CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-838/S-015

Administrative Documents

13 PATENT INFORMATION

13.1 Patent Information

The Patent Information to support this supplemental new drug application is incorporated by reference into this section from NDA 20-838, 01-001-022 (Item-Vol-Page) for ATACAND® (candesartan cilexetil) Tablets and correspondence to Dr. Raymond Lipicky dated 29 June 1998 regarding Time Sensitive Patent Information: Updated Patent Information and Declaration Statement.

14 PATENT CERTIFICATION

The Patent Certification information to support this supplemental new drug application is incorporated by reference into this section from NDA 20-838, 01-001-023 (Item-Vol-Page), for ATACAND® (candesartan cilexetil) Tablets and correspondence sent to Dr. Raymond Lipicky dated 29 June 1998 regarding Time Sensitive Patent Information: Updated Patent Information and Declaration Statement.

EXCLUSIVITY SUMMARY FOR NDA # 20-838 SUPPL #015

Trade Name: ATACAND Generic Name: candesartan cilexetil

Applicant Name: AstraZeneca LP. HFD # 110

Approval Date If Known: September 13, 2002

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 question about the submission.

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

b) Is it an effectiveness supplement?

YES /_X__/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE4_

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 /_X__/ 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:

_____

_____

Form OGD-011347 Revised 10/13/98
cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

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

e) Has pediatric exclusivity been granted for this Active Moiety? **no**

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? (Rx to OTC switches should be answered NO- please indicate as such)

YES /_X__/ NO /___/

If yes, NDA #_20-838_____. Drug Name: Atacand (candesartan cilexetil).

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).

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.

(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:

_____

(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:**

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 **IND #_____** **YES /___/** **NO /___/**

Investigation #2 IND #_____ 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:

_____ _____

_____ _____

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 /___/

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

_____ _____

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"):

_____

_____

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: _____

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 Date
Edward Fromm, Regulatory Health Project Manager

_____
Signature Date
Douglas C. Throckmorton
Director, Division of Cardio-Renal Drug Products

cc: Original NDA Division File HFD-93 Mary Ann Holovac

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

/s/

Doug Throckmorton
9/18/02 08:21:29 AM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 20-838 Supplement Type (e.g. SE5): SE4 Supplement Number: 015

Stamp Date: September 27, 2001 Action Date: July 27, 2002

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

Applicant: AstraZeneca Therapeutic Class: Angiotensin II Antagonist

Indication(s) previously approved: Hypertension

NOTE: No Pediatric Studies are needed as this is a superiority claim versus Cozaar (losartan potassium) in hypertension.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s):_____

Indication #1: _____

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- ☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	kg____	mo.____	yr.____	Tanner Stage____
Max____	kg____	mo.____	yr.____	Tanner Stage____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns

- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960

301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

ction D: Completed Studies

Age/weight range of completed studies:

Min ____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
1-594-7337

ITEM 16 - CERTIFICATION STATEMENT

Re: Atacand NDA 20-838: supplemental NDA

In response to the requirements of the Generic Drug Enforcement Act of 1992, I hereby certify on behalf of AstraZeneca Pharmaceuticals LP, that we did not use and will not use in connection with this application, the services of any person in any capacity debarred under section 306 (a) or (b)

Sincerely,

Cindy M. Lancaster for

Anthony Rogers

Vice President, Regulatory Affairs

Division of Scientific Investigations (DSI)

DSI audits were not requested for this application and DSI did not independently conduct audits of their own.

RHPM NDA Efficacy Supplement Approval/Labeling Review
September 10, 2002

Atacand (candesartan cilexetil) Tablets, 4,8, 16, and 32 mg

NDA 20-838/SE4-015

Sponsor: AstraZeneca L.P.

Classification: SE4 (comparative efficacy claim)

Review Classification: Standard (10 month review)

Indication: Comparative efficacy claim versus Cozaar (losartan potassium) in Hypertension

Date of Application: September 27, 2001

Date of AE Letter: July 26, 2002

Date FPL Submitted: September 3, 2002

Date FPL Received: September 4, 2002

User Fee Goal Date: November 4, 2002

Background

An approvable letter was issued on July 26, 2002 for candesartan cilexetil for a superiority claim versus Cozaar in the treatment of hypertension and other changes to the labeling. After some brief labeling discussions, the firm was informed that they could submit Final Printed Labeling (FPL).

Review

The firm submitted final printed labeling on September 3, 2002, received September 4, 2002. When compared with the last approved labeling supplement (S-016, November 28, 2001) the following changes were noted:

1. Under **CLINICAL PHARMACOLOGY, Special Populations,** *Hepatic Insufficiency*, this subsection has been revised to read as follows:

   The pharmacokinetics of candesartan were compared in patients with mild and moderate hepatic impairment to matched healthy volunteers following a single oral dose of 16 mg candesartan cilexetil. The increase in AUC for candesartan was 30% in patients with mild hepatic impairment (Child-Pugh A) and 145% in patients with moderate hepatic impairment (Child-Pugh B). The increase in Cmax for candesartan was 56% in patients with mild hepatic impairment and 73% in patients with moderate hepatic impairment. The pharmacokinetics after candesartan cilexetil administration have not been investigated in patients with severe hepatic impairment. No initial dosage adjustment is necessary in patients with mild hepatic impairment. In patients with moderate hepatic impairment, consideration should be given to initiation of ATACAND at a lower dose. (See **DOSAGE AND ADMINISTRATION**)

2. Under **CLINICAL PHARMACOLOGY, Clinical Trials**, this section has been updated to include the results of the CLAIM studies that show candesartan cilexetil had a greater effect than losartan potassium in lowering systolic and diastolic blood when both drugs were used at their highest dosage. The exact wording is as follows:

   The antihypertensive effects of candesartan cilexetil and losartan potassium at their highest recommended doses administered once-daily were compared in two randomized, double-blind trials. In a total of 1268 patients with mild to moderate hypertension who were not receiving other antihypertensive therapy, candesartan cilexetil 32 mg lowered systolic and diastolic blood pressure by 2 to 3 mm Hg on average more than losartan potassium 100 mg, when measured at the time of either peak or trough effect. The antihypertensive effects of twice daily dosing of either candesartan cilexetil or losartan potassium were not studied.

   Note: the firm suggested minor editorial corrections to the language for the above section different from what was mentioned in the approvable letter. These corrections, replacing the word "subjects" with the word "patients" and replacing the word "once per day" with "once-daily" were done for consistency. The words "compared with" were replaced with "more than" and "cilexetil" and "potassium" are added to candesartan and losartan in the last sentence. Drs. Throckmorton and Temple said the above changes were acceptable.

3. Under **PRECAUTIONS, General** subsection, a new *Impaired Hepatic Function* subsection has been added that reads as follows:

   Based on pharmacokinetic data which demonstrate significant increases in candesartan AUC and Cmax in patients with moderate hepatic impairment, a lower initiating dose should be considered for patients with moderate hepatic impairment. (See **DOSAGE AND ADMINISTRATION**, and **CLINICAL PHARMACOLOGY, Special Populations**.)

4. Under **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility**, the second paragraph of this subsection has been revised to:

   Candesartan and its O-deethyl metabolite tested positive for genotoxicty in the *in vitro* Chinese hamster lung (CHL) chromosomal aberration assay. Neither compound tested positive in the Ames microbial mutagenesis assay or the *in vitro* mouse lymphoma cell assay. Candesartan (but not its O-deethyl metabolite) was also evaluated *in vivo* in the mouse micronucleus test and *in vitro* in the Chinese hamster ovary (CHO) gene mutation assay, in both cases with negative results. Candesartan cilexetil was evaluated in the Ames test, the *in vitro* mouse lymphoma cell and rat hepatocyte unscheduled DNA synthesis assays and the *in vivo* mouse micronucleus test, in each case with negative results. Candesartan cilexetil was not evaluated in the CHL chromosomal aberration or CHO gene mutation assay.

   Note: Dr. Resnick telephoned the firm on August 21, 2002 to ask them to add the word "synthesis" after "DNA" and delete the word ' — ' after "DNA" from what was suggested for the above paragraph in the approvable letter.

5. Under **PRECAUTIONS, Geriatric Use**, the actual numbers that correspond to the percentages that were 65 and over, and those subjects older than 75 are now listed. The first sentence of this subsection now reads as follows:

   Of the total number of subjects in clinical studies of ATACAND, 21% (683/3260) were 65 and over, while 3% (87/3260) were 75 and over.

6. Under **OVERDOSAGE**, the 2nd paragraph of this section has been deleted and replaced with what was the last paragraph previously. This paragraph reads as follows:

   The most likely manifestation of overdosage with ATACAND would be hypotension, dizziness, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

7. Under **DOSAGE AND ADMINSTRATION**, the sentence "In patients with moderate hepatic impairment, consideration should be given to initiation of ATACAND at a lower dose (See **CLINICAL PHARMACOLOGY, Special Populations**) has been added to the 2nd paragraph of this section.

Comments/Recommendations:

Dr. John Simmons has asked that the chemical name for candesartan cilexetil be revised, under **DESCRIPTION**, to:

(±)-1-Hydroxyethyl 2-ethoxy-1-[*p*-(*o*-1*H*-tetrazol-5-yl-phenyl)benzyl]-7-benzimidazolecarboxylate, cyclohexyl carbonate (ester).

We will ask the firm to make this revision at their next printing.

Dr. Simmons thought that the 4 mg tablet strength should be scored because the 2nd sentence of **DOSAGE AND ADMINISTRATION** reads "Blood pressure response is dose related over the range of 2 to 32 mg." Dr. Throckmorton said that we commonly list the range of doses used from the clinical trials under **DOSAGE AND ADMINISTRATION** and did not think the 4 mg tablet needed to be scored.

Dr. Simmons said that the 8, 16, and 32 mg tablets are basically pink in color and thought that patient confusion could arise because of the similarity of colors among the tablets. AstraZeneca faxed a response on August 28, 2002, in which they said that the tablets, although similar in color, could be distinguished by the size of the tablet and a unique embossing applied to each tablet. Dr. Simmons asked that physical samples of each of the tablets be sent to the Agency for review to help determine how similar in appearance the tablets are to each other. The firm, in the cover letter for the submission of final printed labeling dated September 3, 2002, committed to providing these samples as soon as they are available.

I will draft an approval letter with labeling for Dr. Temple's signature.

/S/

Edward J. Fromm
Regulatory Health Project Manager

dr-ef-9-10-02

RHPM NDA Efficacy Supplement Overview
July 26, 2002

Atacand (candesartan cilextil) -Comparative Efficacy Claim vs. Cozaar (losartan potassium) in Hypertension

NDA 20-838/SE4-015

Applicant: AstraZeneca L.P.

Classification: SE4 (superiority claim)

Review Classification: Standard

Date of Application: September 27, 2001

Receipt Date: September 27, 2001

User Fee Goal Date: July 27, 2002 (10 month)

Background

AstraZeneca, on September 27, 2001, submitted an efficacy supplement for candesartan cilexetil for a comparative efficacy claim versus Cozaar (losartan potassium) for hypertension. This supplement was supported by 3 trials (2 identical, forced-titration trials, Protocols 230 and 231-CLAIM) and protocol 175 (CANDLE). These studies compared regimens of candesartan 16 mg to 32 mg daily with losartan 50 mg to 100 mg daily. The sponsor believes that based on the study results, candesartan gives statistically significantly greater reduction in blood pressures than the losartan regimen when given by forced titration.

This application was presented before the Cardio-Renal Advisory Committee on July 18, 2002 and the Committee recommended unanimously (9-0) that candesartan cilexetil be approved for superior antihypertensive efficacy when compared with losartan.

Meetings

August 19, 1998-DDMAC, Dr. Temple and Dr. Fredd

Review

Medical

Division Director:	Douglas C. Throckmorton, M.D.
Conclusion:	Approvable; Dr. Throckmorton notes that he agrees with the recommendations of the Advisory Committee: " the label for candesartan should be changed to reflect the results from the 230 and 231 trials, supporting greater antihypertensive effect for candesartan at the top approved dose when compared with top approved once daily dose of losartan."
Medical:	Stephen Fredd, M.D.
Conclusion:	Dr. Fredd states in his May 17, 2002 review that "the CANDLE and CLAIM studies do demonstrate that candesartan 16 mg once daily

provides on average more antihypertensive effect (approximately 2 mmg HG for sitting DBP) compared to 50 mg of losartan once daily." However, he notes that since the studies did not include placebo, the 2 mmg HG difference cannot be translated into a difference of "lives saved, strokes or myocardial infarctions prevented, which are the clinical parameters of importance."

Labeling: Dr. Fredd notes in his review several ways of describing the comparison of candesartan to losartan in these studies if the Agency decides that the application should be approved. He also says that the "results of the new PK study in hepatically impaired patients can be included with information on the Child-Pugh scale. The suggested dose modification in hepatically impaired patients can be included. The revised overdose section is acceptable."

Statistical: James Hung, Ph.D.
Labeling: None
Conclusion: Dr. Hung states in his May 17, 2002 review that "the two CLAIM studies showed that the candesartan 16mg to 32 mg regimen gave a statistically significantly greater reduction in blood pressures than the losartan 50 mg to 100 mg regimen when given by forced titration. The difference was 1 to 2.2 mm Hg in trough sitting DBP and about 3.5 mm Hg in trough sitting SBP. The CANDLE study showed that when given by optional titration, the candesartan regimen also gave a statistically significantly greater reduction in trough sitting diastolic blood pressure. The difference was 2.2 mm Hg in trough sitting DBP. The difference in trough sitting SBP was <2 mm Hg, not statistically significant."

Biopharmaceutics
Reviewer: Nhi Nguyen, Pharm.D.
Labeling: Dr. Nguyen suggested relatively minor changes regarding hepatic impairment to the **Special Populations** and **Impaired Hepatic Function** subsections as well as to the **DOSAGE AND ADMINISTRATION** section of the labeling (please see her May 1, 2002 review).
Conclusion: Dr. Nguyen, in her review made no overall approval recommendation other than to suggest some labeling changes as mentioned above.

Pharmacology Not applicable
Reviewer: Anthony Proakis, Ph.D.
Labeling: Based on a re-review of the nonclinical sections of the labeling, Dr. Proakis has suggested the mutagenesis information in the **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility** section of the labeling be revised (please see his review of April 29, 2002).

Chemistry No full review (see Environmental Assessment)

Safety Update: Not needed.

Patent info: Included in package

Pediatric info: Not applicable-not subject to the Pediatric Rule definition for new indication, dosage regimen, etc.

DSI Inspection: Not requested by the Division and not conducted independently by DSI.

Debarment Certification: Included in package

Exclusivity Summary: Not applicable

Environmental Assessment: Sponsor granted Categorical Exclusion

Financial Disclosure: acceptable, see Dr. Karkowsky's July 10, 2002 memo

OPDRA Tradename Review: Not needed, the firm did not change the trade or generic name for this new indication.

DDMAC: At the time of the issuance of the approvable letter, DDMAC had not submitted any written comments regarding the labeling. Dr. Cheryl Cropp was present at a July 25, 2002 internal meeting to discuss the Atacand labeling.

Comments: At an internal meeting on July 25, 2002, Dr. Temple and the Division agreed that the **CLINICAL PHARMACOLOGY, Clinical Trials** subsection would need revision and that Dr. Proakis' changes to the **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection were acceptable. They also said that the sponsor's revisions to the **Special Populations** and **Impaired Hepatic Function** subsections as well as to the **DOSAGE AND ADMINISTRATION** were acceptable.

I will draft an approvable letter with marked-up draft labeling for Dr. Temple's signature.

/S/

Edward J. Fromm
Regulatory Health Project Manager

dr-ef-7-26-02

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(610) 695-1828
Attention:	Ms. Cindy Lancaster
Company Name:	AstraZeneca LP.
Phone:	(610) 695-1348
Subject:	**Approval Letter and Labeling for NDA 20-838/S-015 Atacand (candesartan cilexetil)**
Date:	September 13, 2002
Pages including this sheet:	15
From:	**Edward Fromm**
Phone:	**301-594-5332**
Fax:	**301-594-5494**

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Rockville, MD 20857

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Rockville, MD 20852

Transmitted to FAX Number:	(610) 695-1828
Attention:	Ms. Cindy Lancaster
Company Name:	AstraZeneca
Phone:	(610) 695-1348
Subject:	**Draft Questions for NDA 20-838/S-015 for Atacand (candesartan cilexetil) for July 2002 Cardio-Renal Advisory Committee Meeting**
Date:	June 19, 2002
Pages including this sheet:	**3**
From:	**Edward Fromm**
Phone:	**301-594-5313**
Fax:	**301-594-5494**

Fromm, Edward J

From: Resnick, Charles A
Sent: Wednesday, August 21, 2002 4:24 PM
To: Fromm, Edward J
Cc: Proakis, Anthony G
Subject: Atacand Labeling

Spoke with Cindy Lancaster and David Stong of Astra Zeneca regarding the approvable letter for NDA 20-838/S-015. They wanted to know why we wanted the positive clastogenicity findings for candesartan and its O-deethyl metabolite at the begining of the labeling paragraph that describes the extent and results of their genetic toxicology evaluation. I told them that our intent was to assure that the positive findings were not missed by readers of the labeling.

I took this opportunity to note an error in our approvable letter. I told them that in the next to last sentence of the mutagenesis statement (2nd paragraph of the Carcinogenesis, Mutagenesis, Impairment of Fertility subsection) should have read "unscheduled DNA synthesis". They indicated that they would make the correction in their FPL.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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Rockville, MD 20857

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1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(610) 695-1828
Attention:	Ms. Cindy Lancaster
Company Name:	AstraZeneca
Phone:	(610) 695-1348
Subject:	**Confirmation of Meeting w/FDA** **March 26, 2002** **NDA 20-838/S-015** **Atacand (candesartan cilexetil) Tablets**
Date:	May 10, 2002
Pages including this sheet:	**2**
From:	**Edward Fromm**
Phone:	**301-594-5313**
Fax:	**301-594-5494**

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

Confirmation of Meeting

Drug:	Atacand (candesartan cilexetil) Tablets NDA 20-838/S-015
Sponsor:	AstraZeneca
Subject:	July Cardio-Renal Advisory Committee and Status of FDA Reviews
Date Confirmation Faxed:	May 10, 2002
Meeting Date:	June 12, 2002
Meeting Time:	2:30 to 4:00 P.M.
Location:	Conference Room "F", 5th Floor, 1451 Rockville Pike, Rockville, MD 20857

FDA Participants:

Douglas C. Throckmorton, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D., HFD-110, Medical Team Leader
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
James Hung, Ph.D., HFD-110, Statistician/Team Leader
Nhi Nguyen, Pharm.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Gabriel Robbie, Ph.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist, Acting Team Leader
Ms. Natalia A. Morgenstern, HFD-110, Chief, Project Management Staff
Mr. Edward Fromm, HFD-110, Regulatory Health Project Manager

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
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5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(610) 695-1828
Attention:	Ms. Cindy Lancaster
Company Name:	AstraZeneca
Phone:	(610) 695-1348
Subject:	**Minutes of meeting w/FDA, June 12, 2002** **NDA 20-838/S-015** **Atacand (candesartan cilexetil) Tablets**
Date:	July 9, 2002
Pages including this sheet:	4
From:	**Edward Fromm**
Phone:	**301-594-5313**
Fax:	**301-594-5494**

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

Minutes of a Meeting between AstraZeneca and the FDA

Date: June 12, 2002

Application: NDA 20-838/S-015, Atacand (candesartan cilexetil) Tablets

Indication: Comparative Efficacy Claim versus Cozaar (losartan potassium) in Hypertension

Applicant: AstraZeneca

Subject: Pre-Advisory Committee Meeting

FDA participants

Douglas C. Throckmorton, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
Nhi Nguyen, Pharm.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Mr. Edward Fromm, HFD-110, Project Manager

AstraZeneca

Dr. Steven Miller, Executive Director, Regulatory Affairs
Dr. Howard Hutchinson, Executive Director, Clinical Research
Dr. Cindy Lancaster, Director, Regulatory Affairs
Ms. Patricia Patterson, Associate Director, Regulatory Affairs
Dr. Michael Klibaner, Senior Director, Clinical Research
Dr. Eric Michelson, Senior Director, Clinical Research
Dr. Renli Teng, Senior Director, Clinical Pharmacology
Dr. Conrol Tou, Associate Director, Biostatistical Project Team

Consultants

Dr. W.B. Kannel, Professor of Medicine and Public Health, Boston University School of Medicine
Dr. V. Papademetriou, Professor of Medicine, Georgetown University

Background

AstraZeneca, on September 27, 2001, submitted an efficacy supplement for candesartan cilexetil for a comparative efficacy claim versus losartan potassium for hypertension. This supplement was principally supported by 2 identical, forced-titration trials, Protocols 230 and 231.

The Division asked AstraZeneca to present their application before the July Cardio-Renal Advisory Committee Meeting. The firm agreed to present before the Committee and requested feedback on a draft background package for the meeting as well as the review of the application to date by the Division.

Meeting

Dr. Throckmorton opened the telecon by noting that it important to clear up any numerical discrepancies before the Advisory Committee meeting. He mentioned that the primary medical reviewer for the application, Dr. Stephen Fredd has retired, but in going through Dr. Fredd's review he encountered no numerical differences when comparing it to the sponsor's briefing document. Although not present at the meeting, Dr. Hung noted that Tables

10 and 11 include patients that have 8 week measurements and not the ITT (Intend to Treat) population. The sponsor replied this was a typographical error that will be corrected.

Questions to the Advisory Committee Members

Dr. Throckmorton said that he has a list of draft questions to be presented at the Advisory Committee meeting and will fax a copy to the sponsor after further discussion with Dr. Norman Stockbridge and others within the Division. The final questions (which have to be reviewed by Dr. Temple) will be available just before the Advisory Committee meeting begins. Dr. Throckmorton said that prior to the listing of the actual questions, he would summarize the regulatory background of other sponsors seeking comparative or superiority claims. Some of the questions that follow are likely to be:

-
-
-
-
-

Other Issues

AstraZeneca said they had included in the briefing document a paragraph noting that there were changes in other sections of the labeling (e.g., *Hepatic Insufficiency*) that were not study related and asked if they should still be included. Dr. Throckmorton said inclusion of that paragraph may be confusing to the Committee members and should probably be excluded from the briefing package.

Dr. Karkowsky noted that any study analyses that employs covariates should define these covariates.

AstraZeneca asked if the Division would give a formal presentation at the Advisory Committee Meeting. Dr. Throckmorton said it is likely the Division would give its presentation through the questions to the Committee but he could not rule out a more formal presentation.

Conclusion

Dr. Throckmorton said that, overall, the sponsor's briefing document was acceptable. He said the Division would be faxing a copy of the draft questions for the Advisory Committee to the sponsor shortly. He encouraged the sponsor to speak with himself or the reviewers of the application if questions should arise about their application or the upcoming Advisory Committee meeting.

Minutes Preparation: /s/
Edward Fromm

Concurrence, Chair: /s/ 7.30.02
Douglas C. Throckmorton, M.D.

Drafted/ef: 6-14-02

Rd: AKarkowsky-7-02-02
NNguyen-6-14-02

-COMM. JOURNAL- DATE JUL-09-2002 TIME 08:30

MODE = MEMORY TRANSMISSION START=JUL-09 08:27 END=JUL-09 08:30

FILE NO.=095

STN NO.	COMM.	ONE-TOUCH/ ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	#	916106951828	004/004	00:01:50

-FDA,CDER,OND,ODEI,DCRDP -

-CARDIO RENAL - 301 594 5494-

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
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Rockville, MD 20857

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Rockville, MD 20852

Transmitted to FAX Number:	(610) 695-1828
Attention:	Ms. Cindy Lancaster
Company Name:	AstraZeneca
Phone:	(610) 695-1348
Subject:	**Minutes of meeting w/FDA, June 12, 2002** **NDA 20-838/S-015** **Atacand (candesartan cilexetil) Tablets**
Date:	July 9, 2002
Pages including this sheet:	4
From:	**Edward Fromm**
Phone:	**301-594-5313**
Fax:	**301-594-5494**

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

AstraZeneca LP
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

2. TELEPHONE NUMBER *(Include Area Code)*

(610) 695-1348

3. PRODUCT NAME

Atacand (candesartan cilexetil) Tablets

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

N020838

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4202

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See item 8, reverse side if answered YES)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Cindy M. Lancaster	Director, Regulatory Affairs	SEP 17 2001

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 20-838	Efficacy Supplement Type SE-4 (Comparative Efficacy Claim vs Cozaar (losartan potassium) in HTN	Supplement Number 015	
Drug: Atacand (candesartan cilexetil) Tablets, 4,8, 16, and 32 mg		Applicant: AstraZeneca L.P.	
RPM: E. Fromm		HFD-110	Phone # 594-5332
Application Type: (X) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	11/04/02
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	NA
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	PM-7/26/02 & 9/10/02
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE-7/26/02
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) No
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	NA
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NA
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	NA
• Applicant proposed	NA
• Reviews	NA
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	NA
• Documentation of discussions and/or agreements relating to post-marketing commitments	NA
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	NA
• Pre-NDA meeting (indicate date)	NA
• Pre-Approval Safety Conference (indicate date; approvals only)	NA
• Other	NA

❖ Advisory Committee Meeting	
• Date of Meeting	7/18/02
• 48-hour alert	Not Available
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	NA
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	7/22/02-Div. Director
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	5/17/02
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	NA
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	None
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) *(indicate date for each review)*	5/17/02
❖ Biopharmaceutical review(s) *(indicate date for each review)*	5/1/02
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	NA
• Bioequivalence studies	NA
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	NA
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	Yes-7/19/02
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	NA
❖ Facilities inspection (provide EER report)	Date completed: NA ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed NA ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	4/29/02
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ CAC/ECAC report	