METOPROLOL SUCCINATE- metoprolol succinate capsule, extended release
Sun Pharmaceutical Industries Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use METOPROLOL SUCCINATE EXTENDED-RELEASE CAPSULES safely and effectively. See full prescribing information for METOPROLOL SUCCINATE EXTENDED-RELEASE CAPSULES.
METOPROLOL SUCCINATE extended-release capsules, for oral use
Initial U.S. Approval: 1992

INDICATIONS AND USAGE

Metoprolol succinate extended-release capsules are $beta_1$-selective adrenoceptor blocking agent indicated for the treatment of: (1)

- Hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and non-fatal cardiovascular events, primarily strokes and myocardial infarctions. (1.1)
- Angina Pectoris. (1.2)
- Heart Failure, to reduce the risk of cardiovascular mortality and heart-failure hospitalization in patients with heart failure. (1.3)

DOSAGE AND ADMINISTRATION

- Adult Hypertension: Usual initial dosage is 25 to 100 mg once daily. Titrate weekly (or longer) to optimal blood pressure. (2.1)
- Pediatric Hypertension 6 years of age and older: The recommended starting dose is 1 mg/kg, once daily and titrate to response. Do not exceed a maximum initial dose of 50 mg once daily. (2.1)
- Angina Pectoris: Usual initial dosage is 100 mg once daily. Titrate weekly based on clinical response. (2.2)
- Heart Failure: The recommended starting dose is 25 mg doubled every two weeks to the highest dose tolerated or up to 200 mg. (2.3)

DOSAGE FORMS AND STRENGTHS

- Metoprolol succinate extended-release capsules: 25 mg, 50 mg, 100 mg and 200 mg. (3)

CONTRAINDICATIONS

- Known hypersensitivity to product components. (4)
- Severe bradycardia, greater than first degree heart block, or sick sinus syndrome without a pacemaker. (4)
- Cardiogenic shock or decompensated heart failure. (4)

WARNINGS AND PRECAUTIONS

- Abrupt cessation may exacerbate myocardial ischemia. (5.1)
- Worsening cardiac failure may occur. (5.2)
- Bronchospastic Disease: Avoid beta blockers. (5.3)
- Pheochromocytoma: First initiate therapy with an alpha blocker. (5.4)
- Avoid initiation of high-dose extended-release metoprolol and do not routinely withdraw chronic beta blocker therapy prior to surgery. (5.5, 6.1)
- May mask tachycardia occurring with hypoglycemia. (5.6)
- Abrupt withdrawal in thyrotoxicosis might precipitate a thyroid storm. (5.7)
- May aggravate symptoms of arterial insufficiency. (5.8)

ADVERSE REACTIONS

- Most common adverse reactions: tiredness, dizziness, depression, shortness of breath, bradycardia, hypotension, diarrhea, pruritus, rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-406-7984 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Catecholamine-depleting drugs may have an additive effect when given with beta-blocking agents. (7.1)
- Patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction. (7.2)
- CYP2D6 Inhibitors are likely to increase metoprolol concentration. (7.3)
- Concomitant use of glycosides, clonidine, and diltiazem and verapamil with beta-blockers can increase the risk of bradycardia. (7.4)
- Beta-blockers including metoprolol, may exacerbate the rebound hypertension that can follow the withdrawal of clonidine. (7.4)
- Alcohol interferes with the extended release properties of this product. (7.5)

USE IN SPECIFIC POPULATIONS

- Hepatic Impairment: Consider initiating metoprolol succinate therapy at low doses and gradually increase dosage to optimize therapy, while monitoring closely for adverse events. (8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 1/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Hypertension

Metoprolol succinate extended-release capsules are indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure lowers the risk of fatal and non-fatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including metoprolol.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than 1 drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a

lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (eg, on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

Metoprolol succinate extended-release capsules may be administered with other antihypertensive agents.

1.2 Angina Pectoris

Metoprolol succinate extended-release capsules are indicated in the long-term treatment of angina pectoris, to reduce angina attacks and to improve exercise tolerance.

1.3 Heart Failure

Metoprolol succinate extended-release capsules are indicated to reduce the risk of cardiovascular mortality and heart-failure hospitalization in patients with heart failure.

2 DOSAGE AND ADMINISTRATION

2.1 Hypertension

Adults: The usual initial dosage is 25 mg to 100 mg once daily in a single dose. Adjust dosage at weekly (or longer) intervals until optimum blood pressure reduction is achieved. Dosages above 400 mg per day have not been studied.

Pediatric Hypertensive Patients 6 Years of age or older: The recommended starting dose of metoprolol succinate extended-release capsules is 1 mg/kg once daily, the maximum initial dose should not exceed 50 mg once daily. Adjust dosage according to blood pressure response. Doses above 2 mg/kg (or in excess of 200 mg) once daily have not been studied in pediatric patients *[see Clinical Pharmacology (12.3)]*.

Metoprolol succinate extended-release capsules has not been studied in pediatric patients less than 6 years of age *[see Use in Specific Populations (8.4)]*.

2.2 Angina Pectoris

Individualize the dosage of metoprolol succinate extended-release capsules. The usual initial dosage is 100 mg once daily, given in a single dose. Gradually increase the dosage at weekly intervals until optimum clinical response has been obtained or there is a pronounced slowing of the heart rate. Dosages above 400 mg per day have not been studied. If treatment is to be discontinued, reduce the dosage gradually over a period of 1 to 2 weeks *[see Warnings and Precautions (5)]*.

2.3 Heart Failure

Prior to initiation of metoprolol succinate extended-release capsules, stabilize the dose of other heart failure drug therapy and ensure that the patient is not fluid overloaded. The recommended starting dose of metoprolol succinate extended-release capsules is 25 mg once daily for two weeks. Metoprolol succinate extended-release capsules are not suitable for initial therapy in patients who are expected to require a starting dose less than 25 mg daily. Dosage must be individualized and closely monitored during up-titration. Double the dose every two weeks to the highest dosage level tolerated by the patient or up to 200 mg of metoprolol succinate extended-release capsules. If a patient experiences symptomatic bradycardia, reduce the dose of metoprolol succinate extended-release capsules. If transient worsening of heart failure occurs, consider treating with increased doses of diuretics, lowering the dose of metoprolol succinate extended-release capsules or temporarily discontinuing it. The dose of metoprolol succinate extended-release capsules should not be increased until symptoms of worsening heart failure have been stabilized. Initial difficulty with titration should not preclude later

attempts to introduce metoprolol succinate extended-release capsules.

For patients who are taking metoprolol succinate extended-release tablets at a dose of 25 mg to 200 mg once daily, substitute metoprolol succinate extended-release capsules for metoprolol succinate extended-release tablets, using the same total daily dose of metoprolol succinate in mg.

2.4 Administration

Metoprolol succinate extended-release capsules should be swallowed whole. For patients unable to swallow an intact capsule, alternative administration options are available.

Directions for use with soft food (applesauce, pudding, or yogurt)

For patients with swallowing difficulty, Metoprolol succinate extended-release capsules can be opened and contents can be sprinkled over soft food. The contents of the capsules should be swallowed along with a small amount (teaspoonful) of soft food (such as applesauce, pudding, or yogurt). The drug/food mixture should be swallowed within 60 minutes and not stored for future use.

Nasogastric tube administration

Open and add content of capsule to an all plastic oral tip syringe and add 15 mL of water. Gently shake the syringe for approx. 10 sec to help suspend the granules and promptly deliver through a 12 French or larger nasogastric tube. No granules should be left in the syringe, rinse as required.

3 DOSAGE FORMS AND STRENGTHS

25 mg capsule: Light yellow opaque cap and white opaque body both imprinted with '**RL14**' in black ink containing white to off-white pellets.

50 mg capsule: Dark yellow opaque cap and white opaque body both imprinted with '**RL15**' in black ink containing white to off-white pellets.

100 mg capsule: White opaque cap and white opaque body both imprinted with '**RL16**' in black ink containing white to off-white pellets.

200 mg capsule: Yellow opaque cap and yellow opaque body both imprinted with '**RL17'** in black ink containing white to off-white pellets.

4 CONTRAINDICATIONS

Metoprolol succinate is contraindicated in severe bradycardia, second or third degree heart block, cardiogenic shock, decompensated heart failure, sick sinus syndrome (unless a permanent pacemaker is in place), and in patients who are hypersensitive to any component of this product.

5 WARNINGS AND PRECAUTIONS

5.1 Abrupt Cessation of Therapy

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 succinate, particularly in patients with ischemic heart disease, gradually reduce the dosage over a period of 1 to 2 weeks and monitor the patient. If angina markedly worsens or acute coronary ischemia develops, promptly reinstate metoprolol succinate, and take measures appropriate for the management of unstable angina. Warn patients not to interrupt therapy without their physician's advice. Because coronary artery disease is common and may be unrecognized, avoid abruptly discontinuing metoprolol succinate in patients treated only for hypertension.

5.2 Heart Failure

Worsening cardiac failure may occur during up-titration of metoprolol succinate. If such symptoms occur, increase diuretics and restore clinical stability before advancing the dose of metoprolol succinate *[see Dosage and Administration (2)]*. It may be necessary to lower the dose of metoprolol succinate or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of metoprolol succinate.

5.3 Bronchospastic Disease

PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS. Because of its relative $beta_1$ cardio-selectivity, however, metoprolol succinate 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 succinate. Bronchodilators, including $beta_2$-agonists, should be readily available or administered concomitantly *[see Dosage and Administration (2)]*.

5.4 Pheochromocytoma

If metoprolol succinate 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.

5.5 Major Surgery

Avoid initiation of a high-dose regimen of extended-release metoprolol in patients undergoing non-cardiac surgery, since such use in patients with cardiovascular risk factors has been associated with bradycardia, hypotension, stroke and death.

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.

5.6 Masked Symptoms of Hypoglycemia

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

5.7 Thyrotoxicosis

Beta-adrenergic blockade may mask certain clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of beta-blockade may precipitate a thyroid storm.

5.8 Peripheral Vascular Disease

Beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in labeling:

- Worsening angina or myocardial infarction. *[see Warnings and Precautions (5)]*
- Worsening heart failure. *[see Warnings and Precautions (5)]*
- Worsening AV block. *[see Contraindications (4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed

in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Hypertension and Angina: Most adverse reactions have been mild and transient. The most common (>2%) adverse reactions are tiredness, dizziness, depression, diarrhea, shortness of breath, bradycardia, and rash.

Heart Failure: In the MERIT-HF study comparing metoprolol succinate in daily doses up to 200 mg (mean dose 159 mg once-daily; n=1990) to placebo (n=2001), 10.3% of metoprolol succinate patients discontinued for adverse events vs. 12.2% of placebo patients.

The table below lists adverse reactions in the MERIT-HF study that occurred at an incidence of ≥ 1% in the metoprolol succinate group and greater than placebo by more than 0.5%, regardless of the assessment of causality.

Adverse Reactions Occurring in the MERIT-HF Study at an Incidence ≥ 1% in the Metoprolol Succinate Group and Greater Than Placebo by More Than 0.5%

	Metoprolol Succinate n = 1990 % of patients	Placebo n = 2001 % of patients
Dizziness/vertigo	1.8	1
Bradycardia	1.5	0.4

Post-operative Adverse Events: In a randomized, double-blind, placebo-controlled trial of 8351 patients with or at risk for atherosclerotic disease undergoing non-vascular surgery and who were not taking beta–blocker therapy, metoprolol succinate 100 mg was started 2 to 4 hours prior to surgery then continued for 30 days at 200 mg per day. Metoprolol succinate use was associated with a higher incidence of bradycardia (6.6% vs. 2.4%; HR, 2.74; 95% CI 2.19, 3.43), hypotension (15% vs. 9.7%; HR 1.55; 95% CI 1.37, 1.74), stroke (1% vs. 0.5%; HR 2.17; 95% CI 1.26, 3.74) and death (3.1% vs. 2.3%; HR 1.33; 95% CI 1.03, 1.74) compared to placebo.

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of extended-release metoprolol or immediate-release metoprolol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular: Cold extremities, arterial insufficiency (usually of the Raynaud type), palpitations, peripheral edema, syncope, chest pain and hypotension.

Respiratory: Wheezing (bronchospasm), dyspnea.

Central Nervous System: Confusion, short-term memory loss, headache, somnolence, nightmares, insomnia, anxiety/nervousness, hallucinations, paresthesia.

Gastrointestinal: Nausea, dry mouth, constipation, flatulence, heartburn, hepatitis, vomiting.

Hypersensitive Reactions: Pruritus.

Miscellaneous: Musculoskeletal pain, arthralgia, blurred vision, decreased libido, male impotence, tinnitus, reversible alopecia, agranulocytosis, dry eyes, worsening of psoriasis, Peyronie’s disease, sweating, photosensitivity, taste disturbance.

Potential Adverse Reactions: In addition, there are adverse reactions not listed above that have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to metoprolol succinate.

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, clouded sensorium, and decreased performance on neuropsychometrics.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Laryngospasm, respiratory distress.

7 DRUG INTERACTIONS

7.1 Catecholamine Depleting Drugs

Catecholamine depleting drugs (e.g., reserpine, monoamine oxidase (MAO) inhibitors) may have an additive effect when given with beta-blocking agents. Observe patients treated with metoprolol succinate plus a catecholamine depletor for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

7.2 Epinephrine

While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge and may be unresponsive to the usual doses of epinephrine used to treat an allergic reaction.

7.3 CYP2D6 Inhibitors

Drugs that are strong inhibitors of CYP2D6, such as quinidine, fluoxetine, paroxetine, and propafenone, were shown to double metoprolol concentrations. While there is no information about moderate or weak inhibitors, these too are likely to increase metoprolol concentration. Increases in plasma concentration decrease the cardioselectivity of metoprolol *[see Clinical Pharmacology (12.3)]. Monitor patients closely, when the combination cannot be avoided.*

7.4 Digitalis, Clonidine, and Calcium Channel Blockers

Digitalis glycosides, clonidine, diltiazem and verapamil slow atrioventricular conduction and decrease heart rate. Concomitant use with beta blockers can increase the risk of bradycardia.

If clonidine and a beta blocker, such as metoprolol are coadministered, withdraw the beta-blocker several days before the gradual withdrawal of clonidine because beta-blockers may exacerbate the rebound hypertension that can follow the withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, delay the introduction of beta-blockers for several days after clonidine administration has stopped.

7.5 Alcohol

Metoprolol succinate is released faster from metoprolol succinate extended-release capsules in the presence of alcohol. This may increase the risk for adverse events associated with metoprolol succinate extended-release capsules. Avoid alcohol consumption when taking metoprolol succinate extended-release capsules *[see Clinical Pharmacology (12.3)].*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from published observational studies have not demonstrated an association of adverse developmental outcomes with maternal use of metoprolol during pregnancy (*see Data).* Untreated hypertension and heart failure during pregnancy can lead to adverse outcomes for the mother and the fetus *(see Clinical Considerations).* In animal reproduction studies, metoprolol has been shown to increase post-implantation loss and decrease neonatal survival in rats at oral dosages of 500 mg/kg/day, approximately 24 times the daily dose of 200 mg in a 60-kg patient on a mg/m^2 basis.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical consideration

Disease-associated maternal and/or embryo/fetal risk

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

Stroke volume and heart rate increase during pregnancy, increasing cardiac output, especially during the first trimester. There is a risk for preterm birth with pregnant women with chronic heart failure in 3^{rd} trimester of pregnancy.

Fetal/Neonatal adverse reactions

Metoprolol crosses the placenta. Neonates born to mothers who are receiving metoprolol during pregnancy, may be at risk for hypotension, hypoglycemia, bradycardia, and respiratory depression. Observe neonates for symptoms of hypotension, bradycardia, hypoglycemia and respiratory depression and manage accordingly.

Data

Human Data

Data from published observational studies did not demonstrate an association of major congenital malformations and use of metoprolol in pregnancy. The published literature has reported inconsistent findings of intrauterine growth retardation, preterm birth and perinatal mortality with maternal use of metoprolol during pregnancy; however, these studies have methodological limitations hindering interpretation. Methodological limitations include retrospective design, concomitant use of other medications, and other unadjusted confounders that may account for the study findings including the underlying disease in the mother. These observational studies cannot definitely establish or exclude any drug-associated risk during pregnancy.

Animal Data

Metoprolol has been shown to increase post-implantation loss and decrease neonatal survival in rats at oral dosages of 500 mg/kg/day, i.e. 24 times, on a mg/m^2 basis, the daily dose of 200 mg in a 60-kg patient.

No fetal abnormalities were observed when pregnant rats received metoprolol orally up to a dose of 200 mg/kg/day, i.e. 10 times, the daily dose of 200 mg in a 60-kg patient.

8.2 Lactation

Risk Summary

Limited available data from published literature report that metoprolol is present in human milk. The estimated daily infant dose of metoprolol received from breastmilk range from 0.05 mg to less than 1 mg. The estimated relative infant dosage was 0.5% to 2% of the mother's weight-adjusted dosage *(see*

Data). No adverse reactions of metoprolol on the breastfed infant have been identified. There is no information regarding the effects of metoprolol on milk production.

Clinical consideration

Monitoring for adverse reactions

For a lactating woman who is a slow metabolizer of metoprolol, monitor the breastfed infant for bradycardia and other symptoms of beta blockade such as dry mouth, skin or eyes, diarrhea or constipation. In a report of 6 mothers taking metoprolol, none reported adverse effects in her breastfed infant.

Data

Limited published cases estimate the infant daily dose of metoprolol received from breast milk range from 0.05 mg to less than 1 mg.

In 2 women who were taking unspecified amount of metoprolol, milk samples were taken after one dose of metoprolol. The estimated amount of metoprolol and alpha-hydroxymetoprolol in breast milk is reported to be less than 2% of the mother's weight-adjusted dosage.

In a small study, breast milk was collected every 2 to 3 hours over one dosage interval, in three mothers (at least 3 months postpartum) who took metoprolol of unspecified amount. The average amount of metoprolol present in breast milk was 71.5 mcg/day (range 17.0 to 158.7). The average relative infant dosage was 0.5% of the mother's weight-adjusted dosage.

8.3 Females and Males of Reproductive Potential

Risk Summary

Based on the published literature, beta blockers (including metoprolol) may cause erectile dysfunction and inhibit sperm motility. In animal fertility studies, metoprolol has been associated with reversible adverse effects on spermatogenesis starting at oral dose level of 3.5 mg/kg in rats, which would correspond to a dose of 34 mg/day in humans in mg/m^2 equivalent, although other studies have shown no effect of metoprolol on reproductive performance in male rats.

No evidence of impaired fertility due to metoprolol was observed in rats *[see Nonclinical Toxicology (13.1)]***.**

8.4 Pediatric Use

One hundred forty-four hypertensive pediatric patients aged 6 to 16 years were randomized to placebo or to one of three dose levels of metoprolol succinate (0.2, 1 or 2 mg/kg once daily) and followed for 4 weeks. The study did not meet its primary endpoint (dose response for reduction in SBP). Some pre-specified secondary endpoints demonstrated effectiveness including:

- Dose-response for reduction in DBP,
- 1 mg/kg vs. placebo for change in SBP, and
- 2 mg/kg vs. placebo for change in SBP and DBP.

The mean placebo corrected reductions in SBP ranged from 3 to 6 mmHg, and DBP from 1 to 5 mmHg. Mean reduction in heart rate ranged from 5 to 7 bpm but considerably greater reductions were seen in some individuals *[see Dosage and Administration (2.1)]*.

No clinically relevant differences in the adverse event profile were observed for pediatric patients aged 6 to 16 years as compared with adult patients.

Safety and effectiveness of metoprolol succinate have not been established in patients < 6 years of age.

8.5 Geriatric Use

Clinical studies of metoprolol succinate in hypertension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience in hypertensive patients has not identified differences in responses between elderly and younger patients.

Of the 1,990 patients with heart failure randomized to metoprolol succinate in the MERIT-HF trial, 50% (990) were 65 years of age and older and 12% (238) were 75 years of age and older. There were no notable differences in efficacy or the rate of adverse reactions between older and younger patients.

In general, use a low initial starting dose in elderly patients given their greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

No studies have been performed with metoprolol succinate in patients with hepatic impairment. Because metoprolol succinate is metabolized by the liver, metoprolol blood levels are likely to increase substantially with poor hepatic function. Therefore, initiate therapy at doses lower than those recommended for a given indication; and increase doses gradually in patients with impaired hepatic function.

10 OVERDOSAGE

Signs and Symptoms - Overdosage of metoprolol succinate may lead to severe bradycardia, hypotension, and cardiogenic shock. Clinical presentation can also include: atrioventricular block, heart failure, bronchospasm, hypoxia, impairment of consciousness/coma, nausea and vomiting.

Treatment – Consider treating the patient with intensive care. Patients with myocardial infarction or heart failure may be prone to significant hemodynamic instability. Beta-blocker overdose may result in significant resistance to resuscitation with adrenergic agents, including beta-agonists. On the basis of the pharmacologic actions of metoprolol, employ the following measures.

There is very limited experience with the use of hemodialysis to remove metoprolol, however metoprolol is not highly protein bound.

Bradycardia: Evaluate the need for atropine, adrenergic-stimulating drugs or pacemaker to treat bradycardia and conduction disorders.

Hypotension: Treat underlying bradycardia. Consider intravenous vasopressor infusion, such as dopamine or norepinephrine.

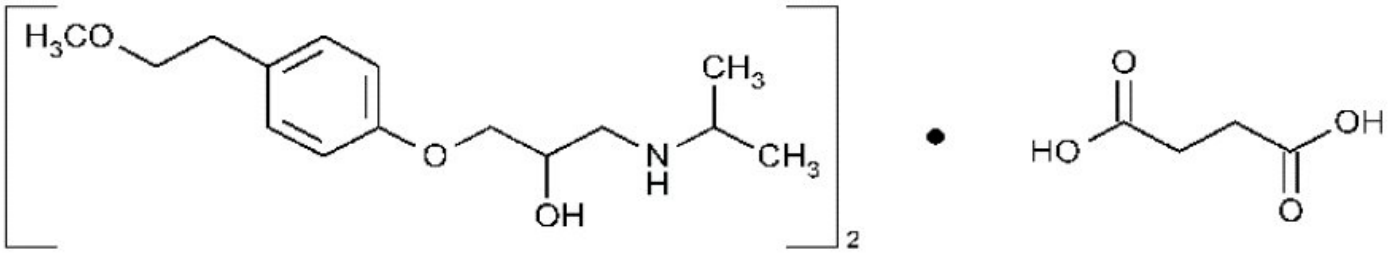
Heart failure and shock: May be treated when appropriate with suitable volume expansion, injection of glucagon (if necessary, followed by an intravenous infusion of glucagon), intravenous administration of adrenergic drugs such as dobutamine, with α_1 receptor agonistic drugs added in presence of vasodilation.

Bronchospasm: Can usually be reversed by bronchodilators.

11 DESCRIPTION

Metoprolol succinate, is a beta$_1$-selective (cardioselective) adrenoceptor blocking agent, for oral administration, available as extended-release capsules. Metoprolol succinate extended-release capsules have been formulated to provide a controlled and predictable release of metoprolol for once-daily administration. The extended-release capsules comprise a multiple unit system containing metoprolol succinate in a multitude of controlled release pellets. Each pellet acts as a separate drug delivery unit and is designed to deliver metoprolol continuously over the dosage interval. The extended-release capsules contain 10.24 mg, 20.48 mg, 40.96 mg, and 81.92 mg of metoprolol free base, present as 23.75 mg, 47.5 mg, 95 mg, and 190 mg of metoprolol succinate and are equivalent to 25 mg, 50 mg, 100 mg, and 200 mg of metoprolol tartrate, USP, respectively. Its chemical name is (±)-1-(Isopropylamino)-3-[p-

(2-methoxyethyl)phenoxy]-2-propanol succinate (2:1) (salt). Its structural formula is:



Metoprolol succinate, USP is a white to off-white powder with a molecular weight of 652.82. It is freely soluble in water, soluble in methanol, sparingly soluble in alcohol, slightly soluble in isopropyl alcohol. Inactive ingredients: ethyl cellulose, hypromellose, polyethylene glycol 400, polyethylene glycol 6000, sugar spheres (corn starch and sucrose), talc and triethyl citrate. The capsule shell and imprinting ink has the following composition: ferric oxide yellow (25 mg, 50 mg and 200 mg), ferrosoferric oxide, gelatin, potassium hydroxide, propylene glycol, shellac and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Metoprolol is a $beta_1$-selective (cardioselective) adrenergic receptor blocking agent. 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.

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

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

Hypertension: The mechanism of the antihypertensive effects of beta-blocking agents has not been 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.

Heart Failure: The precise mechanism for the beneficial effects of beta-blockers in heart failure has not been elucidated.

12.2 Pharmacodynamics

Clinical pharmacology studies have confirmed the beta-blocking activity of metoprolol in man, 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.

The relationship between plasma metoprolol levels and reduction in exercise heart rate is independent of the pharmaceutical formulation. $Beta_1$-blocking effects in the range of 30 to 80% of the maximal

effect (approximately 8 to 23% reduction in exercise heart rate) correspond to metoprolol plasma concentrations from 30 to 540 nmol/L. The relative $beta_1$-selectivity of metoprolol diminishes and blockade of $beta_2$-adrenoceptors increases at plasma concentration above 300 nmol/L.

In five controlled studies in normal healthy subjects, extended-release metoprolol succinate administered once a day, and immediate-release metoprolol administered once to four times a day, provided comparable total $beta_1$-blockade over 24 hours (area under the $beta_1$-blockade versus time curve) in the dose range 100 to 400 mg. In another controlled study, 50 mg once daily for each product, extended-release metoprolol succinate produced significantly higher total $beta_1$-blockade over 24 hours than immediate-release metoprolol. For extended-release metoprolol succinate, the percent reduction in exercise heart rate was relatively stable throughout the entire dosage interval and the level of $beta_1$-blockade increased with increasing doses from 50 to 300 mg daily.

A controlled cross-over study in heart failure patients compared the plasma concentrations and $beta_1$-blocking effects of 50 mg immediate-release metoprolol administered t.i.d., and 100 mg and 200 mg extended-release metoprolol succinate once daily. Extended-release metoprolol succinate 200 mg once daily produced a larger effect on suppression of exercise-induced and Holter-monitored heart rate over 24 hours compared to 50 mg t.i.d. of immediate-release metoprolol.

In other studies, treatment with metoprolol succinate produced an improvement in left ventricular ejection fraction. Metoprolol succinate was also shown to delay the increase in left ventricular end-systolic and end-diastolic volumes after 6 months of treatment.

Although beta-adrenergic receptor blockade is useful in the treatment of angina, hypertension, and heart failure there are situations in which sympathetic stimulation is vital. In patients with severely damaged hearts, adequate ventricular function may depend on sympathetic drive. In the presence of AV block, beta-blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. $Beta_2$-adrenergic blockade results in passive bronchial constriction by interfering with endogenous adrenergic bronchodilator activity in patients subject to bronchospasm and may also interfere with exogenous bronchodilators in such patients.

12.3 Pharmacokinetics

The peak plasma levels following once-daily administration of extended release metoprolol succinate are reduced by 50 to 75% on average compared to a corresponding dose of immediate-release metoprolol tartrate, both when administered once daily or in divided doses. At steady state the average bioavailability of metoprolol following administration of metoprolol succinate, across the dosage range of 50 to 400 mg once daily, was reduced by 25% relative to the corresponding single or divided doses of immediate-release metoprolol tartrate. The bioavailability of metoprolol shows a dose-related, although not directly proportional, increase with dose. The exposure (C_{max} and AUC) of metoprolol succinate extended-release capsule are similar to that of TOPROL-XL® tablet.

Absorption

Plasma levels following oral administration of metoprolol tablet approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism. Peak plasma concentration of metoprolol is attained at 10 hours following administration of metoprolol succinate extended-release capsule.

Effect of food

Compared to fasted state administration, high-fat, high-calorie meal (54.3% fat, 15.6% proteins and 30.1% carbohydrates) did not have a significant effect on the absorption of metoprolol succinate extended-release capsule.

200 mg metoprolol succinate extended release capsule administered under fasting conditions to healthy adults by sprinkling the entire contents on one-tablespoon (15 mL) of applesauce did not significantly affect T_{max}, C_{max}, and AUC of metoprolol.

Distribution

About 12% of the drug is bound to human serum albumin.

Metoprolol crosses the blood-brain barrier and has been reported in the CSF in a concentration 78% of the simultaneous plasma concentration.

Elimination

Elimination is mainly by biotransformation in the liver, and the plasma half-life ranges from approximately 3 to 7 hours.

Metabolism

Metoprolol is a racemic mixture of R- and S- enantiomers, and is primarily metabolized by CYP2D6. When administered orally, it exhibits stereoselective metabolism that is dependent on oxidation phenotype.

Excretion

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 beta-blocking activity.

Following intravenous administration of metoprolol, the urinary recovery of unchanged drug is approximately 10%.

Specific Populations

Pediatric Patients

The pharmacokinetic profile of metoprolol succinate was studied in 120 pediatric hypertensive patients (6 to 17 years of age) receiving doses ranging from 12.5 to 200 mg once daily. The pharmacokinetics of metoprolol were similar to those described previously in adults. Age, gender, race, and ideal body weight had no significant effects on metoprolol pharmacokinetics. Metoprolol apparent oral clearance (CL/F) increased linearly with body weight. Metoprolol pharmacokinetics have not been investigated in patients < 6 years of age.

Drug Interactions

CYP2D6

Metoprolol is metabolized predominantly by CYP2D6. In healthy subjects with CYP2D6 extensive metabolizer phenotype, coadministration of quinidine 100 mg, a potent CYP2D6 inhibitor, and immediate-release metoprolol 200 mg tripled the concentration of S-metoprolol and doubled the metoprolol elimination half-life. In four patients with cardiovascular disease, coadministration of propafenone 150 mg t.i.d. with immediate-release metoprolol 50 mg t.i.d. resulted in steady-state concentration of metoprolol 2- to 5-fold what is seen with metoprolol alone. Extensive metabolizers who concomitantly use CYP2D6 inhibiting drugs will have increased (several-fold) metoprolol blood levels, decreasing metoprolol's cardioselectivity *[see Drug Interactions (7.2)]*.

Alcohol

An *in vitro* dissolution study was conducted to evaluate the impact of alcohol (5, 10, 20 and 40%), on the extended-release characteristics of metoprolol succinate extended-release capsules. The *in vitro* study showed that about 89% of the total metoprolol succinate dose was released at 2 hour at the highest alcohol level (40%), and about 17% of total drug was released at 2 hour with 5% alcohol. Alcohol causes a rapid release of metoprolol succinate from the extended-release capsules that may increase the risk for above events associated with metoprolol succinate extended-release capsules. Consumption of alcohol is not recommended when taking metoprolol succinate extended-release capsules 25 mg, 50 mg, 100 mg and 200 mg.

12.5 Pharmacogenomics

CYP2D6 is absent in about 8% of Caucasians (poor metabolizers) and about 2% of most other populations. CYP2D6 can be inhibited by several drugs. Poor metabolizers of CYP2D6 will have increased (several-fold) metoprolol blood levels, decreasing metoprolol's cardioselectivity.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have been conducted to evaluate the carcinogenic potential of metoprolol tartrate. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg/day (41 times, on a mg/m^2 basis, the daily dose of 200 mg for a 60 kg patient), 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/day (18 times, on a mg/m^2 basis, the daily dose of 200 mg for a 60-kg patient), 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, nor 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 genotoxicity tests performed on metoprolol tartrate (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) and metoprolol succinate (a *Salmonella*/mammalian-microsome mutagenicity test) were negative.

No evidence of impaired fertility due to metoprolol tartrate was observed in a study performed in rats at doses up to 22 times, on a mg/m^2 basis, the daily dose of 200 mg in a 60 kg patient.

14 CLINICAL STUDIES

14.1 Hypertension

In a double-blind study, 1092 patients with mild-to-moderate hypertension were randomized to once daily metoprolol succinate (25, 100, or 400 mg), PLENDIL® (felodipine extended-release tablets), the combination, or placebo. After 9 weeks, metoprolol succinate alone decreased sitting blood pressure by 6 – 8 mmHg /4 - 7 mmHg (placebo-corrected change from baseline) at 24 hours post-dose. The combination of metoprolol succinate with PLENDIL® has greater effects on blood pressure.

In controlled clinical studies, an immediate-release dosage form of metoprolol was an effective antihypertensive agent when used alone or as concomitant therapy with thiazide-type diuretics at dosages of 100 to 450 mg daily. Metoprolol succinate, in dosages of 100 to 400 mg once daily, produces similar β_1-blockade as conventional metoprolol tablets administered two to four times daily. In addition, metoprolol succinate administered at a dose of 50 mg once daily lowered blood pressure 24-hours post-dosing in placebo-controlled studies. In controlled, comparative, clinical studies, immediate-release metoprolol appeared comparable as an antihypertensive agent to propranolol, methyldopa, and thiazide-type diuretics, and affected both supine and standing blood pressure. Because of variable plasma levels attained with a given dose and lack of a consistent relationship of antihypertensive activity to drug plasma concentration, selection of proper dosage requires individual titration.

14.2 Angina Pectoris

In controlled clinical trials, an immediate-release formulation of metoprolol has been shown to be an effective antianginal agent, reducing the number of angina attacks and increasing exercise tolerance.

The dosage used in these studies ranged from 100 to 400 mg daily. Metoprolol succinate, in dosages of 100 to 400 mg once daily, has been shown to possess beta- blockade similar to conventional metoprolol tablets administered two to four times daily.

14.3 Heart Failure

MERIT-HF was a randomized, double-blind study in which 3991 patients with ejection fraction ≤0.40 and NYHA Class II-IV heart failure attributable to ischemia, hypertension, or cardiomyopathy were randomized 1:1 to metoprolol or placebo. The protocol excluded patients with contraindications to beta-blocker use, those expected to undergo heart surgery, and those within 28 days of myocardial infarction or unstable angina. The primary endpoints of the trial were (1) all-cause mortality plus all-cause hospitalization (time to first event) and (2) all-cause mortality. Patients were stabilized on optimal concomitant therapy for heart failure, including diuretics, ACE inhibitors, cardiac glycosides, and nitrates. At randomization, 41% of patients were NYHA Class II; 55% NYHA Class III; 65% of patients had heart failure attributed to ischemic heart disease; 44% had a history of hypertension; 25% had diabetes mellitus; 48% had a history of myocardial infarction. Among patients in the trial, 90% were on diuretics, 89% were on ACE inhibitors, 64% were on digitalis, 27% were on a lipid-lowering agent, 37% were on an oral anticoagulant, and the mean ejection fraction was 0.28. The mean duration of follow-up was one year. At the end of the study, the mean daily dose of metoprolol succinate was 159 mg.

The trial was terminated early for a statistically significant reduction in all-cause mortality (34%, nominal p= 0.00009). The risk of all-cause mortality plus all-cause hospitalization was reduced by 19% (p= 0.00012). The trial also showed improvements in heart failure-related mortality and heart failure-related hospitalizations, and NYHA functional class.

The table below shows the principal results for the overall study population. The figure below illustrates principal results for a wide variety of subgroup comparisons, including US vs. non-US populations (the latter of which was not pre-specified). The combined endpoints of all-cause mortality plus all-cause hospitalization and of mortality plus heart failure hospitalization showed consistent effects in the overall study population and the subgroups. Nonetheless, subgroup analyses can be difficult to interpret and it is not known whether these represent true differences or chance effects.

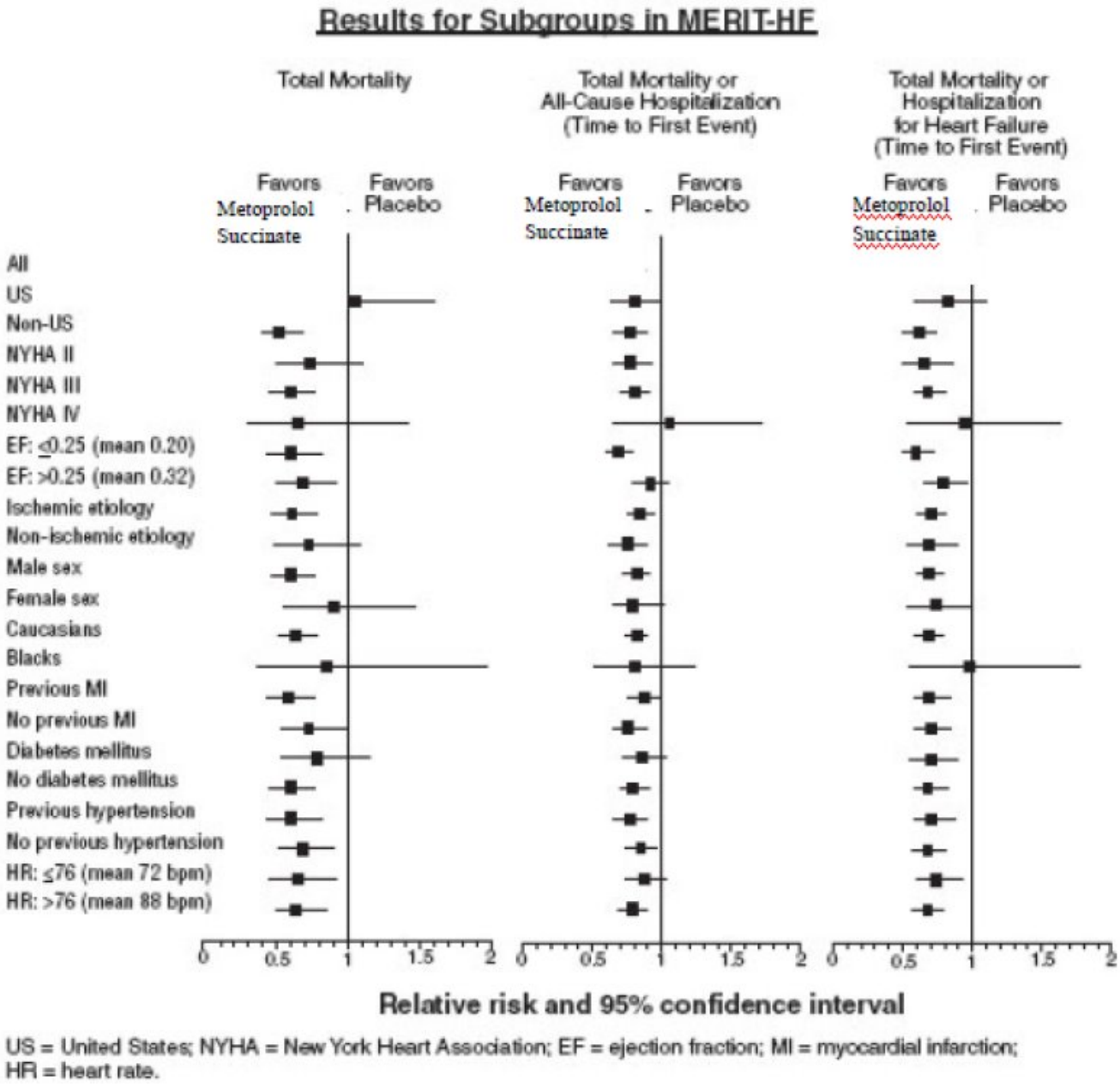
Clinical Endpoints in the MERIT-HF Study

Clinical Endpoint	Number of Patients		Relative Risk (95% Cl)	Risk Reduction With Metoprolol Succinate	Nominal P-value
	Placebo n=2001	Metoprolol Succinate n=1990			
All-cause mortality plus all-caused hospitalization[1]	767	641	0.81 (0.73 to 0.90)	19%	0.00012
All-cause mortality	217	145	0.66 (0.53 to 0.81)	34%	0.00009
All-cause mortality plus heart failure hospitalization[1]	439	311	0.69 (0.60 to 0.80)	31%	0.0000008
Cardiovascular mortality	203	128	0.62 (0.50to 0.78)	38%	0.000022
Sudden death	132	79	0.59 (0.45 to 0.78)	41%	0.0002
Death due to worsening	58	30	0.51	49%	0.0023

heart failure			(0.33 to 0.79)		
Hospitalizations due to worsening heart failure[2]	451	317	N/A	N/A	0.0000076
Cardiovascular hospitalization[2]	773	649	N/A	N/A	0.00028

1. Time to first event

2. Comparison of treatment groups examines the number of hospitalizations (Wilcoxon test); relative risk and risk reduction are not applicable.



US = United States; NYHA = New York Heart Association; EF = ejection fraction; MI = myocardial infarction; HR = heart rate.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each extended-release capsule contains 10.24 mg, 20.48 mg, 40.96 mg, and 81.92 mg of metoprolol

free base, present as 23.75 mg, 47.5 mg, 95 mg, and 190 mg of metoprolol succinate and equivalent to 25 mg, 50 mg, 100 mg, and 200 mg of metoprolol tartrate, USP respectively and are supplied as follows:

25 mg capsule: Light yellow opaque cap and white opaque body both imprinted with '**RL14**' in black ink containing white to off-white pellets.

NDC 10631-008-30 Bottle of 30

50 mg capsule: Dark yellow opaque cap and white opaque body both imprinted with '**RL15**' in black ink containing white to off-white pellets.

NDC 10631-009-30 Bottles of 30

100 mg capsule: White opaque cap and white opaque body both imprinted with '**RL16**' in black ink containing white to off-white pellets.

NDC 10631-010-30 Bottles of 30

200 mg capsule: Yellow opaque cap and yellow opaque body both imprinted with '**RL17'** in black ink containing white to off-white pellets.

NDC 10631-011-30 Bottles of 30

Store at 20° C - 25° C (68° F - 77° F). [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Heart failure patients should be advised to consult their physician if they experience signs or symptoms of worsening heart failure such as weight gain or increasing shortness of breath.

Advise patients if a dose is missed, the patient should take only the next scheduled dose (without doubling it). Patients should not interrupt or discontinue metoprolol succinate extended-release capsules without consulting the physician.

Advise patients (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with metoprolol succinate extended-release capsules 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 succinate extended-release capsules.

Advise patients who are breastfeeding to monitor the infant for bradycardia, dry mouth, skin or eyes, and diarrhea or constipation. *[see Use in Specific Population (8.2)]*.

PLENDIL® and TOPROL-XL® are trademarks of the AstraZeneca group of companies.

Manufactured by:

Ohm Laboratories Inc.

New Brunswick, NJ 08901

Distributed by:

Sun Pharmaceutical Industries, Inc.

Cranbury, NJ 08512

FDA-05

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

NDC 63304-008-30

Metoprolol Succinate

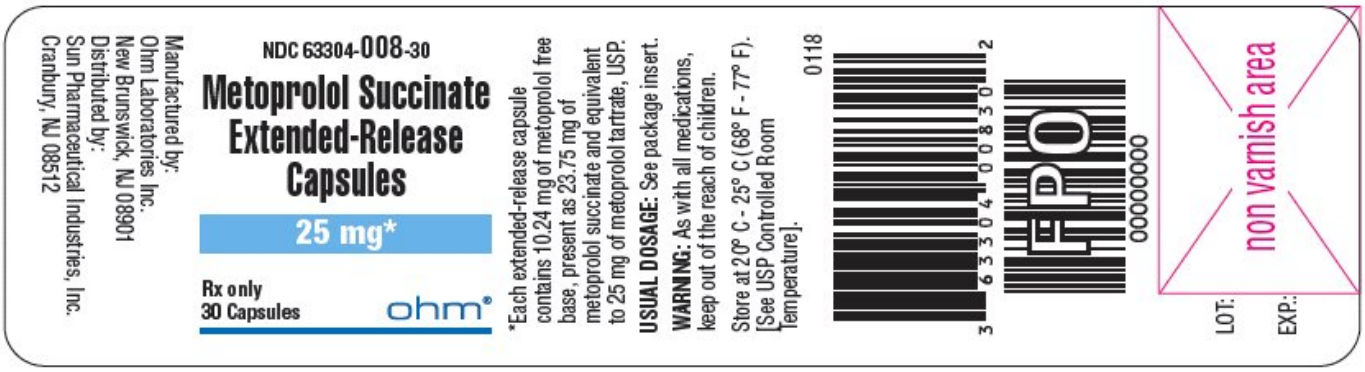
Extended-Release Capsules

25 mg*

Rx only

30 Capsules

ohm®



Package/Label Display Panel

NDC 63304-009-30

Metoprolol Succinate

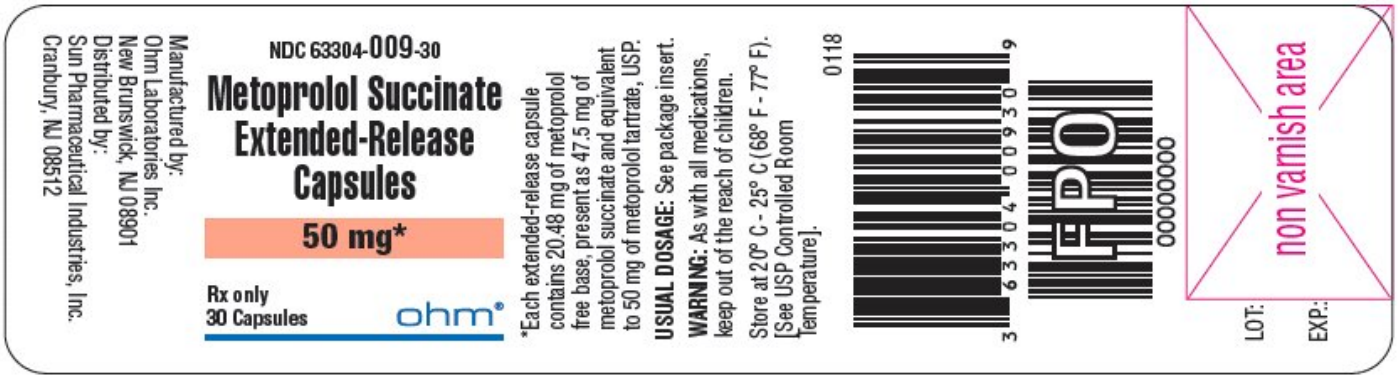
Extended-Release Capsules

50 mg*

Rx only

30 Capsules

ohm®



Package/Label Display Panel

NDC 63304-010-30

Metoprolol Succinate

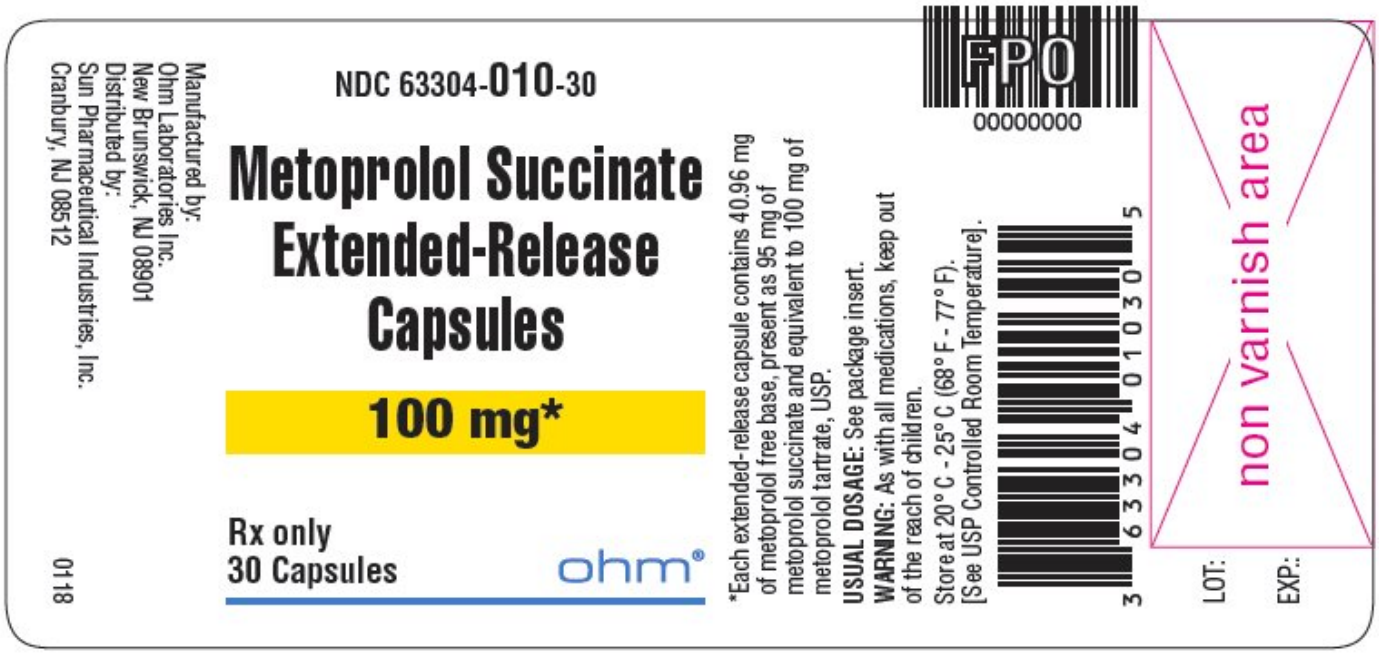
Extended-Release Capsules

100 mg*

Rx only

30 Capsules

ohm®



Package/Label Display Panel

NDC 63304-011-30

Metoprolol Succinate

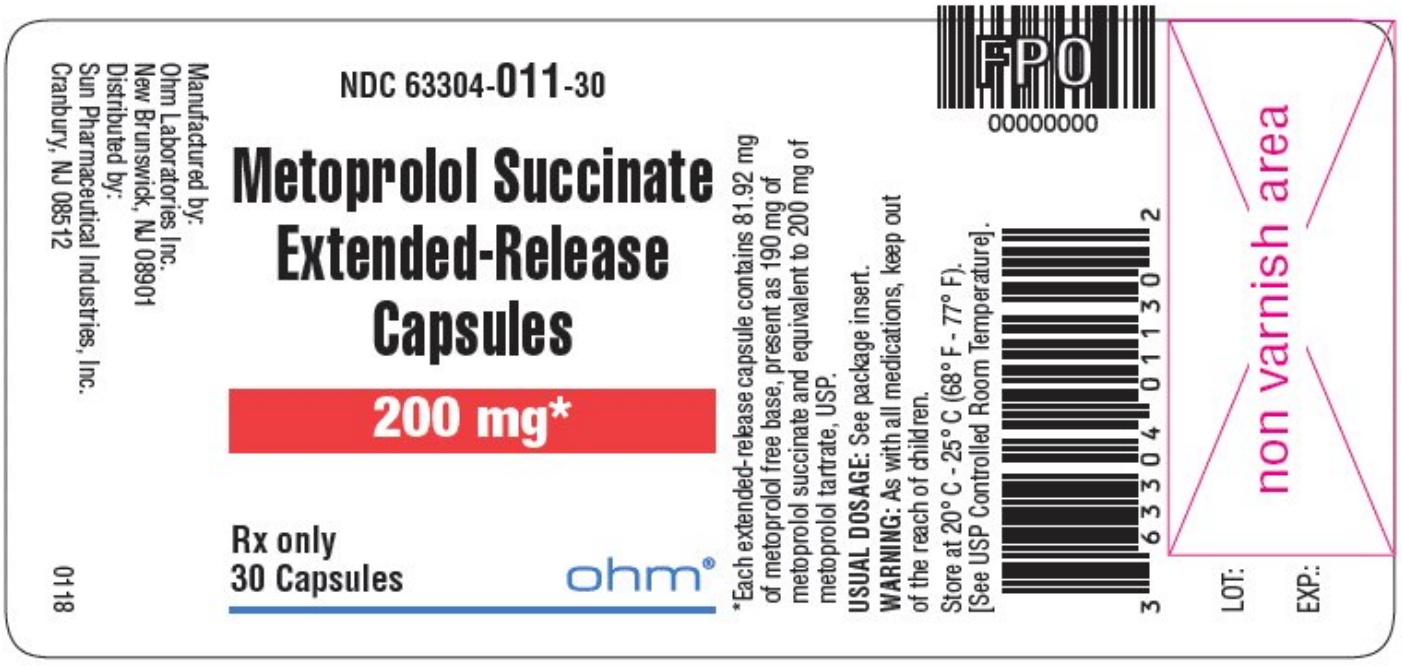
Extended-Release Capsules

200 mg*

Rx only

30 Capsules

ohm®



METOPROLOL SUCCINATE

metoprolol succinate capsule, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:63304-008
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
METOPROLOL SUCCINATE (UNII: TH25PD4CCB) (METOPROLOL - UNII:GEB06NHM23)	METOPROLOL TARTRATE	25 mg

Inactive Ingredients	
Ingredient Name	**Strength**
HYPROMELLOSE 2910 (5 MPA.S) (UNII: R75537T0T4)	
ETHYLCELLULOSE (20 MPA.S) (UNII: BJG0S321QY)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
POLYETHYLENE GLYCOL 6000 (UNII: 30IQX730WE)	
SUCROSE (UNII: C151H8M554)	
STARCH, CORN (UNII: O8232NY3SJ)	
TALC (UNII: 7SEV7J4R1U)	
TRIETHYL CITRATE (UNII: 8Z96QXD6UM)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
SHELLAC (UNII: 46N107B71O)	

TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	

Product Characteristics			
Color	YELLOW (Llight yellow opaque cap and white opaque body)	**Score**	no score
Shape	CAPSULE	**Size**	14mm
Flavor		**Imprint Code**	RL14
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63304-008-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	02/07/2018	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA210428	02/07/2018	

METOPROLOL SUCCINATE

metoprolol succinate capsule, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:63304-009
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
METOPROLOL SUCCINATE (UNII: TH25PD4CCB) (METOPROLOL - UNII:GEB06NHM23)	METOPROLOL TARTRATE	50 mg

Inactive Ingredients

Ingredient Name	Strength
HYPROMELLOSE 2910 (5 MPA.S) (UNII: R75537T0T4)	
ETHYLCELLULOSE (20 MPA.S) (UNII: BJG0S321QY)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
POLYETHYLENE GLYCOL 6000 (UNII: 30IQX730WE)	
SUCROSE (UNII: C151H8M554)	
STARCH, CORN (UNII: O8232NY3SJ)	
TALC (UNII: 7SEV7J4R1U)	
TRIETHYL CITRATE (UNII: 8Z96QXD6UM)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	

POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
SHELLAC (UNII: 46N107B71O)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics			
Color	YELLOW (dark yellow opaque cap and white opaque body)	**Score**	no score
Shape	CAPSULE	**Size**	14mm
Flavor		**Imprint Code**	RL15
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63304-009-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	02/07/2018	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA210428	02/07/2018	

METOPROLOL SUCCINATE

metoprolol succinate capsule, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:63304-010
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
METOPROLOL SUCCINATE (UNII: TH25PD4CCB) (METOPROLOL - UNII:GEB06NHM23)	METOPROLOL TARTRATE	100 mg

Inactive Ingredients

Ingredient Name	Strength
HYPROMELLOSE 2910 (5 MPA.S) (UNII: R75537T0T4)	
ETHYLCELLULOSE (20 MPA.S) (UNII: BJG0S321QY)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
POLYETHYLENE GLYCOL 6000 (UNII: 30IQX730WE)	
SUCROSE (UNII: C151H8M554)	
STARCH, CORN (UNII: O8232NY3SJ)	
TALC (UNII: 7SEV7J4R1U)	
TRIETHYL CITRATE (UNII: 8Z96QXD6UM)	

FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
SHELLAC (UNII: 46N107B71O)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics			
Color	WHITE (opaque cap and white opaque body)	**Score**	no score
Shape	CAPSULE	**Size**	18mm
Flavor		**Imprint Code**	RL16
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63304-010-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	02/07/2018	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA210428	02/07/2018	

METOPROLOL SUCCINATE

metoprolol succinate capsule, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:63304-011
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
METOPROLOL SUCCINATE (UNII: TH25PD4CCB) (METOPROLOL - UNII:GEB06NHM23)	METOPROLOL TARTRATE	200 mg

Inactive Ingredients

Ingredient Name	Strength
HYPROMELLOSE 2910 (5 MPA.S) (UNII: R75537T0T4)	
ETHYLCELLULOSE (20 MPA.S) (UNII: BJG0S321QY)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
POLYETHYLENE GLYCOL 6000 (UNII: 30IQX730WE)	
SUCROSE (UNII: C151H8M554)	
STARCH, CORN (UNII: O8232NY3SJ)	
TALC (UNII: 7SEV7J4R1U)	

TRIETHYL CITRATE (UNII: 8Z96QXD6UM)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
SHELLAC (UNII: 46N107B71O)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	

Product Characteristics

Color	YELLOW (opaque cap and yellow opaque body)	**Score**	no score
Shape	CAPSULE	**Size**	22mm
Flavor		**Imprint Code**	RL17
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63304-011-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	02/07/2018	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA210428	02/07/2018	

Labeler - Sun Pharmaceutical Industries Inc. (146974886)

Registrant - Sun Pharmaceutical Industries Inc. (146974886)

Establishment

Name	Address	ID/FEI	Business Operations
Ohm Laboratories Inc.		184769029	MANUFACTURE(63304-008, 63304-009, 63304-010, 63304-011)

Establishment

Name	Address	ID/FEI	Business Operations
Sun Pharmaceutical Industries Limited		862278942	API MANUFACTURE(63304-008, 63304-009, 63304-010, 63304-011)

Revised: 2/2018 Sun Pharmaceutical Industries Inc.