METOLAR Tablets/ Injection (Metoprolol)

Composition

METOLAR-25
Each uncoated tablet contains..... 25 mg.

METOLAR-50
Each uncoated tablet contains..... 50 mg.

METOLAR-100
Each uncoated tablet contains ..... 100 mg.

METOLAR Injection
Each ml contains Metoprolol tartrate USP 1 mg, Sodium Chloride IP 9 mg and Water for injection q.s. to 1 ml.

Dosage Forms

Tablet and Injection

Pharmacology

Pharmacodynamics

Mechanism of Action
Metoprolol is a $beta_1$-selective (cardioselective) adrenergic receptor blocker. This preferential effect is not absolute, however, and at higher plasma concentrations, Metoprolol also inhibits $beta_2$-adrenoreceptors, chiefly located in the bronchial and vascular musculature.

Clinical pharmacology studies have demonstrated the beta-blocking activity of metoprolol, as shown by (1) reduction in heart rate and cardiac output at rest and upon exercise, (2) reduction of systolic blood pressure upon exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

Hypertension
The mechanism of the antihypertensive effects of beta-blocking agents has not been fully elucidated. However, several possible mechanisms have been proposed: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output; (2) a central effect leading to reduced sympathetic outflow to the periphery; and (3) suppression of renin activity.

Angina Pectoris

By blocking catecholamine-induced increases in heart rate, in velocity and extent of myocardial contraction, and in blood pressure, metoprolol reduces the oxygen requirements of the heart at any given level of effort, thus making it useful in the long-term management of angina pectoris.

Myocardial Infarction
The precise mechanism of action of metoprolol in patients with suspected or definite myocardial infarction is not known.

Beta-Blockade
Relative $beta_1$-selectivity has been confirmed by the following: (1) In healthy subjects, metoprolol is unable to reverse the $beta_2$-mediated vasodilating effects of epinephrine. This contrasts with the effect of nonselective ($beta_1$ plus $beta_2$) beta-blockers, which completely reverse the vasodilating effects of epinephrine. (2) In asthmatic patients, metoprolol reduces forced expiratory volume 1 (FEV_1) and forced vital capacity (FVC) significantly less than a nonselective beta-blocker, propranolol, at equivalent $beta_1$-receptor blocking doses.

Metoprolol has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at doses much greater than required for beta-blockade. Animal and human experiments indicate that metoprolol slows the sinus rate and decreases atrioventricular (AV) nodal conduction.

Significant beta-blocking effect (as measured by reduction of exercise heart rate) occurs within 1 hour after oral administration, and its duration is dose-related. For example, a 50% reduction of the maximum effect after single oral doses of 20, 50, and 100 mg occurred at 3.3, 5.0, and 6.4 hours, respectively, in normal subjects. After repeated oral dosages of 100 mg twice daily, a significant reduction in exercise systolic blood pressure was evident at 12 hours. When the drug was infused over a 10-minute period, in normal volunteers, maximum beta-blockade was achieved at approximately 20 minutes. Equivalent maximal beta-blocking effect is achieved with oral and doses in the ratio of approximately 2.5:1.

There is a linear relationship between the log of plasma levels and reduction of exercise heart rate. However, antihypertensive activity does not appear to be related to plasma levels. Because of variable plasma levels attained with a given dose and lack of a consistent relationship of antihypertensive activity to dose, selection of proper dosage requires individual titration.

In several studies of patients with acute myocardial infarction, followed by oral administration of metoprolol caused a reduction in heart rate, systolic blood pressure, and cardiac output. Stroke volume, diastolic blood pressure, and pulmonary artery end diastolic pressure remained unchanged.

In patients with angina pectoris, plasma concentration measured at one hour is linearly related to the oral dose within the range of 50-400 mg. Exercise heart rate and systolic blood pressure are reduced in relation to the logarithm of the oral dose of metoprolol. The increase in exercise capacity and the reduction in left ventricular ischemia are also significantly related to the logarithm of the oral dose.

Pharmacokinetics

Absorption
The estimated oral bioavailability of immediate release metoprolol is about 50% because of pre-systemic metabolism which is saturable leading to non-proportionate increase in the exposure with increased dose.

Distribution
Metoprolol is extensively distributed with a reported volume of distribution of 3.2 to 5.6 L/kg. About 10% of metoprolol in plasma is bound to serum albumin. Metoprolol is known to cross the placenta and is found in breast milk. Metoprolol is also known to cross the blood brain barrier following oral administration and cerebral spinal fluid (CSF) concentrations close to that observed in plasma have been reported. Metoprolol is not a significant P-glycoprotein substrate.

Metabolism
Metoprolol is primarily metabolized by CYP2D6. Metoprolol is a racemic mixture of R- and S-enantiomers , and when administered orally, it exhibits stereoselective metabolism that is dependent on oxidation phenotype. CYP2D6 is absent (poor metabolizers) in about 8% of Caucasians and about 2% of most other populations. Poor CYP2D6 metabolizers exhibit several fold higher plasma concentrations of metoprolol than extensive metabolizers with normal CYP2D6 activity thereby decreasing metoprolol's cardioselectivity.

Elimination
Elimination of metoprolol is mainly by biotransformation in the liver. The mean elimination half-life of metoprolol is 3 to 4 hours; in poor CYP2D6 metabolizers the half-life may be 7 to 9 hours. Approximately 95% of the dose can be recovered in urine. In most subjects (extensive metabolizers), less than 5% of an oral dose and less than 10% of an IV dose are excreted as unchanged drug in the urine. In poor metabolizers, up to 30% or 40% of oral or IV doses, respectively, may be excreted unchanged; the rest is excreted by the kidneys as metabolites that appear to have no beta-blocking activity. The renal clearance of the stereoisomers does not exhibit stereo-selectivity in renal excretion.

Special Populations
Geriatric Patients: The geriatric population may show slightly higher plasma concentrations of metoprolol as a combined result of a decreased metabolism of the drug in elderly population and a decreased hepatic blood flow. However, this increase is not clinically significant or therapeutically relevant.

Renal Impairment: The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. Consequently, no reduction in dosage is usually needed in patients with chronic renal failure.

Hepatic Impairment: Since the drug is primarily eliminated by hepatic metabolism, hepatic impairment may impact the pharmacokinetics of metoprolol. The elimination half-life of metoprolol is considerably prolonged, depending on severity (up to 7.2 h).

Indications

- Hypertension
- Angina pectoris
- Cardiac arrhythmias, especially supraventricular tachyarrhythmias
- Definite or suspected acute myocardial infarction
- Migraine prophylaxis
- Adjunctive management of thyrotoxicosis

Dosage and Administration

- **Hypertension**

The dosage of metoprolol tablets should be individualized. **METOLAR** tablets should be taken with or immediately following meals.

The usual initial dosage of metoprolol tablets is 100 mg daily in single or divided doses, whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after 1 week of therapy. The effective dosage range of metoprolol tablets is 100-450 mg per day. Dosages above 450 mg per day have not been studied. While once daily dosing is effective and can maintain a reduction in blood pressure throughout the day, lower doses (especially 100 mg) may not maintain a full effect at the end of the 24-hour period, and larger or more frequent daily doses may be required. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. $Beta_1$-selectivity diminishes as the dose of metoprolol is increased.

- **Angina Pectoris**

The dosage of metoprolol tablets should be individualized. **METOLAR** tablets should be taken with or immediately following meals.

The usual initial dosage of metoprolol tablets is 100 mg daily, given in two divided doses. The dosage may be gradually increased at weekly intervals until optimum clinical response has been obtained or there is pronounced slowing of the heart rate. The effective dosage range of metoprolol tablets is 100-400 mg per day. Dosages above 400 mg per day have not been studied. If treatment is to be discontinued, the dosage should be reduced gradually over a period of 1-2 weeks.

- **Cardiac Arrhythmias**
- *Metolar Tablets:* A dosage of 50 mg two or three times daily is usually sufficient. If necessary the dose can be increased up to 300 mg per day administered in divided doses.
- *Metolar Injection:* Initially up to 5 mg should be injected ly at a rate of 1-2 mg/minute. The injection can be repeated at 5-minute intervals until satisfactory response has been obtained. A total dose of 10-15 mg generally proves sufficient. Because of the risk of a pronounced drop of blood pressure, the I.V. administration of carvedilol to patients with a systolic blood pressure below 100 mmHg should only be given with special care.

- **During Anesthesia**

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

- **Myocardial Infarction**
- *Early Treatment:* During the early phase of definite or suspected acute myocardial infarction,

treatment with **METOLAR** should be initiated as soon as possible after the patient's arrival in the hospital. Such treatment should be initiated in a coronary care unit or similar unit immediately after the patient's hemodynamic condition has stabilized.

Treatment in this early phase should begin with the intravenous administration of three bolus injections of 5 mg of metoprolol each; the injections should be given at approximately 2-minute intervals. During the administration of **METOLAR**, blood pressure, heart rate and electrocardiogram should be carefully monitored.

In patients who tolerate the full intravenous dose (15 mg), **METOLAR** tablets 50 mg every 6 hours, should be initiated 15 minutes after the last dose and continued for 48 hours. Thereafter, patients should receive a maintenance dose of 100 mg twice daily. Patients who appear not to tolerate the full dose should be started on metoprolol either 25 mg or 50 mg every 6 hours (depending on the degree of intolerance) 15 minutes after the last dose or as soon as their clinical condition allows. In patients with severe intolerance, treatment with metoprolol should be discontinued.

- *Late Treatment:* Patients with contraindications to treatment during the early phase of suspected or definite myocardial infarction, patients who appear not to tolerate the full early treatment, and patients in whom the physician wishes to delay therapy for any other reason should be started on metoprolol tartrate tablets, 100 mg twice daily, as soon as their clinical condition allows. Therapy should be continued for at least 3 months. Although the efficacy of metoprolol beyond 3 months has not been conclusively established, data from studies with other beta-blockers suggest that treatment should be continued for 1-3 years.

- **Migraine Prophylaxis**

Dose is 100-200 mg daily given in divided doses (morning and evening).

- **Hyperthyroidism**

Usual dose is 50 mg four times daily. The dosage should be progressively reduced as euthyroid state is slowly achieved.

Contraindications

Hypotension, sinus bradycardia, second or third degree heart block, cardiogenic shock, severe peripheral arterial circulatory disorders, sick-sinus syndrome, untreated pheochromocytoma, overt cardiac failure, bradycardia (< 45 beats/minute), continuous or intermittent inotropic therapy acting through beta-receptor agonism, metabolic acidosis, decompensated cardiac failure (pulmonary edema, hypoperfusion or hypotension), uncontrolled heart failure, severe asthma or history of severe bronchospasm and hypersensitivity to metoprolol, other beta-blockers (cross sensitivity between beta-blockers can occur) and related derivatives, or to any of the excipients. Metoprolol is also contraindicated in acute myocardial infarction patients with a heart rate < 45 beats/minute; second- and third-degree heart block; significant first-degree heart block (P-R interval > 0.24 sec); systolic blood pressure < 100 mm Hg; or moderate-to-severe cardiac failure.

Warnings and Precautions

Drug Interactions

Catecholamine Depleting Drugs (eg. Reserpine)
These may have an additive effect when given with beta-blocking agents or monoamine oxidase (MAO) inhibitors. Patients treated with metoprolol plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope or postural hypotension. In addition, possibly significant hypertension may theoretically occur up to 14 days following discontinuation of the concomitant administration with an irreversible MAO inhibitor.

CYP2D6 Inhibitors
Potent inhibitors of the CYP2D6 enzyme may increase the plasma concentration of metoprolol which would mimic the pharmacokinetics of CYP2D6 poor metabolizers. Increase in plasma concentrations of metoprolol would decrease the cardioselectivity of metoprolol. Known clinically significant potent inhibitors of CYP2D6 are antidepressants such as fluvoxamine, fluoxetine, paroxetine, sertraline, bupropion, clomipramine, and desipramine; anti-psychotics such as chlorpromazine, fluphenazine, haloperidol, and 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.

Cytochrome P450 Isoenzyme CYP2D6 Enzyme Inducing Agents (e.g. rifampicin): may reduce plasma concentrations of metoprolol.

Cytochrome P450 Isoenzyme CYP2D6 Enzyme Inhibitors (e.g. cimetidine, alcohol and hydralazine): may increase plasma concentrations.

Clonidine
Beta-adrenergic blockers may also potentiate the hypertensive response to withdrawal of clonidine in patients receiving concomitant cloidie 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. Rebound hypertension that can follow withdrawal of clonidine may be increased in patients receiving concurrent beta-blocker treatment.

Digitalis Glycosides
Concurrent use of digitalis glycosides may result in excessive bradycardia and/or increase in atrioventricular conduction time.

Antihypertensive Agents
The effects of metoprolol and other drugs with an antihypertensive effect on blood pressure are usually additive. Care should be taken when combining with other antihypertensive drugs or drugs that might reduce blood pressure such as tricyclic antidepressants, barbiturates and phenothiazines. However, combinations of antihypertensive drugs may often be used with benefit to improve control of hypertension.

Alpha-adrenergic Agents
Antihypertensive effect of alpha-adrenergic blockers such as guanethidine, betanidine, reserpine, alpha-methyldopa or clonidine may be potentiated by beta-blockers including metoprolol.

Antiarrhythmic Agents

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

Sympathomimetic Ganglion Blocking Agents
Patients receiving concomitant treatment with sympathetic ganglion blocking agents, other beta-blockers (i.e. eye drops), or Mono Amine Oxidase (MAO) inhibitors should be kept under close surveillance.

Calcium Channel Blockers
Increased negative inotropic and chronotropic effects may occur when metoprolol is given together with calcium antagonists of the verapamil and diltiazem type. In patients treated with beta-blockers intravenous administration of calcium antagonists of the verapamil-type should not be given. As with other beta-blockers, concomitant therapy with dihydropyridines e.g. nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.

Lidocaine
Metoprolol may impair the elimination of lidocaine (lignocaine).

Indomethacin and Other Prostaglandin Synthetase Inhibiting Drugs
Concomitant treatment with indomethacin and other prostaglandin synthetase inhibiting drugs may reduce the antihypertensive effect of beta-blockers.

Adrenaline
The administration of adrenaline (epinephrine) to patients undergoing beta-blockade can result in an increase in blood pressure and bradycardia although this is less likely to occur with $beta_1$-selective drugs.

Prazosin
Beta-adrenergic blockers may also potentiate the postural hypotensive effect of the first dose of prazosin, probably by preventing reflex tachycardia.

Nitroglycerin
Nitroglycerin may enhance the hypotensive effect of metoprolol.

Antidiabetic Agents
In diabetic patients who use insulin, beta-blocker treatment may be associated with increased or prolonged hypoglycemia. Beta-blockers may also antagonize 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 diabetes control is maintained.

Non-Steroidal Anti-Inflammatory Drugs
Concurrent treatment with non-steroidal anti-inflammatory drugs such as indomethacin may decrease the antihypertensive effect of metoprolol.

General Anesthetics
Some inhalation anesthetics may enhance the cardiodepressant effect of beta-blockers.

Hydralazine
Concomitant administration of hydralazine may inhibit presystemic metabolism of metoprolol leading to increased concentrations of metoprolol.

Ergot Alkaloid

Concomitant administration wit 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.

Risk of Anaphylactic Reaction
While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Beta$_2$-agonists
Metoprolol will antagonize the beta1-effects of sympathomimetic agents but should have little influence on the bronchodilator effects of beta$_2$-agonists at normal therapeutic doses.

Heart Failure

Beta-blockers, like metoprolol, can cause depression of myocardial contractility and may precipitate heart failure and cardiogenic shock. If signs or symptoms of heart failure develop, treat the patient according to recommended guidelines. It may be necessary to lower the dose of metoprolol or to discontinue it.

Ischemic Heart Disease

Do not abruptly discontinue metoprolol therapy in patients with coronary artery disease. Severe exacerbation of angina, myocardial infarction and ventricular arrhythmias have been reported in patients with coronary artery disease following the abrupt discontinuation of therapy with beta-blockers. When discontinuing chronically administered metoprolol, particularly in patients with coronary artery disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, metoprolol administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue metoprolol therapy abruptly even in patients treated only for hypertension.

Bradycardia

Bradycardia, including sinus pause, heart block, and cardiac arrest have occurred with the use of metoprolol. Patients with first-degree atrioventricular block, sinus node dysfunction, or conduction disorders may be at increased risk. Monitor heart rate and rhythm in patients receiving metoprolol. If severe bradycardia develops, reduce or stop metoprolol.

Exacerbation of Bronchospastic Disease

Patients with bronchospastic disease, should, in general, not receive beta-blockers, including metoprolol. Because of its relative beta$_1$- selectivity, however, metoprolol may be used in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Because beta$_1$- selectivity is not absolute use the lowest possible dose of metoprolol and consider administering metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval.

Bronchodilators, including beta$_2$-agonists, should be readily available or administered concomitantly.

Use During Major Surgery

Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery; however, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Diabetes and Hypoglycemia

Beta-blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Pheochromocytoma

If metoprolol is used in the setting of pheochromocytoma, it should be given in combination with an alpha blocker, and only after the alpha blocker has been initiated. Administration of beta-blockers alone in the setting of pheochromocytoma has been associated with a paradoxical increase in blood pressure due to the attenuation of beta-mediated vasodilatation in skeletal muscle.

Thyrotoxicosis

Metoprolol may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Avoid abrupt withdrawal of beta-blockade, which might precipitate a thyroid storm.

Renal Impairment

No dose adjustment of metoprolol is required in patients with renal impairment.

Hepatic Impairment

Metoprolol blood levels are likely to increase substantially in patients with hepatic impairment. Therefore, metoprolol should be initiated at low doses with cautious gradual dose titration according to clinical response.

Pregnancy

Category C
Upon confirming the diagnosis of pregnancy, women should immediately inform the doctor. Metoprolol has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 11 times the maximum daily human dose of 450 mg, when based on surface area. Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. These limited animal studies do not indicate direct or indirect harmful effects with respect to teratogenicity. There are no adequate and well-controlled studies in pregnant women. The amount of data on the use of metoprolol inn pregnant women is limited. The risk to the fetus/mother is unknown. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lactation

Metoprolol is excreted in breast milk in very small quantities. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug.

Paediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Clinical trials of metoprolol in hypertension did not include sufficient numbers of elderly patients to determine whether patients over 65 years of age differ from younger subjects in their response to metoprolol. Other reported clinical experience in elderly hypertensive patients has not identified any difference in response from younger patients.

In worldwide clinical trials of metoprolol in myocardial infarction, where approximately 478 patients were over 65 years of age (0 over 75 years of age), no age-related differences in safety and effectiveness were found. Other reported clinical experience in myocardial infarction has not identified differences in response between the elderly and younger patients. However, greater sensitivity of some elderly individuals taking metoprolol cannot be categorically ruled out. Therefore, in general, it is recommended that dosing proceed with caution in this population.

Undesirable Effects

Hypertension and Angina

Most adverse effects have been mild and transient.

Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; and hypotension have been reported in about 1 of 100 patients. Gangrene in patients with pre-existing severe peripheral circulatory disorders has also been reported very rarely.

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients. Rhinitis has also been reported.

Gastrointestinal: Diarrhoea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients. Vomiting was a common occurrence. Postmarketing experience reveals very rare reports of hepatitis, jaundice and non-specific hepatic dysfunction. Isolated cases of transaminase, alkaline phosphatase, and lactic

dehydrogenase elevations have also been reported.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Very rarely, photosensitivity and worsening of psoriasis has been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. There have been very rare reports of weight gain, arthritis, and retroperitoneal fibrosis (relationship to metoprolol has not been definitely established).

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with metoprolol.

Myocardial Infarction

Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of metoprolol and placebo, the following adverse reactions were reported:

	Metoprolol	**Placebo**
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.

Potential Adverse Reactions

A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

Postmarketing Experience

The following adverse reactions have been reported during post approval use of metoprolol: confusional state, an increase in blood triglycerides and a decrease in high density Lipoprotein (HDL). Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency.

Overdosage

Acute Toxicity

Several cases of overdosage have been reported, some leading to death.
Oral LD_{50}'s (mg/kg): mice, 1158-2460; rats, 3090-4670.

Signs and Symptoms

Potential signs and symptoms associated with overdosage with metoprolol are bradycardia, hypotension, bronchospasm, and cardiac failure.

Treatment

There is no specific antidote. In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly.

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

Elimination of the Drug: Gastric lavage should be performed.

Other clinical manifestations of overdose should be managed symptomatically based on modern methods of intensive care.

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

Bronchospasm: A $beta_2$-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.

Packaging Information

METOLAR-25: Blister pack of 10 tablets
METOLAR-50: Blister pack of 10 tablets
METOLAR-100: Blister pack of 10 tablets
METOLAR INJECTION: 5 ml in boxes of 5 ampoules

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