

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-882**

**Administrative/Correspondence Reviews**

**EXCLUSIVITY SUMMARY for NDA # 21-882**

Trade Name Exjade

Generic Name deferasirox

Applicant Name Novartis

HFD-180

Approval Date November 2, 2005

**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 X NO    

b) Is it an effectiveness supplement? YES     NO X

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 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:

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 X

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 X

**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 X

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

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 #

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  X  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  X  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  X

- (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  X

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 # 0107

Investigation #2, Study # 0108

Investigation #3, Study # 0109

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 / <u>X</u> /
Investigation #2	YES /___/	NO / <u>X</u> /
Investigation #3	YES /___/	NO / <u>X</u> /

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 <u>X</u>
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Investigation #2                    YES \_\_\_                    NO X  
Investigation #3                    YES \_\_\_                    NO X

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 #1, Study # 0107

Investigation #2, Study # 0108

Investigation #3, Study # 0109

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 # 58,554 YES X NO      Explain:

Investigation #2

IND # 58,554 YES X NO      Explain:

Investigation #3

IND # 58,554 YES X 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 X\_\_\_

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

\_\_\_\_\_  
Signature of Preparer Date  
Title: Regulatory Health Project Manager

\_\_\_\_\_  
Signature of Office or Division Director Date

Remember to cc in DFS:  
HFD-610/Mary Ann Holovac  
HFD-104/PEDS/T.Crescenzi

Form OGD-011347  
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

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Richard Pazdur  
11/3/2005 12:41:02 PM

# PEDIATRIC PAGE

NDA: 21-882

ap Date: April 29, 2005

Action Date: November 2, 2005

HFD-180 Trade and generic names/dosage form: Exjade (deferasorix) Tablets for oral Suspension

Applicant: Novartis Pharmaceuticals Corporation Therapeutic Class: Metal chelator

Number of indications for this application(s): 1

The treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adult and pediatric patients as young as two years of age.

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.

\*\*\*Application has Orphan Product Designation

## 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
- X 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}*

Alice Kacuba  
 Regulatory Health Project Manager

cc: NDA  
 HFD-950/ Terrie Crescenzi  
 HFD-960/ Grace Carmouze  
 (revised 9-24-02)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960  
 301-594-7337**

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/s/

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Alice Kacuba  
11/3/2005 12:48:04 PM

**NDA 21-882**

**Exjade (deferasorix) Tablets for Oral Suspension**

Safety Update-See October 26, 2005 Medical Officer.

Alice Kacuba 10-27-05

Alice Kacuba

Regulatory Health Project Manager

**NDA 21-882**

**Exjade (deferasorix) Tablets for Oral Suspension**

Risk Management-This section is Not Applicable for this application.

Alice Kacuba 10-26-05

Alice Kacuba

Regulatory Health Project Manager



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

OCT 25 2005

Alan R. Cohen, M.D.  
Chairman, Department of Pediatrics  
Children's Hospital of Philadelphia  
34<sup>th</sup> Street & Civic Center Blvd  
Philadelphia, PA 19104

Dear Dr. Cohen:

Between August 2 and 10, 2005, Mr. Mike M. Rashti, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of the following clinical investigations of the investigational drug Exjade (deferasirox) Tablets for Oral Suspension, performed for Novartis Pharmaceuticals:

1. Protocol C1CL670A0107 entitled: "A randomized, comparative, open label phase III trial on efficacy and safety of long-term treatment with ICL670 (5 to 40 mg/kg/day) in comparison with deferoxamine (20 to 60 mg/kg/day) in  $\beta$ -thalassemia patients with transfusional hemosiderosis"
2. Protocol C1CL670A0108 entitled "A multi-center, open label, non-comparative, phase II trial on efficacy and safety of ICL670 (5-40 mg/kg/day) given for at least one year to patients with chronic anemias and transfusional hemosiderosis unable to be treated with deferoxamine"

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Mr. Rashti presented and discussed with you inspectional observations. We acknowledge receipt of your letter dated August 10, 2005, and wish to emphasize the following:

1. You did not document that adequate informed consent was obtained [21 CFR 50.20].

You did not document that the addenda to the consent forms for subjects # 006 and 008 in protocol 107 were obtained. In a letter dated April 23, 2004, the IRB approved the consent form addendum and required using this document immediately.

CFN/FEI:

Field Classification: VAI

Headquarters Classification:

1)NAI

2)VAI- no response required

3)VAI- response requested

4)OAI

Deficiencies noted:

inadequate informed consent form (03)

Deficiency Codes: 03

cc:

HFA-224

HFD-180 Doc.Rm. NDA# 21-882

HFD-180 Review Div.Dir. Harvey

HFD-180 MO Shashaty

HFD-180 PM Kacuba

HFD-46/47 GCP File # 11615

HFD-46/47 GCP Reviewer Malek

HFR-CE150 DIB Baker

HFR-CE1515 Bimo Monitor Tammariello

HFR-CE150 Field Investigator Rashti

GCF-1 Seth Ray

r/d: (REVIEWER) KM-8/25/2005

reviewed: NK: 8/26/05

f/t: 915/05

o:\filename\document name: O\KM\Cohen

**Reviewer Note to Rev. Div. M.O.**

At this site, 11 subjects were screened; one subject (050200009) withdrew consent and ten subjects were enrolled in protocol 0107. In protocol 0108, seven subjects were screened; subject 50500002 was not qualified for the study because liver iron concentration was less than 14 mg Fe/g dw) and 6 subjects entered into the study. The field investigator reviewed all the subjects' records at the site. The inspectional observations include: there was no documentation that addenda to the consent forms for subjects # 006 and 008 in protocol 107 were obtained; the date that the subject 007 signed the assent was not recorded as required on the form. Overall, the data from this site can be used in support of the NDA.

Khairy Malek  
Medical Officer

11 Page(s) Withheld



           § 552(b)(4) Trade Secret / Confidential

           § 552(b)(5) Deliberative Process

           § 552(b)(5) Draft Labeling

17 Page(s) Withheld

         § 552(b)(4) Trade Secret / Confidential

         § 552(b)(5) Deliberative Process

         § 552(b)(5) Draft Labeling

9/29/05



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Oncology Drug Products

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: September 19, 2005**

<b>To:</b> Susan P. Nemeth, Ph.D. Associate Director, Drug Regulatory Affairs	<b>From:</b> Alice Kacuba, R.N., MSN, RAC Certified Regulatory Health Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Medical Imaging and Hematology Products
<b>Fax number:</b> 973-781-5217	<b>Fax number:</b> 301-443-9285
<b>Phone number:</b> 862-778-2003	<b>Phone number:</b> (301) 827-9334 or 7310
<b>Subject:</b> NDA 21-882	

**Total no. of pages including cover:** \_\_\_\_\_

**Comments:** Information Request.

**Documents to be mailed:**                     NO                    YES

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Dr. Nemeth

We have 2 clarifying Information Requests from the CDRH reviewer.

1. For the table of patients measured by the SQUID magnetometer, I assume that these numbers represent distinct patients, so that I can conclude that a total of 865 patients were measured by the SQUID. Is this interpretation correct?
2. For the procedure of lowering of the bed away from the SQUID, I believe that my previous statement of the bed being lowered 7 or 8 cm in a duration of 8 or 10 seconds is still correct then. Please confirm my interpretation.
3. Upon receipt of this request, please let me know an estimated response time.

Thank You.

Alice Kacuba

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/s/

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Alice Kacuba

9/19/2005 05:12:55 PM



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Oncology Drug Products**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: September 9, 2005**

<b>To:</b> Susan P. Nemeth, Ph.D. Associate Director, Drug Regulatory Affairs	<b>From:</b> Alice Kacuba, R.N., MSN, RAC Certified Regulatory Health Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Medical Imaging and Hematology Drug Products
<b>Fax number:</b> 973-781-5217	<b>Fax number:</b> 301-443-9285
<b>Phone number:</b> 862-778-2003	<b>Phone number:</b> (301) 827-9334 or 7310
<b>Subject:</b> NDA 21-882	

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**Total no. of pages including cover:** \_\_\_\_\_

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**Comments:** Attached are Information Requests for NDA 21-882

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**Documents to be mailed:**                     NO                    YES

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Dr. Nemeth

We have 2 information Requests from the CDRH reviewer

Clarifications concerning BLS measurements using the SQUID magnetometer:

1. What is the total number of patients who were measured with the SQUID magnetometer under the present NDA? Table 3-1 on page 22 of 392 (Iron Burden Document) seems to indicate the number of patients who were measured with the SQUID magnetometer in study 107, but no such tables exist for other studies in the NDA.
2. The BLS protocol in the present NDA does not clearly state the distance that the patient's bed was lowered and the duration of time used to lower the bed, during a BLS measurement procedure. The information in IND 58554 seems to indicate 7 or 8 cm for the distance and 8 or 10 seconds for the duration. Please clarify these two parameters.

Upon receipt of this request, please let me know an estimated response time.

Thank You.

Alice Kacuba

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/s/

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Alice Kacuba  
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SEP 21 2005

9

Patricia J. Giardina, M.D.  
525 E 68<sup>th</sup> Street  
New York, NY 10021-4870

Dear Dr. Giardina:

Between July 28 and August 10, 2005, Mr. Thomas P. Hansen, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of the following clinical investigations of the investigational drug Exjade (deferasirox) Tablets for Oral Suspension, performed for Novartis Pharmaceuticals:

1. Protocol C1CL670A0107 entitled: "A randomized, comparative, open label phase III trial on efficacy and safety of long-term treatment with ICL670 (5 to 40 mg/kg/day) in comparison with deferoxamine (20 to 60 mg/kg/day) in  $\beta$ -thalassemia patients with transfusional hemosiderosis"
2. Protocol C1CL670A0108 entitled "A multi-center, open label, non-comparative, phase II trial on efficacy and safety of ICL670 (5-40 mg/kg/day) given for at least one year to patients with chronic anemias and transfusional hemosiderosis unable to be treated with deferoxamine"
3. Protocol C1CL670A0109 entitled "A randomized, multicenter, open label, phase II study to evaluate the safety, tolerability, pharmacokinetics and the effects on liver iron concentration of repeated doses of 10 mg/kg/day of ICL670 relative to deferoxamine in sickle cell disease patients with transfusional hemosiderosis."

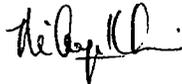
This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

Page 2 - Patricia J. Giardina, M.D.

We appreciate the cooperation shown Investigator Hansen during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,



Ni A. Khin, M.D.  
Branch Chief  
Good Clinical Practice Branch I, HFD-46  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

CFN/FEI:

Field Classification: NAI

Headquarters Classification:

X \_\_\_ 1)NAI

\_\_\_ 2)VAI- no response required

\_\_\_ 3)VAI- response requested

\_\_\_ 4)OAI

cc:

HFA-224

HFD-180 Doc.Rm. NDA# 21-882

HFD-180 Review Div.Dir. Harvey

HFD-180 MO Shashaty

HFD-180 PM Kacuba

HFD-46/47c/r/s/ GCP File # 11602

HFD-46/47 GCP Reviewer Malek

HFR-NE100 DIB Vitillo

HFR-NE1500 Bimo Monitor & Investigator Hansen

GCF-1 Seth Ray

r/d: (REVIEWER) KM-8/23/05

reviewed: NK: 8/23/05

f/t: (REVIEWER)

o:\filename\document name: O:\KM\Giardina

**Reviewer Note to Rev. Div. M.O.**

At this site 13 subjects were enrolled in protocol 0107, 6 subjects in protocol 0108 and one subject in protocol 0109. The FDA field investigator reviewed the records of 6 subjects in protocol 0107, 6 in protocol 0108, and 1 in protocol 0109. No regulatory violations were observed. The data from this study site can be used in support of the NDA.

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§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

8/25/05

TO (Division/Office): <b>Wiley A. Chambers</b> <b>PMSs Maureen Dillon-Parker and Frances LeSane</b>	FROM: Division of GI and Coagulation Drug Products (HFD-180)/ Alice Kacuba <b>(301) 827-9334</b>
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DATE July 27, 2005	IND NO.	NDA NO. 21-882	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT April 29, 2005
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NAME OF DRUG <b>Exjade (deferasorix/ICL 670) orally Disintegrating Tablets</b>	PRIORITY CONSIDERATION <b>Priority review (Going to BPAC on 9-29-05)</b>	CLASSIFICATION OF DRUG <b>Metal Chelator</b>	DESIRED COMPLETION DATE <b>September 1, 2005- can be negotiated</b>
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NAME OF FIRM: **Novartis**

**REASON FOR REQUEST**

**I. GENERAL**

- |   |   |   |
|---|---|---|
| <ul style="list-style-type: none"> <li>• NEW PROTOCOL</li> <li>• PROGRESS REPORT</li> <li>• NEW CORRESPONDENCE</li> <li>• DRUG ADVERTISING</li> <li>• ADVERSE REACTION REPORT</li> <li>• MANUFACTURING CHANGE/ADDITION</li> <li>• MEETING PLANNED BY</li> </ul> | <ul style="list-style-type: none"> <li>• PRE--NDA MEETING</li> <li>• END OF PHASE II MEETING</li> <li>• RESUBMISSION</li> <li>• SAFETY/EFFICACY</li> <li>• PAPER NDA</li> <li>• CONTROL SUPPLEMENT</li> </ul> | <ul style="list-style-type: none"> <li>• RESPONSE TO DEFICIENCY LETTER</li> <li>• FINAL PRINTED LABELING</li> <li>• LABELING REVISION</li> <li>• ORIGINAL NEW CORRESPONDENCE</li> <li>• FORMULATIVE REVIEW</li> <li>••••• OTHER (SPECIFY BELOW):</li> </ul> |
|---|---|---|

**COMMENTS/SPECIAL INSTRUCTIONS:** The purpose of this request is to consult the review of the Ophthalmological complications related to Exjade administration. Is there any risk management program that you might recommend to minimize ophthalmological complications in such patients?

**Background:** Novartis submitted NDA 21-882 to provide for the following indication: the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adult and pediatric patients as young as two years of age. In preclinical studies, cataracts were discovered in animals treated with Exjade. The sponsor paid special attention to eye examinations in patients enrolled in clinical trials (0105, 0106, 0107 [pivotal study], and 0108).

**The HFD-180 Medical Officer is George Shashaty (827-7472), and the Regulatory Project Manager is Alice Kacuba (827-9334).**

This NDA is a fully electronic NDA in CTD format and is available in the edr under NDA 21-882, April 29, 2005 submission. The edr contains a word version of the proposed labeling.

This application will be presented to the Blood Products Advisory Committee (BPAC) on September 29, 2005. We would like to have your consult review by September 1, 2005. This date can be negotiated.

The user fee goal date is November 2, 2005.  
 Thank you for your assistance. Any questions, feel free to call.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

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Alice Kacuba

7/27/05 04:55:05 PM

7/20/05

### NDA REGULATORY FILING REVIEW (Including Memo of Filing Meeting)

NDA # 21-882 Supplement # Efficacy Supplement Type SE-

Trade Name: Exjade  
Established Name: deferasorix  
Strengths: 125, 250, and 500 mg Tablets for Oral Suspension

Applicant: Novartis Pharmaceuticals, Inc.  
Agent for Applicant:

Date of Application: April 29, 2005  
Date of Receipt: May 2, 2005  
Date clock started after UN:  
Date of Filing Meeting: June 6, 2005  
Filing Date: July 1, 2005  
Action Goal Date (optional): November 2, 2005 User Fee Goal Date: November 2, 2005

Indication(s) requested: The treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adult and pediatric patients as young as two years of age.

Type of Original NDA: (b)(1)  (b)(2)   
OR  
Type of Supplement: (b)(1)  (b)(2)

**NOTE:**

- (1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.
- (2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

NDA is a (b)(1) application OR  NDA is a (b)(2) application

Therapeutic Classification: S  P   
Resubmission after withdrawal?  Resubmission after refuse to file?   
Chemical Classification: (1,2,3 etc.) 1  
Other (orphan, OTC, etc.) Orphan

Form 3397 (User Fee Cover Sheet) submitted: YES  NO

User Fee Status: Paid  Exempt (orphan, government)   
Waived (e.g., small business, public health)

**NOTE:** If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the

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This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES  NO   
If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES  NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES  NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES  NO   
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES  NO

- Does the submission contain an accurate comprehensive index? YES  NO

- Was form 356h included with an authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**

- Submission complete as required under 21 CFR 314.50? YES  NO   
If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A  YES  NO   
**If an electronic NDA, all forms and certifications must be in paper and require a signature.**  
Which parts of the application were submitted in electronic format? All except pages with signatures.

Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A  YES  NO

- Is it an electronic CTD (eCTD)? N/A  YES  NO   
**If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments:

- Patent information submitted on form FDA 3542a? YES  NO

- Exclusivity requested? YES, \_\_\_\_\_ Years NO   
**NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.**

- Correctly worded Debarment Certification included with authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

**NOTE:** Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature? YES  NO   
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)  
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section)? Y  NO
- PDUFA and Action Goal dates correct in COMIS? YES  NO   
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 58,554
- End-of-Phase 2 Meeting(s)? Date(s) April 9, 2002 NO   
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) October 1, 2004 NO   
If yes, distribute minutes before filing meeting.

**Project Management**

- Was electronic "Content of Labeling" submitted? YES  NO   
If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES  NO
- Risk Management Plan consulted to ODS/IO? N/A  YES  NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y  NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A  YES  NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A  YES  NO

**If Rx-to-OTC Switch application:**

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A  YES  NO
- Has DOTCDP been notified of the OTC switch application? YES  NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?  
YES  NO

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES  NO   
If no, did applicant submit a complete environmental assessment? YES  NO   
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES  NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES  NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES  NO

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ATTACHMENT

**MEMO OF FILING MEETING**

DATE: June 6, 2005

**BACKGROUND:** Exjade has Orphan Product Designation and Fast Track designation. Exjade was also accepted in to the CMA Pilot-1 Program. The CMC RU was submitted on January 7, 2005. The remainder of the NDA is submitted in the current April 29, 2005 submission. This application is in the edr. CDRH is consulted regarding the use of SQUID. The three clinical protocols were reviewed under IND 58,554 as Special Protocol Assessments.

(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

**ATTENDEES:** Karen Weiss, Flo Houn, Kathy Robie-Suh, George Shashaty, George Mills, Sally Loewke, Ray Frankewich, Eldon Leutzinger, Stella Grosser, Anthony Mucci, Jasti Choudary, Suresh Doddapaneni, Young Choi, Suliman Al-Fayoumi, Khairy Malek, Rafel Rieves, Charles Ho, Alice Kacuba

**ASSIGNED REVIEWERS** (including those not present at filing meeting) :

<u>Discipline</u>	<u>Reviewer</u>
Medical:	George Shashaty
Secondary Medical:	Kathy Robie-Suh
Statistical:	Anthony Mucci
Pharmacology:	Tamal Chakraborti
Statistical Pharmacology:	Ted Guo
Chemistry:	Ray Frankewich
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Suliman Al-Fayoumi
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	Khairy Makek
Regulatory Project Management:	Alice Kacuba
Other Consults:	DDMAC, DMETS, CDRH

Per reviewers, are all parts in English or English translation? YES  NO   
If no, explain:

CLINICAL FILE  REFUSE TO FILE

• Clinical site inspection needed? YES  NO

• Advisory Committee Meeting needed? YES, date if known  X  NO

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?  
N/A  YES  NO

CLINICAL MICROBIOLOGY N/A  FILE  REFUSE TO FILE

STATISTICS	N/A <input type="checkbox"/>	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
BIOPHARMACEUTICS		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
	• Biopharm. inspection needed?		YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>
PHARMACOLOGY	N/A <input type="checkbox"/>	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
	• GLP inspection needed?		YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>
CHEMISTRY		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
	• Establishment(s) ready for inspection?		YES <input checked="" type="checkbox"/> NO <input type="checkbox"/>
	• Microbiology		YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>

ELECTRONIC SUBMISSION:  
Any comments: None

REGULATORY CONCLUSIONS/DEFICIENCIES:  
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
  - No filing issues have been identified.
  - Filing issues to be communicated by Day 74. List (optional): July 15, 2005

ACTION ITEMS:

1.  If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2.  If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3.  Convey document filing issues/no filing issues to applicant by Day 74.

Alice Kacuba  
Regulatory Project Manager, HFD-180

### Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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**Appendix B to NDA Regulatory Filing Review  
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES  NO

*If "No," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES  NO

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

*If "No," skip to question 4. Otherwise, answer part (b).*

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES  NO   
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

*If "Yes," skip to question 6. Otherwise, answer part (c).*

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES  NO

*If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES  NO

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*If "No," skip to question 5. Otherwise, answer part (b).*

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES  NO   
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

**NOTE:** *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

*Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "Yes," skip to question 6. Otherwise, answer part (c).*

- (c) Have you conferred with the Director, Division of Regulatory Policy II, YES  NO   
ORP?

*If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? YES  NO

*If "No," skip to question 6.*

*If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

- (b) Is the approved drug product cited as the listed drug? YES  NO
6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").
7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES  NO
8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES  NO
9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES  NO
10. Are there certifications for each of the patents listed for the listed drug(s)? YES  NO
11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)  
Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)  
Patent number(s):

**NOTE:** *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must subsequently submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)  
Patent number(s):
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).  
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.  
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?  
YES  NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?  
YES  NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?  
N/A  YES  NO
- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?  
N/A  YES  NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).  
YES  NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.  
YES  NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND# \_\_\_\_\_ NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES  NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES  NO

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this page is the manifestation of the electronic signature.**  
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/s/

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Alice Kacuba  
7/20/05 06:36:09 PM  
CSO

**DRAFT**

**NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST**

Application Information	
NDA 21-882	
Drug: Exjade® (deferasorix) Tablets for Oral Suspension	Applicant: Novartis Pharmaceuticals Corporation
RPM: Alice Kacuba	Division of Medical Imaging and Hematology Products      Phone # 301-796-1381
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)            (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p><b>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</b></p> <p><input type="checkbox"/> Confirmed and/or corrected</p>	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
<b>❖ Application Classifications:</b>	
• Review priority	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
• Chem class (NDAs only)	1
• Other (e.g., orphan, OTC)	Orphan product designation
<b>❖ User Fee Goal Date</b>	
	November 2, 2005
<b>❖ Special programs (indicate all that apply)</b>	
	<input type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
<b>❖ User Fee Information</b>	
• User Fee	<input type="checkbox"/> Paid   UF ID number
• User Fee waiver	<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
• User Fee exception	<input checked="" type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
<b>❖ Application Integrity Policy (AIP)</b>	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes     No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes     No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
• Exclusivity Summary	draft
• Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	No
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.	<input type="checkbox"/> Yes, Application # _____ <input checked="" type="checkbox"/> No
Administrative Reviews (Project Manager, ADRA) (July 20, 2005)	X

General Information	
<b>Actions</b>	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(X) Materials requested in AP letter <i>Sponsor will submit prior to 11-2-05. DDMAC aware.</i> ( ) Reviewed for Subpart H
❖ <b>Public communications</b>	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None (X) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ <b>Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))</b>	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	See draft AP letter
• Most recent applicant-proposed labeling ( <i>October 26, 2005</i> )	X
• Original applicant-proposed labeling- <i>April 29, 2005</i>	X
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings ( <i>DMETS=August 4, 2005; DDMAC=September 29, 2005</i> )	X
• Other relevant labeling (e.g., most recent 3 in class, class labeling)- <i>Desferal</i>	X
<b>Labels (immediate container &amp; carton labels)</b>	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed- <i>April 29, 2005, October 27, 2005</i>	X
• Reviews ( <i>DMETS=August 4, 2005, DDMAC=September 29, 2005</i> )	X
❖ <b>Post-marketing commitments</b>	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	X
❖ <b>Outgoing correspondence (i.e., letters, E-mails, faxes)</b>	X
❖ <b>Memoranda and Telecons</b>	X
❖ <b>Minutes of Meetings</b>	
• EOP2 meeting ( <i>April 9, 2002</i> )	X
• Pre-NDA meeting ( <i>October 1, 2004</i> )	X
• Pre-Approval Safety Conference ( <i>November 18, 2005</i> )	Scheduled for November 18, 2005
• Other ( <i>October 23, 2003, June 28, 2004</i> )	X
❖ <b>Advisory Committee Meeting</b>	
• Date of Meeting	September 29, 2005
• 48-hour alert/Quick Minutes	X
❖ <b>Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)</b>	X

Summary Application Review	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (MOTL= 11-2-05, DD= 11-2-05, OD= NA))	X
Clinical Information	
❖ Clinical review(s) (October 26, 2005)	X
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (See MOR dated October 26, 2005)	X
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	draft
❖ Demographic Worksheet (NME approvals only)	NA
❖ Statistical review(s) (October 12, 2005)	X
❖ Biopharmaceutical review(s) (October 11, 2005)	X
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (July 7, 2005, October 12, 2005)	X
❖ Environmental Assessment	
• Categorical Exclusion (October 12, 2005)	X
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report)	Date completed: August 2, 2005 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (X) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (September 29, 2005)	X
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (August 11, 2005, September 8, 2005, September 9, 2005)	X
❖ CAC/ECAC report	X

# Memo

**To:** Brian Harvey, MD  
Director, Division of Gastroenterology Drug Products; HFD-180

**From:** Felicia Duffy, RN, BSN  
Safety Evaluator, Division of Medication Errors and Technical Support  
Office of Drug Safety; HFD-420

**Through:** Alina Mahmud, RPh, MS, Team Leader  
Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Errors and Technical Support  
Office of Drug Safety; HFD-420

**Date:** July 15, 2005

**Re:** ODS Consult 03-0182-1; Exjade (Deferasirox Tablets for Oral Suspension) 125 mg, 250 mg, 500 mg;  
NDA 21-882

---

This memorandum is in response to a June 1, 2005 request from your Division for a re-review of the proprietary name, Exjade. Container labels and package insert labeling were also provided for review and comment for the first time.

The proposed proprietary name, Exjade, was found acceptable by DMETS in a review dated November 17, 2003 (ODS consult #03-0182). Since the November 17, 2003 review, DMETS identified the proprietary name Esgic-Plus as having potential sound-alike similarities to Exjade.

Esgic-Plus may sound similar to Exjade if the "Plus" modifier is omitted. Esgic-Plus is a non-narcotic analgesic with barbiturates indicated for tension headaches. Esgic and Exjade both contain 2 syllables. The first syllable of each name is phonetically similar ("Es" vs. "Ex"). Additionally, the letters "g" and "j" are pronounced the same when the names are spoken. However, the ending of each name is phonetically distinct ("ade" vs. "ic"). Esgic and Exjade are both administered orally. They also share the same dosage form (tablets) and share an overlapping numerical strength (500 mg). Despite these similarities, Esgic and Exjade differ in indication for use (tension headache vs. chronic iron overload), usual dosage (1-2 tablets vs. 20 mg/kg to 30 mg/kg), and frequency of administration (every 4 hours as needed vs. once daily). Although some phonetic similarities exist between Esgic and Exjade, the differentiating product characteristics minimize their potential for confusion.

Review of the insert labeling for Exjade, DMETS has attempted to focus on safety issues relating to possible medication errors.

## A. GENERAL COMMENTS

1. The dosage form appears juxtapose to the net quantity statement. Revise the labels and labeling so that the dosage form appears in conjunction with the established name. Additionally, since there are restrictions in which fluids the tablets can be dispersed, we recommend including this information in close proximity to the product name. We propose the sponsor use following presentation recommended by the CDER Labeling and Nomenclature Committee:

Exjade  
(Deferasirox Tablets for Oral Suspension\*)  
Strength

\*Tablets MUST be dispersed in water or orange juice.  
DO NOT CHEW or SWALLOW WHOLE

2. Since it is not recommended that the product be swallowed whole or chewed, DMETS questions the ramifications if a patient attempts to swallow or chew the tablets. This product is indicated for pediatric patients and most pediatric tablets are chewable tablets. Is there a lack of efficacy or absorption if the tablet is chewed or swallowed whole? Please address the possible ramifications of chewing or swallowing the tablets whole. Additionally, if there is a significant safety issue (e.g., choking hazard), we request the sponsor consider reformulating the product to a powder or suspension for patient safety reasons, especially since this product may be used with pediatric patients.
3. A patient information sheet is not included with Exjade. A brief patient information sheet that includes the directions for use may help to ensure that the product is used properly (e.g. the product is taken on an empty stomach, tablets are not chewed or swallowed whole, type of solution to dissolve tablets in, etc.). The sponsor may want to consider this as an option to increase the safe and proper use of Exjade.

## B. CONTAINER LABEL (professional sample and unit-of-use bottle)

1. See General Comment A1.
2. The — graphic that appears in front of the proprietary name is distracting and may be misinterpreted as the letter “O”. Please delete this graphic in order to avoid confusion.
3. The — color on the — background does not provide sufficient color contrast, thus making the strength difficult to read. We recommend using a different color scheme that provides easier readability.
4. The color of the product strength for the 250 mg and 500 mg tablets are identical. In order to avoid confusion, we recommend clearly differentiating the product strengths from one another by using contrasting color, boxing, or some other means.
5. Relocate the net quantity statement away from the product strength in order to avoid confusion.
6. Since the bottles are unit-of-use, please ensure they have child-resistant caps (CRC) in compliance with the Poison Prevention Act.

## C. PACKAGE INSERT

1. General Comment

The sponsor utilizes the “μg” abbreviation for micrograms. We recommend using “mcg” to abbreviate micrograms in order to avoid confusing “μg” with “mg”. We note that the Joint Commission for Accreditation of Hospitals (JCAHO), 2005 Hospitals National Patient Safety Goals includes the goal: Improve the effectiveness of communication among caregivers. A requirement to meet this goal is that each hospital must “Standardize a list of abbreviations, acronyms and symbols that are not to be

used throughout the organization.” The use of “μ” is specifically listed as a dangerous abbreviation, acronym, or symbol. Other healthcare organizations, such as ISMP have also published similar lists containing symbols that can lead to medication errors. Revise throughout the package insert accordingly. ✓

2. Precautions: Information for Patients subsection

- a. Include the “Do not chew or swallow whole” statement in this section along with the acceptable fluids for dispersion (e.g., disperse in water or orange juice). ☐

☐ This is important information the must be conveyed to the patient.

- b. Repeat the information included in this subsection at the end of the physician insert labeling in accordance with CFR 21 201.57(f)(2). ✓

3. Dosage and Administration section

- a. It is important to inform the user of pertinent information pertaining to the safe and proper use of the drug product in the beginning of the dosage and administration section. Therefore, we recommend adding four bullets that address the following guidelines for Exjade (the four points should be bolded in order to highlight their importance):

- Take Exjade on an empty stomach. ✓
- Do not chew or swallow the tablets whole.
- Tablets **MUST** be dispersed in water or orange juice.
- Do not take Exjade with aluminum-containing antacid products.

- b. The last sentence of the Dosage and Administration section states, “Tablets must not be chewed or swallowed whole.” DMETS questions what the repercussions are if the tablet is chewed or swallowed whole. If there is risk of an adverse event (e.g., choking hazard), then this should be stated in the insert. If the potential for poor absorption or poor efficacy exists if the tablets are chewed or swallowed whole, this should also be stated. ✓

- c. The last paragraph of this section contains a volume that has a trailing zero (7.0 ounces). To avoid confusion, delete the trailing zero since it may be misinterpreted as ☐ J ✓  
As evidenced by our post-marketing surveillance, the use of terminal or trailing zeros could potentially result in a ten-fold medication dose error. Also in accordance with the General Notices (page 12) of the 2000 USP, “In order the minimize the possibility of errors in the dispensing and administration of drugs, the quantity of active ingredient when expressed in whole numbers shall be shown **WITHOUT** a decimal point that is followed by a terminal zero.” We note that the Joint Commission for Accreditation of Hospitals (JCAHO), 2005 Hospitals National Patient Safety Goals includes the goal: Improve the effectiveness of communication among caregivers. A requirement to meet this goal is that each hospital must ‘Standardize a list of abbreviations, acronyms and symbols that are not to be used throughout the organization’. The use of trailing zeroes is specifically listed as a dangerous abbreviation, acronym, or symbol. Other healthcare organizations, such as ISMP have also published similar lists containing symbols that can lead to medication errors.

In summary, DMETS has no objections to the use of the proprietary name, Exjade. We also recommend implementation of the labeling recommendations outlined in this memo that may lead to safer use of the product. ✓  
Additionally, DDMAC finds the proprietary name acceptable from a promotional perspective. We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward. If you have any questions or need clarification, please contact the medication errors Project Manager, Diane Smith at 301-827-1998.

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/s/

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Felicia Duffy  
8/4/05 01:39:09 PM  
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud  
8/4/05 01:43:22 PM  
DRUG SAFETY OFFICE REVIEWER

Denise Toyer  
8/4/05 02:18:46 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
8/4/05 02:34:14 PM  
DRUG SAFETY OFFICE REVIEWER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 21-882

7-14-05

Novartis Pharmaceuticals Corporation  
Attention: Susan P. Nemeth, Ph.D.  
One Health Plaza  
Hanover, NJ 07936-1080

Dear Dr. Nemeth:

Please refer to your April 29, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exjade<sup>®</sup> (deferasorix) Tablets for Oral Suspension.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on July 1, 2005 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Clinical:

1. It appears that in pivotal study 0107 titled "A randomized, comparative, open label phase III trial on efficacy and safety of long-term treatment with ICL-670 (5 to 40 mg/kg/day) in conjunction with deferoxamine (20 to 60 mg/kg/day) in  $\beta$ -thalassemia patients with transfusional hemosiderosis," non-inferiority compared to deferoxamine was not demonstrated for the entire efficacy population.
2. Wording for the proposed indication will depend on the review of the data, as will the proposed transfusion history and serum ferritin levels as determinants of the dosing of the drug.
3. The use of SQUID as a measure of liver iron content appears not to be valid.
4. The size of some of the liver biopsies were less than the one gram that may be required to accurately measure liver iron content.
5. The frequency of adverse events, particularly of the kidney and the skin, appears to be high. These, as well as the other adverse events, will be carefully evaluated to determine the benefit/risk ratio for the clinical use of the drug.

6. The effects of Exjade on morbidity and mortality in iron overloaded patients receiving chronic transfusions for congenital anemias have not been clearly delineated.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We do not expect a response to this letter, and we may not review any such response during the current review cycle.

If you have any questions, call Alice Kacuba, Regulatory Health Project Manager, at (301) 827-9334.

Sincerely,

*{See appended electronic signature page}*

Julieann DuBeau, MSN, RN  
Chief, Project Management Staff  
Division of Gastrointestinal and Coagulation Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Julieann DuBeau  
7/14/05 01:04:56 PM



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation III

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: July 11, 2005**

<b>To:</b> Susan P. Nemeth, Ph.D. Associate Director, Drug Regulatory Affairs	<b>From:</b> Alice Kacuba, R.N., MSN, RAC Certified Regulatory Health Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Gastrointestinal and Coagulation Drug Products
<b>Fax number:</b> 973-781-5217	<b>Fax number:</b> 301-443-9285
<b>Phone number:</b> 862-778-2003	<b>Phone number:</b> (301) 827-9334 or 7310
<b>Subject:</b> <u>NDA 21-882</u>	

**Total no. of pages including cover:** \_\_\_\_\_

**Comments:** Attached are Information Requests from the Pharm/Tox reviewer for NDA  
21-882.

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**Documents to be mailed:**                       NO                      YES

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Dr. Nemeth,

We are requesting that you please submit the historical control data for the rat and mouse for the period covering 3-5 years prior to the end of the in-life phase of the following studies for the same strain of animals and for the same testing facility (Novartis Pharmaceuticals Corporation, East Hannover, NJ 07936):

1. 104-Week oral (gavage) carcinogenicity study (017022) in Wistar Hannover rats (End of in-life phase: May 27, 2003).
2. 26-Week oral (gavage) carcinogenicity study (0270117) in p53 heterozygous mice (End of in-life phase: April 18, 2003).

Upon receipt of this Information Request, please communicate an estimated submission time for your response.

Thank you.

Alice Kacuba

Alice Kacuba, RN, MSN, RAC  
Regulatory Health Project Manager  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180  
ODE III/OND/CDER/FDA  
301-827-9334  
(fax) 301-443-9285  
kacubaa@cder.fda.gov

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/s/

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Alice Kacuba

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Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation III

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: July 11, 2005**

<b>To:</b> Susan P. Nemeth, Ph.D. Associate Director, Drug Regulatory Affairs	<b>From:</b> Alice Kacuba, R.N., MSN, RAC Certified Regulatory Health Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Gastrointestinal and Coagulation Drug Products
<b>Fax number:</b> 973-781-5217	<b>Fax number:</b> 301-443-9285
<b>Phone number:</b> 862-778-2003	<b>Phone number:</b> (301) 827-9334 or 7310
<b>Subject:</b> <u>NDA 21-882</u>	

**Total no. of pages including cover:** \_\_\_\_\_

**Comments:** Attached is an Information Requests for NDA 21-882.

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**Documents to be mailed:**                     NO    YES

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Dr. Nemeth,

I have an additional Information Request:

1. Please address foreign marketing history by stating that the product has not been marketed elsewhere or by providing information on the foreign marketing, such as labeling, etc.

Thank you.

Alice Kacuba

Alice Kacuba, RN, MSN, RAC  
Regulatory Health Project Manager  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180  
ODE III/OND/CDER/FDA  
301-827-9334  
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/s/

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Alice Kacuba

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ORIGINAL  
NEW CORRESP  
NC

Novartis Pharmaceuticals Corporation  
One Health Plaza  
East Hanover, NJ 07936-1080

Susan P. Nemeth, PhD  
Tel. 862-778-2003  
Fax. 973-781-5217

RECEIVED

JUL 13 2005

FDR/CDER

July 11, 2005

Brian Harvey, MD, PhD  
Director  
Division of Gastrointestinal and  
Coagulation Drug Products  
Attn: Division Document Room, 8B-45  
5600 Fishers Lane  
Rockville, MD 20857

NDA 21-882

**EXJADE® (deferasirox) Tablets for Oral  
Suspension**

**General Correspondence: Response to  
Information Request**

Dear Dr. Harvey:

response to an information request received from Ms. Alice Kacuba on July 11, 2005, please note that Exjade (deferasirox, ICL670) is not marketed in any country at this time.

If you have any questions or comments regarding this application, please contact me at (862-778-2003).

Sincerely,

Susan P. Nemeth, PhD  
Associate Director  
Drug Regulatory Affairs

/da

2 Page(s) Withheld

       § 552(b)(4) Trade Secret / Confidential

       § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

**NDA 21-882**

**Exjade (deferasorix) Tablets for Oral Suspension**

Microbiology Review-efficacy-This section is not applicable for this application.

Alice Kacuba 7-11-05

Alice Kacuba

Regulatory Health Project Manager



DISCIPLINE REVIEW LETTER

NDA 21-882/RUC

7-7-05

Novartis Pharmaceuticals Corporation  
Attention: Susan P. Nemeth, Ph.D.  
One Health Plaza  
Hanover, NJ 07936-1080

Dear Dr. Nemeth:

Please refer to your New Drug Application (NDA) for Exjade® (deferasirox) Tablets for Oral Suspension, submitted under the Continuous Marketing Application (CMA)-Pilot 1 program.

We also refer to your January 10, 2005 reviewable unit (RU) for the Chemistry, Manufacturing, and Controls portion of your NDA.

We have completed our review of this RU and have identified the following deficiencies:

Drug Substance

1. Clarify the situations under which you will perform ( ) or the drug substance. ( ) would require review and approval prior to implementation.
2. Tighten the acceptance criterion for particle size in the drug substance based on your batch analysis data. ( )
3. Tighten the acceptance criterion for ( ) Impurities in the drug substance specification to ( ), consistent with the Reporting Threshold in ICH Q3A for a drug for which the potential daily dosage is ( ) or more. Alternatively, provide a rationale for why this cannot be done based on data generated for this drug.
4. Propose an acceptance criterion for ( ) Impurities in the test for ( ) ( ) by HPLC in the drug substance specification that is justified according to batch analysis data and capability of the analytical procedure.
5. Submit results of ( ) chromatogram of the drug substance, using the analytical procedure for assay and accompanying

substances by HPLC. [

6. Provided (a) reference(s) [ ] indicating that the [ ] material that contacts the drug substance when it is stored is safe for use. Specify whether or not the material is [ ] (which is used in stability studies), and provide the name(s) of the suppliers. Also, indicate the material that the [ ] are [ ] used to store stability batches). ]
7. Provide clarification regarding the location of the facility in which the drug substance batches 1030004004 – 1030006004 were manufactured (they were used in the stability study SCR 03-ISL001, referred to as commercial/stability commitment batches). In Section S.4.4 (Batch Analysis) it is indicated that all drug substance batches, including these, were manufactured in the Novartis Basel facility. On pg. 2 of the document entitled Stability Commitment Report - Summary and Conclusion (pg. 523 of the Drug Substance Section), it is indicated that these batches were manufactured at [ ]
8. If you intend to propose the Pratteln, Switzerland site as a manufacturing facility for the drug substance, submit stability data collected using accelerated and room-temperature conditions (refer to ICH Q1A) for batches of drug substance manufactured at the Novartis facility in Pratteln, Switzerland.

#### Drug Product

9. Clarify what the composition of the [ ] used for bulk storage of the drug product is, and what the drug product contact surface of the bags is. Provide references to the Food Additives parts of the CFR indicating that these materials are appropriate for food packaging. Indicate how long the tablets will be stored in the bulk container [ ] before packaging into the containers used for marketing.
10. Adopt the acceptance criteria from <701> for your Disintegration test in your drug product monograph. Specifically, the language (which should replace the current language in the analytical procedure) should be "If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely".
11. Revise your analytical procedure [ ]
12. Justify the use of [ ] to [ ] in the analytical procedure for [ ]  

] Explain whether or not particles larger than [ ] are associated with negative characteristics for a drug product (e. g., bioavailability concerns, drug product quality).

13. Revise the Drug Product Specification such that the limit for Each Unspecified Degradation Product is — commensurate with the Reporting Level in ICH Q3B(R) for a drug whose maximum daily dose — . If it is perceived this is not appropriate, provide a rationale based on release and stability data for the drug product.
14. Propose an acceptance criterion for Total Unspecified Degradation Products in the Drug Product Specification that is justified by batch analysis data and capability of the analytical procedure.
15. Provide a rationale, based on test data, for the acceptance criterion for [ ] test in the Drug Product Specification ([ ])
16. Provide complete information, in Section P.7 of your NDA (Container closure section), about the CR [ ] blister and physician sample packages. Include drawings, specifications, and acceptance criteria, and letters of authorization to the proper Drug Master Files (DMFs).
17. If you intend to propose the Pratteln, Switzerland site as a manufacturing facility for the drug substance, submit stability data collected using accelerated and room-temperature conditions (refer to ICH Q1A) for batches of drug product that were produced using drug substance manufactured at the Novartis facility in Pratteln, Switzerland.
18. Amend your stability protocol to include the tests for [ ]
19. If you have not yet submitted either an Environmental Assessment (EA) or a claim for categorical exclusion from having to submit an EA for this NDA, please do so.

#### Labeling

20. Provide labeling for the following packaging configurations: [ ] blister packs [ ] and, if applicable, cartons; 45 mL HDPE, for 125 mg and 250 mg strengths, 4 count, for physician samples; 90 mL HDPE, for 500 mg strength, 4 count, for physician samples.
21. Provide a statement, preferably in the How Supplied section of the package insert, specifying to the pharmacist the type of container to be used to dispense the drug product (e.g., "Dispense in a tight container as defined in the USP/NF").
22. Remove the words [ ] from the first sentence of the Description section of the package insert. It is stated elsewhere in the labeling that the tablets are intended for oral administration.

In addition, satisfactory inspections of manufacturing facilities are required before this application may be approved. The final recommendations are still pending.

We are providing these comments to you before we complete our review of the complete application to give you preliminary notice of issues that we have identified. These comments are being provided to you in conformance with the guidance "Continuous Marketing Applications: Pilot 1 – Reviewable Units for Fast Track Products under PDUFA" and do not reflect a final decision on the information reviewed. Issues may be added, deleted, expanded upon, or modified as we review the complete application.

If you have any questions, call Alice Kacuba, Regulatory Health Project Manager, at (301) 827-9334.

Sincerely,

*{See appended electronic signature page}*

Liang Zhou, Ph.D.  
Chemistry Team Leader for the  
Division of Gastrointestinal and Coagulation Drug  
Products, (HFD-180)  
DNDC II, Office of New Drug Chemistry  
Center for Drug Evaluation and Research

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/s/

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Liang Zhou  
7/7/05 01:16:27 PM



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation III

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: June 21, 2005**

<b>To:</b> Susan P. Nemeth, Ph.D. Associate Director, Drug Regulatory Affairs	<b>From:</b> Alice Kacuba, R.N., MSN, RAC Certified Regulatory Health Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Gastrointestinal and Coagulation Drug Products
<b>Fax number:</b> 973-781-5217	<b>Fax number:</b> 301-443-9285
<b>Phone number:</b> 862-778-2003	<b>Phone number:</b> (301) 827-9334 or 7310
<b>Subject:</b> NDA 21-882	

**Total no. of pages including cover:**   3  

**Comments:** Information Request for NDA 21-882.

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**Documents to be mailed:**                     NO                    YES

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**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.**

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**Dr. Nemeth,**

**We have several Information Requests (IR) for NDA 21-882. Due to the short review cycle, an expeditious response to them is requested.**

- 1. Please submit the historical control data of the 2-year rat carcinogenicity study (Study #17022) and the 26-week oral gavage carcinogenicity study in p53 heterozygous mice.**
- 2. Please submit the data sets for the carcinogenicity studies in accordance with the guidance documents.**
- 3. Alternatively, please direct us to where this information is located if it has been submitted in the NDA.**
- 3. Upon receipt of this IR, please provide an estimated time when you think that the response will be submitted so that the reviewer can plan.**

**If you have any questions regarding these IRs, please contact me at the numbers listed on Page 1.**

**Thank you.**

**Regards,  
Alice Kacuba**

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/s/

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Alice Kacuba  
6/21/05 06:57:03 PM

3 Page(s) Withheld



\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(5) Draft Labeling

6/20/05

**For Consulting Center Use Only:**

Date Received: \_\_\_\_\_

Assigned to: \_\_\_\_\_

Date Assigned: \_\_\_\_\_

Assigned by: \_\_\_\_\_

Completed date: \_\_\_\_\_

Reviewer Initials: \_\_\_\_\_

Supervisory Concurrence: \_\_\_\_\_

## Intercenter Request for Consultative or Collaborative Review Form

**To (Consulting Center):**

Center: CDRH

Division: Division of Cardiovascular Devices

Mail Code: HFZ-450

Consulting Reviewer Name: Elias Mallis/Charles Ho

Building/Room #: 9200 Corporate/Room 130U

Phone #: 301-443-8517/Ext 177

Fax #:

Email Address:

RPM/CSO Name and Mail Code:

**From (Originating Center):**

Center: CDER

Division: Division of Gastrointestinal and Coagulation Drug Products

Mail Code: HFD-180

Requesting Reviewer Name: Kathy Robie-Suh/George Shashaty

Building/Room #: Parklawn/Room 6B-45

Phone#: 301-827-7472

Fax #: 301-443-9285

Email Address:

RPM/CSO Name and Mail Code: Alice Kacuba. HFD-180

Requesting Reviewer's Concurring

Supervisor's Name: Kathy Robie-Suh

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: June 1, 2005

Requested Completion Date: September 1, 2005

Submission/Application Number: NDA 21-882  
(Not Barcode Number)

Submission Type: NDA  
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product:  Drug-device combination  Drug-biologic combination  Device-biologic combination  
 Drug-device-biologic combination  Not a combination product

Submission Receipt Date: May 2, 2005

Official Submission Due Date: April 29, 2005

Name of Product: Exjade (deferatorix/ICL-670) Dispersible Tablets

Name of Firm: Novartis

Intended Use: iron chelator

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

Electronic NDA which sponsor used SQUID in clinical trials for an NDA for iron overload.

Documents to be returned to Requesting Reviewer?  Yes  No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request:  Consultative Review  Collaborative Review

The sponsor submitted Exjade (deferatorix/ICL670), NDA 21-882 for use as an iron chelator in patients with chronic iron overload. You reviewed a past IND submission from us regarding this drug. Please evaluate the information provided to support the usefulness of SQUID and MRI for assessing body iron burden and liver iron concentration and provide any comments and/or recommendations & indicate whether particular devices for any of the methods discussed have been approved/cleared. I am hopeful that we have massaged the system to get you access to CDER's electronic document room (edr) so that you can view the NDA. We look forward to seeing you at our filing meeting on June 6, 2005 and look forward to working with you on this NDA. This NDA will be presented at a Cardio-Renal Drugs Advisory Committee on September 29, 2005.

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/s/

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Alice Kacuba

6/1/05 07:02:24 PM



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation III

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: June 17, 2005**

<b>To:</b> Susan P. Nemeth, Ph.D. Associate Director, Drug Regulatory Affairs	<b>From:</b> Alice Kacuba, R.N., MSN, RAC Certified Regulatory Health Project Manager <i>AK</i>
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Gastrointestinal and Coagulation Drug Products
<b>Fax number:</b> 973-781-5217	<b>Fax number:</b> 301-443-9285
<b>Phone number:</b> 862-778-2003	<b>Phone number:</b> (301) 827-9334 or 7310

**Subject:** IND 58,554

**Total no. of pages including cover:** 4

**Comments:** Attached is the acknowledgement letter.

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**Documents to be mailed:**                     YES                    NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

6/17/05

NDA 21-882

Novartis Pharmaceuticals Corporation  
Attention: Susan P. Nemeth, Ph.D.  
One Health Plaza  
Hanover, NJ 07936-1080

Dear Dr. Nemeth:

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: Exjade<sup>®</sup> (deferasirox) Tablets

Review Priority Classification: **Priority (P)**

Date of Application: April 29, 2005

Date of Receipt: May 2, 2005

Our Reference Number: NDA 21-882

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 1, 2005 in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be November 2, 2005.

Under 21 CFR 314.102(c), you may request a meeting 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 ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submissions to the

Central Document Room at the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room (CDR)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If your submission only contains paper, send it to one of the following address:

U.S. Postal Service/Courier/Overnight Mail:

Center for Drug Evaluation and Research  
Division of Division of Gastrointestinal and Coagulation Drug Products  
Attention: Division Document Room, 8B-45  
5600 Fishers Lane  
Rockville, Maryland 20857

If you have any questions, call Alice Kacuba, Regulatory Health Project Manager, at (301) 827-9334.

Sincerely,

*{See appended electronic signature page}*

Alice Kacuba, RN, MSN, RAC  
Division of Gastrointestinal and Coagulation Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Alice Kacuba  
6/17/05 03:33:40 PM

**REQUEST FOR CONSULTATION**

TO (Division/Office): ODS, DMETS

FROM: Division of GI and Coagulation Drug  
Products (HFD-180)/ Alice Kacuba  
(301) 827-9334

DATE  
June 1, 2005

IND NO.

NDA NO.  
21-882

TYPE OF DOCUMENT  
New NDA

DATE OF DOCUMENT  
April 29, 2005

NAME OF DRUG  
Exjade (deferasorix/ICL  
670) orally Disintegrating  
Tablets

PRIORITY CONSIDERATION  
Priority Review  
AC meeting on  
September 29, 2005

CLASSIFICATION OF DRUG  
Metal Chelator

DESIRED COMPLETION  
DATE  
September 1, 2005

NAME OF FIRM: Novartis

**REASON FOR REQUEST**

**I. GENERAL**

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE--NDA MEETING        | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

**COMMENTS/SPECIAL INSTRUCTIONS:** The purpose of this request is to obtain safety comments on the labels and a re-consult of the tradename "Exjade" if it is time. Exjade was found not objectionable under a request under the IND 58,554. I do not think that we will be able to approve this NDA this review cycle so I understand that you may not consider re-evaluating the tradename until later. I can keep you posted on the progress. This is an orphan designation and is an oral tablet which make sit more attractive than Desferal so I can not guess if we will be able to approve 1<sup>st</sup> time or not.

**Background:** Novartis submitted NDA 21-882 to provide for the following indication: the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adult and pediatric patients as young as two years of age.

The HFD-180 Medical Officer is George Shashaty (827-7472) , and the Regulatory Project Manager is Alice Kacuba (827-9334).

This NDA is a fully electronic NDA in CTD format and is available in the edr under NDA 21-882, April 29, 2005 submission. The edr contains a word version of the proposed labeling.

The tradename was found acceptable under the IND request and will be re-consulted to DMETS 90 days before Approval).

This application will be presented to the Cardio-Renal Advisory Committee on September 29, 2005.

We would like to have your consult review by September 1, 2005. This date can be negotiated.

user fee goal date is November 2, 2005.

Thank you for your assistance. Any questions, feel free to call me.

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)

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/s/

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Alice Kacuba  
6/1/05 07:48:08 PM

TO (Division/Office): DDMAC, Elaine Hu, Shannon enedetto, HFD-42, Parklawn, Room 17B-17	FROM: Division of GI and Coagulation Drug Products (HFD-180)/ Alice Kacuba (301) 827-9334
---	---

DATE June 1, 2005	IND NO.	NDA NO. 21-882	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT April 29, 2005
NAME OF DRUG Exjade (deferasorix/ICL 670) orally Disintegrating Tablets	PRIORITY CONSIDERATION Priority review (Going to AC on 9-29-05)		CLASSIFICATION OF DRUG Metal Chelator	DESIRED COMPLETION DATE September 1, 2005- can be negotiated

NAME OF FIRM: Novartis

**REASON FOR REQUEST**

**I. GENERAL**

- |   |  |   |
|---|--|---|
| <ul style="list-style-type: none"> <li>• NEW PROTOCOL</li> <li>• PROGRESS REPORT</li> <li>• NEW CORRESPONDENCE</li> <li>• DRUG ADVERTISING</li> <li>• ADVERSE REACTION REPORT</li> <li>• MANUFACTURING CHANGE/ADDITION</li> <li>• MEETING PLANNED BY</li> </ul> | <ul style="list-style-type: none"> <li>• PRE-NDA MEETING</li> <li>• END OF PHASE II MEETING</li> <li>• RESUBMISSION</li> <li>• SAFETY/EFFICACY</li> <li>• PAPER NDA</li> <li>• CONTROL SUPPLEMENT</li> </ul> | <ul style="list-style-type: none"> <li>• RESPONSE TO DEFICIENCY LETTER</li> <li>• FINAL PRINTED LABELING</li> <li>• LABELING REVISION</li> <li>• ORIGINAL NEW CORRESPONDENCE</li> <li>• FORMULATIVE REVIEW</li> <li>• OTHER (SPECIFY BELOW):</li> </ul> |
|---|--|---|

**COMMENTS/SPECIAL INSTRUCTIONS:** The purpose of this request is to consult the review of the labeling to DDMAC. I will be adding the DDMAC reviewer to the team meetings as they are scheduled.

**Background:** Novartis submitted NDA 21-882 to provide for the following indication: the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adult and pediatric patients as young as two years of age.

The HFD-180 Medical Officer is George Shashaty (827-7472), and the Regulatory Project Manager is Alice Kacuba (827-9334).

This NDA is a fully electronic NDA in CTD format and is available in the edr under NDA 21-882, April 29, 2005 submission. The edr contains a word version of the proposed labeling.

The tradename was found acceptable under the IND request and will be re-consulted to DMETS 90 days before Approval).

This application will be presented to the Cardio-Renal Advisory Committee on September 29, 2005. We would like to have your consult review by September 1, 2005. This date can be negotiated. The user fee goal date is November 2, 2005. Thank you for your assistance. Any questions, feel free to call me.

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SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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Alice Kacuba  
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\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(5) Draft Labeling



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

1-25-05

NDA 21-882/RUC-001

Novartis Pharmaceuticals Corporation  
Attention: Susan P. Nemeth, Ph.D.  
One Health Plaza  
Hanover, NJ 07936-1080

Dear Dr. Nemeth:

We have received a reviewable unit (RU) of your new drug application (NDA) submitted under the Continuous Marketing Application (CMA)-Pilot 1 program for the following:

Name of Drug Product: ICL670 (deferasirox) Tablets  
Date of Submission: January 10, 2005  
Date of Receipt: January 10, 2005  
Our Reference Number: NDA 21-882  
Reviewable Unit: RUC-001

Unless we notify you otherwise within 60 days of the above receipt date, we will accept this presubmission as an RU. The user fee goal date for us to complete our review of this RU will be July 10, 2005.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submission to the Central Document Room at the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room (CDR)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180  
Attention: Division Document Room, 8B-45  
5600 Fishers Lane  
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-9334.

Sincerely,

*{See appended electronic signature page}*

Alice Kacuba, RN, MSN, RAC  
Regulatory Health Project Manager  
Division of Gastrointestinal and Coagulation Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Alice Kacuba  
1/26/05 10:07:01 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 58,554

10/18/04

Novartis Pharmaceuticals Corporation  
Attention: Susan Nemeth, Ph.D.  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Dr. Nemeth:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ICL670.

We also refer to the meeting between representatives of your firm and the FDA on October 1, 2004. The purpose of the meeting was as a Pre-NDA meeting.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-9334.

Sincerely,

*{See appended electronic signature page}*

Alice Kacuba, RN, MSN, RAC  
Regulatory Health Project Manager  
Division of Gastrointestinal and Coagulation Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** October 1, 2004

**Time:** 3:00 – 5:00 PM

**Location:** Potomac Conference Room, Parklawn Building

**Application:** IND 58,554, ICL670 Tablets

**Type of Meeting:** Type B; Pre-NDA meeting

**Meeting Chair:** George Shashaty

**Meeting Recorder:** Alice Kacuba

**FDA Attendees, Titles, and Office/Division:**

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Joyce Korvick, M.D.; Acting Division Director

Kathy Robie-Suh, M.D., Ph.D.; Acting Deputy Director

George Shashaty, M.D.; Acting Medical Team Leader, Hematology

Jasti Choudary, B.V.Sc., Ph.D.; Supervisory Pharmacologist

Tamal Chakraborti, Ph.D.; Pharmacology Reviewer

Ray Frankewich, Ph.D.; CMC Reviewer

Alice Kacuba, MSN, R.N., RAC; Regulatory Health Project Manager

Division of Pharmaceutical Evaluation II (HFD-870)

Tein-Mein Chen, Ph.D., Biopharmaceutics Reviewer

Division of Biometrics II (HFD-715)

Stella Grosser, Ph.D.; Statistical Team Leader

Office of Orphan Products (HF-35)

Chris Hood

**External Constituent Attendees and Titles:**

Daniele Alberti, MD	Clinical Research
Peter Marks, MD, PhD	Clinical Research
Romain Sechaud, PhD	Clinical Pharmacology
Insa Gathmann, M.Sc.	Biostatistics
David Parrish, PhD	Toxicology
P.K. Narang, PhD	Drug Regulatory Affairs

Susan Nemeth, PhD	Drug Regulatory Affairs
Ramona Cheng	Technical Research & Development, Reg. CMC
Angelika Stampf, PhD	Technical Research & Development, Reg. CMC
Chin Koemer	Drug Regulatory Affairs
Henry Bloom	Project Team Leader
Renard Capdeville	Clinical Development.

**Background:**

IND 58,554 for ICL670 is being investigated for use as an oral iron chelator. On July 27, 2004, Novartis submitted a meeting request for a Pre-NDA meeting. A subsequent background package was submitted on August 31, 2004. In preparation for today's meeting, the Division sent, by facsimile on September 30, 2004, the Division's responses to the posed questions.

The sponsor used 1 slide during the discussions. That slide is attached to these minutes.

**Regulatory Questions**

The sponsor is proposing to submit a rolling review under the Continuous Marketing Application (CMA) Pilot 1 program. The following questions were discussed and the responses agreed to by the FDA and the sponsor.

**Question 1: Review status**

ICL670 was designated a Fast Track product by FDA on February 21, 2003 as it fulfills the medical need for an oral iron chelator therapy and data are expected to demonstrate that ICL670 is non-inferior to current therapy. Does the FDA agree that priority review may be granted for this NDA in accordance with CDER MAPP 6020.3 Priority Review Policy?

- **The decision regarding priority review status will be made after the application is received. Please request a priority designation in the NDA cover letter for the last reviewable unit.**

**Question 2: Acceptance into Pilot 1 program**

Novartis proposes to begin a rolling submission with the CMC section as described below in accordance with the guidance on the Pilot 1 program. Does the FDA agree to accept this NDA into the Pilot 1 program?

- **The Agency agrees to accept this NDA into the Pilot 1 program.**
- **Your proposed timeline of submitting the CMC reviewable unit in December 2004 and the remaining data as the NDA in March 2005 is acceptable.**
- **The proposed outline for the contents of the reviewable unit on its face appears acceptable.**

- **Please be advised that all manufacturing facilities need to be ready for inspection at the time that the 1<sup>st</sup> reviewable unit is submitted.**
- **Refer to the Guidance for Industry.**

### Question 3: eNDA format

Novartis will provide an eNDA submission for application review and archive purposes. The components and format are described below. Does the FDA agree with the described format?

- **The eNDA submission for application review and archive purposes is acceptable.**
- **Please clarify if you plan to submit a truly electronic CTD (eCTD) or a NDA in CTD format submitted in accordance with the 1999 guidance documents for electronic submissions (Regulatory Submissions in electronic Format: General Considerations and NDAs). If you plan to submit a truly electronic CTD (eCTD) in accordance with M2 eCTD: Electronic Common Technical Document Specification, April 2003, you will need to submit a sample for validation to the electronic document room (edr). This sample would need to be submitted prior to the submission of the first reviewable unit. If you are submitting an NDA in CTD format according to the 1999 guidance documents, please do not refer to the application as an "eCTD" or the edr will reject the submission upon receipt. Refer to the submission as a "NDA submitted according to the Guidance for Industry: Regulatory Submissions in Electronic Format".**

### CMC Questions

#### Question 1: Extension of drug substance retest period by registration stability data

Novartis will submit ( ) registration stability data for three production scale batches of the drug substance in the original submission, and will update with ( ) data early during the review cycle. As per ICH, this should give a ( ) retest period by the action date, based on the fact that the drug substance does not show any change over time for accelerated testing and ( ) long term testing. Will this be acceptable to FDA?

In addition, does FDA agree that the retest period for the drug substance may be extended based on updating the stability data of the registration stability batches?

- **Re-test period will be determined after an evaluation of the available stability data. Your plan to submit data for three production scale batches of drug substance stored at ( ) updated during the review cycle at ( ) appears be acceptable.**

#### Question 2: Extension of drug product shelf life by registration stability data

Novartis will submit ( ) registration stability data on three production scale batches of the drug product in the original submission, and update with an additional ( ) data early during the review cycle. As per ICH, this should give a ( ) expiry by the action date. Will this be acceptable to FDA?

In addition, does FDA agree that the expiry date for the drug product may be extended based on updating the stability data of the registration stability batches?

- **Expiration period will be determined after an evaluation of the available stability data. Your proposal for the submission of the data appears to be acceptable. It is noted that, when microbial testing is performed for the drug product, it is planned for only one of the three stability lots. This should be justified, preferably with data which indicates little or no microbial growth for formulations the same or similar to that of the drug product.**

**Question 3: First three full scale batches covered by registration stability batches**

Novartis proposes that stability data obtained from the primary registration stability batches of commercial production size also satisfies the stability requirement for monitoring the first three full-scale batches. Does the FDA agree?

- **This proposal appears to be acceptable.**

**Question 4: Executed Production Records (R.1.P)**

Novartis plans to submit executed and translated batch records for the 125mg and 500mg dosage strengths. We will in addition submit an untranslated version of the 250mg dosage strength. Is this proposal acceptable to the FDA?

- **This proposal appears to be acceptable.**

**Preclinical Question**

**Question 1: Adequacy of preclinical program**

Novartis has completed an extensive range of nonclinical investigations with ICL670 including in vitro and in vivo pharmacological, pharmacokinetic/ADME and toxicological assessments in several species. Toxicological assessments include repeat dose toxicity in two species up to 39 weeks in duration, genotoxicity, carcinogenicity, and reproductive toxicity studies. In addition, studies requested by the FDA have been completed or are ongoing. Novartis considers this range of studies sufficient to assess the preclinical profile of ICL670 for chronic use in adults and children. Does the FDA agree?

- **Yes.**

**Clinical and Statistical Questions**

**Question 1: Drug-drug interaction studies**

Based on the results of the human ADME 0115 (radiotracer) study and preclinical study results, Novartis believes there is a low likelihood of drug-drug interactions between ICL670 and drugs commonly administered to the target populations. A clinical drug-drug interaction study of ICL670 on digoxin was conducted for safety reasons because digoxin has a narrow therapeutic

window and may be used in the target population. Novartis believes these combined data provide a sufficient analysis of potential drug-drug interactions. Does the FDA agree?

- **The Division agrees. As you have stated, subgroup analysis that includes all concomitant drug administration and the efficacy and safety of ICL 670 should be performed. Please also include the concomitant medication as a covariate in your proposed population PK analysis. It is important to have adequate representation of both genders in this PK analysis. Further drug-drug interaction studies may be suggested based on such analyses.**
- **Please clarify if there are in vitro data investigating microsomal induction potential of ICL670 on CYP isozymes. The sponsor states that they have not performed in-vitro microsomal induction potential assays because no changes in animal or human PK were suggestive of CYP induction. FDA recommends that the sponsor provides, in the NDA, a rationale/justification for why in-vitro induction were not performed.**
- **Please clarify if the proposed to-be-marketed formulation is the same as the clinically tested formulation. The sponsor clarified that Yes, it is. In the NDA, be clear what formulations were used in what study.**

#### **Question 2: Presentation of LIC data from clinical trials**

The clinical trials were performed using measures (biopsy, SQUID) of liver iron content (LIC) in order to demonstrate efficacy. FDA has requested validation of the SQUID methodology for LIC determination. Novartis is in the process of performing these studies and preliminary results indicate that SQUID is a useful technology for assessing relative changes in LIC. Sub-studies to determine the degree of correlation between absolute LIC values measured by SQUID and biopsy are ongoing and will be included in the NDA. Based upon the available data, Novartis proposes that efficacy analyses will be presented for the pivotal studies (0107 and 0108) based upon biopsy alone, SQUID data alone, and biopsy and SQUID data combined. Does the FDA agree?

- **The sponsor may include efficacy analyses for Studies 0107 and 0108 based on biopsy alone, SQUID data alone, and the combined data. However, the standard measure of liver iron concentration (LIC) is liver biopsy. Our review of information submitted by the sponsor suggests that SQUID is an imperfect measure of liver iron concentration and may not be an acceptable method of determining changes in liver iron concentration.**

#### **Question 3: Use of a readily available clinical parameter for ICL670 dosing**

The clinical trials use measures of liver iron content (LIC) to demonstrate efficacy. However, LIC measures such as biopsy and SQUID are not commonly used in clinical practice to manage chelation therapy. Novartis plans to conduct statistical analyses to demonstrate the utility of readily available clinical and/or laboratory parameters (e.g., serum ferritin) for the dosing of ICL670, with the intention of recommending these in the final labeling.

- a. Does the FDA agree with the proposed statistical analyses to assess the degree of correlation between LIC and alternative markers of body iron burden?
  - b. If so, would FDA be willing to consider dosing recommendations for the labeling that have been based on data-driven modeling analyses, and that may be simpler and more practical for physicians than that used in the clinical protocols (e.g., one with a common initial dose followed by adjustment based on serum ferritin)?
- **Serum ferritin is not an accurate marker of LIC because its level is affected by a number of variables that are unrelated to LIC. The Agency will review the statistical analysis of the data that the sponsor has accumulated to determine whether or not there is a degree of correlation between LIC and other laboratory parameters of body iron burden and whether or not dosing recommendations in the labeling can appropriately be made based on laboratory parameters.**

#### **Question 4: Adequacy of statistical analysis plan**

Novartis believes that the proposed statistical analyses will provide sufficient information to assess the safety and efficacy of ICL670 for the indication "treatment of chronic iron overload due to blood transfusions" in both adult and pediatric patients. Does the FDA agree?

- **The proposed statistical analyses will be reviewed for safety and efficacy for each indication and population studied. It should be noted that the measures that are being studied (LIC, ferritin, etc.) are surrogate markers of clinical effectiveness. Evidence demonstrating a reduction in morbidity and/or mortality related to the reduction of elevated iron body iron stores in the diseases being studied is essential. Indications in the labeling will be dependent on the demonstration of such evidence. The sponsor will provide evidence and analyses from the literature that the reduction of an elevated LIC is a predictor for diminution in morbidity and mortality in the conditions studied.**
- **Historical evidence of the effectiveness of desferoxamine should be provided and evaluated in the NDA in order to support the assumptions of the non-inferiority analysis.**

#### **Question 5: Content of summary of clinical safety section**

The Summary of Clinical Safety (SCS) will present data on four groups of patients: thalassemia patients in studies 0106, 0107, 0108 (pooled one year data), thalassemia patients in 0105 (three year data), sickle cell disease patients (six month data), and patients with other rare anemias (one year data). These proposed groupings are based on disease state and duration of exposure. Does the FDA agree to these groupings?

- **The groupings are acceptable. Safety data should also be analyzed in subgroups of age, sex, ethnic group, degree of iron overload, and concomitant clinical conditions.**

**Question 6: Content of summary of clinical efficacy section**

The Summary of Clinical Efficacy (SCE) will summarize the findings by study, rather than use a pooled analysis, due to differences in study design. Data from studies 0105, 0106, 0107, and 0108 will be pooled only for the modeling of iron burden and iron balance. Does the FDA agree with these proposals?

- **The proposals are acceptable.**

**Question 7: Notable laboratory values and patient narratives**

Does the FDA agree with the proposals for summarizing notable laboratory values and providing patient narratives as specified in the briefing book?

- **The proposals for summarizing notable laboratory values and providing patient narratives as specified are acceptable. All notable laboratory values and adverse events should be followed to resolution or irreversibility.**
- **In addition, you should provide, for each patient, information on change from baseline for these clinical laboratory parameters.**
- **Additional analyses may be needed to evaluate potential liver toxicity.**

**Question 8: Case Report Tabulations (CRTs)/SAS Datasets**

Novartis proposes to submit CRTs/SAS datasets from studies 0105E2, 0106, 0107, 0108, and 0109 and the datasets used for population pharmacokinetic, and PK/PD and LIC modeling. Does FDA agree?

- **This is generally acceptable. Please clarify if the safety data will include the laboratory data.**

**Question 9: Case report forms to be submitted**

Does the FDA agree with the proposal below for providing CRF copies?

- **In addition to the proposed CRF copies, CRFs should be submitted on all patients who have any serious adverse event, whether or not believed related to drug administration.**

**Question 10: Submission of sickle cell data**

As agreed previously with FDA during the October 23, 2003 meeting, six month safety data from Study 0109 in adult and pediatric patients with sickle cell disease will be presented in the NDA with one year safety data provided at the 120-Day Safety Update. Novartis proposes to provide these data as an interim safety report in the NDA and a summary safety report in the 120-Day Safety Update. Does the FDA agree that this is acceptable?

- **For study 0109, in the NDA, the sponsor will submit 6 month data on all the ICL treated patients.**
- **For 0109, in the NDA, the sponsor will submit 12 month data on approximately 20-30 ICL treated patients.**
- **For 0109, in the 120 day SU, the sponsor will submit the 12 month data on the remaining 60-70 ICL treated patients.**
- **The FDA reminds the sponsor that it is important to receive this data on or before Day 120 in the review cycle in order to be able to adequately review this indication in sickle cell patients.**
- **For studies 0105, 0106, 0107, and 0108, the NDA will include all data for all of the time points.**

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# Distribution of patients in clinical trials

Age (years)	< 6			6 to < 12			12 to < 16			16 to < 65			≥ 65			Total		
	10	20	30	10	20	30	10	20	30	10	20	30	10	20	30			
Thalassemia																		
0105												24	24			48		
0106	7			13			16					4				40		
0107	6	12	12	18	19	30	25	14	18	45	39	59				297		
0108	1	1		2	2	1	1	5	2	6	14	50			1	86		
Total	14	13	12	33	21	31	42	19	20	79	77	109	0	1	0	471		
Other anemias																		
0108 (MDS)												6	6	8	5	6	16	47
0108 (DBA)	1	2	3	2	3		1	2			1	13				28		
0108 (Other)			3		1			2			1	6	8			23		
Total	1	2	6	2	4	0	1	4	0	7	13	29	5	6	18	98		
0109 SCD	94															95	194	
Overall Total	94															95	763	

\*Initial Dose

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 58,554

7/23/04

Novartis Pharmaceuticals Corporation  
Attention: Susan Nemeth  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Dr. Nemeth:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ICL670.

We also refer to the meeting between representatives of your firm and the FDA on June 28, 2004. The purpose of the meeting was to discuss several issues regarding QTc and the need for a non-rodent study.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-9334.

Sincerely,

*{See appended electronic signature page}*

Alice Kacuba, RN, MSN, RAC  
Regulatory Health Project Manager  
Division of Gastrointestinal and Coagulation Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

## **MEMORANDUM OF MEETING MINUTES**

**Meeting Date:** June 28, 2004

**Time:** 11:00 – 12:30 PM

**Location:** Twinbrook Conference Room, Parklawn Building

**Application:** IND 58,554, ICL670 Tablets

**Type of Meeting:** Type A, to discuss QTc and non-rodent preclinical study

**Meeting Chair:** Kathy Robie-Suh

**Meeting Recorder:** Alice Kacuba

### **FDA Attendees, Titles, and Office/Division:**

#### Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Robert L. Justice, M.D., M.S.; Division Director

Joyce Korvick, M.D.; Deputy Division Director

Kathy Robie-Suh, M.D., Ph.D.; Medical Team Leader, Hematology

George Shashaty, M.D.; Medical Reviewer

Jasti Choudary, B.V.Sc., Ph.D.; Supervisory Pharmacologist

Tamal Chakraborti, Ph.D.; Pharmacology Reviewer

Alice Kacuba, MSN, R.N., RAC; Regulatory Health Project Manager

#### Division of Pharmaceutical Evaluation II (HFD-870)

Tein-Mein Chen, Ph.D., Biopharmaceutics Reviewer

#### Office of New Drugs (HFD-024)

Ken Hastings, Dr.P.H.; Associate Director

#### **External Constituent Attendees and Titles:**

Prem Kumar Narang, Ph.D., F.C.P.; Regulatory Affairs

Susan Nemeth, Ph.D.; Regulatory Affairs (US)

Henry Bloom; International Project Team Leader

Chin Koerner; Regulatory Affairs

Martin P. Bedigian, M.D.; Clinical Research

Peter Marks, MD, Ph.D.; Clinical Research

David Parrish, Ph.D.; Toxicology

Linda Carter; Regulatory Affairs

**Background:**

IND 58,554 for ICL670 is being investigated for use as an oral iron chelator. On May 21, 2004, Novartis submitted two meeting requests. One request was to discuss several clinical questions regarding QTc and the second request was to discuss several issues regarding the preclinical non-rodent study requirement. These two meeting request were granted as one meeting. Subsequent background packages were submitted on June 11, 2004. In preparation for today's meeting, The Division sent, by facsimile, the Division's responses to the posed questions.

**Discussion Points (bullet format):**

Following introductions, the following questions were addressed. The response(s) to each question was agreed to between the Division and the sponsor. [Post-meeting note: A copy of the agreed upon responses was given to the sponsor at the conclusion of the meeting.]

**Clinical Questions**

*1) Novartis considers that the proposed set of quantitative clinical cardiovascular risk assessments (QTc analysis of ECGs from Trial 0107; a focused ECG study in normal volunteers) should suffice to assess QTc prolongation risk for ICL670.*

*Does FDA agree?*

*2) Novartis considers that the design of the normal volunteer study is appropriate to assess the QTc prolongation risk of ICL670.*

*Does FDA agree?*

- **The proposed assessment of QT/QTc prolongation risk for ICL 670 provides a very good starting point for the determination of the risk of this complication.**
- **Consider performing a focused study similar to C1CL670A2122 in a subset of the treated population, including persons with thalassemia major, sickle cell anemia and those with other reasons for hemosiderosis (including both women and children). This would provide information on QT/QTc prolongation in persons with CHF, hepatic dysfunction and in special populations. The sponsor said that they would conduct a subset analysis of the phase 3 study regarding the QT effect in this group of patients. Adequacy of this approach would depend on the results of the normal volunteer study.**
- **Determine the effect of multiple doses of ICL-670 on the QT/QTc interval in normal volunteers because of the potential for accumulation of the drug in myocardial tissue. The sponsor is concerned that acute removal of 200-400 mg of iron may induce toxicity in these subjects. The sponsor asserts that the preclinical data do not show accumulation in cardiac tissue. The adequacy of single dose study will need to be addressed in the application.**

- Electrocardiograms on study subjects should be performed at the same time of day, with standardized activity, food, and posture status. For consistency, a high fat meal should be given to all ICL670 and placebo treatment arms.
- If tolerated, the dose of the drug administered in Study C1CL670A2122 should be greater than 40 mg/kg, since 40 mg/kg is the maximum dose being used in the current clinical studies for efficacy and safety. The sponsor stated that in doses above 40 mg/kg ICL670 was poorly tolerated. There was a 37% incidence of nausea at 80mg/kg. The maximum dose should cover the expected exposure in special populations, e.g., patients with hepatic or renal impairment. The actual maximum dose tested thus far and anticipated in the pivotal clinical trial is 30 mg/kg.
- Clarify whether patients with serious cardiac events (Table 3-1) or with symptoms such as syncope, dizziness, or palpitations were discontinued from the study drug and whether a QT/QTc assessment was performed. In general, when these symptoms occurred, more frequent ECGs were obtained in some of the cases. None of the patients were discontinued from drug due to these symptoms.
- Please submit your final protocol for Study C1CL670A2122 to the Agency for review.

#### Preclinical Questions

*1a) Since there are concerns about the practicality and interpretability of an ICL670 toxicity study in juvenile marmosets, Novartis proposes to conduct a toxicity study in juvenile mice. ICL670-induced hepatobiliary inflammation is clearly observed in adult mice, and the correlation of juvenile development phases between mice and humans is better understood.*

*Does FDA agree to this proposal?*

- Please note that there were no treatment-related gallbladder lesions in the mouse toxicology studies while such effects were clearly present in the marmoset monkey studies.
- Because of potential differences between the rodent and primate in iron handling, it is a valid concern that the toxicity profile of an orally active iron chelator may be poorly characterized or missed if it were to be screened solely in the rodent, prior to human experiment.
- You have stated in a publication that "Marmoset monkey is thus considered to be highly relevant with respect to its iron metabolism and therefore predictive with respect to the pharmacological and toxicological effects of iron chelators" (Nick H et al, *Adv Exp Med Biol.* 2002, 509:185-203).
- However, considering the practical issues, in lieu of the marmoset study, we would consider a full toxicology study in neonatal mice with dosing starting as soon as feasible after birth (day 7 of age), incorporating evaluation of effects on the immune system in these animals out to age of immune competence (days 14, 21, and 42 of age). Please submit a protocol for review. Separate groups will be used for the immunotoxicity assessments

and the toxicology assessments. Consider including a recovery group. The sponsor agree to conduct the proposed mouse study and will include a toxicokinetic assessment.

1b) Since hepatobiliary inflammation is the only sign of ICL670 toxicity seen in marmosets and mice that is not covered by the rat model, Novartis proposes to conduct a study focused on this organ system.

1c) A study design would be used corresponding to that proposed by FDA for the marmoset (appropriate developmental timeframe in the mouse with recovery; no reproductive or behavioral testing).

Does FDA agree to these proposals?

- No. A full toxicology study should be conducted as proposed above.
- Reproductive and behavioral testing are not required.

2) It is likely that the report from the toxicology study in juvenile mice will only be available in mid 2005, after submission of the NDA. Novartis proposes to provide the study report during the ND review.

Does FDA agree?

- No. The report of the neonatal/juvenile animal toxicology study should be included in the NDA submission.
- Please make a proposal for submission of reviewable units under the CMA pilot 1 program.

3) Novartis considers the SPA feedback to still be valid concerning the stated acceptability of the pediatric patient exposure of at least 80 pediatric thalassemic patients in total.

Does the FDA agree?

- Yes, as long as they are evenly distributed among toddlers, older children, and adolescents.

4) If FDA accepts Novartis' above proposal of a mouse model for the juvenile animal study, Novartis assumes that the FDA request for a marmoset juvenile study for the purposes of a Pediatric Written Request would be withdrawn.

Does FDA agree?

- Yes.

Minutes Preparer:

Chair Concurrence:

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Alice Kacuba  
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Kathy Robie-Suh  
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

11/20/03

IND 58,554

Novartis Pharmaceuticals Corporation  
Attention: Robyn B. Sterner, Pharm.D.  
Associate Director, Drug Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Dr. Sterner:

Please refer to the meeting between representatives of your firm and FDA on October 23, 2003. The purpose of the meeting was to obtain the Agency's input on the proposed protocol changes which are intended to improve recruitment and conduct of the study for the purpose of acquiring sufficient data for registration of ICL670.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-4005.

Sincerely,

*{See appended electronic signature page}*

Tanya Clayton, B.S.  
Consumer Safety Officer  
Division of Gastrointestinal & Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

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## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** October 23, 2003

**Time:** 1:30-3:00 PM

**Location:** Parklawn Building, 3<sup>rd</sup> Floor, Conference Room C

**Application:** IND 58,554

**Type of Meeting:** Type A, Clinical

**Meeting Chair:** Kathy Robie Suh, M.D., Ph.D.

**Meeting Recorder:** Tanya Clayton, B.S.

**FDA Attendees, Titles, and Office/Division:**

Division of Gastrointestinal and Coagulation Drug Products

Robert Justice, M.D., MSc.	Division Director
Kathy Robie Suh, M.D., Ph.D.	Medical Team Leader, (Hematology)
George Shashaty, M.D.	Medical Reviewer
Milton Fan, Ph.D.	Statistical Reviewer
Suliman Al Fayoumi, Ph.D.	Biopharmaceutics Reviewer
Tanya Clayton, B.S.	Regulatory Project Manager

**External Constituent Attendees and Titles:**

Novartis Pharmaceuticals Corporation

Robert Miranda	Director, Drug Regulatory Affairs
Peter Marks, M.D., Ph.D.	Senior Clinical Research Physician
Robyn Sterner, PharmD	Associate Director, Drug Regulatory Affairs
Daniele Alberti, M.D.	Clinical Project Leader, Clinical Development
Renaud Capdeville, M.D.	Group Leader, Clinical Development
David Laurie, Ph.D.	Manager, Drug Regulatory Affairs
Christian Mueller, Ph.D.	Statistician, Biostatistics

IND 58, 554

Page 3

**Background:**

On September 24, 2003, the sponsor requested a Type A, clinical meeting for the purpose of obtaining the Agency's input on the proposed protocol changes which are intended to improve recruitment and conduct of the study for the purpose of acquiring sufficient data for registration of ICL670.

A subsequent October 7, 2003 background package was submitted, which contained 10 questions.

Following introductions, the Sponsor provided a brief overview of the development process and proposed study changes.

Discussion Points: (bullet format):

1. Does FDA agree that study 0109 should include adult sickle cell disease patients with iron overload who are not on a regularly scheduled transfusion program?

**Agency's Response**

- Yes, we agree.
2. Does FDA agree to the proposed change  to dosing based on LIC at baseline?

**Agency's Response**

- Yes, we agree.
  - Explain how dosing will be adjusted based on LIC at baseline for those patients enrolled prior to your proposed dosing change. Clarify how these two populations will be handled in the efficacy data analysis.
3. Does FDA agree to the immediate integration of pediatric patients (ages 2-17) into study 0109 as described in the protocol design?

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### Agency's Response

- Yes, we agree.
4. Does FDA agree that the changes to the frequency of SQUID efficacy assessments will still allow evaluation of the effectiveness of ICL670 in this population sufficient to allow extrapolation of the efficacy conclusions from 0107?

### Agency's Response

- The proposed decrease in the frequency of SQUID efficacy assessments is acceptable.
  - Adequacy of the efficacy results from this and other studies conducted will be a review issue to be evaluated after submission of the NDA.
5. Does FDA agree that the reduction in the frequency of safety assessments after three months will still allow sufficient evaluation of safety in this patient population.

### Agency's Response

- Your proposal to reduce the study visit frequency from every two weeks to monthly after patients have completed 12 weeks on therapy is acceptable.
  - Adequacy of the safety results to support approval of the NDA will be a review issue.
6. Does FDA agree to the subanalyses plans to perform subset analyses of the safety and efficacy data in pediatric and adult populations?

### Agency's Response

- Yes, we agree with the proposed subset analyses.
- Stratify randomization by the 3 proposed age groups (adults, children 2 to less than 12 years, adolescents 12 to less than 17 years).
- See also comment under "Additional comments" below.

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7. An interim analysis after patients have completed 24 weeks of treatment is planned that would potentially allow submission of interim safety data from adult and pediatric patients in the initial NDA. Does FDA agree that the proposed size (at least 45 adult and 45 pediatric patients on ICL670) and duration of treatment (24 weeks at time of NDA) of study 0109 are adequate to assess the safety of ICL670 as part of the total information package in the registration program for the specific claim:

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### Agency's Response

- No, we do not agree.
  - Duration of treatment of 24 weeks for study 0109 will not be adequate to assess the safety of ICL670 for the desired claim. At least 52 weeks of therapy is needed.
  - The proposed size (at least 45 adult and 45 pediatric patients on ICL670) seems adequate to support an indication. The exact wording of the indication will depend on the characteristics of the patients studied (e.g., age, transfusion history, prior therapies) and will be a review issue.
  - If you wish to label the drug for patients   
J you should enroll an adequate number of these patients in the study to evaluate outcome in these patients.
  - The Sponsor has explained that they will have 6 month follow up in the original NDA and will provide 1 year follow up data at the 120 day safety update for all sickle cell patients.
  - In the original submission 1 year follow up data will be available for about 30 sickle cell patients and about 550 beta-thalassemia and other anemia patients.
  - This proposal is acceptable to the division.
8. Novartis considers that the intended indication text and claims would be supported by the revised design and patient population of study 0109. Does FDA agree?

### Agency's Response

- See answer for question 7.
- See also comment under "Additional comments" below.

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9. Does FDA agree that the agreements made under the prior SPA for 0109 that are unaffected by this change will still be regarded as valid and binding, including questions 2, 4, 5, 6, 8a, 8b, 9, 10a, 10b, and 12 of that prior SPA?

**Agency's Response**

- Yes, we agree.
- Please also see answer to question 7.

10. Does FDA agree that by integrating children into study 0109 (together with pediatric data from studies 0107 and 0108, plus preclinical data in neonatal and pediatric animals), a Pediatric Study Request should be issued for ICL670, following Novartis submission of a revised PPSR that encompasses all these elements?

**Agency's Response**

- This question can be answered only after reviewing your revised PPSR.
- Your revised PPSR should address all of the elements listed in the July 18, 2003 inadequate letter.
- You should provide any available data and other support for safety and efficacy of ICL670 in your revised PPSR.
- Please clarify whether you will be providing efficacy data in pediatric patients from studies 0106, 0107, and 0108. (The Sponsor clarified that efficacy data will be submitted.)
- Please provide data to clarify the relationship between LIC measured by SQUID and body iron stores as assessed by liver biopsy and usual clinical monitoring tests.
- The Sponsor agrees to provide the background briefing package on methods used in the ICL670 clinical development plan for iron overload assessment by the end of March 2004. The briefing package will address the correlation of various techniques for assessing iron overload (e.g. SQUID, MRI, serum biomarkers).

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**Additional comments:**

- **Note that since all patients will be treated with the test drug or an active comparator in your development plan, the proposed studies are not sufficient in themselves to demonstrate efficacy without reference to external data on the likely outcome without treatment (unless the test drug is superior to the comparator). A thorough evaluation of these external data will be a part of the review of the completed studies, and should not be assumed to have been part of the special protocol assessment.**
- **Sponsor agrees to submit a formal statistical analysis plan for protocol 0108 based on historical control data (e.g. publications, registries, data bases, study patients).**
- **The Sponsor is interested in participating in Pilot 1 initiative.**
- **The Sponsor is planning a rolling submission beginning in November 2004 and ending March 2005. Details will be discussed at a Pre-NDA meeting.**

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Page 8

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Tanya Clayton  
11/20/03 04:19:50 PM



IND 58,554/SN-039

Novartis Pharmaceuticals Corporation  
Attention: Robyn B. Konecne, Pharm.D.  
Associate Director, Drug Regulatory Affairs  
59 Route 10  
East Hanover, NJ 07936-1080

**DRA**  
FEB 07 2003  
**RECEIVED**

Dear Dr. Konecne:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ICL 670 Dispersible Tablets.

We also refer to your December 13, 2002, request, serial number 039, for a special clinical protocol assessment, received December 16, 2002. The protocol (0109) is entitled "An open-label, phase II study to evaluate the safety, tolerability, pharmacokinetics and the effects on liver iron concentration of repeated doses of 10 mg/kg/day of ICL-670 administered to sickle cell disease patients with transfusional hemosiderosis."

We have completed our review of your submission and, based on the information submitted, have the following responses to your questions.

1. Novartis considers that the intended indication text and claims would be supported by the design and patient population of study 0109. The study 0109 would support the following claims:

[ ]  
Does FDA agree?

**Response: Yes. A randomized, open label and two-arm study design enrolling both sickle cell disease patients currently on deferoxamine therapy and patients not previously treated with deferoxamine is acceptable.**

2. Novartis considers that an open label design of study 0109, and the use of an active treatment as reference therapy is appropriate. Does FDA agree?

**Response: Yes. An open-label design and the use of an active treatment as reference therapy are acceptable for this study.**

3. The size of study 0109 has been determined based on the likelihood of detecting common adverse drug reactions in adults with sickle cell disease. Novartis considers that the proposed size ( $\geq 50$  patients on ICL670) and duration of treatment (at least 1 year) in study 0109 are adequate (as part of the total safety information from the registration program) to assess the safety of ICL670 for  sickle cell disease.  
Does FDA agree?

**Response: From a clinical viewpoint, the proposed patient number ( $\geq 50$  patients on ICL670) and duration of treatment (at least 1 year) in study 0109 are acceptable as part of the overall safety information to assess the safety of ICL670 to support the intended indication and claim.**

4. The complications of iron overload toxicity are the same for all patients receiving chronic transfusions. Iron overload in thalassemia is the best characterized condition. Therefore, Novartis considers the conclusions on efficacy of ICL670 (clinical effectiveness, non-inferiority to DFO) from studies 0107 and 0108 can be extrapolated to transfusional iron overload , provided that changes in liver iron content in study 0109 are consistent with the treatment effects in studies 0107 and 0108. Does FDA concur?

**Response: It is acceptable that the majority of patients in the overall development program are thalassemics.**

**Conclusions on efficacy of ICL670 from studies 0107 and 0108 may be applicable to other conditions of transfusional iron overload in anemias**

5. Novartis considers that the proposed primary and secondary objectives are appropriate within the context of study 0109 to assess ICL670 for the intended indication   
 Does FDA agree?

**Response: Yes. Information to validate SQUID as an assessment tool should be submitted in the NDA.**

6. Novartis considers that the definitions of the inclusion/exclusion criteria are appropriate for these patient populations. Does FDA agree?

**Response: The definitions of the inclusion/exclusion criteria are acceptable.**

7. Novartis considers that the initial dose assignments and subsequent adjustments have sufficient basis and are appropriately defined. Does FDA agree?

**Response: Yes. Doses of ICL670 have been based on experience in phase II studies on iron excretion and reduction of liver iron concentration.**

8. a. Novartis considers that the primary measure for assessing clinical efficacy (LIC) and the methods to assess it (SQUID and liver biopsy) are appropriate within the context of study 0109. Does FDA agree?

**Response: Yes. Information to validate SQUID as an assessment tool should be submitted in the NDA.**

8. b. Novartis intends to assess efficacy of ICL670 by measurement of absolute and relative decrease of hepatic liver iron content after one year of treatment, and by total body iron elimination rate. Does FDA agree?

**Response: Yes. It is acceptable to assess efficacy of ICL670 by measurement of absolute and relative decrease of hepatic liver iron content after one year of treatment, and by total body iron elimination rate. Information on clinical laboratory results (including iron studies) and drug dose adjustment during the studies should be carefully and completely documented. Information on compliance with drug dosing should be collected.**

9. Novartis considers that the defined Per Protocol population is appropriate for the primary efficacy analysis. Does FDA agree?

**Response: Yes. The primary efficacy parameter will be the absolute and relative change of liver iron content (LIC) after 1 year treatment. Patients in the per protocol population for the primary efficacy analysis are those randomized patients that have received study drug and who have a LIC assessments at baseline and at least one scheduled post-baseline SQUID assessment. The defined Per Protocol population is acceptable for the primary efficacy analysis.**

**For the patients where no LIC determination is available at 52 weeks, you can use the last value carried forward. However, you should also do a separate analysis for those who have LIC values at 52 weeks. The number of patients and time of the last value assessed should be documented carefully. Disposition and clinical outcome for treated patients who do not have baseline and/or follow-up LIC available, should be provided.**

10. a. Liver biopsy and SQUID, although useful for accurately assessing LIC and iron burden in clinical studies, are not practical methods for use in general practice. Novartis considers that the following points are justified:

- The final approved labeling for ICL670 should not require liver biopsy or SQUID,
- The final approved labeling should recommend the usual clinical monitoring tests for body iron status (and/or those validated in the planned studies).

Does FDA agree with these points?

**Response: Yes. We agree in principle. The exact monitoring recommended in the labeling is dependent on the study results and is a review issue.**

10. b. Novartis considers that the proposed study design is capable of identifying and validating potential additional surrogate markers of iron burden that could be recommended in the final labeling for monitoring and dose adjustment. Does FDA agree?

**Response: Yes. We agree in principle. The exact monitoring recommended in the labeling is dependent on the study results and is a review issue.**

11. Novartis considers that the planned safety assessments will be sufficient to assess ICL670 for the intended patient populations. Does FDA agree?

**Response: The planned safety assessments appear adequate.**

12. Novartis considers that the proposed plans for population pharmacokinetic assessment will be sufficient to assess the effects of hepatic impairment on ICL670. Does FDA concur?

**Response: For population PK analysis, blood samples need to be collected randomly, appropriately, and evenly to cover the entire steady-state dosing interval instead of at fixed time points (at 0, 1, 2, 4, and 8 hrs postdose) during the Visit 9 and 16.**

13. Does FDA consider there is any aspect of the design of study 0109 that might jeopardize the conduct of this study or its usefulness for regulatory approvals?

**Response: See responses to questions 5, 8a, 8b and 9.**

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to our "*Guidance for Industry; Formal Meetings With Sponsors and Applicants for PDUFA Products*"). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at <http://www.fda.gov/cder/guidance/index.htm>. This meeting would be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

If you have any questions, call Alice Kacuba, RN, MSN, RAC, Regulatory Health Project Manager, at (301) 827-1602.

Sincerely,

*{See appended electronic signature page}*

Robert L. Justice, M.D., M.S.  
Director  
Division of Gastrointestinal & Coagulation Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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Robert Justice  
1/30/03 06:09:43 PM



IND 58,554/SN-036

Novartis Pharmaceuticals Corporation  
Attention: Robyn B. Konecne, Pharm.D.  
Associate Director, Drug Regulatory Affairs  
59 Route 10  
East Hanover, NJ 07936-1080

**RECEIVED**

JAN 09 2003

**DRA**

Dear Dr. Konecne:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ICL 670 Dispersible Tablets.

We also refer to your November 18, 2002, request, serial number 036, for a special clinical protocol assessment, received November 19, 2002. The protocol (0107) is entitled "A randomized, comparative, open label phase III trial on efficacy and safety of long-term treatment with ICL-670 (5 to 40 mg/kg/day) in conjunction with deferoxamine (20 to 60 mg/kg/day) in  $\beta$ -thalassemia patients with transfusional hemosiderosis."

We have completed our review of your submission and, based on the information submitted, have the following responses to your questions.

1. Novartis considers that the intended indication text and claims would be supported by the design and patient population of study 0107. Study 0107 is intended to support the following claims as subsets of the following indication:

[ ]

Does FDA agree?

**Response: Depending on the study results, it is acceptable for adult patients. However, it is unacceptable for pediatric patients. No definite number of pediatric patients is specified for inclusion in the study. You estimate that about 50 pediatric patients (age 2 - <18 years) will be enrolled, and only about 25 of those patients will be treated by ICL670. Age distribution of pediatric patients to be enrolled in this study is not specified.**

2. Novartis considers that an open label design of study 0107, using an active comparator as reference therapy, is an appropriate design for this indication. Does FDA agree?

**Response: Yes. An open-label study using an active comparator is an acceptable design for this indication. The person conducting assays of LIC in liver biopsy specimens should be blinded as to patient treatment.**

3. a). The statistical design of study 0107 (non-inferiority of ICL670 vs deferoxamine) was previously agreed with FDA resulting in the planned study size (500 patients). Novartis considers that the proposed number of thalassemic patients on ICL670 (250 patients), and the duration of treatment (at least 1 year) in study 0107 is also adequate (as part of the overall safety information) to assess the safety of ICL670 to support the intended indication and claim. Does FDA agree?

**Response: From a clinical point of view, the proposed 500 thalassemic patients (250 patients on ICL670), and the duration of treatment (at least 1 year) appear to be acceptable to assess the safety of ICL670 as part of the overall safety information.**

3. b). Novartis considers that the extent of pediatric thalassemic patient exposure (>80 patient-years) in the overall proposed development plan is suitable to assess the safety of ICL670 for use in pediatric thalassemic patients. Does FDA agree?

**Response: It is unclear how many pediatric patients will be enrolled and treated with ICL670 in the overall proposed development plan. A total of more than 80 pediatric patients (not patient-years) may be suitable to assess the safety of ICL670 for use in pediatric thalassemic patients. However, those pediatric patients should be relatively evenly distributed by age groups, such as, toddler, older children, and adolescents.**

4. The complications of iron overload toxicity are the same for all ages of thalassemic patients receiving chronic transfusions. Therefore, Novartis considers the following points to be justified:

- Data on clinical response in all ages in study 0107 can be pooled for primary analysis
- Conclusions on efficacy of ICL670 from the pooled data (clinical effectiveness, non-inferiority to deferoxamine) can be extrapolated to all ages of thalassemic patients, provided that changes in liver iron content in study 0107 are consistent between the pooled data and the age subsets. Does FDA concur with these points?

**Response: Although you can pool data in all ages together, you still need to do separate analyses for adult and pediatric patients for both primary and secondary endpoints. Even though efficacy may be extrapolated across ages, safety in the young pediatric population may be different than in adults.**

**Information on the complications and natural history of iron overload (including laboratory parameters and LIC levels) in thalassemic patients should be included in the NDA.**

5. Novartis considers that the proposed primary and secondary objectives of study 0107 are appropriate within the context of study 0107 to assess ICL670 for the intended indication and claims. Does FDA agree?

**Response: Yes. Information to validate SQUID as an assessment tool should be submitted in the NDA.**

6. Novartis considers that the definitions of the inclusion/exclusion criteria are appropriate for this patient population. Does FDA agree?

**Response: The definitions of the inclusion/exclusion criteria are acceptable.**

7. Novartis considers that the initial dose assignments and subsequent adjustments have sufficient basis and are appropriately defined. Does FDA agree?

**Response: Yes. Doses of ICL670 have been based on experience in phase II studies on iron excretion and reduction of liver iron concentration.**

8. a). Novartis considers that the primary measure for assessing clinical efficacy (LIC), and the methods to assess it (liver biopsy and/or SQUID), are appropriate within the context of study 0107. Does FDA agree?

**Response: Yes. Information to validate SQUID as an assessment tool should be submitted in the NDA.**

8. b). Novartis considers that the endpoint definitions of success and failure are appropriate for a clinical study in transfusional iron overload. Does FDA agree?

**Response: Yes, in principle. You should consider stratifying on baseline LIC. Also, you should understand that interpretation of the results of the study may be complicated, particularly for patients in the acceptable range at enrollment. It is possible for a patient in maintenance range to actually increase LIC (up to < 7mg Fe/g dw) and still be called a success. This should be evaluated in the study analysis.**

**Information on clinical laboratory results (including iron studies) and drug dose adjustment during the studies should be carefully and completely documented. Information on compliance with drug dosing should be collected.**

9. Novartis considers that the defined Per Protocol population is appropriate for the primary efficacy analysis. Does FDA agree?

**Response: Yes. Since use of intent-to-treat (ITT) analysis data set is less conservative for non-inferiority analyses. However, an ITT analysis also should be provided.**

10. Novartis considers that the proposed approach of ordered testing is acceptable and could support  $\zeta$   $\int$ . Does FDA agree?

**Response:**  it is justified, is not impeded by the possibility of claiming . Although more than one hypothesis would be tested, the probabilities of errors are appropriately controlled.

11. a). Liver biopsy and SQUID, although useful for accurately assessing LIC and iron burden in clinical studies, are not practical methods for use in general practice. Novartis considers that the following points are justified:

- The final approved labeling for ICL670 should
- The final approved labeling should recommend

Does FDA agree with these points?

**Response:** Yes, in principle. The exact monitoring recommended in the labeling is dependent on the study results and is a review issue.

11. b). Novartis considers that the proposed study design is capable of  that could be recommended in the final labeling for monitoring and dose adjustment. Does FDA agree?

**Response:** Yes, in principle. It will be data dependent. The exact monitoring recommended in the labeling is dependent on the study results and is a review issue.

12. Novartis considers that the planned safety assessments will be sufficient to assess ICL670 for the intended patient populations. Does FDA agree?

**Response:** The planned safety assessments appear adequate. The number of pediatric patients mentioned in the protocol ("about 50") may not provide adequate safety information in the pediatric population.

13. Novartis considers that the proposed plans for population pharmacokinetic assessment will be sufficient to assess the effects of hepatic impairment on ICL670. Does FDA concur?

**Response:** For population PK analysis, blood samples need to be collected randomly, appropriately, and evenly to cover the entire steady-state dosing interval instead of at fixed time points (at 0, 1, 2, 4, and 8 hrs postdose) during the Visit 9 and 16.

As requested previously by the Agency in the EOP2 meeting, the PK of ICL670 in patients with mild, moderate, or severe hepatic impairment should be conducted. Population PK approach is acceptable, however, sufficient patients (per each category according to Child-Pugh classification) should be enrolled and analyzed adequately. Please see FDA guidance "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling" for details.

14. Does FDA consider there is any aspect of the design of study 0107 that might jeopardize the conduct of this study or its usefulness for regulatory approvals?

**Answer: See responses to questions 1, 3b, 4, 8a, and 12.**

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to our "Guidance for Industry; Formal Meetings With Sponsors and Applicants for PDUFA Products"). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at <http://www.fda.gov/cder/guidance/index.htm>. This meeting would be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

If you have any questions, call Alice Kacuba, RN, MSN, RAC, Regulatory Health Project Manager, at (301) 827-1602.

Sincerely,

*{See appended electronic signature page}*

Robert L. Justice, M.D., M.S.  
Director  
Division of Gastrointestinal & Coagulation Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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Robert Justice  
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

1-3-03

IND 58,554/SN-037

Novartis Pharmaceuticals Corporation  
Attention: Robyn B. Konecne, Pharm.D.  
Associate Director, Drug Regulatory Affairs  
59 Route 10  
East Hanover, NJ 07936-1080

Dear Dr. Konecne:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ICL 670 Dispersible Tablets.

We also refer to your November 18, 2002, request, serial number 037, for a special clinical protocol assessment, received November 19, 2002. The protocol (0108) is entitled "A multi-center, open-label, non-comparative, phase II trial on efficacy and safety of ICL-670 (5 to 40 mg/kg/day) given for at least 1 year to patients with chronic anemias and transfusional hemosiderosis unable to be treated with deferoxamine."

We have completed our review of your submission and, based on the information submitted, have the following responses to your questions.

- 1 Novartis considers that the intended indication text and claims would be supported by the design and patient population of study 0108. Study 0108 is intended to support the following claims:

{ }

Does FDA agree?

**Response:** Depending on the study results, it is acceptable for adult patients. However, it is unacceptable for pediatric patients. Number and age distribution of pediatric patients to be enrolled in this study is not specified.

IND 58,554

Page 2

2. Novartis considers that an open label design of study 0108, and the absence of a comparator arm is an appropriate design for this indication. Does FDA agree?

**Response:** An open-label design is acceptable for this study. However, lack of a control arm will be a problem for demonstrating efficacy. You should incorporate an historical control as the comparator arm in the efficacy analyses.

3. The statistical design of study 0108 (superiority to a fixed response rate) was previously agreed with FDA resulting in the planned study size (175 patients). Novartis considers that the proposed patient number, anemia types and duration of treatment (at least 1 year) in study 0108 are also adequate (as part of the overall safety information) to assess the safety of ICL670 to support the intended indication and claim. Does FDA agree?

**Response:** From a clinical viewpoint, the proposed patient number (175 patients), anemia types and duration of treatment (at least 1 year) in study 0108 are acceptable as part of the overall safety information to assess the safety of ICL670 to support the intended indication and claim.

4. The complications of iron overload toxicity are the same for all ages of thalassemic patients receiving chronic transfusions. Iron overload in thalassemia is the best characterized condition. Therefore, Novartis considers the following points to be justified:

- The majority of patients in the overall development program are thalassemics
- Data on clinical response in all anemias and ages in study 0108 can be pooled for primary analysis
- Conclusions on efficacy of ICL670 (clinical effectiveness, non-inferiority to DFO) from studies 0107 and 0108 can be extrapolated to all conditions of transfusional iron overload in anemias.

Does FDA concur with these points?

**Response:** It is acceptable that the majority of patients in the overall development program are thalassemics. Although you can pool data in all ages together, you still need to do separate analysis for adult and pediatric patients for both primary and secondary endpoints. Even though efficacy may be extrapolated across ages, safety in the young pediatric population may be different than in adults.

Conclusions on efficacy of ICL670 from studies 0107 and 0108 may be able to apply to other conditions of transfusional iron overload in anemias.

Information on the complications and natural history of iron overload (including laboratory parameters and LIC levels) in thalassemic patients should be included in the NDA.

5. Novartis considers that the proposed primary and secondary objectives of study 0108 are appropriate within the context of study 0108 to assess ICL670 for the intended indication and claims. Does FDA agree?

IND 58,554  
Page 3

**Response: Yes. Information to validate SQUID as an assessment tool should be submitted in the NDA.**

6. Novartis considers that the definitions of the inclusion/exclusion criteria are appropriate for these patient populations. Does FDA agree?

**Response: The definitions of the inclusion/exclusion criteria are acceptable.**

7. Novartis considers that the initial dose assignments and subsequent adjustments have sufficient basis and are appropriately defined. Does FDA agree?

**Response: Yes, doses of ICL670 have been based on experience in phase II studies on iron excretion and reduction of liver iron concentration.**

8. a). Novartis considers that the primary measure for assessing clinical efficacy (LIC) and the methods to assess it (liver biopsy and/or SQUID) are appropriate within the context of study 0108. Does FDA agree?

**Response: Yes. Information to validate SQUID as an assessment tool should be submitted in the NDA.**

8. b). Novartis considers that the endpoint definitions of success and failure are appropriate for a clinical study in transfusional iron overload. Does FDA agree?

**Response: Yes, in principle. Also, you should understand that interpretation of the results of the study may be complicated, particularly for patients in the acceptable range at enrollment. It is possible for a patient in maintenance range to actually increase LIC (up to < 7mg Fe/g dw) and still be called a success. This should be evaluated in the study analysis.**

**Information on clinical laboratory results (including iron studies) and drug dose adjustment during the studies should be carefully and completely documented. Information on compliance with drug dosing should be collected.**

9. Novartis considers that the definitions of the intention to treat (ITT) population proposed for the primary efficacy analysis, and how missing data is handled are appropriate. Does FDA agree?

**Response: Yes. Analysis on the basis of intention to treat, with missing data considered as failure, is an appropriate analysis for this single-arm study.**

10. a). Liver biopsy and SQUID, although useful for accurately assessing LIC and iron burden in clinical studies, are not practical methods for use in general practice. Novartis considers that the following points are justified:

- The final approved labeling for ICL670 should [

]

- The final approved labeling should recommend

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Does FDA agree with these points?

**Response: Yes, in principle. The exact monitoring recommended in the labeling is dependent on the study results and is a review issue.**

10. b). Novartis considers that the proposed study design is capable of  that could be recommended in the final labeling for monitoring and dose adjustment. Does FDA agree?

**Response: Yes, in principle. The exact monitoring recommended in the labeling is dependent on the study results and is a review issue.**

11. Novartis considers that the planned safety assessments will be sufficient to assess ICL670 for the intended patient populations. Does FDA agree?

**Response: The planned safety assessments appear adequate. However, there is no information available for pediatric plan, such as, how many pediatric patients will be enrolled in each age group.**

12. Does FDA consider there is any aspect of the design of study 0107 that might jeopardize the conduct of this study or its usefulness for regulatory approvals?

**Response: See responses to questions 1, 2, 4, 8a, 8b and 11.**

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to our "Guidance for Industry; Formal Meetings With Sponsors and Applicants for PDUFA Products"). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at <http://www.fda.gov/cder/guidance/index.htm>. This meeting would be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

If you have any questions, call Alice Kacuba, RN, MSN, RAC, Regulatory Health Project Manager, at (301) 827-1602.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.  
Director  
Division of Gastrointestinal & Coagulation Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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Robert Justice  
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 58,554

Novartis Pharmaceuticals Corporation  
Attention: Eileen A. Ryan  
Associate Director Drug Regulatory Affairs  
59 Route 10  
East Hanover, New Jersey 07936-1080

**RECEIVED**

JUN 10 2002

**DRA**

Dear Ms. Ryan:

Please refer to the meeting between representatives of your firm and FDA on April 9, 2002. This was an EOP2 meeting.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-1602.

Sincerely,

*{See appended electronic signature page}*

Alice Kacuba, RN, MSN, RAC  
Regulatory Health Project Manager  
Division of Gastrointestinal & Coagulation Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** April 9, 2002

**Time:** 1-2:30 PM

**Location:** Parklawn Building, Conference Room "K"

**Application:** IND 58,554; ICL 670 Dispersible Tablets

**Type of Meeting:** Type B; End of Phase 2

**Meeting Chair:** Kathy Robie-Suh

**Meeting Recorder:** Alice Kacuba

**FDA Attendees, Titles, and Office/Division:**

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Victor Raczkowski, M.D., MSc; Acting Division Director  
Joyce Korvick, M.D.; Deputy Division Director  
Kathy Robie-Suh, M.D., Ph.D.; Medical Hematology Team Leader  
Ruyi He, M.D.; Medical Reviewer  
Edvardas Kaminskas, M.D.; Medical Reviewer  
Min Lu, M.D.; Medical Reviewer  
Jasti Choudary, B.V.Sc., Ph.D.; Pharmacology Team Leader  
Liang Zhou, Ph.D.; Chemistry Team Leader  
Alice Kacuba, R.N., MSN, RAC; Regulatory Health Project Manager

Division of Biometrics III (HFD-720)

Tom Permutt, Ph.D.; Statistical Team Leader

Division of Pharmaceutical Evaluation II (HFD-870)

Suresh Doddapaneni, Ph.D.; Biopharmaceutics Team Leader

Office of Orphan Products (HF-035)

Jeffery Fritsch; Regulatory Project Manager  
Henry Startzman, M.D.; Medical Review Officer

**External Constituent Attendees and Titles:**

Daniele Alberti, M.D.; Clinical Project Leader, Novartis Clinical Development

Robert DeLap, M.D.; Global Leader, Novartis Clinical Development  
Suzanne Hauffe; Novartis Preclinical Safety  
David Laurie Ph.D.; Regulatory Manager, Novartis DRA  
Robert Miranda; Novartis DRA  
Gerd Rosenkranz, Ph.D.; Novartis Senior Statistical Consultant  
Joachim Schupp, M.D.; International Project Leader, Novartis project Management  
Romain Sechaud, Ph.D.; Pharmacokineticist, Novartis Clinical Pharmacology  
Chin Koerner, M.S., M.Ed.; Novartis Rockville Office Liaison Novartis, DRA  
Donald Schiavo, Ph.D.; Distinguished Research Fellow Novartis Preclinical Safety

**Background:** On February 14, 2002, Novartis submitted a Meeting Request for an End of Phase 2 meeting to discuss ICL 670 Dispersible Tablets. A subsequent background package was submitted on March 12, 2002, which contained specific questions from the firm. ICL 670 is being investigated as an oral iron chelator.

**Discussion Points (bullet format):**

The firm provided a presentation. Please see the firm's April 10, 2002 submission for a copy of the slides presented.

**Question 1:**

As an orally active iron chelator, ICL670 has good potential to address an unmet medical need for the serious disease "chronic iron overload in patients with transfusion-dependent anemias (transfusional hemosiderosis)". Do you agree that ICL670 would qualify for Fast Track Status?

- **You should submit a request for fast track designation. (Refer to Guidance for Industry Fast Track Drug Development Programs - Designation, Development [December 1998] available on Agency's website).**
- **Chronic iron overload in patients with transfusion-dependent anemias is a serious aspect of a serious disease. However, there is an available safe and effective therapy (parenteral Desferal).**
- **There may be a potential unmet medical need in situations where usefulness of Desferal therapy is limited by patient non-compliance (e.g., in the relatively young patients who make up most cases of these diseases), inconvenience (parenteral administration) and patient intolerance (local and systemic effects and risks of infection).**
- **The fast track designation request should include data to define and quantify the extent of the unmet medical need.**
- **The fast track designation should include discussion and supporting documentation to demonstrate that the benefit/risk profile of ICL 670 make it a likely candidate to satisfy the unmet medical need.**

Question 2:

Novartis is planning an Orphan Drug application for ICL670. If ICL670 is successfully designated an Orphan Drug then in accordance with the Pediatric Rule (21 CFR 314.55 (d)) Novartis would be exempt from conducting pediatric studies. However because of the design of the studies it is intended that pediatric patients will be studied in our registration program. We therefore believe that the ICL670 protocols would be adequate for Novartis to receive a Written Request and qualify for pediatric exclusivity.

*Do you concur?*

- You are correct that pediatric studies of orphan drugs are not required under the provisions of the 1998 Pediatric Rule. Therefore, if ICL 670 is granted Orphan Drug designation it will not be required to conduct pediatric studies under that Rule.
- You may still seek pediatric exclusivity for ICL 670 by submitting a Proposed Pediatric Study Request (PPSR). The adequacy of a PPSR would be evaluated at that time. Refer to Guidance for Industry: Qualifying for Pediatric Exclusivity under Section 505A of the FD&C Act published September 1999.
- Based on the protocol outlines provided, it does not appear that the number of pediatric patients to be studied will be sufficient to provide adequate safety and efficacy information in pediatric patients. You will need appropriate distribution across the age ranges.
- The PPSR should provide support for the safety of use of the drug in the pediatric population.

Question 3:

The preclinical safety program includes a complete package (see section 3.2 for completed, ongoing and planned studies) of *in vitro* and *in vivo* mutagenicity tests, reproductive toxicology studies, safety pharmacology studies, acute and chronic toxicology studies up to nine months in duration, together with two carcinogenicity studies. Novartis considers that the preclinical safety program as described is adequate to register ICL670 for chronic use in both adults and children.

*Do you agree?*

- Your list appears to be adequate to support the use of ICL 670 in adults. However, we have concern that toxicity in neonates has not been characterized. Since ICL 670 produces renal toxicity, gastrointestinal tract lesion and ocular toxicity in adult animals, it would be necessary to evaluate whether neonates with direct exposure might have a higher degree of vulnerability. Cardiovascular safety pharmacology of ICL 670 has been studied only in rats. We recommend studies in dogs with respect to effects on cardiac hemodynamics and cardiac conduction. We would also recommend that you

**conduct cardiac electrophysiology studies both in-vitro and in-vivo, employing state of the art models (e.g.; Carlsson et. al., JPET, 282: 220-27, 1997). Consider investigating the mechanism of the ocular toxicity.**

Question 4:

Novartis intends to develop this drug for the broad indication: "the treatment of chronic iron overload in patients with transfusion-dependent anemias (transfusional hemosiderosis)". Novartis believes that the adult and pediatric patient populations that will be included in the registration dossier (i.e. patients with thalassemia major, other transfusion-dependent chronic anemias and sickle cell disease requiring chronic blood transfusions) are representative of transfusion-dependent anemias. Novartis proposes that the planned clinical studies support the wording of this broad indication for registration, and will also permit the promotion of each individual condition studied in the clinical program.

*Do you agree?*

- **Generally the population for which a product is labeled reflects the population in which the drug was studied. The NDA submission should include information to support that the patients in the pivotal studies are representative of the entire population for which you desire labeling.**
- **Clarify whether you are seeking ICL 670 to be a "first line" or "second line" treatment.**

Question 5:

In our ICL670 registration program it is intended to conduct one comparative pivotal study vs deferoxamine (Study 0107) in adult and pediatric thalassemic patients (250 pts/arm) able to be treated with deferoxamine, and one non-comparative pivotal study (Study 0108) in 150 adult and pediatric patients with other transfusion-dependent anemias (excluding sickle cell anemia), or thalassemic patients unable to be treated with deferoxamine. In addition, supportive studies would examine ICL670 in 75 adult patients (Study 0109) and 40 pediatric patients (Study 0110) with sickle cell anemia. The duration of treatment for each of these studies in the registration dossier would be 1 year. Novartis considers that the design and duration of these registration trials are sufficient to assess the long-term safety and efficacy of ICL670 in both adults and children with chronic iron overload in transfusion-dependent anemias.

*Do you agree?*

- **Adequacy of the safety and efficacy databases to support approval of a drug product is data dependent and therefore an issue for review.**

- **Any labeling based on results of clinical studies reflects the population studied. The proposed population for the clinical development plan appears to include relatively few pediatric patients (only 10% in pivotal studies) and many of these may be adolescents.**

Question 6:

Based on phase II results, a dose range for ICL670 has been proposed [  ]  
Novartis considers that the dose range and dose-adjustment criteria proposals for the registration trials are well justified.

*Do you agree?*

- **We agree that there still needs to be additional information obtained to allow for a definition of the initial dose and how dose adjustments will be made.**
- **Please clearly define how the dose adjustment will be made and what a stable dose is.**

Question 7:

Do you consider that the efficacy endpoints and safety monitoring in the registration trials are acceptable to support registration for the broad indication?

- **A binary endpoint of "success" or "failure" of individual patients is desirable. Success and failure should be prospectively defined in the protocols.**
- **Preclinical studies suggest that additional cardiac safety monitoring may be needed.**
- **Description of the safety monitoring in the protocol outlines is sketchy. More specific comments on the proposed monitoring plan can be made when the full protocols are provided.**

Question 8:

Do you consider that the statistical plan for the phase III trials as defined in the Novartis position statement (non-inferiority to comparator; primary analysis; subgroup analysis by disease type and age) is acceptable to support registration?

- **It appears acceptable.**

Question 9:

Desferal (deferroxamine) is the only iron chelator currently approved in the USA for this target indication. The current Desferal USPI states a dose range of 20-40mg/kg/day, while 20-60 mg/kg/day is included in some non-US labeling. In the comparative registration trials a dose range of 20-60 mg/kg/day is planned as this also reflects US clinical practice.

*Do you agree?*

- **It appears appropriate. However, be aware that interpretation of the study results may be problematic if difficult to explain safety and or efficacy effects are seen between higher and lower doses.**
- **In the NDA you should include a thorough justification and support for use of the higher doses.**

Question 10:

Novartis considers that, if the human ADME study (Study 0115) confirms the very low level of renal excretion seen in preclinical studies, then the renal monitoring in the registration studies should suffice and no formal study in renal impairment should be necessary.

*Do you agree?*

- **This approach is acceptable provided that the drug and any active metabolites have a relatively wide therapeutic index and are primarily eliminated via hepatic metabolism or biliary excretion (Please refer to Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function-Study Design, data Analysis, and Impact on Dosing and Labeling).**

Question 11:

Hepatic and cardiac impairment occur frequently in patients with iron overload, and so will be present in a large proportion of patients in the registration studies. Novartis therefore considers that the hepatic and cardiac monitoring in the registration studies should suffice and that no formal study in hepatic impairment or cardiac function should be necessary for this product.

*Do you agree?*

- **Since it appears that the drug is eliminated primarily through metabolism, plasma levels of the drug will be elevated in patients with hepatic impairment. As such, pharmacokinetic data should be obtained in patients with different degrees of hepatic impairment (mild, moderate, and severe).**

**Additional OCPB Comments:**

Since this is a new chemical entity and is likely to be used on a chronic basis, the following information will be expected to be submitted in the NDA:

1. Dose-proportionality in the proposed dosage range, absolute bioavailability, and the food effect on ICL670 absorption using FDA recommended high fat meal.
2. *In vitro* and/or *in vivo* data regarding the potential chelation of ICL670 with constituents other than Fe<sup>+3</sup>.
3. According to animal data, ICL670 is extensively metabolized by CYP 1A1, 1A2, 2D6. Therefore, based on the study results obtained from Study # 0115, drug-drug-interaction (DDI) study(ies) of ICL670 with commonly administered drugs to the target populations should be addressed.
4. According to animal data, ICL670 is highly transferred into milk. Therefore, the secretion of ICL670 into human milk should be addressed.
5. The values of area under the curve (AUC) should be calculated from time zero to infinity and other PK parameters are to be calculated accordingly.
6. Please clarify whether ICL670 and ICL670A (reported in Study # 0101) refer to the same compound.

**Additional information-CMC**

- We recommend that you submit a separate CMC EOP2 meeting request.

Minutes Preparer:

Chair Concurrence:

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Alice Kacuba  
6/3/02 04:03:37 PM

Kathy Robie-Suh  
6/3/02 04:10:07 PM