



NDA 019962/S-041

SUPPLEMENT APPROVAL

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

Dear Mr. Wogan:

Please refer to your supplemental new drug application dated May 28, 2009, received May 28, 2009, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Toprol XL (metoprolol succinate) 25 mg, 50 mg, 100 mg, and 200 mg Extended Release Tablets.

We acknowledge receipt of your submission dated January 14, 2010.

Your submission of January 14, 2010 constituted a complete response to our December 3, 2009 action letter.

This "Changes Being Effected" supplemental new drug application provides for revisions to the **WARNINGS** section of the label to include new language regarding the initiation of high-dose metoprolol prior to surgery. The following changes were made:

1. In **HIGHLIGHTS/WARNINGS AND PRECAUTIONS**, the following text was added as the fourth bullet:

Major Surgery: Avoid initiation of high-dose extended release metoprolol in patients undergoing non-cardiac surgery because it has been associated with bradycardia, hypotension, stroke and death. Do not routinely withdraw chronic beta blocker therapy prior to surgery. (5.5, 6.1)

2. In **ADVERSE REACTIONS/Clinical Trials Experience**, the following text was added:

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, TOPROL-XL 100 mg was started 2 to 4 hours prior to surgery then continued for 30 days at 200 mg per day. TOPROL-XL 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 (1.0% 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.

We have completed our review of this application, as amended, and 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, please submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling (text for the package insert). For administrative purposes, please designate this submission, "SPL for approved NDA 019962/S-041.

PROMOTIONAL MATERIALS

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the following address or by facsimile at 301-847-8444:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

In addition, as required under 21 CFR 314.81(b)(3)(i), you must submit your updated final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA-2253, directly to the above address. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>

LETTERS TO HEALTH CARE PROFESSIONALS

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

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

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:

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Agreed-upon Labeling Text

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-19962	----- SUPPL-41	----- ASTRAZENECA LP	----- TOPROL-XL

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

/s/

Lori A WACHTER
03/19/2010

MARY R SOUTHWORTH
03/19/2010