# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 207968Orig1s000

# SUMMARY REVIEW

# Summary Review for Regulatory Action

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| **Date** | 05/17/17 |
| **From** | Albert Deisseroth MD, PhD, Associate Division Director |
| **Subject** | Division Director Summary Review |
| **NDA #/Supplement#** | NDA 207968 |
| **Applicant** | Novartis Pharmaceuticals Corp. |
| **Date of Submission** | July 21, 2016 |
| **PDUFA Goal Date** | 05/21/17 |
| **Proprietary Name/Proper Name** | Jadenu® Sprinkle |
| **Dosage Forms/Strength** | 14mg per kg body weight once daily for patients with transfusional iron overload<br>7mg per kg body weight once daily for patients with NTDT syndromes |
| **Recommendation** | Accelerated Approval |
| **Recommended Indication** | Treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older.<br>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 (Fe) concentration (LIC) of at least 5 mg Fe per gram of dry weight and a serum ferritin greater than 300 mcg/L. |

| Material Reviewed/Consulted | |
|---|---|
| Medical Officer Review | Andrew Dmytrijuk, MD, and Kathy Robie Suh, MD, PhD |
| Labeling Review | Gini Kwitkowski, RN |
| Non-Clinical | Ramadevi Gudi, PhD and Chris Sheth, PhD |
| Clinical Pharmacology | Sriram Subramaniam, PhD, and Stacy Shord, PhD |
| Clinical Microbiology | Yuansha Chen, PhD |
| OPQ CMC | Amit Mitra, PhD, Sherita McLamore, PhD and Animitro Banerjee, PhD |
| RPM | Suria Yesmin |

# Signatory Authority Review

## 1. Introduction/Executive Summary:

(This section is derived in part from the reviews for NDA 209191 of Dr. Andrew Dmytrijuk, Dr. Ramadevi Gudi, and Dr. Kathy Robie Suh.)

On July 21, 2016, Novartis Pharmaceuticals Corporation submitted NDA 207968 for deferasirox granules under the proposed trade name, JADENU® Sprinkle, for the following indicationa: a. the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older and b. 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. The Sponsor cross references the safety and efficacy of Exjade in NDA 21882 to support the current application for Jadenu Sprinkle NDA 207968.

Exjade in NDA 21882 was first approved by the United States Food and Drug Administration (FDA) in 2005 for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adult and pediatric patients (aged 2 years and over) at doses of up to 40 mg/kg/day.

In 2013, Exjade in sNDA 21882 was also approved for the treatment of chronic iron overload in patients with non-transfusion-dependent thalassemia (NTDT) syndromes aged 10 years and older at doses of up to 20 mg/kg/day.

Jadenu (NDA 206910) was approved in 2015, at a starting dose of 14 mg/kg orally once daily in patients with transfusional iron overload and 7 mg/kg orally once daily in patients with NTDT syndromes.

Exjade and Jadenu were approved under Accelerated Approval regulations and studies for conversion to regular approval have not yet been completed. No clinical efficacy or safety studies were conducted for this most recent application (NDA 207968).

The bioavailability based on area under the curve (AUC) of Jadenu Sprinkle was 52% greater than that of Exjade. The mean Cmax was increased by 34%. After strength-adjustment, 1080 mg of Jadenu Sprinkle was considered equivalent to 1500 mg of Exjade (deferasirox tablets for oral suspension) with respect to the mean AUC under fasting conditions.

The Sponsor therefore proposes a Jadenu Sprinkle starting dose of 14 mg/kg orally once daily in patients with transfusional iron overload and 7 mg/kg orally once daily in patients with NTDT syndromes. The proposed dosing of Jadenu Sprinkle is the same as that of Jadenu. These starting doses of Jadenu Sprinkle are equivalent to the Exjade recommended starting doses: 20 mg/kg orally once daily in patients with transfusional iron overload and 10 mg/kg orally once daily in patients with NTDT syndromes.

The new formulation JADENU® Sprinkle for oral administration is presented as two different dosage forms: granules packaged in sachets and a film-coated tablet (FCT).

Jadenu Sprinkle is a granule formulation of deferasirox, which offers patients with iron overload a potentially more palatable treatment option compared to the approved Exjade which is a dispersible tablet for oral suspension formulation. It is intended that Jadenu Sprinkle be sprinkled onto food. Patients who can't swallow tablets would also have the option of receiving Jadenu Sprinkle or Exjade instead of Jadenu.

**Risk Benefit Assessment**

As stated above, the bioavailability (AUC) of Jadenu Sprinkle (deferasirox granules) was 52% greater than with Exjade (deferasirox tablets for oral suspension). The Cmax for Jadenu Sprinkle did not meet the standard bioequivalence criteria, showing an approximate 34% increase over the Exjade reference formulation of defersirox. This topic was previously discussed with FDA for the Jadenu marketing application at a Type C meeting on July 26, 2013 and it was agreed that a registration of the Jadenu (deferasirox film coated tablet formulation) was possible despite the higher Cmax value (see Meeting Minutes by Patricia Garvey, Regulatory Project Manager in the Division of Hematology Products, final signature date August 5, 2013, in IND 58554). Similarly, registration of Jadenu Sprinkle should also be possible despite the higher Cmax value compared to that of Exjade.

The proposal appears to be reasonable. Similar to Jadenu, the Jadenu Sprinkle dose adjustment during treatment for the indicated patient populations is based on serum ferritin level and LIC which limits potential overexposure to Jadenu. Similar dosing adjustments are also recommended in the Exjade product label (under NDA 21882).

**Regulatory Recommendation of Supervisory Associate Division Director:** Grant Accelerated Approval for the following indications: a. the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older and b. for the treatment of chronic iron overload in patients 10 years of age and older with 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..

## 2. Background:

(This section is derived in part from the review of Dr. Andrew Dmytrijuk.)

Jadenu Sprinkle (deferasirox granules) is an orally bioavailable iron chelator.

The sponsor proposes the same indications for Jadenu Sprinkle as those for Jadenu and Exjade, i.e.:

a. Jadenu Sprinkle is indicated for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. This indication is based on reduction in serum ferritin and LIC. (b) (4) (b) (4)
b. Jadenu Sprinkle is indicated for the treatment of chronic iron overload in patients 10 years of age and older with NTDT syndromes and with a liver iron concentration LIC of at least 5 mg Fe per gram of dry weight and a serum ferritin greater than 300 mcg/L. This indication is based on achievement of an LIC less than 5 mg Fe/g dw. (b) (4) (b) (4)

## 3. CMC/Product Quality Microbiology:

(This section was derived in part from the review of Dr. Amit Mitra.)

Deferasirox is not a new molecular entity. The tablet dosage form for the treatment of iron overload is already approved. 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.

Jadenu is proposed to be used as an iron chelator indicated for treatment of chronic iron overload in patients 2 years of age and older. Each sachet contains 90, 180 or 360 mg deferasirox. The granule dosage form (b) (4) contains deferasirox, microcryslline cellulose, crospovidone, povidone K30, poloxomer 188 (b) (4) (b) (4)

(b) (4) microcrystalline cellulose, crospovidone, magnesium stearate (b) (4). All three strengths have same percentage composition of active and inactive ingredients.

The manufacturing process involves: (b) (4) (b) (4)

All dosage strengths use identical granules and dose proportionately filled into the same size of sachets. The registration batches were manufactured by (b) (4) at pilot scale (approximately (b) (4) units). Each of these batches was packaged into in sachets and placed on long term (25°C/60%RH) and accelerated (40°C/75%RH) stability studies.

The applicant conducted statistical analysis of the 24 months long term data for assay and related substances. The applicant requested a tentative shelf life of 36 months and it may be granted based on satisfactory statistical analysis according to ICH Q1E (evaluation of stability data).

The storage condition is: "Store at 25°C (77°F); excursions are permitted to 15° C-30°C (59° to 86 ° F) [see USP controlled temperature].

**Regulatory Recommendation:** The recommendation of the CMC review was approval with which the Supervisory Associate Division Director agrees.

## 4. Nonclinical Pharmacology/Toxicology:

(This section is derived in part from the review of Dr. Rama Gudi.)

The plasma pharmacokinetics of newly developed formulation variants of deferasirox granules (ICL670) in comparison to commercial Exjade dispersible tablets was investigated in male Beagle dogs. The dogs were administered with single oral doses of 375 mg as four different formulations in a crossover design of 4 periods, with 7-day washout between treatments. The plasma concentrations analysis with ICL670 formulation D (Batch TRD-2692-014) resulted in higher exposure and higher relative bioavailability in comparison with Exjade dispersible tablets. Similar exposure ($AUC_{0-48h}$ and $C_{max}$) values and concentration-time curves were observed with ICL670 Formulation 2, Batch no. TRD-2648-68 in comparison with Exjade dispersible tablets.

**Regulatory Recommendation:** The conclusion of the Pharmatology/Toxicology review is that there are no pharmacology/toxicology issues that would preclude approval of the drug with which the Supervisory Associate Division Director agrees.

## 5. Clinical Pharmacology/Biopharmaceutics:

(This section is derived in part from the review of Dr. Sriram Subramaniam.)

The Office of Clinical Pharmacology recommends approval of this NDA. Key review issues with specific recommendations and comments are summarized below:

• The recommended initial dose is 14 mg/kg/day with an increase up to 28 mg/kg based on serum ferritin for patients with transfusional overload, and an initial dose of 7 mg/kg with an increase up to 14 mg/kg in patients with NTDT and baseline LIC > 15 mg (initial therapy) or > 7

mg (after 6 months of therapy) Fe per gram of liver dry weight. The initial and maximum doses are supported by the RBA study and E-R analysis for safety.

• Jadenu Sprinkle granules is recommended to be taken on an empty stomach or light meal, and administered orally by sprinkling the contents on soft food immediately prior to use. This recommendation is supported by the food effect study.

**Regulatory Recommendation:** The conclusion of the Clinical Pharmacology review is that there are no issues which would preclude approval of the drug with which the Supervisory Associate Division Director agrees.

## 6. Clinical Microbiology:

(This section was derived in part from the review of Dr. Kathy Robie Suh and Dr. Yuansha Chen.)

The Clinical Microbiology Review was conducted by Yuansha Chen (final electronic signature 9/20/2016). The drug product is for oral administration and is non-sterile (no sterility methods employed) and contains no preservative. With regard to patient risk associated with a non-sterile product, the review found the container-closure system adequate for the granule drug product for oral route of administration. The review states the solid dosage form is typically not susceptible to microbiological growth and patient risk from environmental contamination is low. Drug product specification (microbial limits testing) and test method validation/suitability were found to be compliant with USP requirements. The review commented that there is no extended hold time proposed after mixing the drug product with soft food and indicated that there is no concern with the drug product package insert instructions for product administration. The application was found adequate from a Clinical Microbiology perspective.

**Regulatory Recommendation:** The conclusion of the Clinical Microbiology review is that there are no issues which would preclude approval of the drug with which the Supervisory Associate Division Director agrees.

## 7. Clinical/Statistical-Efficacy:

(This section was derived in part from the review of Dr. Andrew Dmytrijuk.)

The sponsor cross references the efficacy of Exjade in NDA 21882 to support the current application for Jadenu Sprinkle NDA 207968. Clinical Reviews of Exjade for the indications listed below were completed by Dr. George Shashaty and Dr. Donna Przepiorka (Clinical Reviewers in

the Division of Hematology Products) on October 26, 2005 (NDA 21882) and January 9, 2013 (NDA 21882 supplement 15), respectively.

Generally, the bioavailability (based on area under the curve (AUC) of Jadenu Sprinkle was 52% greater as compared to Exjade. In bioavailability studies submitted to support the application of Jadenu (deferasirox film coated tablets, NDA 206910) that compared the AUC and Cmax of Jadenu to Exjade, the Cmax was 30% (90% CI: 1.2, 1.4) higher for Jadenu compared to Exjade. However, after strength-adjustment, Jadenu, i.e., 360 mg strength film coated tablet was equivalent to Exjade, i.e., 500 mg strength tablet for oral suspension with respect to the mean AUC under fasting conditions.

From a clinical perspective, the implication of a higher Cmax and bioavailability is that this may increase the risk for adverse reactions which would be similar to those reported for Exjade. However, the Applicant proposes a lower equivalent Jadenu Sprinkle starting dose compared to Exjade. The proposed starting dose of Jadenu Sprinkle is the same as that recommended for Jadenu. Also, proposed dose adjustments for Jadenu Sprinkle, Jadenu and Exjade during treatment are the same and are based on responses in serum ferritin and LIC.

The Clinical Pharmacology review by Dr. Sriram Subramaniam final signature date April 13, 2017 states that The Office of Clinical Pharmacology, Division of Clinical Pharmacology V and Division of Pharmacometrics, has determined that there is sufficient clinical pharmacology information provided in this NDA to support an approval recommendation.

**Regulatory Recommendation:** The conclusion of the clinical efficacy review is that there are no issues to preclude approval of the drug with which the Supervisory Associate Division Director agrees.

## 8. Safety:

(This section has been derived in part from the review of Dr. Andrew Dmytrijuk.)

The review of safety in the studies supporting the Jadenu Sprinkle application in NDA 207968, i.e., studies F2104, F2105, F2106 and F1102, does not raise new or additional safety concerns for Jadenu Sprinkle compared to the marketed Exjade product. These studies were conducted in normal healthy male and female subjects. A similar safety profile for Jadenu Sprinkle is expected compared to the approved Jadenu product. The safety labeling described in the Exjade product label is the same the safety labeling as for the approved Jadenu product label and the proposed Jadenu Sprinkle product label.

**Regulatory Recommendation:** The conclusion of the Safety review is that there are no issues to preclude approval of the drug with which the Supervisory Associate Division Director agrees.

**9. Advisory Committee Meeting**: This product was not taken to an Oncologic Drugs Advisory Committee because there were no issues requiring discussion.

**10. Pediatrics:** A waiver from the need for specific pediatric studies of the film coated tablet formulation (Jadenu) formulation in the requested pediatric age groups should be granted. Similarly, a waiver from the need for specific pediatric studies of the deferasirox granule formulation (Jadenu Sprinkle) in the requested age groups should be granted.

**11. Other Relevant Regulatory Issues:** The existing Postmarketing Requirements (PMR 2888-1 through PMR 2888-9) previously issued for deferasirox under NDA 21882 (Exjade) and NDA 206910 (Jadenu) should be applied to the deferasirox granule formulation (Jadenu Sprinkle).

**12. Labeling:** A label has been negotiated between the FDA and the Applicant.

## 13. Decision/Action/Risk Benefit Assessment:

(This section is derived in part from the review of Dr. Andrew Dmytrijuk.)

The bioavailability of Jadenue Sprinkle is greater than that of Exjade. The Applicant proposed a Jadenue Sprinkle starting dose of 14 mg/kg orally once daily in patients with transfusional iron overload and 7 mg/kg orally once daily in patients with NTDT syndromes. These doses are lower than those recommended for Exjade (20 mg/kg for transfusional iron overload and 10 mg/kg for NTDT syndromes), so as to generate an efficacy and safety profile that resembles Exjade with the exception that the palatability of the Jadenue Sprinkle is greater than that of Exjade.

**14. Regulatory Recommendation of Supervisory Associate Division Director:** Grant Accelerated Approval.

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ALBERT B DEISSEROTH
05/17/2017