DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-962/S-024

AstraZeneca LP
Attention: Cindy M. Lancaster
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Lancaster:

Please refer to your supplemental new drug application dated December 12, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Toprol XL (metoprolol succinate) 25, 50, 100, and 200 mg Extended Release Tablets.

This "Changes Being Effected" supplemental new drug application provides for revisions to the prescribing information based on published literature and post-marketing safety and experience.

This supplement proposes the following changes:

1. The first sentence of the CONTRAINDICATIONS section has been changed from:

   TOPROL-XL is contraindicated in severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, and sick sinus syndrome (unless a permanent pacemaker is in place) (see WARNINGS).

   To:

   TOPROL-XL is contraindicated in severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place) (see WARNINGS) and in patients who are hypersensitive to any component of this product.

2. The following two subsections have been added at the end of the WARNINGS section:

   Peripheral Vascular Disease: Beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in such individuals.
   Calcium Channel Blockers: Because of significant inotropic and chronotropic effects in patients treated with beta-blockers and calcium channel blockers of the verapamil and diltiazem type, caution should be exercised in patients treated with these agents concomitantly.

3. The following sentence has been added at the end of the first paragraph, under the PRECAUTIONS/General subsection:

   In patients with pheochromocytoma, an alpha-blocking agent should be initiated prior to the use of any beta-blocking agent.

4. The first sentence under the PRECAUTIONS/Drug Interactions subsection has been changed from:

   Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents.

   To:

Catecholamine-depleting drugs (eg, reserpine, mono amine oxidase (MAO) inhibitors) may have an additive effect when given with beta-blocking agents.

5. The following has been added at the end of the PRECAUTIONS/Drug Interactions subsection:

   Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are coadministered, the beta blocker should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta-blockers should be delayed for several days after clonidine administration has stopped.

6. The second sentence of the ADVERSE REACTONS/Hypertension and Angina subsection has been changed from:

   The following adverse reactions have been reported for metoprolol tartrate.

   To:

   The following adverse reactions have been reported for immediate release metoprolol tartrate.

7. The Post-Marketing Experience subsection, under the ADVERSE REACTIONS section, has been changed from:

   To:

   The following adverse reactions have been reported with TOPROL-XL in worldwide post-marketing use, regardless of causality:
   Cardiovascular: 2nd and 3rd degree heart block.
   Gastrointestinal: hepatitis, vomiting.
   Hematologic: thrombocytopenia.
   Musculoskeletal: arthralgia.
   Nervous System/Psychiatric: anxiety/nervousness, hallucinations, paresthesia.
   Reproductive, male: impotence.
   Skin: increased sweating, photosensitivity.
   Special Sense Organs: taste disturbances.

An additional change was noted in the proposed labeling:

1. The table in the HOW SUPPLIED section has been changed to add a column entitled "Unit Dose Packages of 100 NDC 0186-". The following continuation of the NDC numbers correspond to the tablet doses: 25 mg: 1088-39; 50 mg: 1090-39; 100 mg: 1092-39; 200 mg: N/A.

We completed our review of this supplemental new drug application. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling submitted electronically December 12, 2002.

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, HF-2
FDA
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:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

{See appended electronic signature page}

Douglas C. Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Doug Throckmorton

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