CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-956

CHEMISTRY REVIEW(S)

NDA 21-956
Metoprolol Succinate and Hydrochlorothiazide

AstraZeneca LP
Division of Cardio-Renal Products

Haripada Sarker, Ph.D.
ONDQA, DPA I

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Chemistry Review Data Sheet

1. NDA 21-956

2. REVIEW #1:

3. REVIEW DATE: 7-26-2006

4. REVIEWER: Haripada Sarker, Ph.D.

1. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original (N-000)	October 28, 2005
Original (N-000)BC	January 5, 2006
Original (N-000)BC	February 27, 2006
Original (N-000)BC	April 19, 2006
Original (N-000)BC – Biopharm. Amendment	May 15, 2006
Original (N-000)BC – Response to comments	June 8, 2006
Original (N-000)BL – Response to labeling comments	June 26, 2006
Original (N-000)BC – Response to CMC comments	July 7, 2006

7. NAME & ADDRESS OF APPLICANT:

Name:	AstraZeneca LP
Address:	1800 Concord Pike P.O. Box 8355 Wilmington, DE 19803
Representative:	Dianne S. Alleva
Telephone:	302-885-8845

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: To be determined
b) Non-Proprietary Name: Metoprolol Succinate Extended Release and Hydrochlorothiazide
c) Code Name/#: N/A
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 3 (new formulation)
- Submission Priority: S

e) Proposed Trade Name: Dutoprol™

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Treatment of Hypertension.

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 25mg/12.5mg; 50mg/12.5mg; 100mg/12.5mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

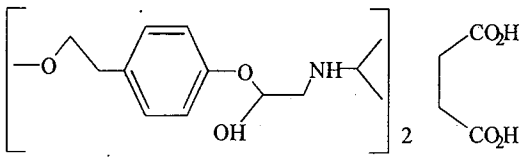
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

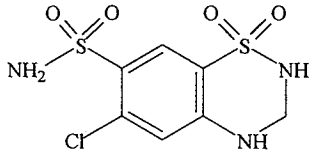
__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Structure:



Metoprolol Succinate



Hydrochlorothiazide (HCT)

Name (drug substance)	Metoprolol	Hydrochlorothiazide USP
Chemical Name (USAN)	(±)-1-(isopropylamino)-3-[p-(2-methoxyethyl)phenoxy]-2-propanol succinate (2:1) (salt)	*2H*-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro-,1,1-dioxide 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide
Chemical Name		
CAS number	98418-47-4	58-93-5
Molecular Weight	652.82	297.74
Molecular Formula	$C_{15}H_{25}NO_3.C_4H_6O_4$	$C_7H_8ClN_3O_4S_2$
Structural formula	As above	As above

17. RELATED/SUPPORTING DOCUMENTS:

A. **DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COM-PLETED	COMMENTS
				3	N/A	N/A	Not reviewed
				4	N/A	N/A	Not reviewed
				4	N/A	N/A	Not reviewed
				4	N/A	N/A	Not reviewed
				4	N/A	N/A	Not reviewed
				1	Adequate	N/A	Reviewed

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

Previous Documents	Document Date
IND 67,095	March 17, 2003
IND 40,602	September 18, 1992
NDA 19-962	December 22, 1989

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	30-June-06	J. D. Ambrogio
Biopharm	Pending	9-SEPT-05	Lydia Velazquez
DMETS/DDMAC	Submitted by CSO	DMETS Pending/DDMAC 13-June-2006	Lisa Hubbard, DDMAC
Methods Validation	No need		Haripada Sarker
EA (Categorical Exclusion)	Acceptable	3-April-06	Haripada Sarker
Microbiology	N/A		N/A

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The Chemistry Review for NDA ———

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for APPROVAL from a chemistry, manufacturing and controls standpoint because:

The applicant addressed all the deficiencies satisfactorily. The following comments regarding shelf-life for the drug product should be included in the action letter:

"A shelf-life of twenty four months for the drug product will be granted based on stability data provided"

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

———™ is a combination product, and formulated as tablets strengths, containing 23.75 mg/6.25 mg, 23.75 mg/12.5 mg, 47.5 mg/12.5 mg and 95 mg/12.5 mg of metoprolol succinate and hydrochlorothiazide respectively as active ingredients. The lowest strength 23.75 mg/6.25 mg will not be marketed in the US, but information is included in the document for completeness. Metoprolol succinate is present in the drug as extended release bead. Inactive ingredients in the combination drug include Silicon dioxide, Ethylcellulose, Hydroxypropyl cellulose ——— Corn starch, Microcrystalline cellulose, ——— and Sodium stearyl Fumarate.

——— Metoprolol extended release tablet (USP) is an approved drug, and Hydrochlorothiazide (USP) immediate release formulations are approved under various NDAs.

All strengths of the drug are controlled by single specifications, except descriptions and API content. The drug product is stored at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F). [See USP Controlled Room Temperature]. The amount of drug product impurity, ——— The applicant proposed 24 months of shelf-life for the drug product. Based on primary and supportive stability data, an expiration dating period of 24 months may be granted for 100 count bottles, and ———

The chemical name of Metoprolol and Hydrochlorothiazide are (±)-1-(isopropylamino)-3-[p-(2-methoxyethyl)phenoxy]-2-propanol succinate (2:1) (salt) and 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro-,1,1-dioxide respectively. Both Metoprolol and Hydrochlorothiazide drug substances are well characterized and have USP monographs. The applicant referred to NDA 19-962 for Metoprolol —, and DMF — for Hydrochlorothiazide — Hydrochlorothiazide — was utilized for number of approved drugs in single or in combination products. No new controls or retest periods are proposed for Metoprolol and Hydrochlorothiazide drug substances.

B. Description of How the Drug Product is Intended to be Used

— ™ tablets of different strengths are supplied as following: — ™ 25/12.5 (NDC 0186-1087-05) yellow, circular, biconvex, film-coated tablet engraved with "A" above "IH" on one side, are supplied in bottles of 100. — 50/12.5 (NDC 0186-1095-05) light orange, circular, biconvex, film-coated tablet engraved with "A" above "IK" on one side, are supplied in bottles of 100. — 100/12.5 (NDC 0186-1097-05) yellow, circular, biconvex, film-coated tablet engraved with "A" above "IL" on one side and scored on the other side, are supplied in bottles of 100. The drug will be administered orally.

The effective doses of Hydrochlorothiazide were 6.25 mg to 25 mg, and metoprolol succinate extended release in doses of 25 to 200 mg. The lowest trade name tablet available is 25/12.5. A 50/6.25 dose can be achieved by splitting the 100/12.5 tablet. Applicant has demonstrated that there is no difference between halved tablets and whole tablets.

C. Basis for Approvability Recommendation

This application is recommended for APPROVAL from the stand point of chemistry, manufacturing and controls because all the deficiencies have been satisfactorily addressed and the office of compliance has provided an overall acceptable recommendation.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Haripada Sarker, Ph.D.
ChemistryBranchChief/Date: Ramesh Sood, Ph.D.
ProjectManagerName/Date: Alisea Sermon

C. CC Block

69 Page(s) Withheld

X Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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

/s/

Haripada Sarker
7/26/2006 10:02:47 AM
CHEMIST

Ramesh Sood
7/26/2006 10:17:10 AM
CHEMIST