

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**19-962/S-013**

**Chemistry Review(s)**

Application: NDA 19962/013      Action Goal:  
Stamp: 10-SEP-1999      District Goal: 05-JUN-2000  
Regulatory Due: 10-JUL-2000      Brand Name: TOPROL-XL (METOPROLOL  
Applicant: ASTRAZENECA      SUCCINATE) TABLETS  
725 CHESTERBROOK BLVD      Estab. Name:  
WAYNE, PA 190875677      Generic Name: METOPROLOL SUCCINATE  
Priority: 2S      Dosage Form: (EXTENDED-RELEASE TABLET)  
Org Code: 110      Strength: 50 MG, 100 MG, 200 MG

Application Comment: ADDITION OF THE ASTRAZENECA FACILITY IN NEWARK, DELAWARE AS AN  
ALTERNATE PACKAGING SITE FOR 100 TABLETS PER BOTTLE OF TOPROL-  
XL 25 MG TABLETS. THE PREVIOUS NAME OF THIS FACILITY WAS ZENECA  
PHARMACEUTICALS. THE NAME WAS CHANGED AFTER THE MERGER OF JUNE  
1, 1999. (on 17-MAR-2000 by R. MITTAL (HFD-110) 301-594-5353)

FDA Contacts: Z. MCDONALD (HFD-110) 301-594-5300 , Project Manager  
R. MITTAL (HFD-110) 301-594-5353 , Review Chemist  
K. SRINIVASACHAR (HFD-110) 301-594-5376 , Team Leader

Overall Recommendation: ACCEPTABLE on 27-MAR-2000 by J. D AMBROGIO (HFD-324) 301-827-  
0062

## Establishment:

ZENECA PHAMACEUTICALS  
587 OLD BALTIMORE PIKE  
NEWARK, DE 19702

DMF No:      AADA:  
Responsibilities: FINISHED DOSAGE PACKAGER  
Profile: TCT      OAI Status: NONE  
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	17-MAR-2000				MITTALR
SUBMITTED TO DO	17-MAR-2000	GMP			FERGUSONS
DO RECOMMENDATION	27-MAR-2000			ACCEPTABLE BASED ON FILE REVIEW	DPAGANO
OC RECOMMENDATION	27-MAR-2000			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

PACKAGING OPERATIONS ARE ACCEPTABLE AT THIS FACILITY.

**APPEARS THIS WAY  
ON ORIGINAL**

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 19-962

REVIEW DATE: 26-JUN-2000

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE
SUPPLEMENT S-013	15-NOV-99	17-NOV-99
AMENDMENT TO S-013	26-JAN-00	28-JAN-00
SNC S-013	02-FEB-00	04-FEB-00
AMENDMENT TO S-013	03-FEB-00	04-FEB-00
AMENDMENT TO S-013	03-MAR-00	04-MAR-00
AMENDMENT TO S-013	13-APR-00	14-APR-00
AMENDMENT TO S-013	17-MAY-00	19-MAY-00

NAME & ADDRESS OF APPLICANT AstraZeneca LP  
725 Chestbrook Blvd  
Wayne PA 19087-5677

Supplements Provides For:

A new strength in conjunction with a new indication of 23.75 mg extended release tablet of metoprolol succinate, corresponding to 25 mg of metoprolol tartrate, USP.

DRUG PRODUCT NAME

Proprietary: TOPROL-XL™  
Non-Propriety/USNAM: Metoprolol Succinate Extended Release Tablets

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL. CATEGORY/INDICATION: Beta-adrenergic blocker/Hypertension, Angina Post MI

DOSAGE FORM: Tablet, controlled Release formulation

STRENGTH: 25 mg.

ROUTE OF ADMINISTRATION: ORAL

DISPENSED: Rx

CHEMICAL NAME, CAS REGISTRY NUMBER, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

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

MOLECULAR FORMULA: C<sub>30</sub>H<sub>50</sub>N<sub>2</sub>O<sub>6</sub>·C<sub>4</sub>H<sub>6</sub>O<sub>4</sub>

MOLECULAR WEIGHT: 653

STRUCTURAL FORMULA:

**CONSULTS:**

Biopharm - Recommended for Approval as the study results show that it is bioequivalent to the commercially available metoprolol succinate CR/XL 50 mg tablet at equivalent doses of 50 mg. Dissolution specifications are same as that for the approved strengths.

**REMARKS/COMMENTS:**

This is an efficacy supplement for the approval of a new lower strength for the new indication of heart failure. The main reason for developing the 23.75 mg strength tablet was to able to start treatment with a lower dose than the strengths already on the market. EER for the alternate packaging facility is ACCEPTABLE.

**CONCLUSIONS & RECOMMENDATIONS:**

The supplement is recommended for approval.

Expiry date of \_\_\_\_\_ for the approved strengths will also be used for the 23.75 mg tablets.

The routine stability program should include a \_\_\_\_\_ interval.

It is recommended that, the storage statement, \_\_\_\_\_ in the package insert and container labels for all strengths of the metoprolol succinate tablets be replaced by the following:

"Store at 25°C (77°F); excursions permitted to 15-30 °C (59-86°F)  
[see USP Controlled Room temperature]"

A change in name of AstraUSA to AstraZeneca should be made in the labeling.

cc:

Orig. NDA

HFD-110/Division File

HFD-110/Ram Mittal/date

HFD-110/ZMcDonald

R/D Init by: KSrinivasachar

JSI  
Ramsharan D. Mittal Ph.D., Review Chemis  
filename: C:\NDA\19962\19962S013.doc

JSI  
6-27-00

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