CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206910Orig1s000

CHEMISTRY REVIEW(S)

CHEMISTRY REVIEWER MEMORANDUM

To:	NDA 206910
From:	Josephine Jee, CMC Reviewer, OLDP
Thru:	Janice Brown, Quality Assessment Lead, ONDP
Date:	17-MAR-2015
Drug:	Jadenu™Film-Coated Tablets (deferasirox)
Route of administration:	Orally
Strength:	90 mg, 180 mg, and 360 mg
Subject:	**Updated Drug Product Specification**

Background

This review covers only the update of the Drug Specification submitted by Novartis dated 12-MAR-2015 (Section 3.2.P.5.1). For further information on NDA 206910, please refer to NDA 206910 CMC Review dated 24-NOV-2014.

In the ICL670 film-coated tablets, the crospovidone level (b) (4) as observed during dissolution when a stirring speed (b) (4) rpm was used. The data from the study of the effect of paddle speed on dissolution rate of ICL670 film-coated tablets clearly indicated that the dissolution rate (b) (4) speed and a paddle speed of (b) (4) rpm is required to observe quantitative dissolution. Since dissolution values of Q (b) (4)% were not consistently observed at the initially proposed Q time point of (b) (4) minutes, use of (b) (4) rpm for dissolution testing was not considered viable for the dissolution test used for routine quality control of ICL670 90 mg, 180 mg and 360 mg film-coated tablets. No trend in the impact of long term storage on dissolution rate has been established as the stability data (b) (4) are currently available only up to (b) (4) months. Based on this data, the final dissolution specification was initially proposed at (b) (4)% (Q) in (b) (4) minutes but has been revised and is now proposed at (b) (4) ***% (Q) in 15 minutes***.

The proposed final dissolution specification is acceptable to B. S. Zolnik, Ph.D., Biopharmaceutics Reviewer, Division of Biopharmaceutics, Office of New Drug Products.

The remaining tests, analytical methods, and acceptance criteria remain the same as in the original submission and reviewed by this reviewer on 24-NOV-2014; see below for updated drug product specifications.

From the CMC perspective, NDA 206910 for Jadenu™Film-Coated Tablets (deferasirox) is recommended for Approval.

Deferasirox (ICL670) 90 mg Film-Coated Tablet Specification:

2 Test specifications

The requirements are valid at release and throughout shelf-life unless indicated otherwise

Test Code	Title of Test, Principle	Requirements	Test performed for	
			Batch release	Stability studies
Description				
10001.01	Appearance by visual examination			
	▪ Shape	Ovaloid, biconvex film-coated tablet with beveled edges	+	+
	▪ Color	Light blue	+	+
	▪ Score	Unscored	+	–
	▪ Debossment	"NVR" on one side and "90" on a slight upward slope in between two debossed curved lines on the other side	+	–
	▪ Approximate size	Length: 10.7 mm Width: 4.2 mm	+	–
Identification				
20601.01	Identity by UV			
	▪ Deferasirox	Corresponds to the reference	+	–
24201.01	Identity of colorants			
	▪ (b) (4) by color reaction	Positive	F_1	–
	▪ (b) (4) by color reaction	Negative	F_1	–
24202.01	Identity of colorants			
	▪ (b) (4) by UV	Positive	F_1	–
53501.01	Identity by HPLC			
	▪ Deferasirox	Corresponds to the reference	+	–
Properties				
10901.01	Mean mass	Target: (b) (4) Range:	+	–

(Cont.)

Test Code	Title of Test, Principle	Requirements	Test performed for	
			Batch release	Stability studies
Performance				
50101.02	Dissolution by HPLC			
	▪ Deferasirox	Not less than (b) (4)% (Q value) of the declared content in 15 minutes, according to Acceptance Table 1 of Ph. Eur. and USP or Acceptance Table 6.10-1 of JP (release testing: levels 1 and 2 only, stability studies: levels 1, 2 and 3)	+	+
50416.02	Uniformity of dosage units by content uniformity by NIR [2)]			
	▪ Deferasirox	Meets the requirements of Ph. Eur. 2.9.47 (Alternative 1)	+	–
50401.01	Uniformity of dosage units by content uniformity by HPLC [3) 4)]			
	▪ Deferasirox	Meets the requirements of Ph. Eur., USP and JP	+	–
Impurities				
53501.01	Degradation products, based on the declared content of Deferasirox, by HPLC			
	▪ Any unspecified degradation product	Not more than (b) (4) %	+	+
	▪ Total unspecified degradation product	Not more than (b) (4)%	+	+
Assay				
53501.01	Assay by HPLC			
	▪ Deferasirox	(b) (4)% - (b) (4)% of the declared content	+	+

+ = Parameter routinely tested

– = Parameter NOT tested

F_n = Parameter tested in a frequency mode:

F_1 = Tests are carried out only on request but at least one batch must be tested in each calendar year in which the product is manufactured.

1) Range is defined as the target of (b) (4)

2) Test 50416, uniformity of dosage units by content uniformity by NIR is performed by analyzing uncoated core tablets.

3) Test 50401, uniformity of dosage units by content uniformity by HPLC is performed by analyzing film-coated tablets.

4) Test 50401, uniformity of dosage units by content uniformity by HPLC, is an alternative to test 50416, uniformity of dosage units by content uniformity by NIR. Uniformity of dosage units by content uniformity by NIR is the primary release method. Uniformity of dosage units by content uniformity by HPLC is an alternative method that will only be used when release by NIR is not possible, such as equipment failure, ongoing method change or legal restriction.

Deferasirox (ICL670) 180 mg Film-Coated Tablet Specification:

2 Test specifications

The requirements are valid at release and throughout shelf-life unless indicated otherwise

Test Code	Title of Test, Principle	Requirements	Test performed for	
			Batch release	Stability studies
Description				
10001.01	Appearance by visual examination			
	▪ Shape	Ovaloid, biconvex film-coated tablet with beveled edges	+	+
	▪ Color	Medium blue	+	+
	▪ Score	Unscored	+	–
	▪ Debossment	"NVR" on one side and "180" on a slight upward slope in between two debossed curved lines on the other side	+	–
	▪ Approximate size	Length: 14 mm Width: 5.5 mm	+	–
Identification				
20601.01	Identity by UV			
	▪ Deferasirox	Corresponds to the reference	+	–
24201.01	Identity of colorants			
	▪ [redacted] (b) (4) by color reaction	Positive	F_1	–
	▪ [redacted] (b) (4) by color reaction	Negative	F_1	–
24202.01	Identity of colorants			
	▪ [redacted] (b) (4) by UV	Positive	F_1	–
53501.01	Identity by HPLC			
	▪ Deferasirox	Corresponds to the reference	+	–
Properties				
10901.01	Mean mass	Target: [redacted] (b) (4) Range:	+	–

Test Code	Title of Test, Principle	Requirements	Test performed for	
			Batch release	Stability studies
Performance				
50101.02	Dissolution by HPLC ▪ Deferasirox	Not less than (b)(4)% (Q value) of the declared content in 15 minutes, according to Acceptance Table 1 of Ph. Eur. and USP or Acceptance Table 6.10-1 of JP (release testing: levels 1 and 2 only, stability studies: levels 1, 2 and 3)	+	+
50416.02	Uniformity of dosage units by content uniformity by NIR [2)] ▪ Deferasirox	Meets the requirements of Ph. Eur. 2.9.47 (Alternative 1)	+	–
50401.01	Uniformity of dosage units by content uniformity by HPLC [3) 4)] ▪ Deferasirox	Meets the requirements of Ph. Eur., USP and JP	+	–
Impurities				
53501.01	Degradation products, based on the declared content of Deferasirox, by HPLC ▪ Any unspecified degradation product ▪ Total unspecified degradation product	 Not more than (b)(4) % Not more than (b)(4)%	 + +	 + +
Assay				
53501.01	Assay by HPLC ▪ Deferasirox	(b)(4)% of the declared content	+	+

+ = Parameter routinely tested

– = Parameter NOT tested

F_n = Parameter tested in a frequency mode:

F_1 = Tests are carried out only on request but at least one batch must be tested in each calendar year in which the product is manufactured.

1) Range is defined as the target of (b)(4)

2) Test 50416, uniformity of dosage units by content uniformity by NIR is performed by analyzing uncoated core tablets.

3) Test 50401, uniformity of dosage units by content uniformity by HPLC is performed by analyzing film-coated tablets.

4) Test 50401, uniformity of dosage units by content uniformity by HPLC, is an alternative to test 50416, uniformity of dosage units by content uniformity by NIR. Uniformity of dosage units by content uniformity by NIR is the primary release method. Uniformity of dosage units by content uniformity by HPLC is an alternative method that will only be used when release by NIR is not possible, such as equipment failure, ongoing method change or legal restriction.

Deferasirox [redacted] 360 mg Film-Coated Tablet Specification:

2 Test specifications

The requirements are valid at release and throughout shelf-life unless indicated otherwise

Test Code	Title of Test, Principle	Requirements	Test performed for	
			Batch release	Stability studies
Description				
10001.01	Appearance by visual examination			
	▪ Shape	Ovaloid, biconvex film-coated tablet with beveled edges	+	+
	▪ Color	Dark blue	+	+
	▪ Score	Unscored	+	–
	▪ Debossment	"NVR" on one side and "360" on a slight upward slope in between two debossed curved lines on the other side	+	–
	▪ Approximate size	Length: 17 mm Width: 6.7 mm	+	–
Identification				
20601.01	Identity by UV			
	▪ Deferasirox	Corresponds to the reference	+	–
24201.01	Identity of colorants			
	▪ [redacted] by color reaction	Positive	F_1	–
	▪ [redacted] by color reaction	Negative	F_1	–
24202.01	Identity of colorants			
	▪ [redacted] by UV	Positive	F_1	–
53501.01	Identity by HPLC			
	▪ Deferasirox	Corresponds to the reference	+	–
Properties				
10901.01	Mean mass	Target: [redacted] Range:	+	–

Test Code	Title of Test, Principle	Requirements	Test performed for	
			Batch release	Stability studies
Performance				
50101.02	Dissolution by HPLC ▪ Deferasirox	Not less than (b) (4) % (Q value) of the declared content in 15 minutes, according to Acceptance Table 1 of Ph. Eur. and USP or Acceptance Table 6.10-1 of JP (release testing: levels 1 and 2 only, stability studies: levels 1, 2 and 3)	+	+
50416.02	Uniformity of dosage units by content uniformity by NIR [2)] ▪ Deferasirox	Meets the requirements of Ph. Eur. 2.9.47 (Alternative 1)	+	–
50401.01	Uniformity of dosage units by content uniformity by HPLC [3) 4)] ▪ Deferasirox	Meets the requirements of Ph. Eur., USP and JP	+	–
Impurities				
53501.01	Degradation products, based on the declared content of Deferasirox, by HPLC ▪ Any unspecified degradation product ▪ Total unspecified degradation product	Not more than (b) (4) % Not more than (b) (4) %	+ +	+ +
Assay				
53501.01	Assay by HPLC ▪ Deferasirox	(b) (4) % - (b) (4) % of the declared content	+	+

+ = Parameter routinely tested

– = Parameter NOT tested

F_n = Parameter tested in a frequency mode:

F_1 = Tests are carried out only on request but at least one batch must be tested in each calendar year in which the product is manufactured.

1) Range is defined as the target of (b) (4)

2) Test 50416, uniformity of dosage units by content uniformity by NIR is performed by analyzing uncoated core tablets.

3) Test 50401, uniformity of dosage units by content uniformity by HPLC is performed by analyzing film-coated tablets.

4) Test 50401, uniformity of dosage units by content uniformity by HPLC, is an alternative to test 50416, uniformity of dosage units by content uniformity by NIR. Uniformity of dosage units by content uniformity by NIR is the primary release method. Uniformity of dosage units by content uniformity by HPLC is an alternative method that will only be used when release by NIR is not possible, such as equipment failure, ongoing method change or legal restriction.

Josephine M. Jee -S

Digitally signed by Josephine M. Jee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300022233, cn=Josephine M. Jee -S
Date: 2015.03.18 12:42:46 -04'00'

Janice T. Brown -A

Digitally signed by Janice T. Brown -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300101685, cn=Janice T. Brown -A
Date: 2015.03.18 12:45:56 -04'00'

CHEMISTRY REVIEW

NDA 206910

Jadenu™ (deferasirox) Film-coated Tablets

Novartis Pharmaceuticals Corporation

Josephine Jee

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I
Branch II

For the Office of Hematology and Oncology Drug Products
Division of Drug Hematology Products

Table of Contents

Table of Contents **2**

Chemistry Review Data Sheet **4**

The Executive Summary **8**

I. Recommendations 8

A. Recommendation and Conclusion on Approvability 8

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 9

II. Summary of Chemistry Assessment 8

A. Description of the Drug Product(s) and Drug Substance(s) 8

B. Description of How the Drug Product is Intended to be Used 9

C. Basis for Approvability or Not-Approval Recommendation 10

III. Administrative 10

A. Reviewer's Signature 10

B. Endorsement Block 10

C. CC Block 10

Chemistry Assessment **11**

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data 11

S DRUG SUBSTANCE [] 11

S.1 General Information 11
S.2 Manufacture 13
S.3 Characterization 14
S.4 Control of Drug Substance 16
S.5 Reference Standards or Materials 17
S.6 Container Closure System 17
S.7 Stability 17

P DRUG PRODUCT 25

P.1 Description and Composition of the Drug Product 25
P.2 Pharmaceutical Development 25
P.3 Manufacture 38
P.4 Control of Excipients 42
P.5 Control of Drug Product 43
P.6 Reference Standards or Materials 54
P.7 Container Closure System 54
P.8 Stability 54

A APPENDICES 63
R REGIONAL INFORMATION 64

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 64
A. Labeling & Package Insert 64
B. Environmental Assessment or Claim of Categorical Exclusion 67

Chemistry Review Data Sheet

1. NDA 206910, **Jadenu™ (deferasirox) Film-Coated Tablets**

2. REVIEW #1

3. REVIEW DATE: 24-NOV-2014

4. REVIEWER: Josephine Jee

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	30-MAY-2014

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DocumentDate
Original NDA 206910	30-MAY-2014

7. NAME & ADDRESS OF APPLICANT:

Name: Novartis Pharmaceuticals Corporation

Address: One Health Plaza, Building 337/B10-6
East Hanover, NJ 07936-1080

Telephone: 862-778-8998

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Not Applicable
b) Non-Proprietary Name (USAN): Deferasirox
Code Name/# (ONDC only):
c) Chem. Type/Submission Priority (ONDC only): ICL670, ICL670-NXA, ICL670-NXB, CGP72670

- Chem. Type: 6
- Submission Priority:

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

10. PHARMACOL. CATEGORY: Treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and for the treatment of chronic iron overload in patients 10 years of age and older with non-transfusion-dependent thalassemia (NTDT) syndromes and with a liver iron and serum ferritin greater than 300 mcg/L.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 90 mg, 180 mg, and 360 mg

13. ROUTE OF ADMINISTRATION: Orally

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

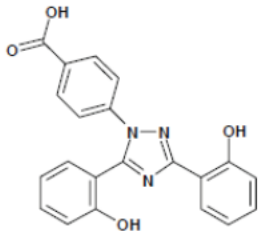
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

4-[3,5-Bis(2-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl]benzoic acid

Chemical Structure of Deferasirox



Empirical Formula: $C_{21}H_{15}N_3O_4$ Molecular Weight: 373 (b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	COD E[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	IV		(b) (4)	3	Adequate	E. Schaefer 12-FEB-2008	
	II			3	Adequate	D.Klein 23-OCT-2012	
	III				Adequate	N. Ni 10-SEP-2012	
	II			3	Adequate	S. Moore 18-SEP-2000	
	III			3	Adequate	G. Holbert 01-FEB-2012	

		Inc.					
(b) (4)	III		(b) (4)	3	Adequate	R. Agarwal 28-JAN-2010	
	III			3	Adequate	G. Holbert 03-FEB-2012	
	III			3	Adequate	21-SEP-2012 F. Frankewich	

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)

[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
IND 58,554	Novartis	Deferasirox Tablet	Active	28-MAR-2002	Iron Chelation Treatment
NDA 21882	Novartis	Exjade (deferasirox	Approved	02-NOV-2005	Treatment of Chronic Iron Overload due to Blood Transfusion

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
None			

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				No statistical analysis of drug product stability data deemed necessary.
EES	Site inspections		OC	Overall Recommendation – Acceptable. See 25-SEP-2014 Recommendation.
Pharm/Tox	Drug substance, drug product impurity qualification (organic and inorganic)		Ramadevi Gudi	Refer to Pharm/Tox Review. Deferasirox DS is the same as the approved NDA 21-882 and no changes have been made since the approved date 02-NOV-2005. Recommendation: Acceptable. See Pharm/Tox Memo dated 26-AUG-2014

Biopharm	In-vivo Bioeqivalence Waiver		Banu Zolnik	Recommendation: Pending
OSE/DMEPA	Labeling consult		N. Vora	Recommendation: Acceptable See Label and Labeling Review dated 23-SEP-2014.
Methods Validation	Method Validation for HPLC methods used for ID, Assay, and Related Substances			Analytical Methods remain the same as NDA 21-882. No validation deemed necessary
EA	Categorical Exclusion (See Review)		J. Jee	***Acceptable***
Microbiology	Oral Dosage Form		B. Riley	Recommendation: Approval See Memo dated 31-JUL-2014

The Chemistry Review for NDA 206910

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From CMC perspective, this application is approvable pending recommendation from Biopharmaceutics. EES has an overall "Acceptable" recommendation for this NDA.

Review of the package insert labeling and container and carton labels are found adequate by DMEPA and CMC.

An expiration dating period of 24-month is granted for Deferasirox Film-Coated Tablets (30 tablets bottle) when stored at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). Protect from moisture. An expiration dating period of 6 months is granted for Deferasirox Film-Coated, Physician Samples (4 tablets bottle).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessment

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

Deferasirox is manufactured by (b) (4). It is proposed as an iron chelating agent and consists of (b) (4). Deferasirox (ICL670) drug substance is a white to slightly yellow powder, (b) (4) that is insoluble in water at room temperature. (b) (4) Complete CMC information regarding deferasirox drug substance has been submitted in *NDA 21882*. This NDA was approved on 02-NOV-2005.

Stability studies on three (3) prototype batches (commercial scale) and four (4) supportive batches at accelerated storage conditions 40°C/75% RH, six (6) months), and at long-term storage conditions (25°C/60% RH), up to 60 months were submitted to support the stability of the drug substance. The assay of one of the three batches was found out of specification at the (b) (4) months period; however, the assay results at the 60 month period met the drug substance specification. In addition, photostability, forced degradation, heat stability and hygroscopicity were studied (b) (4).

The retest date requested for deferasirox is (b) (4) ***months*** ("Do not store (b) (4) C") and it is based on accumulated ICH stability data. Based on the data submitted, the stability data supports the retest period of (b) (4) months and it is granted.

Drug Product

The drug product is an immediate release, film-coated tablets.

The description of the proposed tablets is as follows:

a) Strengths: 90 mg, 180 mg, and 360 mg of deferasirox

b) Color: Light blue, medium blue, and dark blue, respectively
c) Dimension: 10.7 x 4.2 mm, 14 x 5.5 mm, and 17 x 6.7 mm, respectively
d) Other appearance: unscored ovaloid film-coated tablet with beveled edges, debossed with "NVR", on one side and "90", "180", and "360", respectively on a slight upward slope between two debossed curved lines on the other side.

The excipients used in the formulation are USP/NF ingredients: microcrystalline cellulose (b) (4) and (b) (4), crospovidone, povidone K30, magnesium stearate, colloidal silicon dioxide, poloxamer, and opadry blue, a common pharmaceutical colorant.

(b) (4)

The applicant submitted their proposed Quality by Design (QbD) and Quality Risk Management (QRM) principles in the manufacturing process development plan follow. Refer to Memorandum from D. Ghosh, Ph.D. dated Nov 20, 2014.

The stability data for 3 batches each of 90 mg, 180 mg and 360 mg strength covering storage periods up to 12 months in HDPE bottles is submitted in this application. Stability studies conducted under ICH Long-term (25°±2°C/60±5% RH, 12 M), accelerated (40°±2°C/75±5% RH, 6M) as well as 5°C (6M), -20°C (6M), and 50°C (1M) storage conditions demonstrated that the drug is very stable under the intended storage conditions, i.e., 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). Protect from moisture. The proposed 24 month shelf-life is deemed acceptable.

The applicant also provided stability data for 3 batches each of 90 mg, 180 mg, and 360 mg strength covering storage periods up to 3 months in HDPE bottles. Stability studies conducted under ICH Long-term (25°±2°C/60±5% RH, 3 M), and accelerated (40°±2°C/75±5% RH, 3M) storage conditions demonstrated that the drug is very stable under the intended storage conditions, , i.e., 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). Protect from moisture. The applicant did not propose a shelf-life; however, based on the submitted data, a 6-month shelf-life can be granted.

Note: The acceptance criteria for dissolution testing are under review by B. Zolnik, Ph.D., Biopharm. Reviewer. Refer to her review.

B. Description of How the Drug Product is Intended to be Used

Deferasirox is indicated for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. The recommended daily dose of Jadenu for patients 2 years of age and older is as follows:

JADENU Film-coated Tablets (blue oval tablet)

Transfusion-Dependent Iron Overload	
Starting Dose	14 mg/kg/day
Titration Increments	3.5–7 mg/kg
Maximum Dose	28 mg/kg/day
Non-Transfusion-Dependent Thalassemia Syndromes	
Starting Dose	7 mg/kg/day
Titration Increments	3.5–7 mg/kg
Maximum Dose	14 mg/kg/day

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, Novartis Pharmaceuticals Corp. has submitted sufficient CMC _____ information to support approval of the drug. There are no outstanding deficiencies with the application. The referenced NDA 21882 for defesiranox drug substance has been reviewed and found to be adequate to support the NDA. An overall "Acceptable" recommendation was made by the Office of Compliance for the pre-approval inspection of the NDA. However, this application is approvable pending recommendation from Biopharmaceutics recommendation.

III. Administrative

This NDA was submitted in electronic as a 505(b)(1) application. A Quality Overall Summary is included in the application.

A. Reviewer's Signature

Electronically, in DFS

B. **Endorsement Block**

See DFS

C. CC Block

See DFS

53 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

PACKAGE INSERT LABELING:
***Dosage Forms and Strengths*: Acceptable**
Film-coated Tablets, 90 mg, 180 mg, and 360 mg.

***Description* -Acceptable**

***How supplied/Storage and Handling* – Acceptable**

Evaluation: Acceptable
The container labels, sample, physician sample carton labeling, and physician sample container labeling and the package insert submitted in this application are acceptable from the CMC perspective.

B. Environmental Assessment or Claim of Categorical Exclusion

As set forth in 21 CFR Part 25.31(a), action on a New Drug Application is categorically excluded from the requirement to prepare an Environmental Assessment or an Environmental Impact Statement if the action does not increases the use of the active moiety. "Increased use", as defined in 21 CFR Part 25.5(a), will occur if the drug is "administered at higher dosage levels, for longer duration or for different indications than were previously in effect, or if the drug is a new molecular entity."

Novartis Pharmaceuticals Corporation has filed a New Drug Application for a new film-coated tablet formulation of deferasirox. Currently the recommended starting dose of deferasirox as Exjade tablets for oral suspension is 20 mg per kg and is available as 125, 250 and 500 mg dispersible tablets. The new strength-adjusted film-coated tablet will be dosed at a starting dose of 14 mg per kg and will be made available as 90, 180 and 360 mg tablet.

Novartis Pharmaceuticals Corporation certifies that this submission for deferasirox film coated tablets qualifies for a categorical exclusion in accordance with 21 CFR Part 25.31(a) as the concentration of the active moiety, deferasirox, will be not be increased.

Further, Novartis Pharmaceuticals Corporation states that, to the best of its knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment and would thus require the preparation of at least an Environmental Assessment

Evaluation: Adequate. No further action is necessary.

APPEARS THIS WAY ON ORIGINAL

LIST OF COMMENTS
None

ATTACHMENT A:

Application	NDA 206910/000							
Sponsor	NOVARTIS PHARMS CORP							
Status	PN							
FEI	3002653483	(b) (4)	2416082	3002865753	3002653483	3002807776	(b) (4)	2416082
CFN	9692043		2416082	9692042	9692043	9612715		2416082
Establishment	NOVARTIS PHARMA STEIN AG		NOVARTIS PHARMACEUTICALS CORP	NOVARTIS PHARMA STEIN AG	NOVARTIS PHARMA STEIN AG	NOVARTIS RINGASKIDDY PHARMA LTD.		NOVARTIS PHARMACEUTICALS CORP
Address	SCHAFFHAUSERSTRASSE 101 STEIN / CHE SCHAFFHAUSERSTRASSE 101		25 OLD MILL ROAD SUFFERN NY/10901 USA	ROTHAUSWEG SCHWEIZERHALLE / BASEL-LANDSCHAFT CHE ROTHAUSWEG	SCHAFFHAUSERSTRASSE 101 STEIN / CHE SCHAFFHAUSERSTRASSE 101	RINGASKIDDY RINGASKIDDY / IRL CORK		25 OLD MILL ROAD SUFFERN NY/10901 USA
Country	CHE		USA	CHE	CHE	IRL		USA
Profile	TCM		TCM	CSN	CSN	CTL		CTL
Stage	DRUG SUBSTANCE,FINISHED DOSAGE		FINISHED DOSAGE	DRUG SUBSTANCE	DRUG SUBSTANCE,FINISHED DOSAGE	DRUG SUBSTANCE		FINISHED DOSAGE
Process	(b) (4)		PACKAGER,RELEASE TESTER,STABILITY TESTER	MANUFACTURER	(b) (4)	STABILITY TESTER		PACKAGER,RELEASE TESTER,STABILITY TESTER
Last Milestone	OC RECOMMENDATION		OC RECOMMENDATION	OC RECOMMENDATION	OC RECOMMENDATION	OC RECOMMENDATION		OC RECOMMENDATION
Compliance Status	AC		AC	AC	AC	AC		AC
Milestone Date	9/2/2014		6/30/2014	6/30/2014	9/2/2014	6/30/2014		6/30/2014
OAI Alert Status	"NONE"		"NONE"	"NONE"	"NONE"	"NONE"		"NONE"
EER Re eval Date	3/25/2016		2/11/2018	9/25/2015	3/25/2017	3/28/2017		2/11/2017
Overall Recommendation	Acceptable							
Decision Date	10/14/2014 (in Panorama)							
Overall Re eval Date	9/25/2015							

Josephine Jee

Josephine M. Jee -A

Digitally signed by Josephine M. Jee -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=13000222 33, cn=Josephine M. Jee -A
Date: 2014.12.03 11:15:21 -05'00'

Ali Al Hakim

MEMORANDUM

Date: Nov 20, 2014

TO: NDA 206910

FROM:
DEBASIS GHOSH, Ph.D., M. Pharm., Senior Reviewer,
ONDQA/OPS/CDER/FDA

THRU:
ALI AL-HAKIM, Ph.D., Branch Chief, ONDQA/OPS/CDER/FDA

SUBJECT: EVALUATION OF THE PROPOSED MANUFACTURING PROCESS & DESIGN SPACE FOR DRUG PRODUCT

Novartis ('the sponsor') has submitted a New Drug Application (NDA) under 505(b)(1) of FDCA 21 CFR 314.50 for deferasirox (ICL670) film-coated tablets for the treatment of chronic iron overload due to blood transfusions and non-transfusion dependent thalassemia. Deferasirox is an orally active chelator that is selective for ferric ion. The drug was first approved in 2005 under the trademark of Exjade and is currently formulated as a dispersible tablet. In this NDA, Novartis proposed a new dosage form, a film-coated tablet. The sponsor reasoned that tablet is easy to swallow and will improve patient compliance. In addition, based on the bioavailability study, the sponsor proposed a lower strength for film-coated tablets compared to commercially available dispersible Exjade tablets.

The sponsor employed Quality by Design (QbD) and Quality Risk Management (QRM) principles in the manufacturing process development in line with ICHQ8, Q9, and Q10 guidances. The manufacturing process development plan follows classical QbD approach:

- Quality Target Product Profile
- Risk assessment
- Design of experiment (DoE)
- Design space
- Verification at full scale
- Continual verification

Quality Target Product Profile:
The quality target product profile is to develop a physically and chemically stable solid, oral dosage form which is easy to swallow and will improve patient compliance. After carefully considering several

CONCLUSION and RECOMMENDATIONS:

The proposed 'Full Scale Design Space' as described in Sec 3.2.P.3.4 is acceptable. The sponsor considered a (b) (4) approach to define the design space. Inclusion of a non-critical process parameter (b) (4) is justified due to its potential impact on product quality when combined with another variable (b) (4). The proposed control strategy and manufacturing settings for CPPs and non-CPPs are adequate. The proposed plan for continual verification of the manufacturing process during the life cycle of the product is adequate.

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

/s/

DEBASIS GHOSH
11/20/2014

ALI H AL HAKIM
11/20/2014

Overall Manufacturing Inspection Recommendation

Edit Custom Form

Custom Form
Facility Inspection - Overall Application Recommendation

Facility Inspection - Overall Application Recommendation

Facility Inspection - Overall Application Recommendation
Approve

Facility Inspection - Overall Application Re-evaluation Date
9/25/15

Navigation Links

Form Link
http://panorama.fda.gov/task/view?ID=5424761800c2f01b1288bc3549fe8f14&activeTab=content-dashboard__5418eab10003b6cd5f0c5f929c4fa823

Assigned To
Juandria Williams
Edit Assignment

This was done on
Oct 14, 2014
(167 days ago)

Status
Complete

This task is waiting on
Facilities

Last Update	Submitted On
Oct 14, 2014	Sep 25, 2014

Reference Number
2089257