CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207968Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 207968
Review #1

Drug Name/Dosage Form	Jadenu Sprinkle
Strength	90 mg, 180 mg and 360 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Norvartis Pharmaceutical, Corp.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	21-Jul-16	All
Amendment (SD 0011)	06-Jan-17	Process
Amendment (SD 0007)	28-Oct-16	Process
Amendment (SD 0006)	07-Mar-17	Process
Amendment (SD 0010)	17-Jan-17	DP
Amendment (SD 0013)	30-Jan-17	DP
Amendment (SD 0014)	06-Mar-17	DP
Amendment (SD 0015)	22-Mar-17	DP

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Haripada Sarker	Benjamin Stevens
Drug Product	Amit Mitra	Anamitro Banerjee
Process	Yuansha Chen	Neal Sweeney
Microbiology	n/a	n/a
Facility	Wayne Seifert	Ruth Moore
Biopharmaceutics	Banu Zolnik	Okponanabofa Eradiri
Regulatory Business Process Manager	Rabiya Laiq	n/a
Application Technical Lead	Sherita McLamore	n/a
Environmental	Amit Mitra	Anamitro Banerjee

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III	(b) (4)		N/A	No Review	Adequate information provided in the NDA

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	206910	Jadenu Film coated tablets
NDA	21882	Exjade dispersible tablet
IND	58,554	deferasirox dispersible tablet

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of the NDA 207968 for Jadenu® Sprinkle (deferasirox) granules 90, 180 and 360 mg. As part of this action, OPQ grants a (b) (4) re-test period for the drug substance when stored at 25ºC/60%RH and a 36-month drug product expiration period when stored a USP controlled room temperature conditions 15°C to 30°C (59°F to 86°F). There are no outstanding issues and no post-approval quality agreement to be conveyed to the applicant.

II. Summary of Quality Assessments

A. Product Overview

The drug product, Jadenu® Sprinkle (deferasirox) granules, is being developed for Iron overload due to blood transfusions. Deferasirox, is currently approved in a tablet for suspension, film coated tablet (FCT), injectable and in a solution formulation and the drug product has orphan designation. Deferasirox is an oral iron chelator and was the first oral medication approved in the USA for this purpose. The new sprinkle formulation is being developed to improve palatability and patient compliance, and provides administration advantages for patients who are unable to swallow whole tablets. (b) (4) the film coated tablets and the granules contain the same excipients in the same proportions. Crushing the FCT was an option approved in the label to facilitate administration to younger patients and patients that had difficulty in swallowing tablets. The new sprinkle formulation provides administration advantages as there is no need for caregivers to manually crush the tablets. The applicant made reference to NDA 21-882 for the drug substance, NDA 206-910 for the FCT, and IND 58,554 for the original investigation of the active (all of which are owned by the applicant). NDA 21-882 was originally approved on November 2, 2005. NDA 206-910 was approved on March 30, 2015.

The dosing regimen for Jadenu® Sprinkle consists of an initial dose of 14 mg/kg/day up to 28 mg/kg/day for the treatment of transfusion-dependent Iron overload and 7 mg/kg/day up to 14/mg/kg/day for non-transfusion dependent thalassemia syndromes. The drug product should be administered by sprinkling the full dose on soft foods such as yogurt or apple sauce at the same time each day. The transition from the tablets for oral suspension to the granules should be about 30% lower, rounded to the nearest whole sachet.

Based on the information provided in this application (original submission and in responses to information requests), OPQ considers all review issues adequately addressed and potential risks to patient safety, product efficacy, and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 207968 and grants a (b) (4) re-test period for the drug substance and a 36-month drug product expiration period when stored under controlled room temperature in the commercial packaging.

Proposed Indication(s) including Intended Patient Population	Treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older 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 concentration (LIC) of at least 5 milligrams of iron per gram of liver dry weight (mg Fe/g dw) and a serum ferritin greater than 300 mcg/L
Duration of Treatment	Undefined
Maximum Daily Dose	28 mg/kg mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance

Deferasirox drug substance is a white to slightly yellow non-hygroscopic powder. It has no chiral centers. The drug substance is achiral and exhibits polymorphic behavior (b) (4).

Complete CMC information for the deferasirox drug substance is cross-referenced to the approved NDA # 21-882 for Exjade® which is owned by the applicant. Based on the stability data a (b) (4) retest period has been established.

Drug Product

The drug product is presented as white (b) (4) granules containing the active, microcrystalline cellulose, crospovidone, povidone K30, poloxamer 188, magnesium stearate and colloidal silicon dioxide packaged in (b) (4) sachets (b) (4) (b) (4). Each sachet contains 90 mg, 180 mg or 360 mg deferasirox in (b) (4) foil sachet (b) (4) (b) (4). The 90, 180 and 360 mg drug products use identical granules and the same size sachets and differ only in the quantity granules in the sachet. The granule formulated using the same composition as the Jadenu® film coated tablets (b) (4). There are no novel excipients or excipients of human or animal origin used in the formulation. The granule dosage form was developed to improve palatability and patient compliance. For administration, the granule formulation can be sprinkled on soft food such as apple sauce or yogurt and administered orally.

The drug product is manufactured, packaged and release tested (b) (4) (b) (4) at a commercial batch size (b) (4) (b) (4) (b) (4)

The proposed specification for the drug product, together with controls for impurities

in the drug substance are adequate to ensure that the critical quality attributes of this product are well controlled. Twenty-four months of primary stability data was included for 3 pilot scale batches each of the 90, 200 and 400 mg strengths of the drug product. The 90, 200 and 400 mg strengths bracket the 180 and 360 strengths as all strengths use the same granules, are dose proportional and are filled in the same size sachet. The available stability data supports a ***36 month shelf-life when stored under controlled room temperature***.

Process

(b) (4)

(b) (4) The commercial batches will be manufactured in strengths of 90 mg, 180 mg, and 360 mg with a batch size (b) (4) which was the target size of the pre-validation batches. The description of the manufacturing process includes appropriate in-process controls and operating parameters

Biopharmaceutics

The applicant included data from the PK, dose proportionality and food effect studies evaluating the relative bioavailability of deferasirox granules and Exjade tablets and PK/PD analysis in patients. Results of the aforementioned studies will be reviewed by the Office of Clinical Pharmacology (OCP).

The applicant completed a BE study for the 90 mg and requested a biowaiver request for the 180 mg and 360 mg strengths. The biowaiver request for the 180 mg and 360 mg strengths is granted provided OCP finds the outcome of Study F1102 –Part 1 (with the 90 mg strength) is acceptable.

The proposed dissolution method (USP Apparatus 2 (paddle) at 75 rpm) is acceptable.

Facilities

Adequate descriptions were provided for all sites. Following a review of the application, inspectional documents, and pre-approval inspection results, there are no significant, outstanding manufacturing or facility risks that prevent the approval of this application. The Overall Manufacturing Inspection Recommendation is approval.

Environmental Assessment

The applicant claims that NDA, if approved, will increase the use of the active moiety,

deferasirox. However, a claim for categorical exclusion from conducting an environmental impact statement (EIS) or environmental assessment (EA) is made under 21 Code of Federal Regulations (CFR) Sections 25.31(b) on the basis that estimated concentration of the active moiety into the aquatic environment is less than 1 part per billion (ppb).

The claim of categorical exclusion from an environmental assessment is valid since the estimated increase usage of the active moiety is well below the allowable EIC of 1 part per billion (ppb).

The request for categorical exclusion is granted.

C. Special Product Quality Labeling Recommendations (NDA only)

n/a

D. Final Risk Assessment

Included drug product section of this IQA.

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LABELING

{For NDA only}

R Regional Information (NDA 207-968)

1.14 Labeling

1. Package Insert: Is being conducted with the labeling review. ***

(a) "Highlights" Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: Jadenu Sprinkle Established Name: Deferasirox granules	Satisfactory
Dosage form, route of administration	Granules, Oral	Satisfactory
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Granules, 90, 180, 360 mg deferasirox/sachet	Satisfactory

Conclusion: The highlight is satisfactory with respect to proprietary and established name, dosage form and strengths.

(b) "Full Prescribing Information" Section

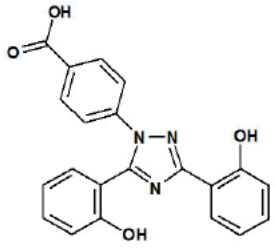
 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Granules	Satisfactory
Strengths: in metric system	90, 180 and 360 mg	Satisfactory
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	White to almost white granules	Satisfactory

Conclusion: This section will be modified according to PLR, if needed.

#11: Description (21CFR 201.57(c)(12))

JADENU (deferasirox) is an iron chelating agent provided as a tablet for oral use. Deferasirox is designated chemically as 4-[3,5-bis(2-hydroxyphenyl)-1H-1,2,4-triazol-1-yl]benzoic acid and has the following structural formula:



Deferasirox is a white to slightly yellow powder. It has a molecular formula $C_{21}H_{15}N_3O_4$ and molecular weight of 373.4.

JADENU granules contain 90 mg, 180 mg, or 360 mg deferasirox. Inactive ingredients include microcrystalline cellulose, crospovidone; povidone (K30), magnesium stearate, colloidal silicon dioxide, poloxamer (188).

Reviewer's Assessment: The paragraph above should read as follows: "JADENU Sprinkle (deferasirox) granules contain---poloxamer (188)" instead of "JADENU granules contain---poloxamer (188)" since the proprietary name is JADENU Sprinkles". The applicant made the changes to the proprietary name as requested in an amendment.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Proprietary name: Jadenu Sprinkles Established name: deferasirox granules	Satisfactory
Dosage form and route of administration	Tablets, Oral	Satisfactory**
Active moiety expression of strength with equivalence statement for salt (if applicable)	"JADENU granules contain 90 mg, 180 mg, or 360 mg deferasirox"	Satisfactory after change to: "JADENU Sprinkle (deferasirox) granules contain 90 mg, 180 mg, or 360 mg deferasirox"
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	See the text above under description section	Satisfactory for oral granule dosage form
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	Iron chelating agent	Satisfactory
Chemical name, structural formula, molecular weight	Yes	Satisfactory
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	Yes	Satisfactory

Conclusion: The applicant has not included the physical properties such as pKa, solubility or pH. This information is also not part of other Jadenu dosage form labelings. However, this information may be important for compounding purposes. Therefore, this item was consulted with the clinical division . Based on the conversation with the OND, the description section was changed from: "Deferasirox is a white to slightly yellow powder. It has a molecular formula C21H15N3O4 and molecular weight of 373.4" to Deferasirox is a white to slightly yellow powder. It has a molecular formula $C_{21}H_{15}N_3O_4$ and molecular weight of 373.4. It is insoluble in water with a pH of 4.1". The applicant made the appropriate changes to the PI.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

JADENU 90 mg granules are white to almost white granules in sachet. They are available in cartons of 30 sachets. (NDC 0078-0727-15).
JADENU 180 mg granules are white to almost white granules in sachet. They are available in cartons of 30 sachets. (NDC 0078-0713-15).
JADENU 360 mg granules are white to almost white granules in sachet. They are available in cartons of 30 sachets. (NDC 0078-0720-15).
Store JADENU granules at 25°C (77°F); excursions are permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture

(b) (4)

Reviewer's Assessment: The proprietary name of the drug product is "Jadenu Sprinkles" and not "Jadenu". The statements in the "How Supplied" section should reflect that. There is no need to add the established name since the other label for Jadenu does not contain the established name. If the established names are to be added, all the labels should be consistent. The reviewer recommends the following language instead of the one above the "How Supplied" section: JADENU Sprinkles, 90 mg granules are white to almost white granules in sachet. They are available in cartons of 30 sachets. (NDC 0078-0727-15). JADENU Sprinkles, 180 mg granules are white to almost white granules in sachet. They are available in cartons of 30 sachets, (NDC 0078-0713-15). JADENU Sprinkles, 360 mg granules are white to almost white granules in sachet. They are available in cartons of 30 sachets, (NDC 0078-0720-15). These changes were included in the latest copy of the label.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	90, 180 and 360 mg granules	Satisfactory
Available units (e.g., bottles of 100 tablets)	90, 180 and 360 mg granules in sachets/30 sachets per carton	Satisfactory
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC number is provided	The drug product is a "granule" and not a "tablet" dosage form. Therefore, shape, scoring, imprinting are not relevant.
Special handling (e.g., protect from light, do not freeze)	The drug product is not light sensitive. It is protected from moisture by packaging in sachets.	Satisfactory
Storage conditions	Store at controlled room temperature, 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].	Satisfactory

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Distributors name and address included: Distributed by: Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936	Satisfactory

Immediate Container Label

90 mg deferasirox granules

Reviewer's Assessment:

The applicant provided the following required items: Established name, dose strength with a wrong statement initially referring it as a base (which is subsequently corrected), route of administration, prescription only, lot #, bar code, and expiration date. DMEPA may have additional comments. These items were included in the revised mock up.

APPEARS THIS WAY ON ORIGINAL

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Proprietary name: Jadenu Sprinkle Established name: deferasirox granules	Satisfactory
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	The term (b) (4) in the expression of strength is incorrect.	The following statement should be changed from (b) (4) to: "each sachet contains 162 mg granule equivalent to 90 mg deferasirox". The revised mock up contains the requested change.
Net contents (21 CFR 201.51(a))	None	Satisfactory
Lot number per 21 CFR 201.18	None	Satisfactory
Expiration date per 21 CFR 201.17	None	Satisfactory
"Rx only" statement per 21 CFR 201.100(b)(1)	None	Satisfactory
Storage (not required)	None	Satisfactory
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	None	Satisfactory
Bar Code per 21 CFR 201.25(c)(2)**	None	Satisfactory
Name of manufacturer/distributor	None	Satisfactory
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Reviewer's Assessment: Change the following statement from [redacted] (b) (4) to: "each sachet contains 162 mg granule equivalent to 90 mg deferasirox". Similar comments apply to sachets for other strengths. In an amendment, the applicant made the requested changes.

Carton Labeling

[redacted] (b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Proprietary name- Jadenu Sprinkles: Satisfactory Established name: Satisfactory	See immediate container label comment
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Not Satisfactory	The applicant was requested to change the following statement from (b) (4) (b) (4) (b) (4) "each sachet contains 162 mg granule equivalent to 90 mg deferasirox". Similar comments apply to sachets for other strengths. The changes were made.
Net contents (21 CFR 201.51(a))	None	Satisfactory
Lot number per 21 CFR 201.18	None	Satisfactory
Expiration date per 21 CFR 201.17	None	Satisfactory
Name of all inactive ingrédients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	The names of inactive ingredients are not required to be present for this solid oral dosage form. However, since this drug product is used in pediatric patients with unknown allergic reactions for individual inactive components, an IR was sent with the request to list all inactive ingredients on the carton label. See the discussion in the Reviewer's comment below.	**See the discussion in the Reviewer's comment below.**
Sterility Information (if applicable)	N/A	**Satisfactory**
"Rx only" statement per 21 CFR 201.100(b)(1)	None	Satisfactory
Storage Conditions	None	Satisfactory

NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	None	Satisfactory
Bar Code per 21 CFR 201.25(c)(2)**	None	Satisfactory
Name of manufacturer/distributor	None	Satisfactory
"See package insert for dosage information" (21 CFR 201.55)	Referenced	Satisfactory
"Keep out of reach of children" (optional for Rx, required for OTC)	None	Satisfactory
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	None	Satisfactory.

Reviewer's Assessment:

The applicant was requested to change the following statement from (b) (4) (b) (4) to: "each sachet contains 162 mg granule equivalent to 90 mg deferasirox". Similar comments apply to sachets for other strengths. This change was made by the applicant in the revised labeling.

The names of inactive ingredients are not required to be present for this solid oral dosage form. However, since this drug product is used in pediatric patients with unknown allergic reactions for individual inactive components, an IR was sent with the request of listing of all inactive ingredients on the carton label. The applicant responded to this deficiency stating that the other dosage forms of deferasirox such as "Exjade (deferasirox) tablet for suspension" and "Jadenu (deferasirox) tablets, film coated" does not have inactive ingredient listed on carton. Also, since it is an oral formulation there is no CFR requirement to place the inactive ingredients on the carton labeling". The applicant wanted to know whether there is a new ruling on this matter". The OPQ responded that the inactive ingredient listing is optional and not required by law.

List of Deficiencies: **None**

Primary Labeling Reviewer Name and Date: Amit K. Mitra, Ph. D/4/7/17

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Anamitro Banerjee, PhD. 4/7/2017

APPEARS THIS WAY ON ORIGINAL

Amit Mitra

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BIOPHARMACEUTICS

Product Background:

NDA: 207698-ORIG-1

Drug Product Name / Strength: Jadenu® Sprinkle (deferasirox) granules, 90 mg, 180 mg and 360 mg

Route of Administration: Oral

Applicant Name: Novartis Pharma Corp

Review Summary:

Deferasirox is an iron chelator indicated for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older and for the treatment of chronic iron overload in patients 10 years of age and older with non-transfusion dependent thalassemia syndromes and with a lower iron (Fe) concentration (LIC) of at least 5 mg Fe per gram of dry weight and serum ferritin greater than 300 mcg/L.

NDA 21882 Exjade® (deferasirox) tablets for oral suspension, 125 mg, 250 mg, and 500 mg, approved on 7/7/2005, is the listed drug.

NDA 206910 Jadenu® (deferasirox) film-coated tablets , 90 mg, 180 mg, and 360 mg, developed by Novartis to overcome the palatability issues observed with Exjade, was approved by FDA on 3/30/2015.

The proposed drug product NDA 207698 Jadenu® Sprinkle (deferasirox) granules is developed for patients who have difficulty swallowing whole tablets. The proposed drug product is to be administered by sprinkling on soft food (e.g. yogurt or apple sauce) immediately prior to use.

In this submission, The Applicant included data from the PK, dose proportionality and food-effect studies (Study F1102 PK study; Study 2106-Food effect; Study 2104-dose proportionality; Study F2105 granules vs Exjade; PK/PD analysis) evaluating the relative bioavailability of deferasirox granules and Exjade tablets and PK/PD analysis in patients. Study F1102-Part 1 is the pivotal study for this application. Results of the aforementioned studies will be reviewed by the Office of Clinical Pharmacology (OCP).

The biowaiver request for the 180 mg and 360 mg strengths is granted provided OCP finds the outcome of Study F1102 –Part 1 (with the 90 mg strength) acceptable.

The following dissolution method and acceptance criterion have been assessed and found acceptable for QC (quality assurance) purposes for batch release and stability testing. The

method below is the same method used in the NDA 206910 Jadenu® (deferasirox) film-coated tablets.

USP Apparatus	Rotation Speed	Medium Volume	Medium/ Temperature	Final Acceptance Criterion
USP II (paddle)	75 rpm	900 mL	Phosphate Buffer pH 6.8 with 0.5% Tween 20 at 37 ± 0.5°C	Q= (b) (4) at 15 min

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 207968 for Jadenu® Sprinkle (deferasirox) granules, 90 mg, 180 mg and 360 mg is recommended for **APPROVAL.**

REVIEW

The Biopharmaceutics review is focused on: 1) The evaluation and acceptability of the dissolution method and acceptance criterion; and 2) Biowaiver request for the 180 mg and 360 mg strengths.

Drug Substance

Deferasirox is a white to slightly yellow powder. Deferasirox is insoluble in water at room temperature. (b) (4)

(b) (4)

(b) (4). The table below shows the solubility of deferasirox in different media and surfactant type. The Applicant chose pH 6.8 Phosphate Buffer with 0.5% Tween 20 as the dissolution media due to higher solubility of deferasirox in this media as compared to the other media tested.

Table 2-3 Solubility of deferasirox as a function of surfactant at pH 6.8 and 7.8

Medium	Solubility (mg/mL) at room temperature (approx. 25°C)
USP buffer pH 6.8	0.04
USP buffer pH 6.8 + 0.4% CTAB	0.02
USP buffer pH 6.8 + 0.5% Tween 20	0.42
USP buffer pH 7.8	Not determined
USP buffer pH 7.8 + 0.5 % LDAO	0.029 (not significant due to gel formation)
USP buffer pH 7.8 + 0.4 % CTAB	0.106
USP buffer pH 7.8 + 0.1 % Tween 20	0.77
USP buffer pH 7.8 + 0.5 % Tween 20	1.38

CTAB Cetyltrimethylammonium bromide
LDAO Lauryldimethylamine-n-dioxide
Tween Polyoxyethylene sorbitan

Drug Product

The proposed drug product, Deferasirox granules are an immediate release dosage form. The composition information is shown below. The proposed drug product is packaged in sachets. The product has three strengths, 90 mg 180 mg, and 360 mg. These three strengths only differ in the amount of granules in the sachet.
The proposed Jadenu® sprinkled granules and the approved Jadenu® contain the same excipients in the same proportions. Jadenu® film coated tablets use the same granule formulation; the granules are compressed to tablet core and coated with coating premix to manufacture Jadenu film-coated tablets.

Table 1. Composition of deferasirox granules, 90 mg, 180 mg and 360 mg

Table 2-1 Composition of Deferasirox 90 mg, 180 mg and 360 mg granules

Ingredient	Amount per 90 mg granules (mg)	Amount per 180 mg granules (mg)	Amount per 360 mg granules (mg)	Function	Reference to standards
(b) (4)					
Deferasirox (b) (4)	90.00	180.00	360.00	Drug substance	Novartis monograph
(b) (4)				(b) (4)	
Microcrystalline cellulose (b)					Ph.Eur., USP/NF
Crospovidone					Ph.Eur., USP/NF
Povidone K30					Ph.Eur., USP/NF
Poloxamer 188					Ph.Eur., USP/NF
					(b) (4)
(b) (4)					
Microcrystalline cellulose, (b) (4)				(b) (4)	Ph.Eur., USP/NF
Crospovidone					Ph.Eur., USP/NF
Magnesium stearate (b) (4)					Ph.Eur., USP/NF
(b) (4)					
Colloidal silicon dioxide					Ph.Eur., USP/NF
					(b) (4)

List Submissions being reviewed:

Original dated 07/21/2016

Dissolution Method and Acceptance Criteria:

The Applicant proposes the approved dissolution method for Jadenu® film coated tablets (NDA 206910). The Applicant provided adequate information to support the validity of the analytical methods used to evaluate the dissolution samples of deferasirox. The detailed information is included in the following link \\cdsesub1\evsprod\nda207968\0000\m3\32-body-data\32p-drug-prod\jadenu-granules\32p5-contr-drug-prod\32p53-val-analyt-proc\val-dissoln-hplc.pdf.

USP Apparatus	Rotation Speed	Medium Volume	Medium/ Temperature	Proposed Acceptance Criterion
USP II (paddle)	75 rpm	900 mL	Phosphate Buffer pH 6.8 with 0.5% Tween 20 at 37 ± 0.5°C	Q= (b) (4) at 15 min

The Applicant evaluated the impact of paddle speed, dissolution medium as part of dissolution method development.

(b) (4)

Reviewer's Assessment

The dissolution method and acceptance criterion are acceptable since the Applicant used the same dissolution method as the approved film coated tablet. Jadenu® film coated tablets use the same granule formulation; (b) (4) (b) (4). Based on the dissolution data the coating did not impact the dissolution profiles of the deferasirox tablets.

In-Vitro Soft-food Interaction Study

Stability of deferasirox was evaluated in plain yogurt and apple sauce by determining the assay and degradation products after mixing with the vehicles over a period of time (0, 0.5, 4 and 24 hours). In addition, the suitability of yogurt and apple sauce as delivery vehicles was evaluated in the registration stability program. Samples from one batch of each strength of deferasirox granules at 0, 6, 12 month in apple sauce and 24 month time point were tested both in apple sauce and yogurt. The in-use stability assessment will be made by the Drug Product Reviewer.

Biowaiver Request

Reviewer's Assessment:

The Applicant's biowaiver request for the 180 mg and 360 mg is granted based on the following reasons:

1) Acceptable BA/BE study on the 90 mg strength (OCP review is pending);
2) All three strengths of the proposed product contain the same granules and only differ in the amount of granules filled in the sachet;
3) Similar dissolution profiles between strengths.

Primary Biopharmaceutics Reviewer Name and Date:

4/10/2017
Banu S. Zolnik, PhD
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products

Secondary Reviewer Name and Date
04/10/2017
Okpo Eradiri, PhD.
Biopharmaceutics Team Lead
Division of Biopharmaceutics
Office of New Drug Products

Banu Zolnik

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Okponanabofa Eradiri

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MICROBIOLOGY

Product Background:

NDA: 207968

Drug Product Name / Strength:
Proprietary: Jadenu Sprinkle
Non-proprietary: Deferasirox
Non sterile granules, 90 mg, 180 mg, 360 mg

Route of Administration: Oral

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

Manufacturing Site:

(b) (4)

Method of Sterilization: N/A. Drug product is non-sterile.

Review Summary:
The submission is recommended for approval on the basis of sterility assurance.

List Submissions being reviewed (table):

Submit	Received	Review Request	Assigned to Reviewer
7/21/2016	7/21/2016	N/A	8/10/2016

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

Product Quality Microbiology Assessment

All of the information in this review relates to patient risk associated with a non-sterile drug product.

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – White to almost white granules.
- **Drug product composition** –

Ingredient	Amount per 90 mg granules (mg)	Amount per 180 mg granules (mg)	Amount per 360 mg granules (mg)	Function
(b) (4)				(b) (4)
Deferasirox (b) (4)	90.00	180.00	360.00	Drug substance
(b) (4) Microcrystalline cellulose (b) (4) Crospovidone Povidone K30 Poloxamer 188 (b) (4)	(b) (4)			(b) (4)
(b) (4)				(b) (4)
(b) (4) Microcrystalline cellulose, (b) (4) Crospovidone Magnesium stearate (b) (4) Colloidal silicon dioxide	(b) (4)			(b) (4)

- **Description of container closure system** –

Deferasirox 90 mg, 180 mg and 360 mg granules will be packaged in sachets, which are made of (b) (4) foil, (b) (4) (b) (4)

Reviewer's Assessment:

The drug product composition and container-closure system were adequately described. The container-closure system is adequate for the granule drug product for oral route of administration.

ADEQUATE

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- **Preservative Effectiveness –**

Drug product contains no preservative. Deferasirox granules is a solid oral dosage form which is typically not susceptible to microbiological growth.

Reviewer's Assessment: ADEQUATE

P.3 Manufacture

P.3.1 Manufacturer

(b) (4)

P.3.3 Description of the Manufacturing Process and Process Controls

- **Environmental monitoring including product bioburden –**

The applicant has not provided a description of environmental monitoring or the area classifications for the commercial production of the subject drug product. However, the subject drug product is a non-sterile granule for oral route. Therefore, patient risk is low from environmental contamination.

Reviewer's Assessment: ADEQUATE

P.5 Control of Drug Product

P.5.1 Specifications

Test	Acceptance Criteria	Method
Total Aerobic Microbial Count	NMT (b) (4) cfu/g	USP <61>
Total Yeast & Mold Count	NMT cfu/g	USP <61>
Escherichia coli	Absent	USP <62>

Suitability of the counting method was validated with *S. aureus*, *P. aeruginosa*, *B. subtilis*, *C. albicans*, A. *brasiliensis*. Grow was comparable with or without the presence of the drug product.

Suitability of the test for *E. coli* was validated. Grow was comparable with or without the presence of the drug product.

Reviewer's Assessment: The drug product specification (microbial limits testing) and test method validation/suitability comply with USP <61>, <62> and <1111>.

ADEQUATE

P.7 Container Closure System See section P.1.

P.8 Stability

P.8.1 Stability Summary and Conclusion

Proposed expiry: 36 months at 25ºC

P.8.2 Post-Approval Stability Protocol and Stability Commitment

Storage condition is 25°C/60% RH. Microbial limits test will be performed for the first three batches of each strength. Thereafter, stability testing will be performed on one batch of each strength annually.

Microbial Enumeration Testing (MET) will be performed at release and at expiry. It is indicated in P.5.6. "justification-of-specifications.pdf" that MET includes TAMC, TYMC and testing for *E. coli*.

Acceptable

P.8.3 Stability Data – See Section P.8.1.

Twenty-four (24) month stability data for 9 lots (3 lots for each strength) are provided. Both TAMC and TYMC met the acceptance criteria at different time points (6 months, 12 months and 24 months) for all lots. *E. coli* was absent at these time points.

Reviewer's Assessment: The submitted stability protocol, commitment and data comply with the Guidance for Industry: (1) Q1A(R2) Stability Testing of New Drug Substances and Products.

ADEQUATE

R REGIONAL INFORMATION

R.1 Executed Batch Record

The batch records for the following exhibit batches are provided: x2020915 (90 mg); x2050915 (180 mg); x2080915 (360 mg).

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)
MODULE 1

A. PACKAGE INSERT

Storage condition is 25°C; excursions permitted to 15-30ºC; protect from moisture.

JADENU granules should be administered by sprinkling the full dose on soft food (e.g. yogurt or apple sauce) immediately prior to use and administered orally.

Reviewer's Assessment: There is no extended hold time proposed after mixing the drug product with soft food. There is no concern with the drug product package insert instructions for product administration.

ADEQUATE

Primary Microbiology Reviewer Name and Date:

Yuansha Chen, Ph.D.

CDER/OPQ/OPF/DMA

11/15/2016

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Neal J. Sweeney, Ph.D.

CDER/OPQ/OPF/DMA

11/15/16

Neal Sweeney

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Yuansha Chen

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Sherita McLamore

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