CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-838

CHEMISTRY REVIEW(S)

K. Bongiovanni

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

JUN 1 - 1998

NDA #: 20-838 **CHEM.REVIEW #:** 4 **REVIEW DATE:** May 29, 1998

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	30-Apr-97	30-Apr-97	05-May-97
Amendment (BZ)	05-May-98	05-May-98	18-May-98
" (BC)	12-May-98	13-May-98	21-May-98
" "	22-May-98	22-May-98	22-May-98
" "	22-May-98	22-May-98	29-May-98

Amendment provides for:

Amendment (BZ) - Response to FDA concerns voiced at May 8, 1998 meeting with Drs. Ahmed A. El-Tahtawy and Ameeta Parekh regarding dissolution specifications.
" (BC) - Submission of a product specific, in-process, sampling plan, as requested in Agency letter dated April 28, 1998.
" " - Submission of camera-ready proof labeling.
" " - Submission of updated methods validation package.

NAME & ADDRESS OF APPLICANT:

Address:	Astra Merck 725 Chesterbrook Blvd. Wayne, PA 19087-5677
Responsible Official:	Daniel J. Cushing
Phone:	(610) 695-1370
FAX:	(610) 695-1828

DRUG PRODUCT NAME:

Proprietary:	ATACAND™ Tablets (US and Europe) BLOPRESS™ Tablets (Japan)
Nonproprietary:	Candesartan cilexetil tablets
CAS Registry Number:	145040-37-5
Code Names:	TCV-116(Takeda)and H 212/91(Astra Merck)
Chemical type/Therapeutic Class:	1S

ANDA SUITABILITY PETITION/DESI/PATENT STATUS: (01-001-022)- Satisfactory

See previous reviews for this information.

PHARMACOL.CATEGORY/INDICATION: Treatment of hypertension, non-peptide, AT_1-subtype Angiotensin II Receptor Antagonist.

DOSAGE FORM:	Tablet 32 mg
STRENGTHS:	4, 8, 16 mg/tablet
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	Rx

REMARKS/COMMENTS:

The information submitted is complete according to Dr. Ahmed A. El-Tahtawy. The firm will revise the specifications for the 32 mg. tablet later, based on a review of their production batches.

The firm has submitted a product specific sampling plan and revised methods validation package.

CONCLUSIONS & RECOMMENDATIONS:

These amendments are recommended for approval. The firm has fulfilled all requests and commitments.

5/29/98

Joseph T. Piechocki, Ph.D.
Review Chemist

cc:
Orig. NDA 20-838
HFD-110/Division File
HFD-110/PiechockiJ/5/29/98
HFD-100/BongiovaniK
District
HFD-102

R/D Init. by: Dr. Kasturi Srinivasachar 20838R04.doc

K Srinivasachar 6-1-98

APPEARS THIS WAY
ON ORIGINAL

BOLUS IV INJ

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

MAR 31 1998

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-838 **CHEM.REVIEW #:** 4 **REVIEW DATE:** Mar. 25, 1998

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	30-Apr-97	30-Apr-97	05-May-97
Amendment (BC)	19-Mar-98	19-Mar-98	20-Mar-98

Amendments provide for:

Amendment (BC)-Response to FDA CMC deficiencies noted in Agency letters dated 1/16/98 and 3/10/98.
-Updated 24 months stability data.

NAME & ADDRESS OF APPLICANT:

Address: Astra Merck
725 Chesterbrook Blvd.
Wayne, PA 19087-5677
Responsible Official: Daniel J. Cushing
Phone: (610) 695-1370
FAX: (610) 695-1828

Proprietary: **ATACAND™ Tablets** (US and Europe)
BLOPRESS™ Tablets (Japan)
Nonproprietary: Candesartan cilexetil tablets
CAS Registry Number: 145040-37-5
Code Names: TCV-116(Takeda)and H 212/91(Astra Merck)
Chemical type/Therapeutic Class: 1S

ANDA Suitability Petition/DESI/Patent Status: (01-001-022)- Satisfactory

See previous reviews for this information.

PHARMACOL.CATEGORY/INDICATION: Treatment of hypertension, non-peptide, AT_1-subtype Angiotensin II Receptor Antagonist.

DOSAGE FORM: Tablet
STRENGTHS: 4, 8, 16 mg/tablet
ROUTE OF ADMINISTRATION: Oral
DISPENSED: __X__ Rx _____ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT

See previous reviews for this information.

Molecular Formula: $C_{33}H_{34}N_6O_6$
Molecular Weight: 610.67
Chemical Name: ±)-1-(cyclohexyloxycarbonyloxy) ethyl 2-ethoxy-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate

SUPPORTING DOCUMENTS:

See previous reviews for this information.

RELATED DOCUMENTS (if applicable):

See previous reviews for this information.

CONSULTS:

None

REMARKS/COMMENTS:

The information submitted seems complete, except for the sampling plan.

CONCLUSIONS & RECOMMENDATIONS:

The firm needs to submit their sampling SOP's for review. This is a minor problem poses no safety or efficacy concerns for the consumer and therefore it is recommended this item not delay approval of the extended expiration date. It is suggested that an Approvable letter be issued, requiring the firm to commit to remedy this in their first future submission to this document.

Joseph T. Piechocki, Ph.D.
Review Chemist

cc:

Orig. NDA 20-838
HFD-110/Division File
HFD-110/PiechockiJ/3/25/98
HFD-100/BongiovaniK
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HFD-810/CHoiberg

R/D Init. by: JHShort 20838R03.doc

APPEARS THIS WAY
ON ORIGINAL

FEB 18 1998

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-838 **CHEM.REVIEW #:** 3 **REVIEW DATE:** 3-Feb-98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	30-Apr-97	30-Apr-97	05-May-97
Amendment (BZ)	15-Jul-97	16-Jul-97	17-Jul-97
Amendment	12-Aug-97	13-Aug-97	14-Aug-97
Amendment (BC)	30-Sep-97	01-Oct-97	06-Oct-97
Amendment (BZ)	02-Dec-97	03-Dec-97	03-Dec-97
Amendment (BC)	10-Dec-97	11-Dec-97	15-Dec-97
Amendment (BC)	19-Dec-97	19-Dec-97	24-Dec-97

Amendments provide for:

Amendment 12-Aug-97 had been previously reviewed.

Amendment (BZ) July 15, 1997 Submission of dissolution data for clinical and marketed batches.

Amendment (BC) (30-Sep-97) Submission of updated stability data for:
1. 18 months data for drug substance produced at the Takeda Modified Plant 1.
2. 6 months data for drug substance produced at Takeda's Plant No. 2.
3. 18 months data and statistical analysis for 4, 8 and 16 mg Atacand™ tablets.

Amendment (BZ) (02-Dec-97) Submission of an electronic copy of dissolution data from clinical and commercial batches.

Amendment (BC) (10-Dec-97) Submission of original methods validation procedures.

Amendment (BC) (19-Dec-97) Submission of an additional dosage strength, 32 mg.

NAME & ADDRESS OF APPLICANT:

Address: Astra Merck
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

Responsible Official: Daniel J. Cushing
Phone: (610) 695-1370
FAX: (610) 695-1828

Proprietary: **ATACAND™ Tablets** (US and Europe)
BLOPRESS™ Tablets (Japan)

Nonproprietary: Candesartan cilexetil

CAS Registry Number: 145040-37-5

Code Names: TCV-116(Takeda)and H 212/91(Astra Merck)

Chemical type/Therapeutic Class: 1S

APPEARS THIS WAY
ON ORIGINAL

REMARKS/COMMENTS:

None

CONCLUSIONS & RECOMMENDATIONS:

Not approvable. Deficiencies will be conveyed to applicant.

2/3/98

Joseph T. Piechocki, Ph.D.
Review Chemist

JH Short 2/17/98

cc:

Orig. NDA 20-838
HFD-110/Division File
HFD-110/PiechockiJ/2-3-98
HFD-100/BongiovanniK
District

20838r03.doc

R/D Init. by: JShort 20838R03.doc

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K. Bergmann
DEC 31 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-838 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 15-DEC-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	30-Apr-97	30-Apr-97	05-May-97
Amendment (BZ)	15-Jul-97	16-Jul-97	17-Jul-97
Amendment	12-Aug-97	13-Aug-97	14-Aug-97
Amendment (BC)	30-Sep-97	01-Oct-97	06-Oct-97
Amendment (BZ)	02-Dec-97	03-Dec-97	03-Dec-97
Amendment (BC)	10-Dec-97	11-Dec-97	15-Dec-97

Amendments provide for:

Amendment 12-Aug-97 had been previously reviewed.

Amendment (BZ) July 15, 1997 Submission of dissolution data for clinical and marketed, batches.

Amendment (BC) (30-Sep-97) Submission of updated stability data for:
1. 18 months data for drug substance produced at the Takeda Modified Plant 1.
2. 6 months data for drug substance produced at Takeda's Plant 2.
3. 18 months data and statistical analysis for 4, 8 and 16 mg Atacand™ tablets.

Amendment (BZ) (02-Dec-97) Submission of an electronic copy of dissolution data from clinical and commercial batches.

Amendment (BC) (10-Dec-97) Submission of original methods validation procedures.

NAME & ADDRESS OF APPLICANT:

Address: Astra Merck
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

Responsible Official: Daniel J. Cushing
Phone: (610) 695-1370
FAX: (610) 695-1828

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BLOPRESS™ Tablets (Japan)

Nonproprietary: Candesartan cilexetil tablets

CAS Registry Number: 145040-37-5

Code Names: TCV-116(Takeda)and H 212/91(Astra Merck)

Chemical type/Therapeutic Class: 1S

APPEARS THIS WAY
ON ORIGINAL

REMARKS/COMMENTS:

The additional stability data submitted data seems complete and analyzed.

CONCLUSIONS & RECOMMENDATIONS:

It is recommended that the extension of the expiration date to 24 months be approved. The firm needs to explain the positive slope for their assay values of their stability samples. This minor problem poses no safety or efficacy concerns for the consumer and therefore it is recommended this item not delay approval of the extended expiration date.

The trademark is acceptable but inspection reports on the nds manufacturer and Astra the product manufacturer have not been completed. The inspection of Astra has been completed but the report not finalized.

12/23/97

Joseph T. Piechocki, Ph.D.
Review Chemist

cc:

Orig. NDA 20-838
HFD-110/Division File
HFD-110/PiechockiJ/12/15/97
HFD-100/BongiovaniK
District
HFD-102/

20838r02.doc

R/D Init. by: RJWolters 20838R02.doc

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SEP 4 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-838 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 22-Aug-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	30-Apr-97	30-Apr-97	05-May-97
Amendment	12-Aug-97	13-Aug-97	14-aug-97

NAME & ADDRESS OF APPLICANT:

Address: Astra Merck
725 Chesterbrook Blvd.
Wayne, PA 19087-5677
Responsible Official: Daniel J. Cushing
Phone: (610) 695-1370
FAX: (610) 695-1828

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BLOPRESS™ Tablets (Japan)
Nonproprietary: Candesartan cilexetil tablets
CAS Registry Number: 145040-37-5
Code Names: TCV-116(Takeda)and H 212/91(Astra Merck)
Chemical type/Therapeutic Class: 1S

ANDA Suitability Petition/DESI/Patent Status: (01-001-022)

Patent Status				
Patent Number	**Expiration Date**	**Type**	**Owner**	**Authorized Representative to Receive Notice of Patent Certification**
5,196,44	April 18, 2011	drug; drug product; method of use	Takeda Chemical Industries	Astra Merck Inc.
5,508,297	Feb. 24, 2014	method of use	Takeda Chemical Industries	Astra Merck Inc.
5,534,534	July 9, 2013	drug product	Takeda Chemical Industries	Astra Merck Inc.

Patent Declaration Statement is submitted on p. 01-001-023 of Vol. 1.1.

8/27/97

Joseph T. Piechocki, Ph.D.
Review Chemist

9/4/97

cc:

Orig. NDA 20-838
HFD-110/Division File
HFD-110/PiechockiJ/7/ /97
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HFD-102/

R/D Init. by: RJWolters 20838R01.doc

APPEARS THIS WAY
ON ORIGINAL

JAN 15 1998

DIVISION OF CARDIO-RENAL DRUGS
Review of Chemistry, Manufacturing and Controls

NDA 20-838	EA Review		Complete Jan 15, 1998
Submission Type	Document Date	CDER Date	Topics
Amend to Pending Application	January 9, 1998	Jan 13, 1998	Confirmation that maximum production

Name and Address of Applicant

Astra Merck	Daniel J Cushing	(610) 695-1370
725 Chesterbrook Blvd.	Donald F Dwyer	(610) 695-1291
Wayne, PA 19087-5677	FAX	(610) 695-1828

Drug Product Name
Proprietary **Atacand Tablets**
Pharmacological Category: Angiotensin II Subtype 1 Receptor Antagonist
Indication: Treatment of Hypertension
Dosage Form: Tablet for oral administration
Strength: 4 mg, 8 mg, 16 mg and 32 mg candesartan cilexetil
Dispensed: Rx only
Chemical name, molecular formula and molecular weight:
Generic Name: **candesartan cilexetil**
Chemical name: (±)-1-(Cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-caboxylate
Molecular formula: $C_{33}H_{34}N_6O_6$ Molecular Weight: 610.67

Related Documents:
(1) Memo of a T-Con dated January 7, 1998, attached
(2) Page 76 dated Nov 12, 1998 from Amendment to NDA 20-838 submitted Dec 19, 97, attached

Remarks and Comments:
Based on confirmation that maximum production of the drug substance in any of the first 5 years after approval of the NDA is and the absence of extraordinary circumstances, the request for categorical exclusion is granted.

Recommendations and Conclusions: **No Action Indicated**

Jan 15, 1998

Florian Zielinski
Review Chemist, Office of New Drug Chemistry I
Jan 15, 1998

Distribution:
Original: NDA 20-838
HFD 110 Division File
HFD 810 Joe Piechocki
HFD 810 Florian Zielinski
HFD 110 Kathleen Bongiovanni
Initialed by James H Short JHShort 1/15/98

File name: NDA 20838 Candesartan EA Review