



NDA 019962/S-044

**SUPPLEMENT APPROVAL**

AstraZeneca LP  
Attention: Ian Wogan  
Regulatory Affairs Director  
1800 Concord Pike  
PO Box 8355  
Wilmington DE, 19803-8355

Dear Mr. Wogan:

Please refer to your Supplemental New Drug Application (sNDA) dated October 30, 2013, received October 30, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Toprol XL (metoprolol succinate) controlled release tablets 25, 50, 100 and 200 mg.

This "Prior Approval" supplemental new drug application provides for revisions to the "Overdose" section.

The following has been added or ~~deleted~~:

Under **Section 10 OVERDOSE**,

Signs and Symptoms - Overdosage of TOPROL-XL 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. Seek consultation with a regional poison control center and a medical toxicologist as needed. 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: ~~Administer intravenous atropine; repeat to effect. If the response is inadequate, consider intravenous isoproterenol or other positive chronotropic agents.~~

Evaluate the need for transvenous pacemaker insertion. 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  $\alpha_1$  receptor agonistic drugs added in presence of vasodilation.

Bronchospasm: ~~Can usually be reversed by bronchodilators. Administer a beta<sub>2</sub> agonist, including albuterol inhalation, or an oral theophylline derivative.~~ Cardiac Failure: ~~Administer diuretics or digoxin for congestive heart failure. For cardiogenic shock, consider IV dobutamine, isoproterenol, or glucagon.~~

## **APPROVAL & LABELING**

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARY R SOUTHWORTH  
05/06/2014