

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

16-295/S-036

Administrative Documents

EXCLUSIVITY SUMMARY for NDA # 16-295 SUPPL # 036

Trade Name Droxia Generic Name hydroxyurea

Applicant Name Bristol-Myers Squibb Company HFD- 150

Approval Date June 26, 2003

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 /_X_/

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

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

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 /_X_/

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.

This was a Phase 4 commitment study to assess the influence of renal function on the pharmacokinetics of hydroxyurea in adults with sick cell disease.

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 /_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?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 /___/ NO /___/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 9 (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 9. 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 9.

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 9:**

- (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: _____

/S/

Signature of Preparer
Christy Cottrell
Consumer Safety Officer

Date

/S/

Signature of Division Director
Richard Pazdur, M.D.

Date

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

/s/

Christy Cottrell
6/26/03 02:14:14 PM

Richard Pazdur
6/26/03 03:37:28 PM

**DIVISION OF ONCOLOGY DRUG PRODUCTS
CSO LABELING REVIEW**

NDA: NDA 16-295/SE2-036
NDA 16-295/SE2-036 BL
NDA 16-295/SE2-036 AB

DRUG: Droxia® (hydroxyurea capsules, USP)
Hydrea® (hydroxyurea capsules, USP)

SPONSOR: Bristol –Myers Squibb Company

DATE OF SUBMISSION: August 20, 2002, received August 27, 2002
September 19, 2002, received September 26, 2002 (BL)
February 19, 2003, received February 20, 2003 (AB)

BACKGROUND:

This supplement proposes changes to the labeling based on data obtained from a study conducted to determine the influence of renal impairment on the pharmacokinetics of hydroxyurea in adults with sickle cell disease. This was a Phase 4 commitment study requested in the Approval letter for SE1-029 and SCS-030 dated February 25, 1998.

The sponsor submitted a labeling amendment submission (BL) on September 19, 2002, and a major amendment (AB) on February 19, 2003. The major amendment also contained updated labeling.

I compared the proposed labeling from the February 19, 2003, major amendment to the most recently approved final printed labeling for S-034 dated April 4, 2001.

DISCUSSION:

The only changes and/or discrepancies found were those that were proposed and identified by the sponsor in this supplement. All of the proposed changes were reviewed by Dr. Anne Zajicek. Please see her review dated June 25, 2003 for acceptability of the changes and any Division recommendations for further revisions.

RECOMMENDATIONS:

Based on the recommendations in Dr. Zajicek's review, an Approval letter will issue for NDA 16-295/SE2-036.



Christy Cottrell
Consumer Safety Officer

concurrency:



Dotti Pease
Chief, Project Management Staff

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

/s/

Christy Cottrell
6/26/03 01:57:39 PM
CSO

Dotti Pease
6/26/03 02:19:07 PM
CSO

Redacted 4

pages of trade

secret and/or

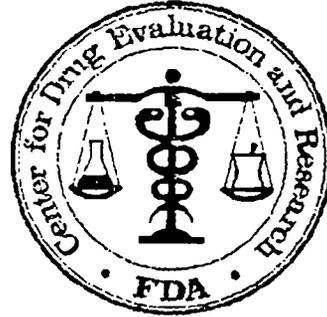
confidential

commercial

information

- in D+S.

FAX



FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: Steven Knapp

From: Christy Cottrell

Fax: by e-mail

Fax: (301) 594-0499

Phone:

Phone: (301) 594-5761

Pages, including cover sheet: 4

Date: 6-23-03

Re: NDA 16-295/S-036 for Droxia (hydroxyurea)

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you

Steve,

Please refer to your pending supplemental NDA 16-295/S-036 for Droxia (hydroxyurea). Included in this fax are the Division's recommended labeling changes for this supplement. Please let me if these changes are acceptable no later than close of business on Wednesday, June 25, 2003.

1. In the **CLINICAL PHARMACOLOGY** section, **Pharmacokinetics** subsection, **Metabolism** sub-subsection, you proposed the following changes (shown as single underline for added text and ~~strikethrough~~ for deleted text):

“Metabolism

[

]

We recommend the following revisions to your proposal (shown as double underline for added text and ~~strikethrough~~ as deleted text):

“Metabolism

Up to 60% of an oral dose undergoes conversion through metabolic pathways that are not fully characterized. One pathway is probably saturable hepatic metabolism.

Another minor pathway may be degraded ation by urease found in intestinal bacteria. Acetohydroxamic acid was found in the serum of three leukemic patients receiving hydroxyurea and may be formed from hydroxylamine resulting from action of urease on hydroxyurea.”

FDA comment: The submitted study showed 60% non-renal elimination.

2. In the **CLINICAL PHARMACOLOGY** section, **Special Populations** subsection, **Renal Insufficiency** sub-subsection, you proposed the following changes (shown as single underline for added text and ~~strikethrough~~ for deleted text):

“Renal Insufficiency

Γ

]

We recommend the following revisions to your proposal (shown as double underline for added text and ~~strikethrough~~ for deleted text):

“Renal Insufficiency

As renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage of hydroxyurea in patients with renal impairment. In adult patients with sickle cell disease, an open-label, non-randomized, single dose, multi-center study was conducted to assess the influence of renal function on the pharmacokinetics of hydroxyurea. Patients in the study with normal renal function (creatinine clearance (CrCl) > 80 mL/min); and mild (CrCl 50-80 mL/min), or severe (<30 mL/min) renal impairment received hydroxyurea ...”

FDA Comment: Clarifies the meaning of normal renal function.

3. In the **DOSAGE AND ADMINISTRATION** section, **Renal Insufficiency** subsection, you proposed the following revisions (shown as single underline for added text and ~~strikethrough~~ for deleted text):

“Renal Insufficiency

1

J

We recommend the following revisions to your proposal (shown as double underline for added text and ~~strikethrough~~ for deleted text):

“Renal Insufficiency

As renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage of DROXIA in patients with renal impairment.-

The results of a single dose study of the influence of renal function on the pharmacokinetics of hydroxyurea in adults with sickle cell disease suggest that the initial dose of hydroxyurea should be reduced by 50%, to 7.5 mg/kg/d, when used to treat patients with renal impairment (creatinine clearance < 60ml/min). (See PRECAUTIONS and CLINICAL PHARMACOLOGY). Close monitoring of hematologic parameters is advised in these patients.

<u>Creatinine Clearance</u> <u>(mL/min)</u>	<u>Recommended Droxia® Initial Dose</u> <u>(mg/kg daily)</u>
<u>≥ 60</u>	<u>15</u>
<u>< 60 or</u> <u>ESRD*</u>	<u>7.5</u>

FDA comment: Reprint of table will re-state the dosage recommendation for patients with renal dysfunction at defined by creatinine clearance < 60 ml/min.

4. All other proposed changes are acceptable.

Again, please let me know by **close of business on Wednesday, June 25th**, if these recommended revisions are acceptable. If you have any questions, feel free to call me at (301) 594-5761.

Thanks,

Christy Cottrell

APPEARS THIS WAY
ON ORIGINAL

4-9-03 Request for additional PK demographic information.txt
From: Cottrell, Christy
Sent: Wednesday, April 09, 2003 4:59 PM
To: 'steven.knapp@bms.com'
Subject: FW: Droxia; NDA 16-295/S-036/Demographic Info

See the attached request for additional information from the Biopharm reviewer for NDA 16-295/S-036.

Christy

-----Original Message-----

From: Zajicek, Anne
Sent: Wednesday, April 09, 2003 4:56 PM
To: Cottrell, Christy
Subject: RE: Droxia; NDA 16-295/S-036/Demographic Info

Hi Christy-Could you ask BMS to send individual demographics for each patients? I need individual demographics, not demographics grouped by renal function. Thank you-Anne

-----Original Message-----

From: Cottrell, Christy
Sent: Wednesday, March 19, 2003 1:08 PM
To: Zajicek, Anne
Subject: FW: Droxia; NDA 16-295/S-036/Demographic Info

FYI...as requested.

Christy

-----Original Message-----

From: steven.knapp@bms.com [mailto:steven.knapp@bms.com]
Sent: Wednesday, March 19, 2003 1:04 PM
To: Cottrell, Christy
Subject: Droxia; NDA 16-295/S-036/Demographic Info

Demography data attached...if you need a password to open it, use no password is being provided to modify the data table, only to read it. The creatinine clearances are simply 24 hour urine collections (there were no calculations). These are the last data pieces from your recent request (the Pk spreadsheet was sent a few weeks back).

"WorldSecure Server <cder.fda.gov>" made the following annotations on 03/19/03 13:04:57

4-9-03 Request for additional PK demographic information.txt

[INFO] -- Access Manager:

This message was sent from Bristol-Myers Squibb, Co. across the Internet in encrypted format and was successfully decrypted, unless otherwise noted.

=====
=====

From: Cottrell, Christy
Sent: Monday, March 03, 2003 3:48 PM
To: 'Steven J Knapp'
Subject: NDA 16-295 Droxia
Steve,

On a separate note....we received the info for the Droxia NDA 16-295/S-036. The biopharm reviewer would like you to submit the raw PK data (times and concentrations) for each patient, as well as serum creatinine, height, weight, sex and age, and method of calculating creatinine clearance (we are assuming Cockcroft-Gault).

Thanks,
Christy

APPEARS THIS WAY
ON ORIGINAL

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 16-295	Efficacy Supplement Type SE2	Supplement Number 036
Drug: Droxia (hydroxyurea capsules, USP)		Applicant: Bristol-Myers Squibb Company
RPM: Christy Cottrell		HFD- 150 Phone # (301) 594-5761
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		N/A
• Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Dates		June 27, 2003 (10-month)
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input checked="" type="checkbox"/> Other [Clinical data = NO]
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		N/A
• OC clearance for approval		N/A
❖ 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.		<input type="checkbox"/> Verified N/A
❖ Patent		
• Information: Verify that patent information was submitted		<input type="checkbox"/> Verified N/A
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (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).		<input type="checkbox"/> Verified N/A
❖ Exclusivity Summary (approvals only)		Included
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)		N/A

General Information	
❖ Actions	
• Proposed action	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	<input type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> Not applicable
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> 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)	Included
• Most recent applicant-proposed labeling	Included
• Original applicant-proposed labeling	Included
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>)	Included DDMAC review - May 6, 2003 CSO review- June 26, 2003
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	N/A
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
• Outgoing correspondence (i.e., letters, E-mails, faxes)	Included
• Memoranda and Telecons	N/A
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
• Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	N/A
❖ Clinical review(s) <i>(indicate date for each review)</i>	N/A
❖ Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>	N/A
❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Included
❖ Statistical review(s) <i>(indicate date for each review)</i>	N/A
❖ Biopharmaceutical review(s) <i>(indicate date for each review)</i>	Included Review dated June 25, 2003
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i>	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) <i>(indicate date for each review)</i>	N/A
❖ Environmental Assessment	
• Categorical Exclusion <i>(indicate review date)</i>	N/A
• Review & FONSI <i>(indicate date of review)</i>	N/A
• Review & Environmental Impact Statement <i>(indicate date of each review)</i>	N/A
❖ Micro (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>	N/A
❖ Facilities inspection (provide EER report)	Date completed: N/A () Acceptable () Withhold recommendation
❖ Methods validation	() Completed N/A () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	N/A
❖ CAC/ECAC report	N/A

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

/s/

Christy Cottrell
6/26/03 02:08:32 PM

Not applicable

Clinical data = NO