METOPROLOL TARTATE- metoprolol tartate tablet
Northwind Pharmaceuticals

Metoprolol Tartrate

Information for Patients

Information for Patients

Patients should be advised to take metoprolol regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue metoprolol without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with metoprolol has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking metoprolol.

Drug Interactions

Catecholamine-depleting drugs: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents or monoamine oxidase (MAO) inhibitors. Observe patients treated with Metoprolol Tartrate plus a catecholamine depletor 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.

Digitalis glycosides and beta blockers: Both digitalis glycosides and beta blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia. Monitor heart rate and PR interval.

Calcium channel blockers: Concomitant administration of a beta-adrenergic antagonist with a calcium channel blocker may produce an additive reduction in myocardial contractility because of negative chronotropic and inotropic effects.

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.

General Anesthetics:Some inhalation anesthetics may enhance the cardiodepressant effect of beta blockers (see WARNINGS, Major Surgery).

CYP2D6 Inhibitors: Potent inhibitors of the CYP2D6 enzyme may increase the plasma concentration of Metoprolol Tartrate which would mimic the pharmacokinetics of CYP2D6 poor metabolizer (see Pharmacokinetics section). 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; antipsychotics 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.

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

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 Tartrate. 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 Tartrate concurrently, and clonidine treatment is to be discontinued, stop Metoprolol Tartrate several days before clonidine is withdrawn. Rebound hypertension that can follow withdrawal of clonidine may be increased in patients receiving concurrent beta-blocker treatment.

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have been conducted to evaluate carcinogenic potential. In a 2-year study in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, or in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.

Reproduction toxicity studies in mice, rats and rabbits did not indicate teratogenic potential for metoprolol tartrate. Embryotoxicity and/or fetotoxicity in rats and rabbits were noted starting at doses of 50 mg/kg in rats and 25 mg/kg in rabbits, as demonstrated by increases in preimplantation loss, decreases in the number of viable fetuses per dose, and/or decreases in neonatal survival. High doses were associated with some maternal toxicity, and growth delay of the offspring in utero, which was reflected in minimally lower weights at birth. The oral NOAELs for embryo-fetal development in mice, rats, and rabbits were considered to be 25, 200, and 12.5 mg/kg. This corresponds to dose levels that are approximately 0.3, 4, and 0.5 times, respectively, when based on surface area, the maximum human oral dose (8 mg/kg/day) of metoprolol tartrate. Metoprolol tartrate has been associated with reversible adverse effects on spermatogenesis starting at oral dose levels of 3.5 mg/kg in rats (a dose that is only 0.1-times the human dose, when based on surface area), although other studies have shown no effect of metoprolol tartrate on reproductive performance in male rats.

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 (see Carcinogenesis, Mutagenesis, Impairment of Fertility).

There are no adequate and well-controlled studies in pregnant women. The amount of data on the use of

metoprolol in 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.

Nursing Mothers

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

Fertility: The effects of Metoprolol Tartrate on the fertility of human have not been studied.

Metoprolol Tartrate showed effects on spermatogenesis in male rats at a therapeutic dose level, but had no effect on rates of conception at higher doses in animal fertility studies (see Carcinogenesis, Mutagenesis, Impairment of Fertility).

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical trials of metoprolol tartrate USP, 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 tartrate. Other reported clinical experience in elderly hypertensive patients has not identified any difference in response from younger patients.

In worldwide clinical trials of metoprolol tartrate 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 tartrate cannot be categorically ruled out. Therefore, in general, it is recommended that dosing proceed with caution in this population.

Adverse Reactions

ADVERSE REACTIONS

Hypertension and Angina

Most adverse effects have been mild and transient.

Central Nervous System: 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 (see WARNINGS). Rhinitis has also been reported.

Gastrointestinal: Diarrhea 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. Post-marketing 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 described in the CLINICAL PHARMACOLOGY section, 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 postapproval use of Metoprolol Tartrate: 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.

Online drug information link

For complete manufacturer's drug information please visit this online link:

http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=c9a87c39-4baf-43e2-b6bc-3634f1eb77cf

Indication and usage

INDICATIONS AND USAGE

Hypertension

Metoprolol tartrate tablets are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents.

Angina Pectoris

Metoprolol tartrate tablets are indicated in the long-term treatment of angina pectoris.

Myocardial Infarction

Metoprolol tartrate injection and tablets are indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment with intravenous metoprolol tartrate can be initiated as soon as the patient’s clinical condition allows (see DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS). Alternatively, treatment can begin within 3 to 10 days of the acute event (see DOSAGE AND ADMINISTRATION).

Contraindications

Hypertension and Angina

Metoprolol tartrate is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

Hypersensitivity to metoprolol and related derivatives, or to any of the excipients; hypersensitivity to other beta-blockers (cross sensitivity between beta-blockers can occur).

Sick-sinus syndrome.

Severe peripheral arterial circulatory disorders.

Myocardial Infarction

Metoprolol is contraindicated in patients with a heart rate < 45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg; or moderate-to-severe cardiac failure (see WARNINGS).

Hypertension and Angina

Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, fully digitalize patients and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, metoprolol should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents,

exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered metoprolol, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1 to 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.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS, including Metoprolol tartrate. Because of its relative beta1 selectivity, however, metoprolol may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta1 selectivity is not absolute, a beta2-stimulating agent should be administered concomitantly, and the lowest possible dose of metoprolol tartrate should be used. In these circumstances it would be prudent initially to administer 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).

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

Myocardial Infarction

Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with metoprolol, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, metoprolol should be discontinued.

Bradycardia: Metoprolol produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25 to 0.5 mg) should be administered intravenously. If treatment with atropine is not successful, metoprolol should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

AV Block: Metoprolol slows AV conduction and may produce significant first- (P-R intervals ≥ 0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, metoprolol should be discontinued and atropine (0.25 to 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, 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 AV block, treatment should be directed at reversing these (see above).

Precautions

General

Start at a low dose and uptitrate slowly in patients with impaired hepatic function.

LABEL

NDC: 51655-535-52

Mfg: 57664-166-58

Metoprolol Tartate 50 MG

30 Tablets

Rx Only

Lot# NW43360001

Exp Date: 1/2016

Each tablet contains Metoprolol Tartate, USP ....50 MG

Dosage: See package outsert for full prescribing information.

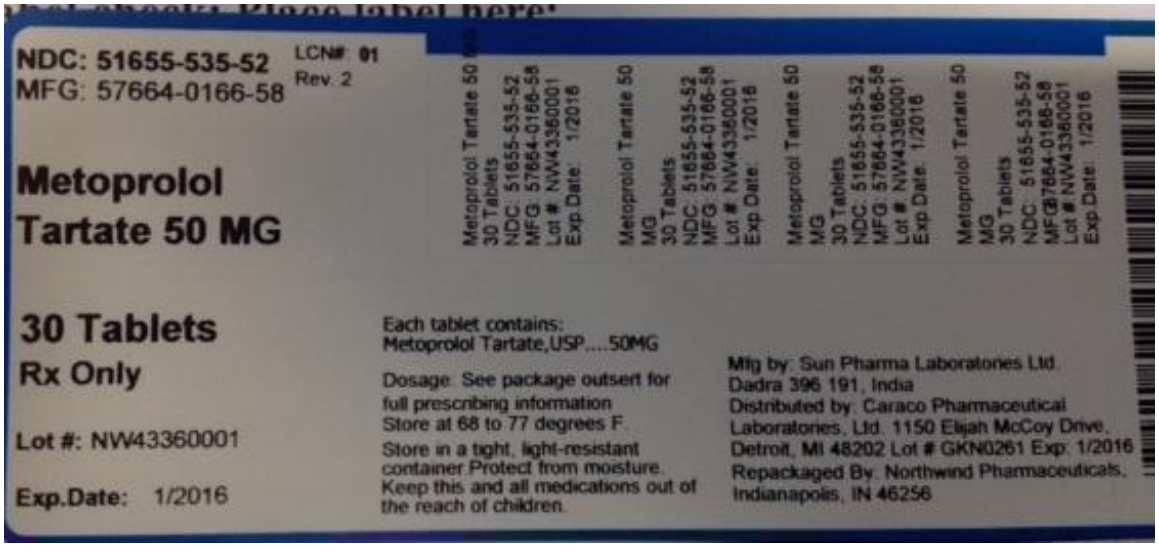
Store at 68 to 77 degrees F.

Store in a tight, Light-resistant container. Protect from moisture. Keep this and all medication out of the reach of children.

Mfg by: Sun Pharma Laboratories Ltd. Dadra 396 191 India

Distributed by: Caraco Pharmaceuticals Laboratories, Ltd 1150 Elijah McCoy Drive, Detroit MI 48202 Lot# GKN0261 Exp 1/2016

Repackaged by: Northwind Pharmaceuticals, Indianapolis, IN 46256



NDC: 51655-535-25

Mfg: 57664-166-58

Metoprolol Tartate 50 MG

60 Tablets

Rx Only

Lot#

Exp Date:

Each tablet contains Metoprolol Tartate, USP ....50 MG

Dosage: See package outsert for full prescribing information.

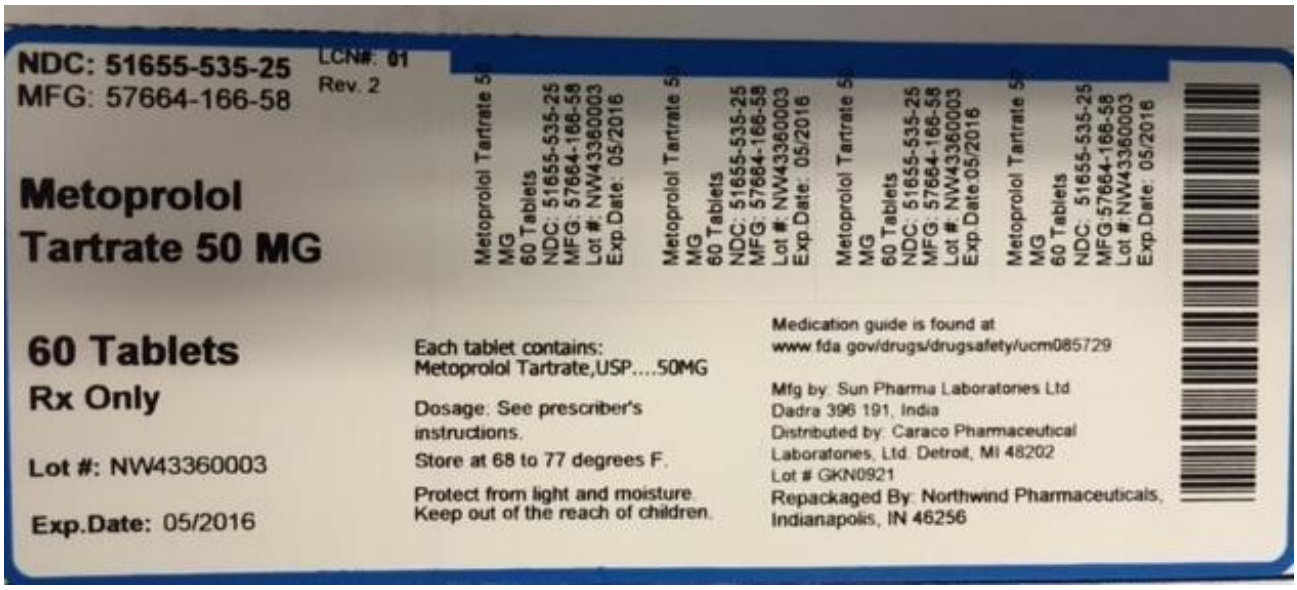
Store at 68 to 77 degrees F.

Store in a tight, Light-resistant container. Protect from moisture. Keep this and all medication out of the reach of children.

Mfg by: Sun Pharma Laboratories Ltd. Dadra 396 191 India

Distributed by: Caraco Pharmaceuticals Laboratories, Ltd 1150 Elijah McCoy Drive, Detroit MI 48202
Lot#

Repackaged by: Northwind Pharmaceuticals, Indianapolis, IN 46256



NDC: 51655-535-26

Mfg: 57664-166-58

Metoprolol Tartate 50 MG

90 Tablets

Rx Only

Lot#

Exp Date:

Each tablet contains Metoprolol Tartate, USP ....50 MG

Dosage: See package outsert for full prescribing information.

Store at 68 to 77 degrees F.

Store in a tight, Light-resistant container. Protect from moisture. Keep this and all medication out of the

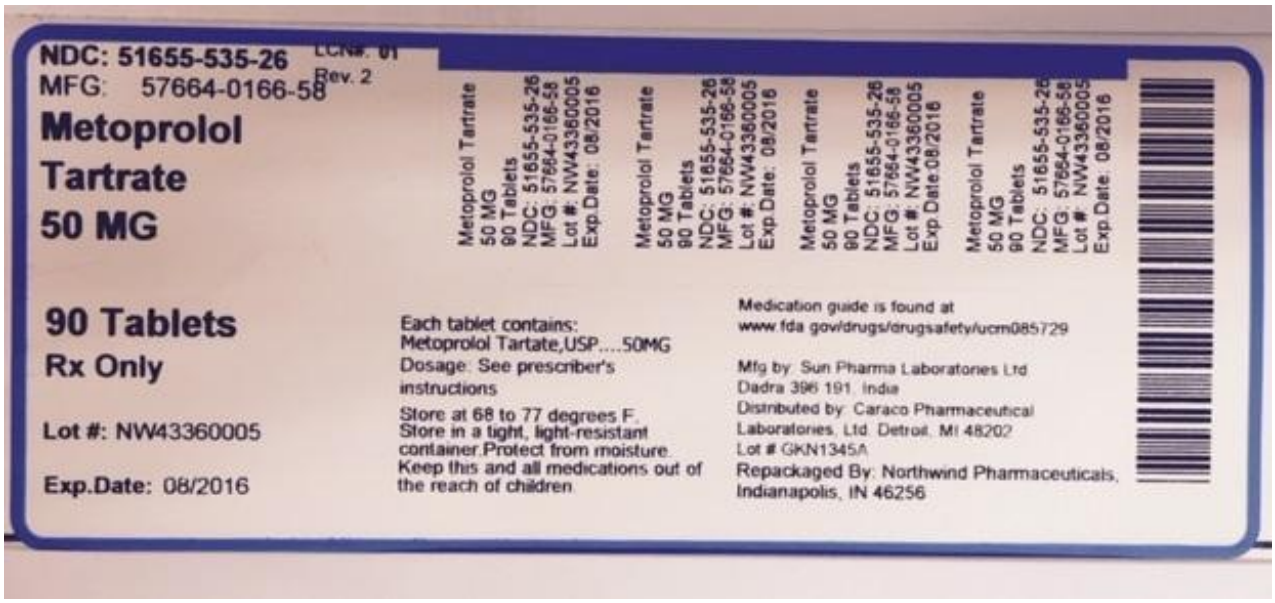
reach of children.

Medication guide is found at www.fda.gov/drugs/drugsafety/ucm085729

Mfg by: Sun Pharma Laboratories Ltd. Dadra 396 191 India

Distributed by: Caraco Pharmaceuticals Laboratories, Ltd 1150 Elijah McCoy Drive, Detroit MI 48202
Lot#

Repackaged by: Northwind Pharmaceuticals, Indianapolis, IN 46256



METOPROLOL TARTATE

metoprolol tartate tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:51655-535(NDC:57664-166)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
METOPROLOL TARTRATE (UNII: W5S57Y3A5L) (METOPROLOL - UNII:GEB06NHM23)	METOPROLOL TARTRATE	50 mg

Product Characteristics			
Color	white	**Score**	no score
Shape	OVAL	**Size**	11mm
Flavor		**Imprint Code**	166
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:51655-535-52	30 in 1 BOTTLE, DISPENSING		

2	NDC:51655-535-25	60 in 1 BOTTLE, DISPENSING		
3	NDC:51655-535-26	90 in 1 BOTTLE, DISPENSING		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA074644	06/02/2014	

Labeler - Northwind Pharmaceuticals (036986393)

Registrant - Northwind Pharmaceuticals (036986393)

Establishment

Name	Address	ID/FEI	Business Operations
Northwind Pharmaceuticals		036986393	repack(51655-535)

Revised: 4/2015 Northwind Pharmaceuticals