, beta-blockers, including metoprolol, should be given only with caution to patients with first degree atrioventricular block (see A9. Contraindication).

If the patient develops increasing bradycardia (heart rate less than 50 to 55 beats/min) the dosage should be gradually reduced, or treatment gradually withdrawn (see A9. Contraindication).

Myocardial infarction

In patients with myocardial infarction, if significant hypotension occurs, metoprolol should be discontinued, and the hemodynamic status of the patient and the extent of myocardial ischemia carefully assessed. Intensive hemodynamic monitoring may be required and appropriate treatment modalities should be instituted. If hypotension is associated with significant bradycardia or atrioventricular block, treatment should be directed at reversing these.

Peripheral circulatory disorders

Metoprolol should be used with caution in patients with peripheral arterial circulatory disorders (for example, Raynaud's disease or phenomenon, intermittent claudication), because beta-blocker treatment may aggravate such conditions (see A9. Contraindication).

Pheochromocytoma

In patients known to have, or suspected of having, a pheochromocytoma, metoprolol should always be given in combination with an alpha-blocker and only after the alpha-blocker has been initiated (see A9. Contraindication).

Anesthesia and surgery

Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery. The impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures. If a patient treated with metoprolol needs general anesthesia, the anesthetist should be informed that the patient is receiving a beta-blocker. An anesthetic agent with as little cardiodepressant effect as possible should be used (see A11. Interactions With Other Medicaments). If it is thought necessary to withdraw beta-blocker, including metoprolol, therapy before surgery, this should be done gradually and completed about 48 hours before the general anesthetic.

Abrupt withdrawal

Metoprolol treatment should not be stopped suddenly, especially in patients with ischemic heart disease. To prevent exacerbation of angina pectoris, the dosage should be gradually reduced over 1 to 3 weeks and, if necessary, replacement therapy should be initiated at the same time.

Anaphylactic reactions

Anaphylactic reactions precipitated by other agents may be particularly severe in patients taking beta-blockers, and may be resistant to normal doses of adrenaline. Whenever possible, beta-blockers, including metoprolol, should be avoided for patients who are at increased risk of anaphylaxis.

Prinzmetal's angina

Beta-blockers may increase the number and duration of angina attacks in patients with Prinzmetal's angina (variant angina pectoris). Relatively selective $beta_1$-receptor blockers, such as metoprolol, can be used in such patients, but only with the utmost care.

Thyrotoxicosis

Beta-blockers mask some of the clinical signs of thyrotoxicosis. Therefore, where metoprolol is administered to patients having, or suspected of developing, thyrotoxicosis, both thyroid and cardiac function should be monitored closely.

Oculomucocutaneous syndrome

The full oculomucocutaneous syndrome, has not been reported with metoprolol. However, part of this syndrome (dry eyes either alone or, occasionally, with skin rashes) has occurred. In most cases the symptoms cleared when metoprolol treatment was withdrawn. Patients should be observed carefully for potential ocular effects. If such effects occur, discontinuation of metoprolol should be considered.

Interactions

Calcium channel blocker of the verapamil (phenylalkylamine) type should not be given intravenously to patients receiving metoprolol because there is a risk of cardiac arrest in this situation (see A11. Interactions With Other Medicaments).

Special populations

Hepatic impairment

Metoprolol undergoes substantial hepatic first-pass metabolism, and is mainly eliminated by means of hepatic metabolism (see section 5.2 Pharmacokinetic properties). Therefore, hepatic impairment may increase the systemic bioavailability of metoprolol and reduce its total clearance, leading to increased plasma concentrations.

Geriatric patients

Elderly patients should be treated cautiously. An excessive decrease in blood pressure or pulse rate may reduce the blood supply to vital organs to inadequate levels.

Warnings

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, fructose intolerance or sucrase-isomaltase insufficiency should not take this medicinal product.

Interactions With Other Medicaments

Observed interactions resulting in concomitant use not being recommended

Calcium channel blockers (IV use)

Calcium channel blockers such as verapamil and diltiazem may potentiate the depressant effects of beta-blockers on blood pressure, heart rate, cardiac contractility and atrioventricular conduction. A calcium channel blocker of the verapamil (phenylalkylamine) type should not be given intravenously to patients receiving metoprolol because there is a risk of cardiac arrest in this situation (see A10. Warning and Precautions).

Interactions to be considered

Interactions resulting in effects on metoprolol

Other antihypertensive drugs

The effects of metoprolol and other antihypertensive drugs on blood pressure are usually additive. Patients receiving concurrent treatment with catecholamine depleting drugs, other beta-blockers (including those in form of eye drops, such as timolol), or monoamine oxidase (MAO) inhibitors, should be carefully monitored. In addition, possibly significant hypertension may theoretically occur up to 14 days following discontinuation of the concomitant administration with an irreversible MAO inhibitor.

Calcium channel blockers (oral use)

Concomitant administration of a beta-adrenergic antagonist with a calcium channel blocker may produce an additive reduction in myocardial contractility due to negative chronotropic and inotropic effects. Patients taking an oral calcium channel blocker of the verapamil type in combination with metoprolol should be closely monitored.

Anti-arrhythmic drugs

Beta-blockers may potentiate the negative inotropic effect of anti-arrhythmic agents and their effect on atrial-conduction time. Particularly, in patients with pre-existing sinus node dysfunction, concomitant administration of amiodarone may result in additive electro-physiologic effects including bradycardia, sinus arrest and atrioventricular block. Anti-arrhythmic agents such as quinidine, tocainide, procainamide, ajmaline, amiodarone, flecainide and disopyramide may potentiate the effects of metoprolol on heart rate and atrioventricular conduction.

Nitroglycerin

Nitroglycerin may enhance the hypotensive effect of metoprolol.

General anesthetics

Some inhalation anesthetics may enhance the cardiodepressant effect of beta-blockers (see A10. Warning and Precautions).

CYP2D6 inhibitors
Potent inhibitors of this enzyme may increase the plasma concentration of metoprolol. Strong inhibition of CYP2D6 would result in the change of phenotype into poor metabolizer (phenocopying, see section 5.2 Pharmacokinetic properties). Caution should therefore be exercised when co-administering potent CYP2D6 inhibitors with metoprolol. Known clinically significant potent inhibitors of CYP2D6 are antidepressants such as fluvoxamine, fluoxetine, paroxetine, sertraline, bupropion, clomipramine, desipramine, antipsychotics such as chlorpromazine, fluphenazine, haloperidol, thioridazine, antiarrhythmics such as quinidine or propafenone, antiretrovirals such as ritonavir, antihistamines such as diphenhydramine, antimalarials such as hydroxychloroquine or quinidine, antifungals such as terbinafine.
Hydralazine
Concomitant administration of hydralazine may inhibit presystemic metabolism of metoprolol leading to increased concentrations of metoprolol.
Digitalis glycosides
Concurrent use of digitalis glycosides may result in excessive bradycardia and/or increase in atrioventricular conduction time. Monitoring heart rate and PR interval is recommended.
Sympathomimetics
Concomitant administration of sympathomimetic drugs such as adrenaline, noradrenaline, isoprenaline, ephedrine, phenylephrine, phenylpropanolamine, and xanthine derivatives (including antitussives or nose and eye drops) with a beta-blocker may enhance the pressor response resulting in hypertension due to mutual inhibition of therapeutic effects. However, this is less likely with therapeutic doses of $beta_1$-selective drugs than with non-selective beta-blockers.
Non-steroidal anti-inflammatory drugs
Concomitant administration of non-steroidal anti-inflammatory drugs including COX-2 inhibitors with a beta-blocker may decrease the antihypertensive effect of metoprolol, possibly as a result of the inhibition of renal prostaglandin synthesis and sodium and fluid retention caused by non-steroidal anti-inflammatory drugs.
Hepatic enzyme inducers
Enzyme-inducing drugs may affect plasma concentrations of metoprolol. For example, the plasma concentration of metoprolol is lowered by rifampicin.
Interactions resulting in effects on other drugs
Anti-adrenergic agents
Antihypertensive effect of alpha-adrenergic blockers such as guanethidine, betanidine, reserpine, alpha-methyldopa or clonidine may be potentiated by beta-blockers. Beta-adrenergic blockers may also potentiate the postural hypotensive effect of the first dose of prazosin, probably by preventing reflex tachycardia. On the contrary, beta adrenergic blockers may also potentiate the hypertensive response to withdrawal of clonidine in patients receiving concomitant clonidine and beta-adrenergic blocker. 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.
Antidiabetic drugs and insulin
Beta-blockers may interfere with the usual hemodynamic response to hypoglycemia and produce a rise in blood pressure associated with severe bradycardia. In diabetic patients who use insulin, beta-blocker treatment may be associated with increased or prolonged hypoglycemia. Beta-blockers may also antagonise the hypoglycemic effects of sulfonylureas. The risk of either effect is less with a $beta_1$-selective drug such as metoprolol than with a non-selective beta-blocker. However, diabetic patients receiving metoprolol should be monitored to ensure that diabetic control is maintained (see A10. Warning and Precautions).
Lidocaine (xylocaine)
Metoprolol may reduce the clearance of lidocaine, leading to increased lidocaine effects.
Prazosin
The acute postural hypotension that can follow the first dose of prazosin may be increased in patients already taking a beta-blocker, including metoprolol.
Ergot alkaloid
Concomitant administration with beta-blockers may enhance the vasoconstrictive action of ergot alkaloids.
Dipyridamole
In general, administration of a beta- blocker should be withheld before dipyridamole testing, with careful monitoring of heart rate following the dipyridamole injection.
Alcohol
Metoprolol may modify the pharmacokinetic parameters of alcohol.

Pregnancy and Lactation
Women of child-bearing potential
Upon confirming the diagnosis of pregnancy, women should immediately inform the doctor.
Pregnancy
There is a limited amount of data on the use of metoprolol in pregnant women. Experience with metoprolol in the first trimester of pregnancy is limited, but no fetal malformations attributable to metoprolol have been reported. However, beta-blockers may reduce placental perfusion.
Limited animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. The risk to the fetus/mother is unknown.
Metoprolol should be given to pregnant women only if clearly needed.
In the case of treatment with metoprolol during pregnancy, the lowest possible dose should be used, and treatment discontinuation should be considered 2 to 3 days before delivery to avoid increased uterine contractility and effects of beta-blockade in the newborn baby (for example, bradycardia, hypoglycemia).
Breast-feeding
Small quantities of metoprolol are secreted into breast milk: with therapeutic doses, an infant consuming 1 L of breast milk daily would receive a dose of less than 1 mg of metoprolol. Nevertheless, breast-fed infants should be closely observed for signs of beta-blockade.

Side Effects

Dizziness, fatigue or visual impairment may occur during treatment with metoprolol and may adversely affect the patient's ability to drive or use machines.

Tabulated summary of adverse drug reactions from clinical trials
Adverse drug reactions from clinical trials are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III):
Very common ≥ 1/10
Common ≥ 1/100 and < 1/10
Uncommon ≥ 1/1000 and < 1/100
Rare ≥ 1/10,000 and < 1/1000
Very rare < 1/10,000
Blood and lymphatic system disorders
Very rare: Thrombocytopenia
Psychiatric disorders
Rare: Depression nightmares
Very rare: Personality disorder, hallucinations
Nervous system disorders
Common: Dizziness, headache
Rare: Depressed level of consciousness, somnolence, insomnia, paresthesia
Eye disorders
Very rare: Visual impairment (e.g. blurred vision), dry eyes, eye irritation
Ear and labyrinth disorders
Very rare: Tinnitus, in doses exceeding those recommended hearing disorders (e.g. hypoacusis or deafness)
Cardiac disorders
Common: Bradycardia
Rare: Cardiac failure, arrhythmias, palpitation
Very rare: Conduction disorders, chest pain
Vascular disorders
Common: Orthostatic hypotension (occasionally with syncope)
Rare: Edema, Raynaud's phenomenon
Very rare: Gangrene in patients with pre-existing severe peripheral circulatory disorders

Respiratory, thoracic and mediastinal disorders
Common: Exertional dyspnea
Rare: Bronchospasm (which may occur in patients without a history of obstructive lung disease)
Very rare: Rhinitis

Gastrointestinal disorders
Common: Nausea and vomiting, abdominal pain
Rare: Diarrhea or constipation
Very rare: Dry mouth, retroperitoneal fibrosis (relationship to metoprolol has not been definitely established)

Hepatobiliary disorders
Very rare: Hepatitis

Skin and subcutaneous tissue disorders
Rare: Rash (in the form of urticaria, psoriasiform and dystrophic skin lesions)
Very rare: Photosensitivity reaction, hyperhydrosis, alopecia, worsening of psoriasis

Musculoskeletal and connective tissue disorders
Rare: Muscle spasms
Very rare: Arthritis

Reproductive system and breast disorders
Very rare: Erectile dysfunction, libido disorder, Peyronie's disease (relationship to metoprolol has not been definitely established)

General disorders and administration site conditions
Common: Fatigue

Investigations
Very rare: Weight increase, liver function test abnormal

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)
The following adverse reactions have been derived from post-marketing experience with metoprolol via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Nervous system disorders
Confusional state

Investigations
Blood triglycerides increased, High Density Lipoprotein (HDL) decreased

Symptoms And Treatment of Overdose
Signs and symptoms
An overdosage of metoprolol may lead to severe hypotension, sinus bradycardia, atrioventricular block, myocardial infarction, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness (or even coma), convulsions, nausea, vomiting, and cyanosis and death.
Concomitant ingestion of alcohol, antihypertensives, quinidine, or barbiturates aggravates the signs and symptoms.
The first manifestations of overdose appear 20 minutes to 2 hours after ingestion of metoprolol.
The effects of massive overdose may persist for several days, despite declining plasma concentrations.
Management
Patients should be admitted to hospital and, generally, should be managed in an intensive care setting, with continuous monitoring of cardiac function, blood gases, and blood biochemistry. Emergency supportive measures such as artificial ventilation or cardiac pacing should be instituted if appropriate. Even apparently well patients who have taken a small overdose should be closely observed for signs of poisoning for at least 4 hours.
In the event of a potentially life-threatening oral overdose, use induction of vomiting or gastric lavage (if within 4 hours after ingestion of metoprolol) and/or activated charcoal to remove the drug from the gastrointestinal tract. Hemodialysis is unlikely to make a useful contribution to metoprolol elimination.
Other clinical manifestations of overdose should be managed symptomatically based on modern methods of intensive care. The beta-blocker withdrawal phenomenon (see A10. Warning and Precautions) may occur after overdose.

Storage Condition
Store in a cool dry place, not above 30°C.
Keep medicines out of reach of children
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Pack size
Pack of 20's, 50's and 100's
(2x10's, 5 x10's, 10 x10's 2x25's, 4x25's tablets per box)
not all pack size are marketed

Shelf Life
Please refer to outer package

Manufactured by
Salutas Pharma GmbH
Otto-von-Guericke-Allee 1
D-39179 Barleben

For
Hexal AG
Industriestraße 25
83607 Holzkirchen, Germany

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