DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 017963/S-068

SUPPLEMENT APPROVAL

U.S. Pharmaceuticals Holdings I, LLC
Attention: Matthew C. Sandoval
C/O Wood Creek Capital Management LLC
157 Church Street 20th Floor
New Haven CT 06510

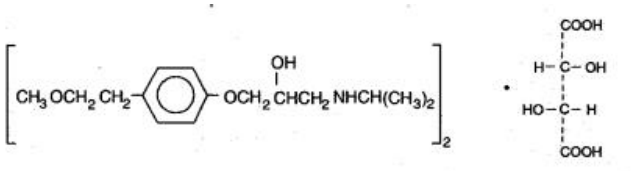
Dear Mr. Sandoval:

Please refer to your Supplemental New Drug Application (sNDA) dated August 14, 2012, received August 14, 2012 submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lopressor (metoprolol tartrate) 50 mg / 100 mg Tablets.

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.

In **INDICATIONS AND USAGE**;

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 alone or in conjunction with intravenous Lopressor. Oral Lopressor therapy can be initiated after intravenous Lopressor therapy or, alternatively, oral

treatment can begin within 3 to 10 days of the acute event (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 **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.

~~**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.

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

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.~~

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

CYP2D6 Inhibitors: Potent inhibitors of the CYP2D6 enzyme may increase the plasma concentration of Lopressor which would mimic the pharmacokinetics of CYP2D6 poor metabolizer (see Pharmacokinetics section). Increase in plasma concentrations of metoprolol would decrease the cardioselectivity of metoprolol. Known clinically significant potent inhibitors of CYP2D6 are antidepressants such as fluvoxamine, fluoxetine, paroxetine, sertraline,bupropion, clomipramine, and desipramine; antipsychotics such as chlorpromazine, fluphenazine, haloperidol, and thioridazine; antiarrhythmics such as quinidine or propafenone; antiretrovirals such as ritonavir; antihistamines such as diphenhydramine; antimalarials such as hydroxychloroquine or quinidine; antifungals such as terbinafine.

In **DOSAGE AND ADMINISTRATION;**

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~~30698-458-01

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~~30698-459-01

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