DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-962/S-038

AstraZeneca LP
Attn: Paula R. Clark, Director
Regulatory Affairs
1800 Concord Pike
Box 8355
Wilmington, DE 19803-8355

Dear Ms Clark:

Please refer to your supplemental new drug application dated August 11, 2008 received August 11, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TOPROL XL (metoprolol succinate) 25 mg, 50 mg, 100 mg, and 200 mg Extended Release Tablets.

We acknowledge receipt of your submission dated October 30, 2008.

This "Changes Being Effected" supplemental new drug application provides for revisions to the **WARNINGS** and **OVERDOSAGE** sections of the label as follows:

1. In the **WARNINGS** section, the following paragraph has been added:

   Pheochromocytoma: If TOPROL-XL 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-medicated vasodilatation in skeletal muscle.

2. In the **OVERDOSAGE/Treatment** section, the second paragraph ***Bradycardia*** has been changed from:

   Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

   To:

   Atropine should be given intravenously. If the response is inadequate, isoproterenol or any other agent with positive chronotropic properties may be given cautiously. Under some circumstances, transvenous pacemaker insertion may be necessary.

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

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the attached agreed upon labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, designate this submission "**SPL for approved supplement NDA 19-962/S-038**"

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

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:

Lori Anne Wachter RN, BSN
Regulatory Project Manager
(301) 796 3975

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Agreed-upon labeling text

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

/s/

Norman Stockbridge

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