APPLICATION NUMBER:

207968Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW
<table>
<thead>
<tr>
<th><strong>Date</strong></th>
<th>May 16, 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>From</strong></td>
<td>Kathy M. Robie Suh, M.D., Ph.D.</td>
</tr>
<tr>
<td><strong>Subject</strong></td>
<td>Cross-Discipline Team Leader Review</td>
</tr>
<tr>
<td><strong>NDA</strong></td>
<td>207968</td>
</tr>
<tr>
<td><strong>Applicant</strong></td>
<td>Novartis Pharmaceuticals Corp</td>
</tr>
<tr>
<td><strong>Date of Submission</strong></td>
<td>July 21, 2016</td>
</tr>
<tr>
<td><strong>PDUFA Goal Date</strong></td>
<td>July 21, 2016</td>
</tr>
<tr>
<td><strong>Proprietary Name / Established (USAN) names</strong></td>
<td>JADENUR® (deferasirox) Sprinkle/ deferasirox</td>
</tr>
<tr>
<td><strong>Dosage forms / Strength</strong></td>
<td>Granules for oral administration: 90 mg, 180 mg, and 360 mg</td>
</tr>
<tr>
<td><strong>Proposed Indication(s)</strong></td>
<td>Treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. 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</td>
</tr>
<tr>
<td><strong>Recommended:</strong></td>
<td>Approval</td>
</tr>
</tbody>
</table>
1. Introduction

Exjade (deferasirox) tablets for oral suspension and Jadenu (deferasirox) Tablets for oral use are approved in the United States for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older and for the treatment of non-transfusion dependent thalassemia (NTDT) syndromes in patients 10 years of age and older. Exjade was first registered in the United States on November 2, 2005. Exjade is a dispersible tablet which must be dispersed in water (or orange juice or apple juice) and the liquid swallowed. Jadenu is a film-coated tablet.

Exjade and Jadenu were approved under Accelerated Approval regulations and studies for conversion to regular approval have not yet been completed.

The current application provides for a new granule formulation of deferasirox which is sprinkled on soft food and then consumed. The granules are packaged in a sachet. The dosing for the new formulation (Jadenu Sprinkle) granules is the same as for the film-coated tablet (Jadenu). The granule formulation provides an additional dosing option for patients who have difficulty swallowing whole tablets.

This 505(b)(1) new drug application is based in part on prior documentation submitted to the applicant’s NDA 21882 for Exjade and NDA 206910 for Jadenu. The basis for this NDA is pharmacokinetic (PK) comparability of the new product with the currently marketed deferasirox formulations. The applicant has submitted quality (chemistry, manufacturing and controls)(CMC) information, biopharmaceutics information on deferasirox in humans, and clinical pharmacology (pharmacokinetic/pharmacodynamics)(PK/PD) studies in healthy volunteers. Safety information from these studies and from post-marketing experience of deferasirox is included in the application. No clinical efficacy and safety studies were conducted for this application.

2. CMC/Device

In this NDA the sponsor is seeking approval of a new formulation of deferasirox. The major chemistry, manufacturing and controls (CMC) review findings are summarized below.

Regarding the overall Chemistry, Manufacturing and Controls (CMC) review Dr. Sherita McLamore, Application Technical Lead (review signed 4/19/2017) provides the following summary of the major findings and conclusions of the review:
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 re-test period for the drug substance when stored at 25°C/60%RH and a 36-month drug product expiration period when stored under 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. 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 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.
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.

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 [redacted] test period has been established.

Drug Product
The drug product is presented as white [redacted] granules containing the active, microcrystalline cellulose, crospovidone, povidone K30, poloxamer 188, magnesium stearate and colloidal silicon dioxide packaged in [redacted] sachets. Each sachet contains 90 mg, 180 mg or 360 mg deferasirox in [redacted] foil sachet. 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 Jadex® film coated tablets. 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 at a commercial batch size [redacted].

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**

The commercial batches will be manufactured in strengths of 90 mg, 180 mg, and 360 mg with a batch size 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.
Cross Discipline Team Leader Review
NDA 207968

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.

Additional detail from the individual CMC reviews is provided below:

The Drug Substance (DS) Quality Assessment review was conducted by Haripada Sarker (signed 4/10/2017). Regarding the drug substance, the review states that the DS information is cross-referenced to commercially available drug, deferasirox, which was approved as Exjade (NDA 21882), and based on the information provided for deferasirox in this NDA the DS section supports the NDA 207968. The DS review indicated there were no outstanding issues.

The Drug Product (DP) Quality Assessment review was conducted by Amit Mitra (signed 4/7/2017). The review describes the manufacturing process as involving:

(b) The granule dosage form contains deferasirox, microcrystalline cellulose, crospovidone, povidone K30, poloxamer 188, microcrystalline cellulose, crospovidone, magnesium stearate and silica. All three strengths have same % composition of active and inactive ingredients.” The review states all dosage strengths use identical granules that are dose proportionately filled into the sachets. Stability studies were conducted and the review states, “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 conditions specify storage at 25°C (77°F) with excursions permitted to
Cross Discipline Team Leader Review
NDA 207968

15°C-30°C (59°F to 86°F). Compatibility of deferasirox 90, 200, and 400 mg granules with yogurt was assessed. The review states, “The stability was assessed by determination of the assay and degradation products of ICL670 granules after dispersion and storage with the selected vehicle over specified period of time (6 and 24 hours). No substantial change in these attributes over the 24 hours’ time period was found.”

The reviewer comments that, “Most of the drug excipient compatibility data were obtained via prior knowledge from film coated tablets and dispersible tablets.” The review states that the excipients are compendial. Regarding impurities the reviewer states the following:

Reviewer’s Assessment: The applicant has not adopted an elemental impurities specification or conducted a PDE assessment for safety related to elemental impurities. The applicant was requested to adopt a specification for elemental impurities based on the recommendation of ICH-Q3D. In an amendment, dated 17-JAN-2017, the applicant provided the following response: “A risk assessment for elemental impurities was conducted to evaluate the potential presence of elemental impurities in deferasirox (ICL670) 90 mg, 180 mg, and 360 mg granules, complying with requirements defined in ICH Q3D and USP <232> guidelines. Because the maximum level of elemental impurities potentially present in the excipients, drug substance, facilities, and packaging is less than \( \text{of the permitted limit for each elemental impurity for oral administration (according to ICH Q3D Option 2a, assuming that the daily dose of drug product is } \text{grams per day), it can be concluded that there is no need to establish the specification limits for elemental impurities. The current product specification appropriately reflects the requirements of ICH Q3D and USP <232>“. The applicant also provided the detailed risk assessment report as recommended by ICH Q3D. The risk assessment based on common causes and actual batch data of the drug product suggest, that no specification for elemental impurities is necessary. The reviewer concludes that according to the current regulatory standard, no specification for elemental impurities is necessary.

Regarding the container closure the DP review describes that the sachets are made of foil.
The reviewer’s assessment is that “The container/closure information provided in the NDA in conjunction with the referenced DMF (with quality control information of individual components of the sachet laminate), and the stability data for the drug product meets the recommendation provided in “Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics” specifically solid oral dosage form.”

Dr. Mitra’s DP Quality Assessment review recommended approval and did not propose any post-marketing commitments or risk management measures. Labeling recommendations for Quality Assessment were provided.

The application was found acceptable from a Process perspective (review by Rakhi Shah, signed 2/10/2017). The review summarizes:

“The drug product will be produced at [REDACTED] and microbial testing of the drug product will be performed at [REDACTED]. The Drug Product is an immediate release oral granule. There is no USP monograph for the Drug Substance or Drug Product. The Drug Product Manufacturing Process [REDACTED]. The Drug Product is manufactured using a common blend.”

The Process review identified a deficiency in that in-process controls (IPC) for the mean and individual fill weights of the drug product were found not to be adequate to ensure that the drug product complies with the assay specification [REDACTED] % as indicated by the failure to comply with the assay specification during stability studies. The review describes the problem as follows:

The sponsor was advised to tighten IPC to ensure compliance with the assay specifications. The sponsor did not tighten the in-process control limits but rather made “changes [to] improve the process enough such that it is not necessary as demonstrated by successful pre-validation and validation campaigns with no out of specification release testing [REDACTED] in IPC.” The changes are summarized below:
An improved control strategy was implemented (0006-1.11.1 cmc-response-fda page 7).

The review found the effect of these measures acceptable stating: “The applicant stated that the above listed process changes will result in acceptable manufacturing as noted by acceptable pre-validation release testing and few IPC failures. The applicant also passed release testing during registration batches and has not significantly reduced the number of IPC failures. The applicant has significantly improved the yield by reducing the number of rejected sachets.” The review consulted with the clinical review team which did not feel there are clinical concerns.

Overall, the application was found acceptable from a Process perspective.

Facilities Review was conducted by Wayne Seifert, Office of Pharmaceutical Quality (signed 3/29/2017). The review encompassed five facilities. All were found acceptable for approval as summarized below:

<table>
<thead>
<tr>
<th>Establishment Name and Address</th>
<th>FEI Number</th>
<th>Responsibilities and profile codes</th>
<th>Initial Risks Identified</th>
<th>Final Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novartis Pharma Stein AG Schaffhauserstrasse 101 Stein, Switzerland CH-4332</td>
<td>5000653483</td>
<td>CSN - Manufacturing of deferasirox (b)(4)</td>
<td>Medium – The current inspection conducted 10/16/2015 was a post approval inspection with coverage for profiles (b)(4) (b)(4)</td>
<td>Approval</td>
</tr>
</tbody>
</table>

Reference ID: 4098542
3. Nonclinical Pharmacology/Toxicology

The non-clinical Pharmacology/Toxicology primary review of this application was conducted by Ramadevi Gudi, Ph.D. (final signature, 5/2/2017). No additional non-clinical toxicology studies for deferisirox were submitted in this application.

The Pharmacology/Toxicology Review describes that the Applicant submitted nonclinical pharmacokinetic studies in dogs with various formulations of ICL670 (Exjade). The review summarizes the findings of those studies as follows:
The Pharmacology/Toxicology review found the NDA to be approvable from a pharmacology/toxicology perspective.

4. Clinical Pharmacology/Biopharmaceutics

The Division of Biopharmaceutics primary review was completed by BS Zolnik (4/11/2017). The review summarizes:

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 bioequivalence 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 dissolution method (same as for NDA 206910 Jadenu film-coated tablets) and acceptance criterion were assessed and found to be acceptable for QC (quality assurance) purposes for batch release and stability testing. The review states that based on the dissolution data the coating did not impact the dissolution profiles of the deferasirox tablets. The review concluded, “From the Biopharmaceutics perspective, NDA 207968 for Jadenu® Sprinkle (deferasirox) granules, 90 mg, 180 mg and 360 mg is recommended for APPROVAL.”

The FDA Clinical Pharmacology review of this application was conducted by Sriram Subramaniam, Ph.D. (final signature, 4/13/2017).

The review summarized that comparison of the pharmacokinetics of Jadenu Sprinkle granules with Exjade revealed the following:
The BA (based on dose-adjusted AUC) of deferasirox following administration of Jadenu Spring granules was 52% higher than that of Exjade tablets.

The mean AUC_{inf} following a single 1080 mg dose of Jadenu Sprinkle granules was similar to that of a 1500 mg dose of Exjade tablets under fasting condition; however, the mean C_{max} following a dose of Jadenu Sprinkle granules was 34% higher as compared to Exjade tablets. The difference is not clinically meaningful based on E-R analysis for safety. Similarly, the mean C_{max} was higher following the same dose of Jadenu tablets and it was concluded that the differences in exposure were not clinically meaningful.

The mean AUC_{inf} and C_{max} of deferasirox with a soft meal (e.g., yogurt and apple sauce) or low-fat meal (~450 calories with fat content ~30% of total calories), were similar to those under fasting conditions. Also, the increase in mean AUC_{inf} with a high-fat meal (~1000 calories with fat content > 50% of total calories) was within 1.2-fold with no changes in mean C_{max} compared to that under fasting conditions.

This review found the NDA to be approvable from a clinical pharmacology perspective, pending labeling agreement between the Applicant and the Agency and acceptable findings of inspection of the clinical conduct of the relative bioavailability (RBA) study by the Office of Study Integrity and Surveillance (OSIS). (The completed OSIS inspection of the analytical site for the application was acceptable). The Clinical Pharmacology Review made the following recommendations:

- 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 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 dw. 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.

There were no requests for post-marketing requirements of commitments from Clinical Pharmacology review.

### 5. Clinical Microbiology

The Clinical Microbiology primary 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.

6. Clinical/Statistical- Efficacy

The primary Clinical Review of this application was conducted by Andrew Dmytrijuk, M.D., (final signature 5/1/2017). No new clinical efficacy studies were conducted for this application. The Clinical Review discusses that the current application for Jadenu Sprinkle cross-references the safety and efficacy findings for Exjade in NDA 21882 and some information from NDA for Jadenu film-coated tablets (NDA 206910). Exjade and Jadenu are approved for:

- Treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older.
- 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

Clinical Reviews of Exjade for the two approved indications were completed by George Shashaty, M.D. and Donna Przepiorka, M.D. (10/26/2005 and 1/9/2013, respectively).

The clinical review notes that because the bioavailability of the Jadenu Sprinkle product (based on AUC) is greater than that of Exjade [see section 4 Clinical Pharmacology/Biopharmaceutics above], “the sponsor proposes a Jadenu 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 approved starting dose of Exjade is 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 review explains and comments that, “Notably, 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 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. Therefore, the starting dose of Jadenu is 14 mg/kg orally once daily in patients with transfusional iron overload and 7 mg/kg orally once daily in patients with NTDT syndromes (see Clinical Pharmacology Review by Vicky Hsu, Ph.D. for NDA 206910 final signature date February 3, 2015). The difference of 4% in Cmax in Jadenu Sprinkle compared to Jadenu is not clinically significant.”

As there were no clinical efficacy data submitted in this application no Statistical Review was conducted.

7. Safety
The Clinical Review of the safety aspects of this application was conducted by Andrew Dmytrijuk, M.D., (final signature 5/1/2017).

The review notes that all the available clinical safety information for Jadenu Sprinkle in is normal subjects. There are no clinical data in patients treated with Jadenu Sprinkle.

Regarding safety of Jadenu the Clinical Review comments, “Review of safety in the studies supporting the Jadenu Sprinkle application 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 for the proposed Jadenu Sprinkle product label.”

8. Advisory Committee Meeting

No advisory committee meeting was held for this application.

9. Pediatrics

No pediatric patients were studied for the current NDA. Pediatric patients were included in studies for the initial approval of Exjade (NDA 21882) and approval of the supplemental indication in non-transfusion-dependent thalassemia.

As noted in the Clinical Review (5/1/2016) the sponsor requested a waiver of requirement for pediatric studies of Jadenu Sprinkle under PREA in patients age 0 to < 2 years with chronic iron overload due to blood transfusions on the basis that iron overload requiring treatment chelation is rare in patients below 2 years of age. The sponsor also requests a waiver of pediatric studies of Jadenu Sprinkle in patients age 0 to 9 years with chronic iron overload in patients with NTDT syndromes on the basis that studies in patients 0-9 years in the NTDT setting were impossible or highly impractical. The Clinical Review comments as follows:

“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 for the approved Jadenu product label and the proposed Jadenu Sprinkle product label. Jadenu Sprinkle is exempt from PREA requirements because of the deferasirox Orphan Designation. However, the existing Postmarketing Requirements (PMRs) and Postmarketing commitments (PMCs) for pediatric studies of deferasirox under NDA 21882 (Exjade) and NDA 206910 (Jadenu) should be completed and studies may be modified to allow use of the deferasirox granule formulation (Jadenu Sprinkle).”
10. **Other Relevant Regulatory Issues**

Proprietary name review by Leeza Rahimi (signed 11/22/2016) found the proposed name Jadenu Sprinkle acceptable. The proprietary name was granted (letter issued 11/22/2016).

The Office of Study Integrity and Surveillance (OSIS) inspection of the clinical portions of Study ICL670F1102 conducted by Souseikai Sumida Hospital, Tokyo, Japan found the clinical data from the site to reliable and gave a final inspection classification of No Action Indicated (NAI) (inspection by Yiyue Zhang, final report 4/14/2017).

OSIS inspection review of the conduct of the bioanalytical portion of the bioequivalence studies for the NDA study at [REDACTED] did not identify any significant issues and final classification of the inspection was No Action Indicated (NAI (Xikui Chen, 2/17/2017)). Data were deemed acceptable for review.

11. **Labeling**

The sponsor included proposed labeling in the submission.

Final wording for the labeling for the indications has been developed by the DHP review team with discussion and consideration of the recommendations from each of the review disciplines and consulting review divisions and with negotiation with the sponsor.

Labeling recommendations were provided by the Office of Prescription Drug Promotion (OPDP) (Rachael Conklin, final signature 3/8/2017). Recommendations included comments for Dosage and Administration and Patient Counseling Information. See the OPDP review for detailed recommendations. The review concurred with recommendation for the carton and container labeling provided by DMEPA.

The Division of Medication Error Prevention and Analysis (DMEPA) review was done by Leeza Rahimi (final signature 2/22/2017). The review found the carton and container labels acceptable from a medication error perspective. The review provided recommendations for labeling, mainly for 2 Dosage and Administration section and 17 Patient Counseling Information regarding sprinkling the product on food. Also, a recommendation was made for the sponsor to change placement of the serial number on the cartons to minimize possible confusion with the lot number.

12. **Recommendations/Risk Benefit Assessment**

Regarding benefit/risk for approval of Jadenu Sprinkle the Clinical Review (Andrew Dmytrijuk, M.D., 5/1/2017) states the following.
The recommendation for the approval of Jadenu Sprinkle is based on the safety and efficacy of the marketed Exjade (deferasirox) product and the available Jadenu Sprinkle supportive safety information from the pharmacokinetic (PK) and bioavailability studies F2104, F2105, F2106 and F1102. No new or additional safety concerns were identified in this Clinical Review of NDA 207968 for Jadenu Sprinkle. Overall, the risk benefit assessment favors the approval of Jadenu Sprinkle for the same indications as those of Exjade, i.e., for patients with transfusional iron overload and NTDT syndromes.

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. The sponsor proposes an equivalent 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 compared to Exjade. The proposed dosing of Jadenu Sprinkle is the same as that of Jadenu. The starting dose of Jadenu Sprinkle is equivalent to the Exjade recommended starting dose, i.e., 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 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 (approved August 12, 2016 under NDA 21882).

The Clinical Review recommended that the outstanding post-marketing requirements/commitments for Exjade should apply as well to Jadenu Sprinkle. For studies to fulfill these remaining post-marketing requirements patients may receive Exjade, Jadenu, or Jadenu Sprinkle. The postmarketing requirements along with timelines are shown below. The review comments that except for the study to fulfill PMR 2888-1 the remaining studies are ongoing.

PMR 2888-1  Establish a registry for children aged 2 to < 6 years to enroll approximately 200 patients receiving deferasirox and follow them for 5 years. Collect data at least monthly for renal function and blood pressure and yearly for growth and development, and analyze the data for adverse renal reactions and delayed growth and development. Submit your monitoring scheme for our review and comment.

The timetable you submitted on March 27, 2015, states that you will conduct this study according to the following schedule:

| Final Report Submission: | 02/2016 |

Reference ID: 4098542
PMR 2888-3  Conduct a trial to assess the long-term efficacy (and safety) of deferasirox treatment to a target LIC of 3 mg Fe/g dw followed by one or more treatment holidays until the LIC is ≥5 mg Fe/g dw in patients with NTDT. Follow-up of all subjects for up to 5 years is necessary.

The timetable you submitted on March 27, 2015, states that you will conduct this study according to the following schedule:

Trial Completion: 05/2019  
Final Report Submission: 11/2019

PMR 2888-4  Conduct a prospective, randomized trial in at least 210 patients with low to intermediate risk myelodysplastic syndromes (MDS) receiving deferasirox for transfusional iron overload (approximately 140 patients) or placebo (approximately 70 patients) to determine the efficacy and safety of deferasirox in this population. The trial will continue for 3 years from the date the last patient is enrolled.

The timetable you submitted on March 27, 2015, states that you will conduct this study according to the following schedule:

Trial Completion: 03/2018  
Final Report Submission: 09/2018

PMR 2888-5  Conduct a study, using your established registry, to evaluate the risk of growth inhibition in children (aged 10 to <18 years old at enrollment) with NTDT and treated with deferasirox for documented iron overload. Follow at least 40 children for up to 5 years to assess and analyze the long-term safety of treatment with deferasirox, including an assessment of growth, compared to children on a regular transfusion program receiving deferasirox (based on historical data).

Provide annual interim reports on enrollment and outcomes.

The timetable you submitted on March 27, 2015, states that you will conduct this study according to the following schedule:

Interim Report Submission: 12/2015  
Interim Report Submission: 12/2016  
Interim Report Submission: 12/2017  
Interim Report Submission: 12/2018  
Interim Report Submission: 12/2019  
Interim Report Submission: 12/2020  
Study Completion: 06/2021  
Final Report Submission: 12/2021
There is no recommendation for post-market risk evaluation and mitigation strategies (REMS) for this application.
In conclusion, the application is acceptable for approval for treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older and 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, with agreed-upon final wording of the labeling and post-marketing requirements. Because the current approval of the Exjade application used as reference for clinical efficacy and safety is under Accelerated Approval, approval of Jadenu Sprinkle should also be under Accelerated Approval regulations.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATHY M ROBIE SUH
05/16/2017