

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

19-962/S-013

Pharmacology Review(s)

Z. Mc Donnell

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NDA 19-962 /S-013

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

A. DeFelice,
February 1, 2000

SUPPLEMENT 013 DATED: September 10, 1999.
CENTER RECEIPT DATE: September 10, 1999.
REVIEWER RECEIPT DATE: September 13, 1999.

SPONSOR: AstraZeneca LP

DRUG: Toprol-XL (Metoprolol succinate)

CHEMICAL NAME: 1-isopropylamino-3-[p-(2-methoxyethyl) phenoxy]-2-propanol
(2:1) succinate.

MOLECULAR WEIGHT: 652.8

FORMULATION: Extended release tablets containing 47.5, 95, or 190 mg of metoprolol succinate equivalent to 50, 100, or 200 mg of metoprolol tartrate, USP, respectively. Inactive ingredients comprised of GRAS excipients.

CATEGORY: Selective Beta-1 adrenoceptor antagonist devoid of appreciable intrinsic sympathomimetic or membrane-stabilizing activities.

PROPOSED INDICATION: Congestive heart failure. Approved previously for treatment of essential hypertension and angina pectoris as the **succinate** salt (Toprol-XL: AstraZeneca), **tartrate** salt (Lopressor: CibaGeigy, now Novartis; NDAs 17963 and 18704), and **fumarate** salt (Lopressor SR: Ciba Geigy, now Novartis; NDA 19786 OROS formulation).

PROPOSED DOSING REGIMEN: Up to 200 mg once daily, i.e., one-half the MRHD for the other approved indications.

INTRODUCTION: Toprol-XL, i.e., metoprolol succinate, was approved in 1992 for sole or combination therapy of primary hypertension, and for long-term treatment of angina pectoris. The fumarate salt, as an extended release OROS formulation, is also available by prescription. For the proposed new CHF indication, it is intended to be used combined with diuretics, ACE-inhibitors, and/or digitalis i.e., as tested in the phase III clinical trials which comprise approximately 4500 CHF patients. Clinical efficacy and safety in patients with hypertension and/or angina pectoris is based on 13 years world-wide marketing experience.

Preclinical pharmacology and toxicology of metoprolol **tartrate** has been previously reviewed by Dr. C. Resnick (NDA 17963 : reviews dated 12/22/77 and 3/19/82); and that of metoprolol **succinate** by Dr. W. VanArsdel (NDA 19962 : review dated 8/28/1990).

NONCLINICAL PHARMACOLOGY and TOXICOLOGY:

Sponsor refers to their prior NDA 19-962 (Metoprolol CR; AB Hassle, Astra Group, Molndal, Sweden) for all nonclinical pharmacology, toxicology, and ADME studies of metoprolol succinate. According to sponsor, no additional nonclinical pharmacology, toxicology, or disposition studies of metoprolol succinate were conducted by AstraZeneca beyond those that were performed, and submitted, for NDA 19-962. Sponsor further states that they conducted a comprehensive search of the nonclinical metoprolol literature and found no citations of new toxicological findings relevant to metoprolol succinate safety. An inventory of previously submitted animal toxicology studies of metoprolol tartrate and succinate includes acute toxicity in three species; lifetime carcinogenicity studies in mouse and rat; one-year study in dog; segment

I, II, and III reproductive toxicity studies in rats and rabbits; genotoxicity studies (dominant lethal, mice; clastogenicity in somatic cells; salmonella/ mammalian microsome mutagenicity assays; nucleus anomaly test in somatic interphase nuclei), and ADME studies.. These studies were interpretable, and supported approval of metoprolol in 1992 for other cardiovascular indications.

Sponsor did not study metoprolol in an animal model of congestive heart failure to support the proposed new indication. However sponsor previously performed a cardiovascular safety (pharmacology) study pertinent to the current CHF indication, and identified dose-related myocardial depressant activity of metoprolol (Hassle's report no 220-0147). [Direct cardiac depressant activity of phenoxy isopropyl amino propanols , such as metoprolol and propranolol, is usually attributed to membrane-stabilizing i.e., local anesthetic, activity.] However, as calculated from data included in Dr VanArsdel's NDA 19-962 review of 8/28/90, the metoprolol dosage causing cardiac depression (i.e., approx. 40% reduction in blood pressure and LV dp/dt) in anesthetized dogs is 15 micromoles/Kg of either the succinate or tartrate salt vs. 0.22 micromoles/Kg required for beta-blockade (i.e., approx. 40% inhibition of the beta adrenoceptor - mediated tachycardic effect of cardioaccelerator nerve stimulation). Accordingly, the safety ratio for cardiac depressant activity vs. beta-blocking activity in the dog (15/0.22) is approx. 70. This supports the statement in the Clinical Pharmacology portion of the labelling that membrane-stabilizing activity is detectable only at plasma concentrations much greater than required for beta-blockade

RECOMMENDATION: Approval from the pre-clinical standpoint. No new safety pharmacology or toxicology studies were performed, or are needed, for the proposed congestive heart failure indication.. However, a propos the new CHF indication , Sponsor had previously established that, at least in the healthy anesthetized dog, direct myocardial depressant activity occurs only at an exposure several orders of magnitude greater than that affording targeted pharmacological activity.

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