DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 018704/S-026

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Jia Yifeng
Regulatory Manager
One Health Plaza,
East Hanover, NJ, 07936

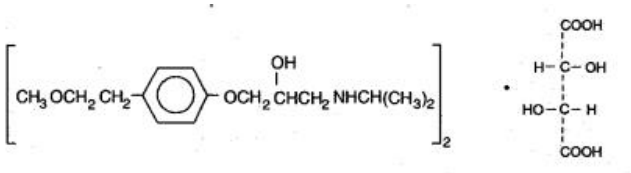
Dear Ms. Yifeng:

Please refer to your Supplemental New Drug Application (sNDA) dated January 12, 2012, received January 12, 2012 submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lopressor (metoprolol tartrate) 5 mg / 5 ml injection.

This "Prior Approval" supplemental new drug application provides for the following content changes, additional minor changes were made throughout;

In **DESCRIPTION**;

Lopressor, metoprolol tartrate USP, is a selective beta$_1$-adrenoreceptor blocking agent, available ~~as 50- and 100-mg tablets for oral administration and~~ in 5-mL ampuls for intravenous administration. Each ampul contains a sterile solution of metoprolol tartrate USP, 5 mg, and sodium chloride USP, 45 mg, and water for injection USP. Metoprolol tartrate USP is (±)-1-(Isopropylamino)-3-[*p*-(2-methoxyethyl)phenoxy]-2-propanol L-(+)-tartrate (2:1) salt, and its structural formula is



Metoprolol tartrate USP is a white, practically odorless, crystalline powder with a molecular weight of 684.82. It is very soluble in water; freely soluble in methylene chloride, in chloroform, and in alcohol; slightly soluble in acetone; and insoluble in ether.

~~*Inactive Ingredients:* Tablets contain cellulose compounds, colloidal silicon dioxide, D&C Red No. 30 aluminum lake (50-mg tablets), FD&C Blue No. 2 aluminum lake (100-mg tablets), lactose, magnesium stearate, polyethylene glycol, propylene glycol, povidone, sodium starch glycolate, talc, and titanium dioxide.~~

In **CLINICAL PHARMACOLOGY;**

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

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

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

~~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 <u>proper dosage requires individual titration</u>.~~

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

~~In patients with angina pectoris, plasma concentration measured at 1 hour is linearly related to the oral dose within the range of 50-400 mg. Exercise heart rate and systolic blood pressure are reduced in relation to the logarithm of the oral dose of metoprolol. The increase in exercise capacity and the reduction in left ventricular ischemia are also significantly related to the logarithm of the oral dose.~~

Pharmacokinetics

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

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

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

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

Special populations

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

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

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

Clinical Studies:

Hypertension

In controlled clinical studies, Lopressor has been shown to be an effective antihypertensive agent when used alone or as concomitant therapy with thiazide-type diuretics, at oral dosages of 100-450 mg daily. In controlled, comparative, clinical studies, Lopressor has been shown to be as effective an antihypertensive agent as

propranolol, methyldopa, and thiazide-type diuretics, to be equally effective in supine and standing positions.

Angina Pectoris

In controlled clinical trials, Lopressor, administered orally two or four times daily, has been shown to be an effective antianginal agent, reducing the number of angina attacks and increasing exercise tolerance. The oral dosage used in these studies ranged from 100-400 mg daily. A controlled, comparative, clinical trial showed that Lopressor was indistinguishable from propranolol in the treatment of angina pectoris.

In **INDICATIONS AND USAGE**;

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

~~***Angina Pectoris***~~

~~Lopressor is indicated in the long-term treatment of angina pectoris.~~

Myocardial Infarction

Lopressor ampuls ~~and tablets~~ are indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality when used in conjunction with oral Lopressor maintenance therapy. Treatment with intravenous Lopressor can be initiated as soon as the patient's clinical condition allows (see DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS).

~~. Treatment with intravenous Lopressor 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).~~

In **CONTRAINDICATIONS;**

~~***Hypertension and Angina***~~

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

Hypersensitivity to Lopressor 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

Lopressor 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).

In **WARNINGS;**

Heart Failure

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

~~***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 give a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, withdraw Lopressor.~~

Ischemic Heart Disease~~:~~

Do not abruptly discontinue Lopressor therapy in patients with coronary artery disease. ~~Following abrupt cessation of therapy with certain be~~Severe exacerbation of angina, myocardial infarction and ventricular arrhythmias have been reported in patients with coronary artery disease following the abrupt discontinuation of therapy with beta-blockers. ~~ta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred.~~ When discontinuing chronically administered Lopressor, particularly in patients with coronary artery~~ischemic heart~~ disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Lopressor 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 Lopressor therapy abruptly even in patients treated only for hypertension.

Use During Major Surgery

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

Bradycardia

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

Exacerbation of Bronchospastic Diseases

: Patients with bronchospastic disease PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS, should, in general, not receive beta blockers, including Lopressor. Because of its relative $beta_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Because Since $beta_1$ selectivity is not absolute use, a $beta_2$ stimulating agent should be administered concomitantly, and th the lowest possible dose of Lopressor and consider should be used. In these circumstances it would be prudent initially to administering Lopressor 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). Bronchodilators, including $beta_2$ agonists, should be readily available or administered concomitantly.

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 Lopressor 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:

Lopressor 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.

~~***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 give a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, withdraw Lopressor.~~

~~***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 Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Lopressor 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 Lopressor therapy abruptly even in patients treated only for hypertension.~~

~~Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS, including Lopressor. Because of its relative beta$_1$ selectivity, however, Lopressor 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 beta$_2$ stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor 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 Lopressor 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 Lopressor, monitor the hemodynamic status of the patient. If heart failure occurs or persists despite appropriate treatment, discontinue Lopressor.~~

~~***Bradycardia:*** Lopressor 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 (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, discontinue Lopressor and consider cautious administration of isoproterenol or installation of a cardiac pacemaker.~~

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

~~If heart block occurs, discontinue Lopressor and administer atropine (0.25-0.5 mg) intravenously. If treatment with atropine is not successful, consider administration of isoproterenol or installation of a cardiac pacemaker.~~

~~***Hypotension:*** If hypotension (systolic blood pressure ≤90 mmHg) occurs, discontinue Lopressor, and assess the hemodynamic status of the patient and the extent of myocardial damage. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Institute appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities. If hypotension is associated with sinus bradycardia or AV block, direct treatment at reversing these (see above).~~

In **PRECAUTIONS;**

Risk of Anaphylactic Reactions

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.

Information for Patients

~~Advise patients to take Lopressor 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 Lopressor 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 Lopressor 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 Lopressor.

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 Lopressor 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.~~

Geriatric Use

~~Clinical trials of Lopressor 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 Lopressor. Other reported clinical experience in elderly hypertensive patients has not identified any difference in response from younger patients.~~

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

In **ADVERSE REACTIONS;**

Hypertension and Angina

These adverse reactions were reported for treatment with oral Lopressor. Most adverse effects have been mild and transient.

and

Myocardial Infarction

These adverse reactions were reported from treatment regimens where intravenous Lopressor was administered, when tolerated.

In **DOSAGE AND ADMINISTRATION;**

~~***Hypertension***~~

~~Individualize the dosage of Lopressor tablets. Lopressor tablets should be taken with or immediately following meals.~~

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

~~***Angina Pectoris***~~

~~The dosage of Lopressor tablets should be individualized. Lopressor tablets should be taken with or immediately following meals.~~

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

Myocardial Infarction

Early Treatment: During the early phase of definite or suspected acute myocardial infarction, initiate treatment with Lopressor 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.

Begin treatment in this early phase with the intravenous administration of three bolus injections of 5 mg of Lopressor each; give the injections at approximately 2-minute intervals. During the intravenous administration of Lopressor, monitor blood pressure, heart rate, and electrocardiogram.

In patients who tolerate the full intravenous dose (15 mg), initiate Lopressor tablets, 50 mg every 6 hours, 15 minutes after the last intravenous dose and continue for 48 hours. Thereafter, the maintenance dosage is 100 mg orally twice daily. ~~(see *Late Treatment* below).~~

Start patients who appear not to tolerate the full intravenous dose on Lopressor tablets 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, discontinue Lopressor (see WARNINGS).

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

Special populations

Pediatric patients: No pediatric studies have been performed. The safety and efficacy of Lopressor in pediatric patients have not been established.

Renal impairment: No dose adjustment of Lopressor is required in patients with renal impairment.

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

Geriatric patients (>65 years): 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.

Method of administration:

Parenteral administration of Lopressor (ampoule) should be done in a setting with intensive monitoring.

Note: **Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.**

~~For oral treatment, the tablets should be swallowed un-chewed with a glass of water. Lopressor should always be taken in standardized relation with meals. If the physician asks the patient to take Lopressor either before breakfast or with breakfast, then the patient should continue taking Lopressor with the same schedule during the course of therapy.~~

In **HOW SUPPLIED;**

~~***Lopressor® Tablets***~~

~~***metoprolol tartrate tablets, USP***~~

~~***Tablets 50 mg*** – capsule-shaped, biconvex, pink, scored (imprinted GEIGY on one side and 51 twice on the scored side)~~

~~Bottles of 100.....NDC 0078-0458-05~~

~~***Tablets 100 mg*** – capsule-shaped, biconvex, light blue, scored (imprinted GEIGY on one side and 71 twice on the scored side)~~

~~Bottles of 100.....NDC 0078-0459-05~~

~~Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from moisture and heat.~~

~~*Dispense in tight, light-resistant container (USP).*~~

Lopressor® Injection

metoprolol tartrate injection, USP

Ampuls 5 mL – each containing 5 mg of metoprolol tartrate

Carton of 10 ampuls.....NDC 0078-0400-01

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from light and heat.

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY R SOUTHWORTH
03/14/2013