CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-882

Chemistry Review(s)
NDA 21-882

Exjade® (deferasirox) Tablets for Oral Suspension

Novartis Pharmaceuticals Corp.

Raymond P. Frankewich, Ph.D.

Division of GI and Coagulation Drug Products (HFD-180)
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I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data ..................................................................................................................... NA
   S DRUG SUBSTANCE [deferasirox, Novartis Pharmaceuticals Corp.] ...................... NA
   P DRUG PRODUCT [Exjade® Tablets for Oral Suspension, 125, 250, and 500 mg] ................ NA
   A APPENDICES .................................................................................................... NA
   R REGIONAL INFORMATION ............................................................................. NA

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .................... NA
   A. Labeling & Package Insert ............................................................................... NA
   B. Environmental Assessment Or Claim Of Categorical Exclusion ....................... NA

III. List Of Deficiencies To Be Communicated ............................................................ NA
Chemistry Review Data Sheet

1. NDA or ANDA 21-882
2. REVIEW #: 2
3. REVIEW DATE: October 10, 2005
4. REVIEWER: Raymond P. Frankewich, Ph.D.
5. PREVIOUS DOCUMENTS:

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7. NAME & ADDRESS OF APPLICANT:

Name: Novartis Pharmaceuticals Corporation
Address: One Health Plaza
         East Hanover, NJ 07936-1080
Representative: Susan P. Nemeth, Ph.D., Associate Director, Drug Regulatory Affairs
Telephone: (862) 778-2003
8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: None®
   b) Non-Proprietary Name (USAN): deferasirox
   c) Code Name/# (ONDC only): ICL670 / 201530-41-8 (CAS Registry Number)
   d) Chem. Type/Submission Priority (ONDC only):
      • Chem. Type: 1
      • Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: NA for 505(b)(1).

10. PHARMACOL. CATEGORY: Metal chelator (code: 8016400)

11. DOSAGE FORM: Tablet (Tentative: Tab Soluble, code 507; see Executive Summary)

12. STRENGTH/POTENCY: 125, 250, and 500 mg

13. ROUTE OF ADMINISTRATION: (Oral, code 001)

14. Rx/OTC DISPENSED: _X_Rx  ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
   _____SPOTS product – Form Completed
   _____X_Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLEcular FORMULA, MOLEcular WEIGHT: See Section S.1 below.
17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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1. Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

2. Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

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18. STATUS: NOTE: The CMC section of this NDA was submitted as a Reviewable Unit on January 10, 2005. The rest of the NDA was submitted on
April 29, 2005. As a result, many of the consult reviews below will be listed as pending.

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19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes  ____ No  If no, explain reason(s) below:
The Chemistry Review for NDA 21-882

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
   From CMC perspective, approval is recommended for this application.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
   None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)
   Drug substance is known as deferasirox, which is the non-proprietary name designated by USAN. The deferasirox molecule consists of three substituted phenyl groups, all covalently bonded (radiating from) a triazole structure. In this NDA deferasirox is proposed as an iron chelator.

   At room temperature and atmospheric pressure, deferasirox appears as a white to slightly yellow powder. It is optically active.

   Deferasirox has no chiral centers, and is not optically active.

   Deferasirox is highly water-insoluble. It is highly lipid-soluble, and is observed to possess good permeability.

   The drug product is a tablet in three proposed strengths: 125 mg, 250 mg, and 500 mg. The tablet(s) should be placed in an appropriate amount of liquid (described in package insert) and stirred until a suspension is obtained. The patient is to drink the resulting suspension. According to the package insert, doses should be calculated so that whole tablets will be used (calculated to the nearest whole tablet). When the suspension is prepared in water, the suspension appears white and opaque. During development of the drug, tests results were obtained that indicated several liquids could be used (see section P.2.6, Pharmaceutical Development/Compatibility).

   The proposed name of the drug product is Exjade® (deferisirox) Tablets for Oral Suspension. At this time, the dosage form name “Tablet for Oral Suspension” does not exist in CDER Data Standards Manual C-DRG-00201, revision no. 2 (latest revision is
dated 2000; this manual establishes dosage form names). However, in 2003, discussions were initiated with Capt. William A. Hess, Lexicographer/Center Consultant, the person responsible for maintaining Manual C-DRG-00201. Capt. Hess indicated it was possible to revise Manual C-DRG-00201 so that this and perhaps other appropriate dosage form names could be provided for. At this time, it is the understanding of the review division that this will be accomplished at an appropriate time.

B. Description of How the Drug Product is Intended to be Used
The administration of the drug product is described above. The proposed indication is treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis). It is to be used for both adult patients and for pediatric patients aged 2 years and over.

Package insert (Dosage and Administration section) indicates that after swallowing the suspension, any residue should be resuspended in liquid and swallowed. It is also indicated that tablets should not be swallowed whole.

It was determined that ☑ for this drug substance,

☑ The applicant indicates that ☑ of the drug substance; it is indicated that ☑ was necessary because ☑

C. Basis for Approvability or Not-Approval Recommendation
The reasons for the recommendation of approval are as follows:

- Inspections of all facilities are complete. Overall Compliance recommendation (dated August 2, 2005) is Acceptable;
- It has been indicated that the Proposed Dosage Form name (Tablet for Oral Suspension) will be added to CDER Data Standards Manual C-DRG-00201 (see section II A above);
- Satisfactory responses by the firm to 19 information requests, sent to the applicant in a letter dated July 7, 2005. Responses to those requests, and evaluation of those responses, are provided in this review.
III. Administrative

A. Reviewer’s Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block
17 Page(s) Withheld

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

☐ § 552(b)(5) Deliberative Process

☐ § 552(b)(5) Draft Labeling
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ray Frankewich  
10/12/2005 12:41:16 PM  
CHEMIST

Liang Zhou  
10/12/2005 12:47:39 PM  
CHEMIST
NDA 21-882

Exjade® (deferasirox) Tablets for Oral Suspension

Novartis Pharmaceuticals Corp.

Raymond P. Frankewich, Ph.D.

Division of GI and Coagulation Drug Products (HFD-180)
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    C. Basis for Approvability or Not-Approval Recommendation .................................... 9
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    A. Reviewer’s Signature ................................................................................................. 10
    B. Endorsement Block ................................................................................................. 10
    C. CC Block .................................................................................................................. 10
Chemistry Assessment ...................................................................................................... 11
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   P  DRUG PRODUCT [Exjade® Tablets for Oral Suspension, 125, 250, and 500 mg] ............ 64
   A  APPENDICES ........................................................................................................... 109
   R  REGIONAL INFORMATION ..................................................................................... 109
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   A. Labeling & Package Insert ....................................................................................... 109
   B. Environmental Assessment Or Claim Of Categorical Exclusion ................................. 113
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1. NDA or ANDA 21-882

2. REVIEW #: 1

3. REVIEW DATE: July 6, 2005

4. REVIEWER: Raymond P. Frankewich, Ph.D.

5. PREVIOUS DOCUMENTS:

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6. SUBMISSION(S) BEING REVIEWED:

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7. NAME & ADDRESS OF APPLICANT:

   Name: Novartis Pharmaceuticals Corporation
   Address: One Health Plaza
            East Hanover, NJ 07936-1080
   Representative: Susan P. Nemeth, Ph.D., Associate Director, Drug Regulatory Affairs
   Telephone: (862) 778-2003
8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: None®
   b) Non-Proprietary Name (USAN): deferasirox
   c) Code Name/# (ONDC only): ICL670 / 201530-41-8 (CAS Registry Number)
   d) Chem. Type/Submission Priority (ONDC only):
      • Chem. Type: 1
      • Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NA for 505(b)(1).

10. PHARMACOL. CATEGORY: Metal chelator (code: 8016400)

11. DOSAGE FORM: Tablet (Tentative: Tab Soluble, code 507; see Executive Summary)

12. STRENGTH/POTENCY: 125, 250, and 500 mg

13. ROUTE OF ADMINISTRATION: (Oral, code 001)

14. Rx/OTC DISPENSED: _X_Rx   ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    _____SPOTS product – Form Completed
    ___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: See Section S.1 below.

17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs:

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1 Action codes for DMF Table:
1 - DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 - Type 1 DMF
3 - Reviewed previously and no revision since last review
4 - Sufficient information in application
5 - Authority to reference not granted
6 - DMF not available
7 - Other (explain under "Comments")

2 Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

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18. STATUS: NOTE: The CMC section of this NDA was submitted as a Reviewable Unit on January 10, 2005. The rest of the NDA was submitted on April 29, 2005. As a result, many of the consult reviews below will be listed as pending.

**ONDC:**

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19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. _____ Yes _____ No If no, explain reason(s) below:

Appears This Way
On Original
The Chemistry Review for NDA 21-882

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
   Approvable for CMC. Pending issues are EER, and responses to information requests in DR letter.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
   None at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)
   Drug substance is known as deferasirox, which is the non-proprietary name designated by USAN. The deferasirox molecule consists of three substituted phenyl groups, all covalently bonded (radiating from) a triazole structure. In this NDA deferasirox is proposed as an iron chelator.

   At room temperature and atmospheric pressure, deferasirox appears as a white to slightly yellow powder.

   Deferasirox has no chiral centers, and is not optically active.

   Deferasirox is highly water-insoluble. It is highly lipid-soluble, and is observed to possess good permeability.

   The drug product is a tablet in three proposed strengths: 125 mg, 250 mg, and 500 mg. The tablet(s) should be placed in an appropriate amount of liquid (described in package insert) and stirred until a suspension is obtained. The patient is to drink the resulting suspension. According to the package insert, doses should be calculated so that whole tablets will be used (calculated to the nearest whole tablet). When the suspension is prepared in water, the suspension appears white and opaque. During development of the drug, tests results were obtained that indicated several liquids could be used (see section P.2.6, Pharmaceutical Development/Compatibility).

   The proposed name of the drug product is Exjade® (deferasirox) Tablets for Oral Suspension. At this time, the dosage form name "Tablet for Oral Suspension" does not
exist in CDER Data Standards Manual C-DRG-00201, revision no. 2 (latest revision is
dated 2000; this manual establishes dosage form names). However, in 2003,
discussions were initiated with Capt. William A. Hess, Lexicographer/Center
Consultant, the person responsible for maintaining Manual C-DRG-00201. Capt. Hess
indicated it was possible to expand Manual C-DRG-00201 so that appropriate dosage
form names could be provided for. This issue will be considered further, and any
decisions or results will be reported in future CMC reviews.

B. Description of How the Drug Product is Intended to be Used
The administration of the drug product is described above. The proposed indication is
treatment of chronic iron overload due to blood transfusions (transfusional
hemosiderosis). It is to be used for both adult patients and for pediatric patients aged 2
years and over.

Package insert (Dosage and Administration section) indicates that after swallowing the
susension, any residue should be resuspended in liquid and swallowed. It is also
indicated that tablets should not be swallowed whole.

It was determined that for this drug substance,
substance. The applicant indicates that of the drug substance; it is indicated that was necessary because

C. Basis for Approvability or Not-Approval Recommendation
The primary reason for the Approvable recommendation is because of the outstanding
inspections (see section P.3.1, Drug Product Manufacturers). Inspection was scheduled
for the Novartis Basel facility (CFN# 9692042, drug substance manufacturer) for May
30 – June 1, 2005 (for CSN profile). Inspections were scheduled for the Novartis Stein
facility (CFN# 9692043, drug product manufacturer, drug substance for June 6 – 9, 2005 (for the CRU and TCM profiles). The inspection of which performs the drug product, was scheduled for June 3, 2005.

Another outstanding issue is the name of the dosage form, discussed above.

There are a total of 19 information requests (that do not involve labeling) are listed in
the section of this review entitled List Of Comments To Be Communicated in Action
Letter. These requests will be sent to the applicant. It is expected that these issues will
be addressed in this review cycle. The most important issues appearing in the List of
Comments are these:

• Clarification and justification of some of the parameters and acceptance criteria for
the tests. For a dosage form of this kind, in which a tablet is to be dispersed in liquid, these tests are important
indicators of bioavailability of the drug substance;
• Whether or not the tests \( \mathcal{X} \) will be performed for stability evaluation of annual batches of drug product, and for stability evaluation for post-approval changes (comment no. 18);

• It does not appear that any stability data has been submitted for drug substance manufactured at one of the proposed sites for drug substance manufacturing (located at Pratteln, Switzerland). It also does not appear that any stability data for drug product manufactured with drug substance produced at the Pratteln, Switzerland site has been submitted.

III. Administrative

A. Reviewer’s Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block
Page(s) Withheld

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

☐ § 552(b)(5) Deliberative Process

☐ § 552(b)(5) Draft Labeling
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ray Frankewich
7/6/05 03:00:41 PM
CHEMIST

Liang Zhou
7/6/05 03:47:36 PM
CHEMIST
NDA 21-882
Exjade (deferasorix) Tablets for Oral Suspension

Environmental Assessment-See October 12, 2005 cmc review for the request for categorical exclusion form conducting an Environmental Assessment.

Alice Kacuba 10:16:05
Regulatory Health Project Manager
NDA 21-882
Exjade (deferasorix) Tablets for Oral Suspension

Methods Validation - This section is Not Applicable for this application.

Alice Kacuba 10-17-05

Alice Kacuba
Regulatory Health Project Manager
NDA 21-882
Exjade (deferasorix) Tablets for Oral Suspension

Statistical Review-stability-This section is not applicable for this application.

Alice Kacuba 7-11-05
Alice Kacuba
Regulatory Health Project Manager
NDA 21-882
Exjade (deferasorix) Tablets for Oral Suspension

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

Alice Kacuba 7.11.05

Alice Kacuba
Regulatory Health Project Manager
ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application: NDA 21882/000
Org Code: 180
Priority: 1P

Sponsor: NOVARTIS
Brand Name: EXJADE (DEFERASIRIX)
Estab. Name:
Generic Name: DEFERASIRIX

Stamp Date: 02-MAY-2005
PDUFA Date: 02-NOV-2005

Dosage Form: (TABLET)
Action Goal:

Strength: 125 MG, 250 MG, 500 MG
District Goal: 01-JAN-2006

FDA Contacts:
A. KACUBA Project Manager (HFD-180) 301-827-9334
R. FRANKIEWICH Review Chemist (HFD-180) 301-827-7310
L. ZHOU Team Leader (HFD-180) 301-827-1251

Overall Recommendation: ACCEPTABLE on 02-AUG-2005 by S. ADAMS (HFD-322) 301-827-9052

Establishment:
CFN:

FEI:

DMF No:

Responsibilities:

Profile: TCM
OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 22-MAR-05
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
Establishment : NOVARTIS PHARMA INC
LICHSTRASSE 35, ST. JOHANN SITE
BASEL, CH

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 29-MAR-95
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : NOVARTIS PHARMA INC
CORK
RINGASKIDDY, CORK, IE

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile: CTL
Last Milestone: OC RECOMMENDATION
Milestone Date: 29-MAY-05
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CPN: 9692042 FEI: 3002865753
NOVARTIS PHARMA STEIN AG
SCHWEIZERHALLE, BASEL, SZ

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CSN
Last Milestone: OC RECOMMENDATION
Milestone Date: 20-JUL-05
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CPN: 9692043 FEI: 3002653483
NOVARTIS PHARMA STEIN AG
SCHAFFHAUSERSTRASSE
STEIN, , SZ

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE FINISHED DOSAGE MANUFACTURER

Profile: CRU
Last Milestone: OC RECOMMENDATION
Milestone Date: 02-AUG-05
Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Profile : TCM

OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 02-MAR-05

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 2416082    FBI : 2416082

NOVARTIS PHARMACEUTICALS CORP

OLD MILL RD

SUPTERN, NY 10901

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Profile : CTL

OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 22-MAR-05

Decision : ACCEPTABLE

Reason : BASED ON PROFILE
ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile : TCM

OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 22-MAR-05

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : [ ]

FEI : [ ]

DMF No: [ ]

AADA: [ ]

Responsibilities: [ ]

Profile : CTL

OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 02-AUG-05

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION