PRODUCT MONOGRAPH

PrNTP-METOPROLOL

(METOPROLOL tartrate tablets USP)

50 mg, and 100 mg TABLETS

β-Adrenoceptor Blocking Agent

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PRODUCT MONOGRAPH

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(METOPROLOL tartrate tablets USP)
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THERAPEUTIC CLASSIFICATION

β-adrenoceptor blocking agent

ACTIONS AND CLINICAL PHARMACOLOGY

NTP-METOPROLOL (metoprolol tartrate) is a β-adrenoceptor blocking agent. *In vitro* and *in vivo* animal studies have shown that it has a preferential effect on β_1-adrenoreceptors, chiefly located in cardiac muscle. This preferential effect is not absolute, however, and at higher doses, NTP-METOPROLOL also inhibits β_2-adrenoreceptors, chiefly located in the bronchial and vascular musculature. It is used in the treatment of hypertension and angina pectoris and to reduce mortality in patients with myocardial infarction.

The mechanism of the antihypertensive effect has not been established. Among the factors that may be involved are:

a) competitive ability to antagonize catecholamine-induced tachycardia at the β-receptor sites in the heart, thus decreasing heart rate, cardiac contractility and cardiac output;
b) inhibition of renin release by the kidneys;
c) inhibition of the vasomotor centres.

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. However, in patients with heart failure, beta-adrenoceptor blockade may increase oxygen requirements by increasing left ventricular fibre length and end-diastolic pressure.

The mechanisms involved in reducing mortality in patients with acute myocardial infarction are not fully understood.

Pharmacokinetics
In man, absorption of metoprolol is rapid and complete. Plasma levels following oral administration, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism.

Intersubject plasma levels achieved are highly variable after oral administration, although they show

good reproducibility within each individual. Peak plasma concentrations are attained after approximately 1.5-2 hours with conventional metoprolol formulations, and after approximately 4-5 hours with sustained-release formulations. Upon repeated oral administration, the percentage of the dose systemically available is higher than after a single dose and also increases dose-dependently. Ingestion together with food may raise the systemic availability of an oral dose by approximately 30-40%. Only a small fraction of the drug (about 12%) is bound to human serum albumin. Elimination is mainly by biotransformation in the liver, and the plasma half-life averages 3.5 hours (extremes: 1 and 9 hours). The total clearance rate is approximately 1 L/min and the protein binding rate is approximately 5-10%. Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no clinical significance.

The systemic availability and half-life of metoprol inpatients with renal failure do not differ to a clinically significant degree from those in normal subjects. The excretion of metabolites, however, is reduced. Significant accumulation of metabolites was observed in patients with a GFR of approximately 5 mL/min, but this accumulation does not influence the β-blocking effects of metoprolol. Consequently, no reduction in dosage is usually needed in patients with chronic renal failure.

Elderly subjects show no significant changes in the plasma concentrations of metoprolol as compared with young persons. However, plasma concentrations of the major pharmacologically active metabolites were higher in the elderly.

Liver cirrhosis may increase the bioavailability of metoprolol and reduce its total clearance.

Pharmacodynamics

Significant β-blocking effect (as measured by reduction of exercise heart rate) occurs within one hour after oral administration, and its duration is dose-related. For example, a 50% reduction of the maximum registered 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.

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.

Studies in hypertiensive and angina patients have shown plasma levels of 28-46 ng/mL, 12 hours after regular tablets.

Two separate single dose bioavailability studies comparing NTP-METOPROLOL film-coated tablets with Lopresor® film-coated tablets and also NTP-METOPROLOL uncoated tablets with Betaloc® uncoated tablets were carried out in 12 normal volunteers. The dose administered was one tablet of 100 mg of metoprolol tartrate. The pharmacokinetic data calculated for each of the metoprolol tartrate formulations are tabulated below:

TABLE OF COMPARATIVE BIOAVAILABILITY DATA
NTP-METOPROLOL (**film-coated tablets**)
(1 x 100 mg)

Parameters	**NTP-METOPROLOL**	**Lopresor®**
AUC_{0-16} (ng•h/mL)	496	500
C_{max} (ng/mL)	103	100
T_{max}(h)	1.7	1.8
$T_{1/2}$(h)	2.18	2.51

TABLE OF COMPARATIVE BIOAVAILABILITY DATA
NTP-METOPROLOL (**uncoated tablets**)
(1 x 100 mg)

Parameters	**NTP-METOPROLOL**	**Betaloc®**
AUC_{0-24} (ng•h/mL)	843	844
C_{max} (ng/mL)	119	116
T_{max}(h)	2.1	1.8
$T_{1/2}$(h)	4.46	4.19

INDICATIONS AND CLINICAL USE

Hypertension
NTP-METOPROLOL (metoprolol tartrate) is indicated in patients with mild or moderate hypertension. It may be used alone or in combination with other antihypertensive agents. See DOSAGE AND ADMINISTRATION.

The combination of metoprolol with a diuretic or peripheral vasodilator has been found to be compatible and generally more effective than metoprolol alone. Limited experience with other antihypertensive agents has not shown evidence of incompatibility with metoprolol.

NTP-METOPROLOL is not recommended for the emergency treatment of hypertensive crises.

Angina Pectoris
NTP-METOPROLOL is indicated for the long-term treatment of angina pectoris due to ischemic heart disease.

Myocardial Infarction
NTP-METOPROLOL is indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality.

In patients with proven myocardial infarction, treatment can begin within 3 to 10 days of the acute event (see DOSAGE AND ADMINISTRATION). Data are not available as to whether benefit would ensue if the treatment is initiated later.

Clinical trials have shown that patients in whom the myocardial infarction was unconfirmed, received no benefit from early metoprolol therapy.

CONTRAINDICATIONS

NTP-METOPROLOL (metoprolol tartrate) should not be used in the presence of:
1. known hypersensitivity to metoprolol and related derivatives;
2. sinus bradycardia;
3. sick sinus syndrome;
4. second- and third-degree A-V block;
5. right ventricular failure secondary to pulmonary hypertension;
6. overt heart failure;
7. cardiogenic shock;
8. severe peripheral arterial circulatory disorders;
9. anesthesia with agents that produce myocardial depression, e.g. ether.

Myocardial Infarction Patients - Additional Contraindications
NTP-METOPROLOL is contraindicated in patients with a heart rate 45 beats/min; significant heart block greater than first degree (PR interval 20.24 sec); systolic blood pressure100 mmHg; or moderate to severe cardiac failure (see WARNINGS).

WARNINGS

Cardiac Failure
Special caution should be exercised when administering metoprolol to patients with a history of heart failure. Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with β-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. The positive inotropic action of digitalis may be reduced by the negative inotropic effect of metoprolol tartrate when the two drugs are used concomitantly. The effects of β-blockers and digitalis are additive in depressing A-V conduction. This also applies to combinations with calcium antagonists of the verapamil type or some antiarrhythmics (see Drug Interactions).

In patients without a history of cardiac failure, continued depression of the myocardium over a

period of time can, in some cases, lead to cardiac failure and/or hypotension (systolic blood pressure ≤90 mmHg). Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, metoprolol therapy should be reduced or withdrawn.

Abrupt Cessation of Therapy
Patients with angina should be warned against abrupt discontinuation of NTP-METOPROLOL. There have been reports of severe exacerbation of angina, and of myocardial infarction or ventricular arrhythmias occurring in patients with angina pectoris, following abrupt discontinuation of β-blocker therapy. The last two complications may occur with or without preceding exacerbation of angina pectoris. Therefore, when discontinuation of metoprolol is planned in patients with angina pectoris or previous myocardial infarction, the dosage should be gradually reduced over a period of at least 10 to 14 days, in diminishing doses, to 25 mg once a day for the last 6 days. During this period the patient should be carefully observed. In situations of greater urgency, metoprolol tartrate therapy should be discontinued stepwise and under conditions of closer observation. If angina markedly worsens or acute coronary insufficiency develops, it is recommended that treatment with NTP-METOPROLOL be reinstituted promptly, at least temporarily.

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 NTP-METOPROLOL therapy abruptly even in patients treated only for hypertension.

Oculomucocutaneous Syndrome
Various skin rashes and conjunctival xerosis have been reported with β-blockers, including metoprolol tartrate. Oculomucocutaneous syndrome, a severe syndrome whose signs include conjunctivitis sicca and psoriasiform rashes, otitis, and sclerosing serositis has occurred with the chronic use of one β-adrenergic-blocking agent (practolol). This syndrome has not been observed with metoprolol or any other such agent. However, physicians should be alert to the possibility of such reactions and should discontinue treatment in the event that they occur.

Severe Sinus Bradycardia
Severe sinus bradycardia may occur with the use of metoprolol from unopposed vagal activity remaining after blockade of β_1-adrenergic receptors. Very rarely a pre-existing A-V conduction disorder of moderate degree may become aggravated, possibly leading to A-V block. In such cases, dosage should be reduced. Atropine, isoproterenol or dobutamine should be considered in patients with acute myocardial infarction.

Thyrotoxicosis
Although metoprolol has successfully been used for the symptomatic (adjuvant) therapy of thyrotoxicosis, possible deleterious effects from long-term use of metoprolol have not been adequately appraised. β-blockade may mask the clinical signs of continuing hyperthyroidism or complications, and give a false impression of improvement. Therefore, abrupt withdrawal of metoprolol tartrate may be followed by an exacerbation of the symptoms of hyperthyroidism,

including thyroid storm.

Cardiac Failure
Depression of the myocardium with NTP-METOPROLOL may lead to cardiac failure (see general WARNINGS above). Special caution should be exercised when administering NTP-METOPROLOL to patients with a history of cardiac failure or those with a minimal cardiac reserve. Should failure occur, treatment should be as described in WARNINGS.Severe Sinus

Bradycardia
See General Warnings for severe sinus bradycardia.

A-V Conduction
Metoprolol slows A-V conduction and may produce significant first- (PR interval ≥ 0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, NTP-METOPROLOL should be discontinued and atropine (0.25 - 0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension
If hypotension (systolic blood pressure ≤90 mmHg) occurs, NTP-METOPROLOL should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or A-V block, treatment should be directed at reversing these (see above).

PRECAUTIONS

Bronchospastic Diseases

Patients with bronchospastic diseases should, in general, not receive β-blockers.
Because of its relative β_1-selectivity, however, NTP-METOPROLOL (metoprolol tartrate) may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since β_1-selectivity is not absolute, a β_2-stimulating agent should preferably be administered concomitantly, and the lowest possible dose of NTP-METOPROLOL should be used. In these circumstances it would be prudent initially to administer NTP-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 (see DOSAGE AND ADMINISTRATION).

Because it is unknown to what extent β_2-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should not be used prophylactically in patients with proven or

suspected acute myocardial infarction. If bronchospasm not related to congestive heart failure occurs, NTP-METOPROLOL should be discontinued. A theophylline derivative or a β_2-agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and β_2-agonists may produce serious cardiac arrhythmias.

Diabetes and Hypoglycemia
NTP-METOPROLOL should be administered with caution to diabetic patients subject to spontaneous hypoglycemia (most of these patients are insulin treated). B-adrenergic blockers may mask the premonitory signs and symptoms of acute hypoglycemia, but this is mainly attributed to unselective β-adrenergic blockers.

Liver Function
NTP-METOPROLOL should be used with caution in patients with impaired liver function. Liver function tests should be performed at regular intervals during long-term treatment. Dose adjustment is normally not needed in patients suffering from liver cirrhosis because metoprolol has low protein binding (5-10%). When there are signs of serious impairment of liver function (e.g., shunt-operated patients) a dose reduction should be considered.

Allergen Immunotherapy
There may be increased difficulty in treating an allergic type reaction in patients on β-blockers. In these patients, the reaction may be more severe due to pharmacologic effects of the β-blockers and problems with fluid changes. Epinephrine should be administered with caution since it may not have its usual effects in the treatment of anaphylaxis. On the one hand, larger doses of epinephrine may be needed to overcome the bronchospasm, while on the other these doses can be associated with excessive alpha-adrenergic stimulation with consequent hypertension, reflex bradycardia and heart-block, and possible potentiation of bronchospasm. Alternatives to the use of large doses of epinephrine include vigorous supportive care such as fluids and the use of β-agonists including parenteral salbutamol or isoproterenol to overcome bronchospasm and norepinephrine to overcome hypotension.

Patients Undergoing Surgery
It is not advisable to withdraw β-adrenoceptor blocking drugs prior to surgery in the majority of patients especially in those with risk of overt or silent coronary heart disease. However, care should be taken to avoid using anesthetic agents that may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1-2 mg i.v.).

Some patients receiving β-blocking drugs have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported.

Since metoprolol is a competitive inhibitor of β-adrenoceptor agonists, its effects may be reversed, if necessary, by sufficient doses of such agonists as isoproterenol or dobutamine.

Peripheral Artery Disorders
Metoprolol may aggravate the symptoms of peripheral arterial circulatory disorders, mainly due to

its blood pressure lowering effect.

Phaeochromocytoma
Where a β-blocker is prescribed for a patient known to be suffering from a phaeochromocytoma, an α-blocker should be given concomitantly.

Reaction Time
β-blockers may adversely affect the patient's reaction time. Patients should be advised to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with NTP-METOPROLOL has been determined.

Usage in Pregnancy
Metoprolol crosses the placental barrier. Since metoprolol has not been studied in human pregnancy, the drug should not be given to pregnant women. The use of any drug in patients of child-bearing potential requires that the anticipated benefit be weighed against the possible hazards.

Nursing Mothers
Metoprolol is excreted in breast milk in very small quantities. Caution should be exercised when NTP-METOPROLOL is administered to a nursing woman.

Usage in Children
The safety and efficacy of NTP-METOPROLOL in children has not been established.

Usage in the Elderly
Caution is indicated when using NTP-METOPROLOL in elderly patients. An excessively pronounced decrease in blood pressure or pulse rate may cause the blood supply to vital organs to fall to inadequate levels.

Drug Interactions

Antihypertensives
NTP-METOPROLOL dosage should be adjusted according to the individual requirements of the patient especially when used concomitantly with other antihypertensive agents (see DOSAGE AND ADMINISTRATION).

MAO Inhibitors and Adrenergic Neuron Blockers
Patients receiving MAO inhibitors or catecholamine-depleting drugs (such as reserpine or guanethidine) should be closely monitored because the added β-adrenergic-blocking action of NTP-METOPROLOL may produce an excessive reduction of sympathetic activity. NTP-METOPROLOL should not be combined with other β-blockers.

Calcium Entry Blockers
As with other β-blockers, NTP-METOPROLOL should not be given to patients receiving calcium antagonists of the verapamil type. However, in exceptional cases, when in the opinion of the

physician concomitant use is considered essential, such use should be instituted gradually in a hospital setting under careful supervision. Negative inotropic, dromotropic, and chronotropic effects may occur when NTP-METOPROLOL is given together with calcium antagonists. Verapamil and diltiazem may reduce the clearance of metoprolol.

Antiarrhythmic Agents
B-blockers may enhance the negative inotropic and negative dromotropic effect of anti-arrhythmic agents such as quinidine and amiodarone.

Clonidine Withdrawal Syndrome
The hypertensive crisis which may follow the withdrawal of clonidine may be accentuated in the presence of β-blockade. It has been proposed that withdrawal of the β-blocker several days before the clonidine may reduce the danger of rebound effects.

Oral Anti-Diabetics
The dosage of oral anti-diabetics may have to be readjusted in patients receiving β-blockers (see PRECAUTIONS).

Indomethacin
Concurrent treatment with indomethacin may decrease the antihypertensive effect of β-blockers.

Hepatic Enzyme-Inducers and Enzyme-Inhibitors
Hepatic enzyme-inducing and enzyme-inhibiting substances may exert an influence on the plasma level of metoprolol. The plasma concentration of metoprolol is lowered by rifampicin, and may be raised by cimetidine, ranitidine, propafenone and hydralazine.

Lidocaine
Metoprolol may reduce the clearance of lidocaine.

ADVERSE REACTIONS

Adverse reactions have generally been mild and reversible. The following events have been reported as adverse events in clinical trials or reported from routine use. In many cases, a relationship to treatment with metoprolol has not been established.

The most common adverse events reported are exertional tiredness, gastrointestinal disorders and disturbances of sleep patterns. The most serious adverse events reported are congestive heart failure, bronchospasm and hypotension.

Reported adverse events according to organ systems are:

Cardiovascular

Congestive heart failure (see WARNINGS)

Secondary effects of decreased cardiac output which include:
syncope, vertigo, lightheadedness and postural hypotension
Severe bradycardia
Lengthening of PR interval
Second and third degree A-V block
Sinus arrest
Cardiac arrhythmias
Palpitations
Chest pains
Edema
Cold extremities
Claudication
Gangrene in patients with pre-existing severe peripheral circulatory disorders
Hot flushes

In a placebo controlled study in patients with acute myocardial infarction, the incidences of the following cardiovascular reactions were:

	Metoprolol	Placebo
Hypotension (systolic BP< 90mmHg)	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 (PR ≥0.26 sec)	5.3%	1.9%
Heart Failure	27.5%	29.6%

Central Nervous System

Headache
Dizziness
Mental depression
Lightheadedness
Concentration impaired
Anxiety
Weakness
Fatigue
Sedation
Somnolence or insomnia
Vivid dreams/nightmares
Vertigo
Paresthesia
Hallucination
Nervousness

Impotence/sexual dysfunction
Amnesia/memory impairment
Confusion

Gastrointestinal

Diarrhea
Constipation
Flatulence
Heartburn
Nausea and vomiting
Abdominal pain
Dryness of mouth
Hepatitis

Respiratory

Shortness of breath
Wheezing
Bronchospasm
Status asthmaticus
Rhinitis

Allergic/Dermatological (see WARNINGS)

Skin rash (exanthema, urticaria, psoriasiform and dystrophic skin lesions)
Sweating
Pruritus
Photosensitivity

Eye, Ear, Nose and Throat (EENT)

Blurred vision and non-specific visual disturbances
Dry and/or itching eyes
Conjunctivitis
Tinnitus
Hearing difficulties in doses exceeding those recommended
Taste disturbances

Miscellaneous

Muscle cramps
Exertional tiredness
Weight gain
Loss of hair
Arthritis
Peyronie's disease

Clinical Laboratory

The following laboratory parameters have been rarely elevated: transaminases, BUN, alkaline phosphatase and bilirubin. Isolated cases of thrombocytopenia and leukopenia have been reported.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms
The most common signs to be expected with overdosage of a β-adrenoceptor blocking agent are hypotension, bradycardia, congestive heart failure, bronchospasm and hypoglycemia. Atrioventricular block, cardiogenic shock and cardiac arrest may develop. In addition, impairment of consciousness (or even coma), nausea, vomiting and cyanosis may occur.

Concomitant ingestion of alcohol, antihypertensives, quinidine, or barbiturates aggravate the signs andsymptoms.

The first manifestations of overdosage set in 20 minutes to 2 hours after drug administration.

Treatment
If overdosage occurs, in all cases therapy with NTP-METOPROLOL (metoprolol tartrate) should be discontinued and the patient hospitalized and observed closely. Remove any drug remaining in the stomach by induction of emesis or gastric lavage. In addition, if required, the following therapeutic measures are suggested:

Bradycardia and Hypotension: Initially 1-2 mg of atropine sulfate should be given intravenously. If a satisfactory effect is not achieved, norepinephrine or dopamine may be administered after preceding treatment with atropine (see PRECAUTIONS concerning the use of epinephrine in β-blocked patients). In case of hypoglycemia glucagon (1-10 mg) can also be administered.

Heart Block (second- or third-degree): Isoproterenol or transvenous cardiac pacemaker.

Congestive Heart Failure: Conventional therapy.

Bronchospasm: Intravenous aminophylline or β_2-agonist.

Hypoglycemia: Intravenous glucose.

It should be remembered that metoprolol is a competitive antagonist of isoproterenol and hence, large doses of isoproterenol can be expected to reverse many of the effects of excessive doses of NTP-METOPROLOL. However, the complications of excess isoproterenol, e.g. hypotension and tachycardia, should not be overlooked.

DOSAGE AND ADMINISTRATION

Hypertension
NTP-METOPROLOL (metoprolol tartrate) is usually used in conjunction with other antihypertensive agents, particularly a thiazide diuretic, but may be used alone (see INDICATIONS).

The dose must always be adjusted to the individual requirements of the patient, in accordance with the following guidelines.

NTP-METOPROLOL treatment should be initiated with doses of 50 mg b.i.d. If an adequate response is not seen after one week, dosage should be increased to 100 mg b.i.d. In some cases the daily dosage may need to be increased by further 100 mg increments at intervals of not less than two weeks up to a maximum of 200 mg b.i.d., which should not be exceeded. The usual maintenance dose is within the range of 100-200 mg daily.

When NTP-METOPROLOL is combined with another antihypertensive agent which is already being administered, NTP-METOPROLOL should be added initially at a dose of 50 mg b.i.d. After one or two weeks the daily dosage may be increased if required, in increments of 100 mg, at intervals of not less than two weeks, until adequate blood pressure control is obtained.

Angina Pectoris
The recommended dosage range for NTP-METOPROLOL in angina pectoris is 100-400 mg per day in divided doses.

Treatment should be initiated with 50 mg b.i.d. for the first week.

If response is not adequate, the daily dosage should be increased by 100 mg for the next week. The usual maintenance dose is 200 mg/day.

The need for further increases should be closely monitored at weekly intervals and the dosage increased in 100 mg increments to a maximum of 400 mg/day in two or three divided doses.

A NTP-METOPROLOL dose of 400 mg/day should not be exceeded.

Myocardial Infarction
In addition to the usual contraindications:

ONLY PATIENTS WITH SUSPECTED ACUTE MYOCARDIAL INFARCTION WHO MEET THE FOLLOWING CRITERIA ARE SUITABLE FOR THERAPY AS DESCRIBED BELOW:	
Systolic blood pressure Heart Rate PR Interval Rales	≥100 mmHg ≥45 beats per min <0.24 seconds

Adequate Peripheral Circulation	<10 cm

Early Treatment
During the early phase of definite or suspected acute myocardial infarction, treatment with metoprolol can be initiated as soon as possible after the patient's arrival in the hospital. Such treatment should be initiated in a coronary care 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 intravenous administration of metoprolol, blood pressure, heart rate, and electrocardiogram should be carefully monitored. If any of the injections are associated with adverse cardiovascular effects, intravenous administration should be stopped immediately and the patient should be observed carefully and appropriate therapy instituted.

In patients who tolerate the full intravenous dose (15 mg), NTP-METOPROLOL tablets, 50 mg every 6 hours should be initiated 15 minutes after the last intravenous dose and continued for 48 hours. Thereafter, patients should receive a maintenance dosage of
100 mg twice daily (see **Late Treatment** below).

Patients who appear not to tolerate the full intravenous dose should be started on either
25 mg or 50 mg every 6 hours (depending on the degree of intolerance) 15 minutes after the last intravenous dose or as soon as their clinical condition allows. In patients with severe intolerance, treatment with NTP-METOPROLOL should be discontinued (see WARNINGS).

Late Treatment (for proven myocardial infarction patients only)
Patients with contraindications to treatment during the early phase of 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 NTP-METOPROLOL tablets, 100 mg twice daily, as soon as their clinical condition allows. Treatment can begin within 3 to 10 days of the acute event. Therapy should be continued for at least 3 months. Although the efficacy of treatment with metoprolol beyond 6 months has not been conclusively established, data from studies with other β-blockers suggest that the treatment should be continued for 1 to 3 years.

Impaired liver function
Dose adjustment is normally not needed in patients suffering from liver cirrhosis because metoprolol has low protein binding (5-10%). When there are signs of serious impairment of liver function (e.g., shunt-operated patients) a dose reduction should be considered.

PHARMACEUTICAL INFORMATION

Drug Substance

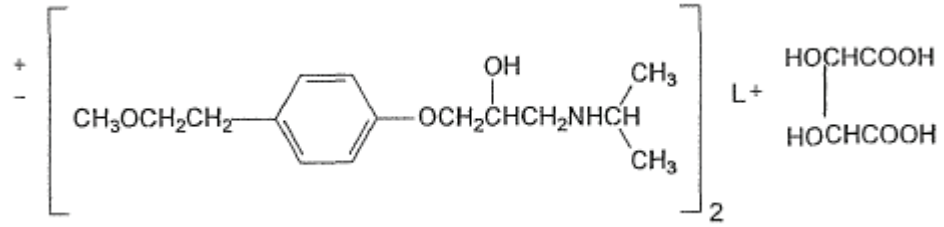
Proper Name: Metoprolol tartrate USP

Molecular Formula: $(C_{15}H_{25}NO_3)_2 \bullet C_4H_6O_6$

Molecular Weight: 684.82

Chemical Name: (±)-1-(isopropylamino)-3-[p-(2-methoxyethyl)phenoxy]-2-propanol L-(+)-tartrate (2:1) (salt).

Structural Formula:



Description: Metoprolol tartrate is a white, odourless, crystalline powder with a bitter taste.

Solubility: Very soluble in water; freely soluble in methylene chloride and in alcohol; slightly soluble in acetone; insoluble in ether.

Composition

Each NTP-METOPROLOL (metoprolol tartrate) 100 mg **film-coated** tablet contains: 100 mg of metoprolol tartrate active ingredient with the following inactive ingredients: silicon dioxide, lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, corn starch, magnesium stearate, hypromellose, titanium dioxide, macrogol and FD&C blue #2.

Each NTP-METOPROLOL (metoprolol tartrate) 50 mg **film-coated** tablet contains: 50 mg of metoprolol tartrate active ingredient with the following inactive ingredients: silicon dioxide, lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, corn starch, magnesium stearate, hypromellose, titanium dioxide, macrogol, D&C red #30 and FD&C yellow #6.

Each NTP-METOPROLOL (metoprolol tartrate) 100 mg **uncoated** tablet contains: 100 mg of metoprolol tartrate active ingredient with the following inactive ingredients: silicon dioxide, lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, corn starch and magnesium stearate.

Each NTP-METOPROLOL (metoprolol tartrate) 50 mg **uncoated** tablet contains: 50 mg of

metoprolol tartrate active ingredient with the following inactive ingredients: silicon dioxide, lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, corn starch and magnesium stearate.

Stability and Storage Recommendations
Store bottles between 15 to 30°C and unit dose boxes between 15 to 25°C . Protect from heat, light and humidity.

AVAILABILITY OF DOSAGE FORMS

NTP-METOPROLOL (metoprolol tartrate) Film-Coated Tablets:

100 mg: Light blue coloured, capsule-shaped, bi-convex, scored, film-coated tablets; embossed **N | 100** on the scored side, plain on the reverse side. Available in bottles of 100 and 500 and unit dose boxes of 100 tablets.

50 mg: Pink coloured, capsule-shaped, bi-convex, scored, film-coated tablets; embossed **N | 50** on the scored side, plain on the reverse side. Available in bottles of 100 and 500 and unit dose boxes of 100 tablets.

NTP-METOPROLOL (metoprolol tartrate) Uncoated Tablets:

100 mg: White, round, bi-convex, scored, compressed uncoated tablets engraved **N / 100** on the scored side, and plain on the reverse side. Available in bottles of 100 and 500 tablets.

50 mg: White, round, bi-convex, scored, compressed uncoated tablets engraved **N / 50** on the scored side, and plain on the reverse side. Available in bottles of 100 and 500 tablets.

PHARMACOLOGY

Effect on the Cardiovascular System
Metoprolol produced dose-dependent reductions in heart rate and contractile force responses to sympathetic nerve stimulation in the anesthetized cat. The ED_{50} value for blockade of the chronotropic response to nerve stimulation was approximately 7 times less than that for isoproterenol stimulation. Metoprolol reduced the heart rate in conscious dogs at rest and during exercise. With the exception of PR interval prolongation, ECG complexes were not changed.

In anesthetized cats, intravenous doses up to 2.0 mg/kg did not significantly influence the pressor response to intravenous epinephrine.

In anesthetized cats, intravenously-administered metoprolol antagonized the hind limb vasodilating response to intra-arterial isoproterenol in much higher doses (ED_{50} 5 mg/kg) than required to block the increase in chronotropic response (ED_{50} 0.4 mg/kg) or increase in contractile force (ED_{50} 0.2 mg/kg).

In 5 healthy volunteers, intravenously-administered 10 mg doses of metoprolol reduced exercise-induced tachycardia by 13% and systolic blood pressure during exercise by 13%. The decrease in mean blood pressure after epinephrine was abolished by metoprolol, whereas the increase in systolic blood pressure was reduced by 50%; vascular resistance in the forearm was unchanged after metoprolol.

In healthy volunteers, intravenous metoprolol 0.15 mg/kg significantly lowered cardiac output by 1.3 litre/min at rest, and 3.6 litre/min during exercise. The mean decreases in heart rate were 9 and 16 beats/min during rest and exercise, respectively. Right atrial pressure was significantly increased during rest and exercise. Oxygen consumption was not significantly influenced by drug administration. Significant increases in the calculated arteriovenous oxygen differences were observed (6 and 20 mL/litre at rest and during exercise, respectively).

Studies in reserpinized cats showed that metoprolol was devoid of β-receptor stimulating (intrinsic) activity. In cumulative doses up to 0.85 mg/kg, the drug did not significantly influence heart rate or contractile force.

A single oral dose of 40 mg of metoprolol administered to17 anginal patients 90 minutes before testing, increased total work performed from 5994 to 8462 k.p.m. (40%). Times to onset of pain and appearance of ST depression were similarly increased from 11.8-16.9 min and 9.9-13.9 min respectively.

Effects on Pulmonary Function
The effects on specific airways resistance (SR_{aw}) of single oral doses of 100 mg of metoprolol were assessed in 6 healthy volunteers and in 12 patients with bronchial asthma. No bronchodilator was used. Metoprolol did not have a significant effect on SR_{aw} in the normal subjects, but in the asthmatic patients, SR_{aw} was significantly increased. Similar findings were

observed with an 80 mg dose of propranolol.

In a controlled study, 17 patients with bronchial asthma received concomitantly a bronchodilator (terbutaline) with 50 mg or 100 mg b.i.d. of metoprolol. The $FEV_{1.0}$ values fell only in the high dose group, indicating some β_2-blocking effect.

Other Effects
Metoprolol showed a negligible local anesthetic effect on the isolated sciatic nerve of the frog and in the intracutaneous wheal test in guinea pigs. The cardiostimulant effects of ouabain, glucagon and theophylline were not affected by doses of 2-3 mg/kg in the anesthetized cat. The same dosage of metoprolol was found to be devoid of anticholinergic, ganglionic blocking, antihistaminic and alpha-receptor blocking properties in cats.

Metoprolol inhibited the increase in plasma renin activity induced by furosemide.

The effects of metoprolol on isoproterenol-stimulated metabolic effects showed inhibition of the increase in liberation of glycerol, glucose, insulin and free fatty acids.

TOXICOLOGY

Acute Toxicity

Species	Sex	Route	Solutions	LD_{50} (mg/kg)
mouse	male	i.v.	1%	69.4 ± 5.1
mouse	female	i.v.	1%	79.9 ± 4.5
mouse	male	p.o.	23%	2460 ± 210
mouse	female	p.o.	25%	2300 ± 200
rat	male	i.v.	5%	71.9 ± 4.4
rat	female	i.v.	5%	74.3 ± 4.4
rat	male	p.o.	50%	4670 ± 1210
rat	female	p.o.	50%	3470 ± 580

The toxic symptoms in rats included: sedation, piloerection, ataxia, irritation, spasm and lacrimation. Rats were unconscious before death, which occurred within 5-10 min after intravenous injection and 6-20 h after oral administration.

In mice the most pronounced symptoms were: sedation, hypersensitivity, irritation, spasms and ptosis. Convulsions were seen before death, which occurred within 5 minutes after intravenous injection.

No symptoms of toxicity were detectable 24 h after administration in surviving animals.

Subacute Toxicity

Subacute Toxicity in Animals

Species	Strain	Sex M	Sex F	No. of Groups	No. of Animals/Group	Dose mg/kg/day	Route	Duration of study	Toxic Effects
Rats	Sprague-Dawley	40	40	4	10M 10F	Saline, 10,50,100 mg/kg/day (after 14 days, high dose incr to 200 mg/kg/day)	p.o.	5 weeks	Slight incr in hematocrit & slight decr in blood sugar in high dose females
Dogs	Beagle	1	1	1	1M 1F	40 mg/kg x 3 days, incr by 20 mg/kg/day to 140 mg/kg x 6 days to 160 mg/kg/day	p.o.	3 weeks	Disturbance of balance; incr abdominal muscular tone, mydrialysis, hyperemia in visible mucous membranes. One dog died at dose level of 140 mg/kg.day.
Dogs	Beagle	1	2	2	1M 2F	80 mg/kg b.i.d./one day; 2 days later, single dose of 100 mg/kg 20 mg/kg/b.i.d., incr every 5 days by 20 mg/kg/b.i.d. up to 120 mg/kg/b.i.d.	p.o. p.o	3 days 4 weeks	Disturbance of balance; vomiting, prostration, dyspnea, loss of consciousness, death Vomiting; incr salivation, tremor, ataxia, one dog died at highest dose.
Dogs	Beagle	4	4	4	1M 1F	0, 5, 20, 40 mg/kg/day	p.o.	4 weeks	None
Dogs	Beagle	3	3	3	1M 1F	Saline, 0.5, 5 mg/kg/day	i.v.	2 weeks	Prolonged PR interval in ECG.
Dogs	Beagle	2	2	2	1M 1F	Saline, 5 mg/kg/day	i.v.	2 weeks	Prolonged PR interval in ECG.

Chronic Toxicity

Chronic Toxicity in Animals

Species	Strain	Sex M	Sex F	No. of Groups	No. of Animals/Group	Dose mg/kg/day	Route	Duration of study	Toxic Effects
Rats	Sprague-Dawley	60	60	4	15M 15F	Saline, 10, 100, 200 mg/kg/day. High dose increased to 200 mg/kg.day after 13 weeks	p.o.	6M	None
Dogs	Beagle	11	11	Cont. 1 Active 3	2M 2F 3M 3F	0,5,20,40 mg/kg/b.i.d. After 7 W, high dose incr to 50 mg/kg/b.i.d.; after 3 M, intermediate dose increased to 30 mg/b.i.d. and high dose to 80 mg/b.i.d.	p.o.	6M	Bradycardia, incr. PR interval and QT interval in ECG.
Dogs	Beagle	24	24	Cont. 1 Active 3	6M 6F 6M 6F	0, 10, 60 mg/kg/day. High level dogs rec'd 120 mg/day on day 1, 60 mg/kg on days 3 to 8, 90 mg/kg/day on days 9 to 22 and 105 mg/kg/day for balance	p.o.	1Y	2 high dosed dogs died on Day 1, otherwise, none.

Teratology and Reproduction

Rat (Sprague-Dawley Strain)

Doses of 10, 50 and 200 mg/kg were administered orally to groups of 20 pregnant rats on days 6-15 of gestation. Treatment with metoprolol did not adversely affect any of the parameters studied.

Rabbit (New Zealand White Strain)

Doses of 5, 12.5 and 25 mg/kg were administered orally to groups of 20 pregnant rabbits on days 6-18 of gestation. Parameters studied were not significantly affected, although litter size was lower and fetal loss higher in the high dose group. The incidence of fetal abnormality was unaffected by treatment.

Rat (Sprague-Dawley Strain)

Doses of 10, 50 and 200 mg/kg were administered orally to groups of 50 rats from day 15 of gestation through lactation to 21 days post partum. Parameters studied in litter and parent animals were not adversely affected.

Rat (Charles River CD Strain)

Doses of 50 and 500 mg/kg were administered orally to groups of 10 male and 20 female rats. Males were treated for 63 days prior to mating and during the mating period. The females were treated for 14 days prior to mating, during mating and throughout the gestation and lactation periods to 21 days post partum, with an interim sacrifice at day 13 of gestation. The only significant finding in this study was a slight reduction of intrauterine growth in rats at 50 and 500 mg/kg/day and a higher frequency of stillbirths in the high dose group.

Carcinogenicity Studies

Metoprolol was administered to 3 groups of 60 male and 60 female Charles River Sprague-Dawley rats at dietary levels of 50, 200 and 800 mg/kg per day for 78 weeks. A fourth group received 2-AAF (positive control) and the fifth was the negative control group. The incidence of nodules and masses observed at necropsy were comparable between the treated and control groups. The only histopathological changes noted were an increased incidence of impaction of pulmonary alveoli by septal cells in all the treated animals and an increase in biliary hyperplasia in the high and intermediate metoprolol-treated groups. The strain of rats was susceptible to the known carcinogen 2-AAF; a statistically higher incidence of neoplasms, primarily hepatomas, was present.

A similar study in Swiss albino mice at doses of 75, 150 and 750 mg/kg/day for 78 weeks showed that the tumors were distributed with equal frequency in the treated and control groups. The strain was susceptible to the known carcinogen.

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