

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number     **20-838****

**ADMINISTRATIVE DOCUMENTS**  
**CORRESPONDENCE**

**Environmental Assessment**

*No. in BC 12-19-97*

**1. Date**

November 12, 1997

**2. Name of Applicant**

Astra Merck Inc.

**3. Address of Applicant**

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

**4. Description of Proposed Action**

**Requested Action - Catagorical Exclusion**

Astra Merck is filing an amendment to NDA 20-838 requesting the approval of candesartan cilexetil tablets, 32 mg, in addition to the 4 mg, 8 mg and 16 mg doses already requested in NDA 20-838, submitted on April 30, 1997. Drug substance will be manufactured at the Takeda Fine Chemicals facility in Hikari City, Japan. As with the 4 mg, 8 mg and 16 mg doses, drug product formulation of candesartan cilexetil tablet, 32 mg, will take place at Astra Production Tablets, in Sodertalje, Sweden. Packaging of candesartan cilexetil tablets will take place at Merck & Co.

Astra Merck is requesting a catagorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR 25.31(b). The production of candesartan cilexetil tablets meets the requirements of a catagorical exclusion under 21 CFR 25.31(b) because the estimated concentration of candesartan cilexetil at the point of entry, referred to as the Expected Introduction Concentration (EIC), into the aquatic environment will be below 1 part per billion (ppb). To the best of the firm's knowledge no extraordinary circumstances exist in regards to this action.

*Dec 24, 1997  
Horvath and Kathy B. und...  
this to be a "request for catagorical  
exclusion" for all drug products  
covered by NDA 20-838.  
this info will be conveyed to Joe P...  
Horvath*



NDA 20-838

JUN 2 - 1998

Astra Merck Inc.  
Attention: Daniel J. Cushing, Ph.D.  
725 Chesterbrook Blvd.  
Wayne, PA 19087-5677

Dear Dr. Cushing:

We acknowledge receipt on May 22, 1998 of your May 22, 1998 amendments (two) that complete the resubmission of your new drug application for Atacand (candesartan cilexetil) 4, 8, 16 and 32 mg Tablets.

This resubmission contains the following additional information submitted in response to our April 28, 1998 action letter:

- May 8, 1998 - Dissolution specifications
- May 12, 1998 - Product-specific sampling plan
- May 18, 1998 - Final printed package inserts
- May 20, 1998 - Patient Information - Protocols 153 and 175
- May 22, 1998 - Revised methods validation data
- May 22, 1998 - Camera-ready proofs of container labels

We consider this a complete, class 1 response to our April 28, 1998 action letter. For this fiscal year, our performance goals are to have 90% of class 1 resubmissions acted upon within 6 months (the secondary user fee goal date), and 30% acted upon within 2 months (the primary user fee goal date). The primary user fee goal date for this application is July 22, 1998 and the secondary user fee goal date is November 22, 1998.

If you have any questions concerning this NDA, please contact:

Ms. Kathleen Bongiovanni  
Regulatory Health Project Manager  
(301) 594-5334

Sincerely yours,

Natalia A. Morgenstern  
Chief, Project Management Staff  
Division of Cardio-Renal Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

cc

Orig. NDA

HFD-110

DISTRICT OFFICE

HFD-110/KBongiovanni

sb/5/28/98;5/29/98;5/29/98

R/D: NMorgenstern/5/29/98

ACKNOWLEDGEMENT - AC

**APPEARS THIS WAY  
ON ORIGINAL**



DEPARTMENT OF HEALTH & HUMAN SERVICES

*K. Bongiovanni*  
Public Health Service

Food and Drug Administration  
Rockville MD 20857

NDA 20-838

MAR 10 1998

Astra-Merck Inc.  
Attention: Daniel J. Cushing, Ph.D.  
725 Chesterbrook Blvd.  
Wayne, PA 19087-5677

Dear Dr. Cushing:

Please refer to your pending April 30, 1997 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Atacand (candesartan cilexetil) 4, 8, 16, and 32 mg Tablets.

We also refer to your amendments dated July 15, August 12, September 30, December 2, 10 and 19, 1997.

We have completed our review of the chemistry, manufacturing and controls section of your submissions and have identified the following deficiencies:

**THIS PAGE  
WAS  
DETERMINED  
NOT  
TO BE  
RELEASABLE**

If you have any questions, please contact:

Ms. Kathleen Bongiovanni  
Regulatory Health Project Manager  
(301) 594-5334

Sincerely yours,

Raymond J. Lipicky, M.D.  
Director  
Division of Cardio-Renal Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

cc:  
Original NDA  
HFD-110  
HFD-810/ONDC Division Director (only for CMC related issues)  
HFD-110/KBongiovanni  
~~sb/2/24/98; 3/6/98~~  
R/D: JPiechocki  
JShort/2/24/98  
NMorgenstern/3/6/98

INFORMATION REQUEST (IR)

**APPEARS THIS WAY  
ON ORIGINAL**



NDA 20-838

JAN 16 1998

Astra Merck Inc.  
Attention: Daniel J. Cushing, Ph.D.  
725 Chesterbrook Blvd.  
Wayne, PA 19087-5677

Dear Dr. Cushing:

Please refer to your pending April 30, 1997 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Atacand (candesartan cilexetil) Tablets.

We also refer to your amendments dated July 15, August 12, September 30, December 2 and 10, 1997.

We have completed our review of the chemistry, manufacturing and controls section of your submission and have identified the following deficiencies:



We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Ms. Kathleen Bongiovanni  
Regulatory Health Project Manager  
(301) 594-5334

Sincerely yours,

Raymond J. Lipicky, M.D.  
Director  
Division of Cardio-Renal Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

cc:

Original NDA

HFD-110

HFD-810/ONDC Division Director (only for CMC related issues)

~~HFD-110/KBongiovanni;1/6/98~~

sb/1/6/98;1/12/98

R/D: JPiechocki

JShort/1/8/98

NMorgenstern/1/9/98

INFORMATION REQUEST (IR)

**APPEARS THIS WAY  
ON ORIGINAL**



Food and Drug Administration  
Rockville MD 20857

NDA 20-838

SEP 26 1997

Astra Merck Inc.  
Attention: Daniel J. Cushing, Ph.D.  
725 Chesterbrook Blvd.  
Wayne, PA 19087-5677

Dear Dr. Cushing:

Please refer to your pending April 30, 1997 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Atacand (candesartan cilexetil) Tablets.

We also refer to your amendment dated August 12, 1997.

We have completed our review of the chemistry, manufacturing and controls section of your submission and have identified the following deficiencies:

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

**Ms. Kathleen Bongiovanni**  
**Regulatory Health Project Manager**  
**(301) 594-5334**

Sincerely yours,

**Raymond J. Lipicky, M.D.**  
**Director**  
**Division of Cardio-Renal Drug Products**  
**Office of Drug Evaluation I**  
**Center for Drug Evaluation and Research**

cc:

Original NDA

~~HFD-110~~

~~HFD-110/KBongiovanni~~

~~sb/9/11/97;9/23/97~~

R/D: JPiechocki/9/22/97

RWolters/9/22/97

GBuehler for NMorgenstern/9/23/97

INFORMATION REQUEST

**APPEARS THIS WAY  
ON ORIGINAL**



DEPARTMENT OF HEALTH & HUMAN SERVICES

*K. Bongiovanni*  
Public Health Service

NDA 20-838

Food and Drug Administration  
Rockville MD 20857

MAY 9 1997

Astra Merck Inc.  
Attention: Daniel J. Cushing, Ph.D.  
725 Chesterbrook Blvd.  
Wayne, PA 19087-5677

Dear Dr. Cushing:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Atacand (candesartan cilexetil) Tablets

Therapeutic Classification: 1S

Date of Application: April 30, 1997

Date of Receipt: April 30, 1997

Our Reference Number: NDA 20-838

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 29, 1997 in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations and in accordance with the policy described in the Center for Drug Evaluation and Research Staff Manual Guide CDER 4820.6, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Please request the meeting at least 15 days in advance. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact:

Ms. Kathleen Bongiovanni  
Regulatory Health Project Manager  
(301) 594-5334

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

Natalia A. Morgenstern  
Chief, Project Management Staff  
Division of Cardio-Renal Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

JUN - 4 1998

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

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DATE: MAY 22 1998

FROM: Medical Team Leader, HFD-110

SUBJECT: NDA 20-838 Atacand (candesartan cilexetil) Tablets  
Astra Merck, Inc.

TO: Director, Office of Drug Evaluation I

We are returning the Atacand (candesartan cilexetil) Tablets package to you for final signature on the approval letter.

The April 28, 1998 approvable letter requested final printed labeling identical to the enclosed marked-up draft labeling and the product-specific sampling plan.

At our May 8, 1998 labeling meeting with Astra-Merck, we requested case report forms from patients who died or discontinued due to adverse events for Protocols 153 and 175 (to support the 32 mg tablet strength). The firm submitted the percentage of patients who discontinued due to an adverse event for Protocols 153 and 175 (there were no deaths in the trials).

Ms. Bongiovanni asked for the case report forms from those patients, but since the case report forms are still with the contract research organization conducting the trials, the firm asked whether tabular summaries would be sufficient. These were submitted by facsimile and on paper (see attached). I believe they are acceptable, but if you would like us to review the case report forms, the firm will submit them.

Our Biopharmaceutists have discussed the dissolution specification with the firm, and they have agreed to the specifications noted in the approval letter.

Astra Merck submitted the product-specific sampling plan in an amendment dated May 12, 1998, and it is acceptable.

The final printed labeling contains the revisions we agreed to in our May 8, 1998 meeting. In the PRECAUTIONS, Geriatric Use subsection, we asked the firm to fill in the correct amount the blood pressure was lowered in this population, using raw means. I agree with the "12/6 mm Hg" figure.

We believe that the application is now ready for approval.

Charles Ganley, M.D.

cc:

NDA 20-838

HFD-110

HFD-110/KBongiovanni

kb/5/20/98.

**APPEARS THIS WAY  
ON ORIGINAL**

JUN - 4 1998

## RHPM Review of Labeling

NDA: 20-838 Atacand (candesartan cilexetil) 4, 8, 16, and 32 mg Tablets

Date of submission: May 18, 1998

Date of receipt: May 18, 1998

Applicant: Astra Merck Inc.

**Background:** On April 28, 1998, Dr. Temple signed an approvable letter for NDA 20-838, requesting final printed labeling identical to the enclosed marked-up draft labeling, requesting the product-specific sampling plan referred to in the March 19, 1998 amendment, and setting the dissolution specification

On May 8, 1998, Drs. Temple, Lipicky, Ganley, U, and I met with the firm to discuss the marked-up labeling from the approvable letter. We agreed to revisions of the labeling and requested case report forms from patients who died or discontinued due to adverse events for Protocols 153 and 175 (see Minutes).

On May 8, 1998, Drs. Parekh and El-Tahtawy met with the firm to discuss the dissolution specification. In their submission dated May 8, 1998, the firm notes that the following dissolution specifications will be used:

4 and 8 mg:  
16 and 32 mg:

Astra Merck submitted the product-specific sampling plan in an amendment dated May 12, 1998.

In a submission dated May 18, 1998, the firm submitted final printed labeling and the percentage of patients who discontinued due to an adverse event for Protocols (there were no deaths in the trials). I called Ms. Cindy Lancaster on May 19, 1998, and asked for the case report forms from those patients. Elliott Berger, Ph.D. returned the call and asked whether tabular summaries would be sufficient, since the case report forms are still with the contract research organization conducting the trials. He sent a copy of the available information by facsimile on May 19, 1998 (attached). Dr. Ganley said that he thought the tabular summaries were adequate.

**Review:** I have reviewed the submitted final printed labeling. I could find no differences from the draft labeling included with the approvable letter other than minor editorial revisions, with the following exception, where we asked the firm to provide information:

In the PRECAUTIONS, Geriatric Use subsection, we asked the firm to fill in the correct amount the blood pressure was lowered in this population, using raw means. Dr. Ganley agreed with the "12/6 mm Hg" figure.

**Recommendation:** I will prepare an approval letter for this NDA for Dr. Temple's signature.

---

Kathleen F. Bongiovanni

6-1-98



cc: NDA 20-838  
HFD-110  
HFD-111/KBongiovanni  
HFD-111/SBenton

kb/5/20/98, 5/1/98.

**APPEARS THIS WAY  
ON ORIGINAL**

EXCLUSIVITY SUMMARY for NDA # 20838 SUPPL # \_\_\_\_\_

Trade Name Atacand Tablets Generic Name Candesartan cilexetil

Applicant Name Astra-Merck Inc HFD- 3110

Approval Date \_\_\_\_\_

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA? YES /  / NO /  /

b) Is it an effectiveness supplement? YES /  / NO /  /

If yes, what type? (SE1, SE2, etc.) \_\_\_\_\_

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.") YES /  / NO /  /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

\_\_\_\_\_  
\_\_\_\_\_

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

\_\_\_\_\_  
\_\_\_\_\_

d) Did the applicant request exclusivity?

YES /  / NO /  /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

not specified

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /  / NO /  /

If yes, NDA # \_\_\_\_\_ Drug Name \_\_\_\_\_

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /  / NO /  /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

APPEARS THIS WAY  
ON ORIGINAL

**PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**  
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / \_\_\_ /      NO /  /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # \_\_\_\_\_  
NDA # \_\_\_\_\_  
NDA # \_\_\_\_\_

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / \_\_\_ /      NO / \_\_\_ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # \_\_\_\_\_  
NDA # \_\_\_\_\_  
NDA # \_\_\_\_\_

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /\_\_\_/      NO /\_\_\_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /\_\_\_/      NO /\_\_\_/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /\_\_\_/      NO /\_\_\_/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /\_\_\_/      NO /\_\_\_/

If yes, explain: \_\_\_\_\_

---

- (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /\_\_\_/      NO /\_\_\_/

If yes, explain: \_\_\_\_\_

---

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # \_\_\_\_\_

Investigation #2, Study # \_\_\_\_\_

Investigation #3, Study # \_\_\_\_\_

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____	Study # _____
NDA # _____	Study # _____
NDA # _____	Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____	Study # _____
NDA # _____	Study # _____
NDA # _____	Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #\_\_, Study # \_\_\_\_\_

Investigation #\_\_, Study # \_\_\_\_\_

Investigation #\_\_, Study # \_\_\_\_\_

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1  
 IND # \_\_\_\_\_ YES /\_\_\_/ ! NO /\_\_\_/ Explain: \_\_\_\_\_  
 !  
 !

Investigation #2  
 IND # \_\_\_\_\_ YES /\_\_\_/ ! NO /\_\_\_/ Explain: \_\_\_\_\_  
 !  
 !

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  
 YES /\_\_\_/ Explain \_\_\_\_\_ ! NO /\_\_\_/ Explain \_\_\_\_\_  
 !  
 !

\_\_\_\_\_  
 !  
 !  
 \_\_\_\_\_



Investigation #2  
 YES /\_\_\_/ Explain \_\_\_\_\_ NO /\_\_\_/ Explain \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /\_\_\_/ NO /\_\_\_/

If yes, explain: \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

\_\_\_\_\_  
 Signature  
 Title: Regulatory Health Project Manager

3-25-98  
 Date

\_\_\_\_\_  
 Signature of Division Director

4/3/98  
 Date

cc: Original NDA                      Division File                      HFD-85 Mary Ann Holovac

**I. PATENT INFORMATION**

The patent information for candesartan cilexetil is provided in this section. Three patents have been identified as pertinent to candesartan cilexetil and its proposed indication for the treatment of hypertension, the subject of this New Drug Application (NDA 20-838).

Patent information as per Title 21 CFR §314.53(c)(1) is summarized below. In addition, a declaration statement is provided in accordance with Title 21 CFR §314.53(c)(2).

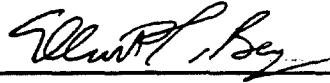
**TABLE 13-1  
Summary of Patent Information**

<u>Patent Number</u>	<u>Patent Expiration Date</u>	<u>Type of Patent</u>	<u>Patent Owner</u>	<u>Authorized Representative to Receive Notice of Patent Certification</u>
5,196,444	April 18, 2011	drug; drug product; method of use	Takeda Chemical Industries	Astra Merck Inc.
5,508,297	February 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.

**II. PATENT DECLARATION STATEMENT**

**DECLARATION**

The undersigned declares that Patent Numbers 5,196,444, 5,508,297, and 5,534,534 cover the formulation, composition, and/or method of use of candesartan cilexetil. This product is the subject of this application for which approval is being sought.



Elliott T. Berger, Ph.D.

Executive Director

Regulatory Affairs

Astra Merck Inc.

**APPEARS THIS WAY  
ON ORIGINAL**



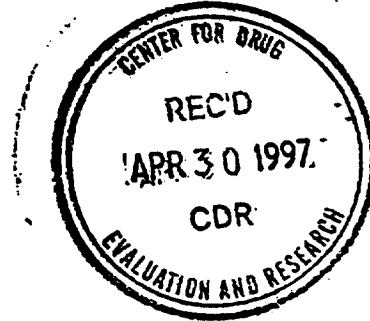
Exclusivity request -  
pg 3

DANIEL J. CUSHING, Ph.D., F.C.P.  
Director, Regulatory Liaison

ASTRA MERCK

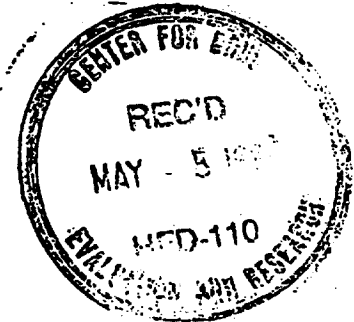
725 Chesterbrook Blvd.  
Wayne, PA 19087-5677  
610 695-1370  
Fax 610 695-1828

April 30, 1997



Raymond J. Lipicky, M.D., Director  
Division of Cardio-Renal Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room  
12420 Parklawn Drive  
Rockville, MD 20852

Dear Dr. Lipicky:



NDA 20-838  
ATACAND™ (candesartan cilexetil) Tablets  
Original New Drug Application

In accordance with 21 CFR 314, and section 505(b) of the Federal Food, Drug and Cosmetic Act, Astra Merck Inc. is submitting an Original New Drug Application for ATACAND™ (candesartan cilexetil) Tablets for the treatment of hypertension.

This Original New Drug Application consists of data from a clinical program conducted under \_\_\_\_\_ and from several clinical trials in hypertensive patients and in normal subjects conducted outside the U.S. by Takeda Chemical Industries, Ltd. and Astra Hässle AB. The safety and efficacy of candesartan cilexetil in the treatment of hypertension are supported by four (4) primary controlled clinical trials and several other controlled and uncontrolled clinical trials. The safety profile of candesartan cilexetil is further supported by a full analysis of safety data from all clinical trials and a complete list of all known deaths and non-fatal serious adverse events residing in the safety databases of Takeda Chemical Industries, Ltd., Astra Hässle AB and Astra Merck Inc.

Candesartan cilexetil is also under development in combination with hydrochlorothiazide for the treatment of hypertension under \_\_\_\_\_ and for the treatment of congestive heart failure under \_\_\_\_\_

Raymond J. Lipicky, M.D.

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This application is formatted in accordance with 21 CFR 314.50. This application consists of an "archival" copy (blue binder) which consists of 259 printed volumes. We have also included five review copies. Each review copy includes administrative documentation, an overall Index to the Contents of the Application (Item 1), the Synopsis of the Application (Item 2) and the specific technical items as listed below.

Item 3 Chemistry, Manufacturing and Controls  
(red binder) - 7 volumes

Item 4 Samples and Labeling  
(red binder) - 2 volume

Item 5 Nonclinical Pharmacology and Toxicology Documentation  
(yellow binder) - 31 volumes

Item 6 Human Pharmacokinetics and Bioavailability Documentation  
(orange binder) - 24 volumes

Item 8 Clinical Documentation  
(light brown binder) - 126 volumes

Item 10 Statistical Documentation  
(green binder) - 74 volumes

FDA correspondence dated February 20, 1997 granted a waiver allowing for submission of NDA Items 11 and 12 in electronic format only and not as a paper submission. Subsequently, in FDA correspondence dated March 12, 1997, a waiver was granted for the omission of Item 11 entirely since the same information will be provided as full data sets from the world wide clinical database in SAS transport format. In total this NDA consists of 498 volumes, 259 of which are provided as printed volumes and the remaining 239 volumes are provided as the electronic version of Item 12.

As required by Section 306(k)(1) of the Generic Drug Enforcement Act [21 U.S.C. 335a(k)(1)], we hereby certify that in connection with this application, Astra Merck Inc. did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

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In accordance with 21 CFR 314.50(j), we are hereby claiming exclusivity. Since candesartan cilexetil has not previously been approved under section 505(b) of the Act, we hereby reference 314.108 (b)(2) to support the exclusivity claim.

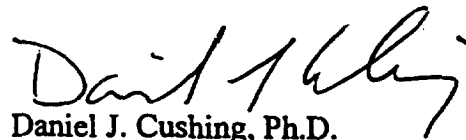
Documentation is on file that indicates original subject records were reviewed during the course of monitoring activities for verification of case report forms for all controlled clinical studies. In addition, all international studies were performed in accordance with the directives stated in the Declaration of Helsinki.

We consider the submission of this information to be confidential and proprietary and request that the Food and Drug Administration not make its existence public without first obtaining written permission from Astra Merck Inc.

We are also providing a full copy of the Chemistry, Manufacturing and Controls Technical Section and Methods Validation Section (Items 3 and 4, respectively) to the Philadelphia District Office of the Food and Drug Administration.

If you have any questions or require any additional information concerning this Original New Drug Application please contact me directly at (610/695-1370) or, in my absence, Donald F. Dwyer, RAC, Regulatory Project Manager at (610/695-1291).

Sincerely yours,



Daniel J. Cushing, Ph.D.  
Director  
Regulatory Liaison

Enclosures  
Hand Delivery

Desk Copy: Ms. Mary Ann Holovac, Drug Information Services, HFD-85, Rm 8B-37  
(letter/patent information only)

Ms. Kathleen Bongiovanni, RHPM, HFD-110, letter only

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one is prepared at the time of the last action.

BLA # 20-838 Supplement #        Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD: 110 Trade and generic names/dosage form: Atacand (candesartan cilexetil) Tablets Action: AP AE NA

Applicant Astra-Merck Therapeutic Class IS

Indication(s) previously approved       

Pediatric information in labeling of approved indication(s) is adequate  inadequate

Proposed indication in this application treatment of hypertension

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS?  Yes (Continue with questions)  No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

Neonates (Birth-1month)  Infants (1month-2yrs)  Children (2-12yrs)  Adolescents(12-16yrs)

1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.

a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

c. The applicant has committed to doing such studies as will be required.

(1) Studies are ongoing,

(2) Protocols were submitted and approved.

(3) Protocols were submitted and are under review.

(4) If no protocol has been submitted, attach memo describing status of discussions.

d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE 4 COMMITMENTS IN THE ACTION LETTER? \_\_\_ Yes  No  
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from CHARLES GANLEY, MD (e.g., medical view, medical officer, team leader)

Reg. Health Proj. Mgr. 3/26/98  
Signature of Preparer and Title Date

cc: Orig NDA/BLA # 20-838  
HFD-110 /Div File  
NDA/BLA Action Package / R. S. Ungiovanni  
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

Hyper tension is not a common disease in the pediatric population.  
Consequently, the sponsor is not required to perform studies in this group of patients.

ND 3/26/98



RHPM NDA Overview  
May 20, 1998

**NDA 20-838**      Atacand (candesartan cilexetil) 4, 8, and 16 mg Tablets

**Sponsor:**            Astra-Merck Inc.

**Date of Application:**    April 30, 1997  
**Date of Receipt:**        April 30, 1997  
**User Fee Goal Date:**    April 30, 1998  
**Date of Approvable letter:** April 28, 1998

**STATUS:**

**Medical and Medical/Statistical Reviews**

Steven Caras, M.D., Ph.D.      Review completed 8-8-97

Stephen Fredd, M.D./Kooros Mahjoob, Ph.D. - efficacy      Review completed 1-29-98  
Labeling: not reviewed  
Conclusion: approvable

Khin U, M.D. - safety      .Review completed 1-26-98; additional reviews: 3-23-98,  
3-31-98 (two), 5-8-98.  
Labeling: recommendations included in marked-up draft  
Conclusion: approvable

**Biopharmaceutics Review:**

Biopharmaceutist: Ahmed El-Tahtaway, Ph.D.      Review completed 4-3-98  
(Team Leader: Ameeta Parekh, Ph.D.)

Labeling: revisions included in marked-up draft  
Conclusion: Approvable. Revised Q spec from May 8, 1998 discussion with Astra-Merck included in approval letter.

**Chemistry-**

Joseph Piechocki, Ph.D.

Dates of completion:

Review 1: 9-4-97;    IR letter issued 9-26-97  
Review 2: 12-31-97; IR letter issued 1-16-98  
Review 3: 2-18-98; IR letter issued 3-10-98  
Review 4: 3-31-98;  
Review 5: 6-1-98;

Labeling: acceptable

cGMP Inspections: acceptable

Methods validation: ongoing

Conclusion: approvable. SOPs requested in approvable letter submitted May 12, 1998.

**Environmental Assessment:**    see FZielinski review 1-15-98; EA categorical exclusion granted.

**Pharmacology-**

Anthony Proakis, Ph.D. Review completed 2-17-98

CAC: Presented at 2-10-98 Exec CAC Mtg. Rat and mouse studies acceptable; no evidence of biologically significant carcinogenic potential in either species.

Labeling: recommendations starting on page 127 of review

Conclusion: approvable

**Statistics (preclin):**

Reviewer: Lu Cui, Ph.D.: Review completed 1-12-98

**Safety Update:** Aug 29, 1997

**Patent info:** included in package

**Exclusivity:** form included in package

**Debarment Certification:** included in package

**DSI Inspections-** Antoine El Hage, Ph.D. : three NAI and one VAI.

**CDER Labeling & Nomenclature Committee:**

Acceptable 9-7-97.

**Labeling:** FPL (package inserts) included in 5-18-98 submission;  
camera-ready proofs for carton and container labeling submitted 5-22-98.

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Kathleen F. Bongiovanni

6-2-98

cc:

NDA 20-838

HFD-110

HFD-110/SBenton

HFD-110/KBongiovanni

APPEARS THIS WAY  
ON ORIGINAL