

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

NDA 19-962/S-002

Trade Name: Toprol XL ER Tablets

Generic Name(s): (metoprolol succinate)

Sponsor: Astra Pharmaceutical Products, Inc.

Agent:

Approval Date: June 24, 1992

Indication: Provides for revised FPL

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NDA 19-962/S-002

Approval Letter(s)

NDA 19-962/S-002

JUN 24 1992

ASTRA Pharmaceutical Products, Inc.
Attention: Joseph J. Anisko, Ph.D.
50 Otis Street
Westborough, MA 01581-4500

Dear Dr. Anisko:

We acknowledge the receipt on June 2, 1992 of your June 1, 1992 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Toprol XL (metoprolol succinate) Tablets.

The supplemental application provides for final printed labeling revised as follows:

1. The **Ischemic Heart Disease** subsection under **WARNINGS** has been enclosed in a black box.
2. The following statement has been added to the **DOSAGE AND ADMINISTRATION** section:

Toprol XL tablets are scored and can be divided; however, the whole or half tablet should be swallowed whole and not chewed or crushed.

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Should you have any questions, please contact:

Ms. Zelda McDonald
Consumer Safety Officer
Telephone: (301) 443-4730

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:

Original NDA

HFD-110

HFD-110/CSO

HFD-80/DDIR

HFD-232 (with labeling)

HFD-110/ZMcDonald/6/4/92;6/8/92

sb/6/4/92;ml/6/16/92

R/D: RWolters/6/8/92

WVanArsdel/6/8/92

ADeFelice/6/8/92

CDuarte/6/10/92

NMorgenstern/6/15/92

Approval Date: January 10, 1992

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

19-962/S-002

Approved Labeling

TOPROL XL™ TABLETS

JUN 24 1992

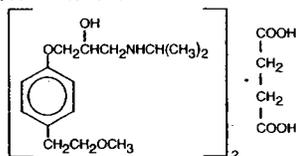
(Metoprolol succinate)

Extended Release Tablets

Tablets: 50 mg, 100 mg, and 200 mg

DESCRIPTION

Toprol XL, metoprolol succinate, is a beta₁-selective (cardioselective) adrenergic receptor blocking agent, for oral administration, available as extended release tablets. Toprol XL has been formulated to provide a controlled and predictable release of metoprolol for once daily administration. The tablets comprise a multiple unit system containing metoprolol succinate in a multitude of controlled release pellets. Each pellet acts as a separate drug delivery unit and is designed to deliver metoprolol continuously over the dosage interval. The tablets contain 47.5 mg, 95 mg and 190 mg of metoprolol succinate equivalent to 50, 100 and 200 mg of metoprolol tartrate, USP, respectively. Its chemical name is (±)1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate (2:1) (salt). Its structural formula is:



Metoprolol succinate is a white crystalline powder with a molecular weight of 652.8. It is freely soluble in water; soluble in methanol; sparingly soluble in ethanol; slightly soluble in dichloromethane and 2-propanol; practically insoluble in ethyl-acetate, acetone, diethylether and heptane. Inactive ingredients: Silicone dioxide, Cellulose compounds, Acetyltributyl citrate, Maize starch, Lactose powder, Polyvidone, Magnesium stearate, Polyethylene glycol, Titanium dioxide, Paraffin.

CLINICAL PHARMACOLOGY

Metoprolol is a beta₁-selective (cardioselective) adrenergic receptor blocking agent. This preferential effect is not absolute, however, and at higher plasma concentrations, metoprolol also inhibits beta₂-adrenoceptors, chiefly located in the bronchial and vascular musculature. Metoprolol has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at plasma concentrations much greater than required for beta-blockade. Animal and human experiments indicate that metoprolol slows the sinus rate and decreases AV nodal conduction.

Clinical pharmacology studies have confirmed the beta-blocking activity of metoprolol in man, as shown by (1) reduction in heart rate and cardiac output at rest and upon exercise, (2) reduction of systolic blood pressure upon exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

The relative beta₁-selectivity of metoprolol has been confirmed by the following: (1) In normal subjects, metoprolol is unable to reverse the beta₂-mediated vasodilating effects of epinephrine. This contrasts with the effect of nonselective beta-blockers, which completely reverse the vasodilating effects of epinephrine. (2) In asthmatic patients, metoprolol reduces FEV₁ and FVC significantly less than a nonselective beta-blocker, propranolol, at equivalent beta₁-receptor blocking doses.

In five controlled studies in normal healthy subjects, the same daily doses of Toprol XL and immediate release metoprolol were compared in terms of the extent and duration of beta₁-blockade produced. Both formulations were given in a dose range equivalent to 100-400 mg of immediate release metoprolol per day. In these studies, Toprol XL was administered once a day and immediate release metoprolol was administered once to four times a day. A sixth controlled study compared the beta₁-blocking effects of a 50 mg daily dose of the two formulations. In each study, beta₁-blockade was expressed as the percent change from baseline, in exercise heart rate following standardized submaximal exercise tolerance tests at steady state. Toprol XL administered once a day, and immediate release metoprolol administered once to four times a day, provided comparable total beta₁-blockade over 24 hours (area under the beta₁-blockade versus time curve) in the dose range 100-400 mg. At a dosage of 50 mg once daily, Toprol XL produced significantly higher total beta₁-blockade over 24 hours than immediate release metoprolol. For Toprol XL, the percent reduction in exercise heart rate was relatively stable throughout the entire dosage interval and the level of beta₁-blockade increased with increasing doses from 50 to 300 mg daily. The effects at peak/trough (i.e. at 24 hours post dosing) were; 14/9, 16/10, 24/14, 27/22 and 27/20% reduction in exercise heart rate for doses of 50, 100, 200, 300 and 400 mg Toprol XL once a day, respectively. In contrast to Toprol XL immediate release metoprolol given at a dose of 50-100 mg once a day, produced a significantly larger peak effect on exercise tachycardia, but the effect was not evident at 24 hours. To match the peak to trough ratio obtained with Toprol XL over the dosing range of 200 to 400 mg, a t.i.d. to q.i.d. divided dosing regimen was required for immediate release metoprolol.

The relationship between plasma metoprolol levels and reduction in exercise heart rate is independent of the pharmaceutical formulation. Using the E_{max} model, the maximal beta₁-blocking effect has been estimated to produce a 28.3% reduction in exercise heart rate. Beta₁-blocking effects in the range of 30-80% of the maximal effect (corresponding to approximately 8-23% reduction in exercise heart rate) are expected to occur at metoprolol plasma concentrations ranging from 30-540 nmol/L. The concentration-effect curve begins reaching a plateau between 200-300 nmol/L, and higher plasma levels produce little additional beta₁-blocking effect. The relative beta₁-selectivity of metoprolol diminishes and blockade of beta₂-adrenoceptors increases at higher plasma concentrations.

Although beta-adrenergic receptor blockade is useful in the treatment of angina and hypertension, there are situations in which sympathetic stimulation is vital. In patients with severely damaged hearts, adequate ventricular function may depend on sympathetic drive. In the presence of AV block, beta-blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta₂-adrenergic blockade results in passive bronchial constriction by interfering with endogenous adrenergic bronchodilator activity in patients subject to bronchospasm and may also interfere with exogenous bronchodilators in such patients.

Hypertension

The mechanism of the antihypertensive effects of beta-blocking agents has not been elucidated. However, several possible mechanisms have been proposed: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output; (2) a central effect leading to reduced sympathetic outflow to the periphery; and (3) suppression of renin activity.

In controlled clinical studies, an immediate release dosage form of metoprolol has been shown to be an effective antihypertensive agent when used alone or as concomitant therapy with thiazide-type diuretics at dosages of 100-450 mg daily. Toprol XL, in dosages of 100 to 400 mg once daily, has been shown to possess comparable β_1 -blockade as conventional metoprolol tablets administered two to four times daily. In addition, Toprol XL administered at a dose of 50 mg once daily has been shown to lower blood pressure 24-hours post-dosing in placebo controlled studies. In controlled, comparative, clinical studies, immediate release metoprolol appeared comparable as an antihypertensive agent to propranolol, methyldopa, and thiazide-type diuretics, and affected both supine and standing blood pressure. Because of variable plasma levels attained with a given dose and lack of a consistent relationship of antihypertensive activity to drug plasma concentration, selection of proper dosage requires individual titration.

Angina Pectoris

By blocking catecholamine-induced increases in heart rate, in velocity and extent of myocardial contraction, and in blood pressure, metoprolol reduces the oxygen requirements of the heart at any given level of effort, thus making it useful in the long-term management of angina pectoris. However, in patients with heart failure, beta-adrenergic blockade may increase oxygen requirements by increasing left ventricular fiber length and end-diastolic pressure.

In controlled clinical trials, an immediate release formulation of metoprolol has been shown to be an effective antianginal agent, reducing the number of angina attacks and increasing exercise tolerance. The dosage used in these studies ranged from 100 to 400 mg daily. Toprol XL, in dosages of 100 to 400 mg once daily, has been shown to possess comparable β_1 -blockade as conventional metoprolol tablets administered two to four times daily.

Pharmacokinetics

In man, absorption of metoprolol is rapid and complete. Plasma levels following oral administration of conventional metoprolol tablets, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism. Metoprolol crosses the blood-brain barrier and has been reported in the CSF in a concentration 78% of the simultaneous plasma concentration.

Plasma levels achieved are highly variable after oral administration. Only a small fraction of the drug (about 12%) is bound to human serum albumin. Elimination is mainly by biotransformation in the liver, and the plasma half-life ranges from approximately 3 to 7 hours. Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no clinical significance. Following intravenous administration of metoprolol, the urinary recovery of unchanged drug is approximately 10%. The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. Consequently, no reduction in dosage is usually needed in patients with chronic renal failure.

In comparison to conventional metoprolol, the plasma metoprolol levels following administration of Toprol XL are characterized by lower peaks, longer time to peak and significantly lower peak to trough variation. The peak plasma levels following once daily administration of Toprol XL average one-fourth to one-half the peak plasma levels obtained following a corresponding dose of conventional metoprolol, administered once daily or in divided doses. At steady state the average bioavailability of metoprolol following administration of Toprol XL, across the dosage range of 50 to 400 mg once daily, was 77% relative to the corresponding single or divided doses of conventional metoprolol. Nevertheless, over the 24 hour dosing interval, β_1 -blockade is comparable and dose-related (see CLINICAL PHARMACOLOGY). The bioavailability of metoprolol shows a dose-related, although not directly proportional increase with dose and is not significantly affected by food following Toprol XL administration.

INDICATIONS AND USAGE

Hypertension

Toprol XL tablets are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents.

Angina Pectoris

Toprol XL tablets are indicated in the long-term treatment of angina pectoris.

CONTRAINDICATIONS

Hypertension and Angina

Toprol XL is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS

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 hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Toprol XL should be administered cautiously. Both digitalis and Toprol XL slow AV conduction.

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, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Toprol XL should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Toprol XL, particularly in patients with 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, Toprol XL 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 Toprol XL therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS. Because of its relative beta₁-selectivity, however, Toprol XL may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta₁-selectivity is not absolute, a beta₂-stimulating agent should be administered concomitantly, and the lowest possible dose of Toprol XL should be used (see DOSAGE AND ADMINISTRATION).

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Toprol XL like other beta-blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta-blockers.

Diabetes and Hypoglycemia: Toprol XL should be used with caution in diabetic patients if a beta-blocking agent is required. Beta-blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade, which might precipitate a thyroid storm.

PRECAUTIONS

General

Toprol XL should be used with caution in patients with impaired hepatic function.

Information for Patients

Patients should be advised to take Toprol XL regularly and continuously, as directed, preferably 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 Toprol XL without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Toprol XL 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 Toprol XL.

Laboratory Tests

Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

Drug Interactions

Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Toprol XL plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have been conducted to evaluate the carcinogenic potential of metoprolol tartrate. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg/day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg/day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor. All mutagenicity tests performed on metoprolol tartrate (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) and metoprolol succinate (a Salmonella/mammalian-microsome mutagenicity test) were negative.

No evidence of impaired fertility due to metoprolol tartrate was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.

Pregnancy Category C

Metoprolol tartrate has been shown to increase post-implantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when metoprolol tartrate is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Metoprolol is excreted in breast milk in very small quantities. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Toprol XL is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

Risk Of Anaphylactic Reactions

While taking beta-blockers, patients with a history of severe anaphylactic reactions 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.

ADVERSE REACTIONS

Hypertension and Angina

Most adverse effects have been mild and transient. The following adverse reactions have been reported for metoprolol tartrate.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, somnolence, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; syncope; chest pain; and hypotension have been reported in about 1 of 100 patients (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see WARNINGS).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, digestive tract disorders and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, decreased libido and tinnitus have also been reported. There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explainable. The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with metoprolol.

Potential Adverse Reactions

A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Toprol XL.

Central Nervous System: Reversible mental depression progressing to cataplexy; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

OVERDOSAGE

Acute Toxicity

No overdosage has been reported with Toprol XL and no specific overdosage information was obtained with this drug, with the exception of animal toxicology data. However, since Toprol XL (metoprolol succinate salt) contains the same active moiety, metoprolol, as conventional metoprolol tablets (metoprolol tartrate salt), the recommendations on overdosage for metoprolol conventional tablets are applicable to Toprol XL.

Signs and Symptoms

Potential signs and symptoms associated with overdosage with metoprolol are bradycardia, hypotension, bronchospasm, and cardiac failure.

Treatment

There is no specific antidote.

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly. On the basis of the pharmacologic actions of metoprolol tartrate, the following general measures should be employed.

Elimination of the Drug: Gastric lavage should be performed.

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

Hypotension: A vasopressor should be administered, e.g., levarterenol or dopamine.

Bronchospasm: A beta₂-stimulating agent and/or a theophylline derivative should be administered.

Cardiac Failure: A digitalis glycoside and diuretics should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol or glucagon may be considered.

DOSAGE AND ADMINISTRATION

Toprol XL is an extended release tablet intended for once-a-day administration. When switching from immediate release metoprolol tablet to Toprol XL, the same total daily dose of Toprol XL should be used.

As with immediate release metoprolol, dosages of Toprol XL should be individualized and titration may be needed in some patients.

Toprol XL tablets are scored and can be divided; however, the whole or half tablet should be swallowed whole and not chewed or crushed.

Hypertension

The usual initial dosage is 50 to 100 mg daily in a single dose, whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after 1 week of therapy. Dosages above 400 mg per day have not been studied.

Angina Pectoris

The dosage of Toprol XL should be individualized. The usual initial dosage is 100 mg daily, given in a single dose. The dosage may be gradually increased at weekly intervals until optimum clinical response has been obtained or there is a pronounced slowing of the heart rate. Dosages above 400 mg per day have not been studied. If treatment is to be discontinued, the dosage should be reduced gradually over a period of 1-2 weeks (see WARNINGS).

HOW SUPPLIED

Tablets 50 mg:

Contain 47.5 mg of metoprolol succinate equivalent to 50 mg of metoprolol tartrate, USP

Are white, biconvex, round, film-coated

Engraved A_{ms} on one side and scored on the other

Bottles of 100 NDC 0186-1090-05

Tablets 100 mg:

Contain 95 mg of metoprolol succinate equivalent to 100 mg of metoprolol tartrate, USP

Are white, biconvex, round, film-coated

Engraved A_{ms} on one side and scored on the other

Bottles of 100 NDC 0186-1092-05

Tablets 200 mg:

Contain 190 mg of metoprolol succinate equivalent to 200 mg of metoprolol tartrate, USP

Are white, biconvex, oval, film-coated

Engraved A_{ms} and scored on one side

Bottles of 100 NDC 0186-1094-05

Store at controlled room temperature 15°-30°C (59°-86°F).

Manufactured by:

Astra Pharmaceutical Production, AB

Södertälje, Sweden

Manufactured for:

ANTRA © Astra Pharmaceutical Products, Inc.
Westborough, MA 01581

5/92 (2)

JUN 24 1992

CSO Review of Final Printed Labeling
NDA 19-962/S-002

Date of Submission: June 1, 1992
Date of Review: June 4, 1992
Applicant Name: Astra Pharmaceutical Products, Inc.

Product Name: Toprol XL (metoprolol succinate) Tablets

Evaluation:

This submission provides for final printed labeling in accordance with our supplement request letter dated April 2, 1992 wherein we asked that the Ischemic Heart Disease subsection under the WARNINGS section be enclosed in a black box. We had inadvertently failed to enclose that section in a black box at the time of approval of the application.

The revised labeling also includes the addition of the following statement to the DOSAGE AND ADMINISTRATION section:

"Toprol XL tablets are scored and can be divided; however, the whole or half tablet should be swallowed whole and not chewed or crushed."

This statement was requested by Dr. Wolters in a telephone conversation with Dr. Anisko. Dr. Wolters and I subsequently agreed with Dr. Anisko that the statement could be added when this supplement was submitted.

There are no other changes from the last approved labeling.

Recommendation:

An acknowledge and approve letter should issue for S-002 as set forth under CFR 314.70 (c) (2) (i) [To add or strengthen a warning] and (iii) [To add or strengthen and instruction about dosage and administration that is intended to increase the safe use of the product].

Zelda McDonald
Zelda McDonald, CSO

cc: Orig. NDA
HFD-110
HFD-111/McDonald
HFD-111/Benton