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

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

SUBMISSION TYPE  DOCUMENT DATE  CDER DATE  ASSIGNED DATE
ORIGINAL
Amendment (BZ)  30-Apr-97  30-Apr-97  05-May-97
Amendment (BC)  12-May-98  12-May-98  18-May-98
Amendment (BZ)  22-May-98  22-May-98  21-May-98
Amendment (BC)  22-May-98  22-May-98  22-May-98
Amendment (BZ)  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.
Amendment (BC) - Submission of a product specific, in-process, sampling plan,
Amendment (BZ) - Submission of camera-ready proof labeling.
Amendment (BC) - 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, AT1-
subtype Angiotensin II Receptor Antagonist.

DOSAGE FORM: Tablet
STRENGTHS: 32mg
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.

Joseph T. Piechocki, Ph.D.
Review Chemist

5/29/98

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

R/D Init. by: Dr. Kasturi Srinivasachar

K.Drinko
6-1-98

APPEARS THIS WAY ON ORIGINAL
CDIVISION OF CARDIO-RENAI DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

**NDA #1: 20-838**
**CCHM REVIEW #: 4**
**REVIEW DATE: Mar. 25, 1998**

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**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
  - 145040-37-5
- 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, AT₁-subtype Angiotensin II Receptor Antagonist.

**DOSEAGE FORM:** Tablet
**STRENGTH:** 4, 8, 16 mg/tablet
**ROUTE OF ADMINISTRATION:** Oral
**DISPENSED:** ☐ RX ☐ OTC

**STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT**

See previous reviews for this information.

Molecular Formula: C₃₁H₃₁N₄O₇
Molecular Weight: 610.67
Chemical Name: (+)-1-(cyclohexyloxy carbonyloxy) 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.

Joséph T. Piechocki, Ph.D.
Review Chemist

CC:
Orig. NDA 20-838
HFD-110/Division File
HFD-110/PiechockiJ/3/25/98
HFD-100/BongiovaniiK
District
HFD-810/CHoiberg

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

APPEARS THIS WAY ON ORIGINAL
DIVISION OF CARDIO-RENAI DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-838
Chem. Review #: 3
Review Date: 3-Feb-98

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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) 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) Submission of an electronic copy of dissolution data from clinical and commercial batches.
- Amendment (BC) Submission of original methods validation procedures.
- Amendment (BC) 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)
Nonproprietary: BLOPRESS™ Tablets (Japan)
CAS Registry Number: Candesartan cilexetil 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.

Joseph T. Piechocki, Ph.D.
Review Chemist

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

R/D Init. by: JShort

APPEARS THIS WAY ON ORIGINAL
DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

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

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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) Submission of updated stability data for:
(30-Sep-97) 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) Submission of an electronic copy of dissolution data from
(02-Dec-97) clinical and commercial batches.
Amendment (BC) Submission of original methods validation procedures.
(10-Dec-97)

NAME & ADDRESS OF APPLICANT:

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

Daniel J. Cushing
(610) 695-1370
(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
REMARKS/COMMENTS:
The additional stability data submitted 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.

Joseph T. Piechocki, Ph.D.
Review Chemist

12/23/97

CC:
Orig. NDA 20-838
HFD-110/Division File
HFD-110/Piechocki J/12/15/97
HFD-100/Bongiovani K
District
HFD-102/

R/D Init. by: RJWolters 20838r02.doc

20838R02.doc
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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Code Names: TCV-116(Takeda)and H 212/91(Astra Merck)

Chemical type/Therapeutic Class: 1S

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

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Patent Declaration Statement is submitted on p. 01-001-023 of Vol. 1.1.
cc:
Orig. NDA 20-838
HFD-110/Division File
HFD-110/Piechocki 7/ 97
HFD-100/Bongiovanik
District
HFD-102/

R/D Init. by: RJWolters

APPEARS THIS WAY ON ORIGINAL
DIVISION OF CARDIO-RENAAL DRUGS
Review of Chemistry, Manufacturing and Controls

NDA 20-838
EA Review
Complete Jan 15, 1998

Submission Type: Document Date: November 9, 1998
Amend to Pending: January 9, 1998
Application: CDER Date: Jan 13, 1998

Confirmation that maximum production

Name and Address of Applicant
Astra Merck
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

Daniel J Cushing
Donald F Dwyer
FAX
(610) 695-1291
(610) 695-1828

Drug Product Name
Atacand Tablets
Proprietary

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: (4S)-1-[(4-chlorophenyl)carbonyl]ethyl 2-ethoxy-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate
Molecular formula: C₃₅H₃₄N₂O₆
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

File name: NDA 20838 Candesartan EA Review

NDA 20838 Candesartan EA Review