Cross-Discipline Team Leader Review

Date	December 11, 2018
From	Kathy M. Robie-Suh, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 21882 /S-028; NDA 206910 /S-009; NDA 207968 /S-004
Applicant	Novartis Pharmaceutical Corp
Date of Submission	June 15, 2018
PDUFA Goal Date	December 15, 2018
Proprietary Name / Established (USAN) names	Exjade (deferasirox) tablets for oral suspension; Jadenu (deferasirox) film-coated tablets; Jadenu Sprinkle (deferasirox) granules
Dosage forms / Strength	Exjade (deferasirox) tablets for oral suspensión, 125 mg, 250 mg, 500 mg; Jadenu (deferasirox) film-coated tablets, 90 mg, 180 mg, 360 mg; Jadenu Sprinkle (deferasirox) granules, 90 mg, 180 mg, 60 mg
Indication(s)	No new indication is being sought with this sNDA. Currently approved: For the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older; 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
Recommended:	Approval [Note: no new indication]

1. Introduction

Exjade, Jadenu and Jadenu Sprinkle are three formulations of deferasirox (ICL670) which is an orally active iron chelator first approved November 2, 2005 (Exjade, NDA 21882) for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older. Exjade was subsequently (January 23, 2013) approved for treatment of iron overload in patients age 10 years and older with non-transfusion-dependent thalassemia syndromes and with a liver iron concentration of ≥5 mg Fe per gram dry weight and a serum ferritin >300 mcg/L. The Jadenu (NDA 206910 and Jadenu Sprinkle (NDA 207968) formulations were subsequently developed and were approved on 3/30/2015 and 5/18/2017, respectively. Both indications for all three products are approved under Accelerated Approval (Subpart H) provisions. The transfusional hemosiderosis indication was converted to regular approval on 5/11/2018.

In this submission the sponsor submits pediatric supplemental NDA (SE8 supplement) for Priority review. For all three products the submission includes the interim report for a clinical study, Study CICL670F2202 (F2202), titled *"A Randomized, Open-Label, Multicenter, Two Arm, Phase 2 Study To Evaluate Treatment Compliance, Efficacy And Safety Of An Improved Deferasirox Formulation (Granules) In Pediatric Patients With Iron Overload"*, and requests pediatric exclusivity determination in response a Written Request (WR) for pediatric studies that was issued for deferasirox on May 29, 2018. The detailed Clinical Review of this supplement has been completed by Dr. Andrew Dmytrijuk (final signature 12/06/2018) and the detailed Statistical Review for the application has been completed by Haiyan Chen, Ph.D. (final signature 11/30/2018). .

2. Background

An original Written Request (WR) for pediatric studies was issued for deferasirox on December 17, 2014. The WR requested the sponsor to conduct and submit the report for a single study (Study 1) of deferasirox in pediatric patients age 2 years and older with any transfusion-dependent anemia requiring chelation therapy due to iron overload. Patients were to be chelation treatment naïve. The study was to be a randomized, open label, study of 48-weeks treatment duration comparing treatment compliance and changes in serum ferritin levels in patients treated with the deferasirox granule and deferasirox dispersible tablet (DT) formulations. (The sponsor developed the granule formulation to improve palatability of deferasirox which was anticipated to improve compliance and thereby enhance effectiveness of chelation therapy among patients, particularly pediatric patients, requiring iron chelation therapy). The WR stipulated: "A sufficient number of patients must be enrolled to ensure that the study is adequately powered to detect a statistically significant and clinically relevant improvement in compliance and difference in change in serum ferritin from baseline to 48 weeks between the two treatment arms. Male and female children and adolescents aged ≥ 2

and < 18 years at enrollment will be included in this study. Patients must be chelation naïve." Important safety assessments for the study were to include ophthalmologic evaluations (distance visual acuity, applanation tonometry, lens photography, and wide angle fundus photography of the retina and optic nerve), cardiac evaluations (echocardiography and ECG) and adverse events of renal, liver and gastrointestinal toxicity. Reports of studies to address the WR were to be submitted to the Agency on or before January 1, 2018. The sponsor designed and initiated Study F2202 to address the WR. However, the sponsor experienced enrollment difficulties with the study and despite multiple interactions with the Agency regarding sponsor proposals to amend the WR (e.g., fewer ICT-naïve patients, shorter treatment duration for efficacy assessment), it was not possible to reach agreement on protocol modifications that would potentially allow faster patient accrual while still maintaining a reasonable ability to provide useful information on the effectiveness of the two formulations in pediatric patients. Because of enrollment difficulties, including problems finding patients not previously treated with ICT, the study was unable to accrue the protocol-proposed target number of patients during the time the WR was in effect and the WR expired on January 1, 2018.

The sponsor submitted preliminary results which included assessments at 24 weeks for patients enrolled in the ongoing F2202 study to the Agency in March 2018 along with a new Proposed Pediatric Study Request (PPSR). Agency preview of those topline results determined that it was unlikely that additional data at 48 weeks of treatment would substantively affect the overall results of the study. Agency preview of top line data [from Study F2202] determined that full submission and review of 24-week data from the study to support the efficacy of the product in treatment of iron overload in pediatric patients was warranted. Consequently, a new WR was issued on May 29, 2018 indicating that a response to WR based on the 24-week data was reasonable. (See May 5, 2018 Teleconference Memorandum signed in DARRTS May 16, 2018). The current submission is the sponsor's pediatric supplement in response to the May 29, 2018 WR.

> [Note: The WR also required to the sponsor to submit a final report for PMR 750-1 to "Establish a registry for children aged 2 to <6 years to enroll approximately 200 patients and follow them for 5 years. Data collection will be at least monthly for renal function and blood pressure and yearly for growth and development. Submit your monitoring scheme for our review and comment." The final report for Study CICL670A2411 titled "*A 5 year observational study (registry) of children aged 2 to <6 years at enrollment with transfusional hemosiderosis treated with deferasirox"* was submitted on January 29, 2016 to address PMR 750-1. Based on the findings of the study and at FDA request a clinical prior approval labeling supplement with draft labeling was subsequently submitted on July 13, 2017 (NDA 21882/S-025; NDA 206910/S-006; NDA 207968/S-001) and the supplements were approved on May 11, 2018].

3. CMC/Device

No new CMC information was included in this supplement resubmission and there was no CMC review for this submission.

4. Nonclinical Pharmacology/Toxicology

No new Pharmacology/Toxicology studies were submitted for this supplement. The Non-clinical Pharmacology/Toxicology (P/T) review signoff of the submission was completed by Ramadevi Gudi (review noted NAI, 10/10/2018).

5. Clinical Pharmacology/Biopharmaceutics

The Office of Clinical Pharmacology Review was conducted by Sriram Subramaniam (final signature in DARRTS 11/29/2018). The review summarized the pharmacokinetics (PK) and pharmacodynamics (PD) results of Study F2202 as follows:

> PK and pharmacodynamics (PD) were characterized in an open-label trial in pediatric patients (age range: 2 years to 13 years, median 2 years, N=71) with chelation naïve transfusion dependent anemia. Starting doses of 20 mg/kg DT or 14 mg/kg granules were orally administered once daily, with dose adjustment based on serum ferritin. The results showed that the pre-dose deferasirox concentrations (surrogate for area under the curve within dosing interval: AUC_{tau}) and the 3 hour post-dose (maximal concentrations: C_{max}) were comparable between the formulations across visits. The E-R relationships between the pre-dose and 3 hour post-dose concentrations and change in serum ferritin levels, serum creatinine, creatinine clearance (CLcr), estimated-glomerular filtration rate (e-GFR), and urine protein to creatinine ratio (UPCR), were comparable for the two formulations across visits. Study CICL670F2202 was not designed to compare efficacy because of the small sample size of the trial.

The review stated, "The Office of Clinical Pharmacology has reviewed the information contained in the sNDAs. These supplements fulfill the clinical pharmacology components of the WR and are approvable from a clinical pharmacology perspective." Regarding labeling the review recommended the following:

> **2. Summary of Labeling Recommendations**
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> - Section 8.4 Pediatric Use included a description of Study CICL670F2202 and the high level clinical summary results. No PK information is added.
> - No changes to Section 12.3 Pharmacokinetics as the PK of deferasirox in pediatric patients and the relative bioavailability of the DT and granule formulations have been characterized and appropriately labeled.

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

The Clinical Review for efficacy of this application was conducted by Andrew Dmytrijuk, M.D., (final signature 12/06/2018) and the Statistical Review was conducted by Haiyan Chen, Ph.D. (final signature 11/30/2018).

As described in the Clinical Review, the sponsor submitted a report for Study CICL670F2202 (F2202), titled "A Randomized, Open-Label, Multicenter, Two Arm, Phase 2 Study to Evaluate Treatment Compliance, Efficacy And Safety Of An Improved Deferasirox Formulation (Granules) In Pediatric Patients With Iron Overload" and requests pediatric exclusivity determination for deferasirox. The primary objective of the study is to evaluate patient compliance (using stick packs or tablet counts) and change in serum ferritin over time for both formulations of deferasirox (granule formulation vs. dispersible tablets) in pediatric patients with iron overload with any transfusion-dependent anemia requiring chelation therapy due to iron overload, and having a treatment goal to reduce iron burden as measured by serum ferritin. Randomization was stratified by age groups (≥2 to <10 years, 10 to <18 years) and by prior Iron Chelation Therapy (ICT) (Yes/No). Study drug dosing was according to the approved product label.

The study intended an enrollment of 216 patients (96 treatment naïve and 120 patients with previous ICT) randomized 1:1 to either of the two formulations. The key inclusion criteria are as follows.

- Iron chelation therapy (ICT)-naïve and previously treated male and female children and adolescents ages ≥ 2 and < 18 years.
- Any transfusion-dependent anemia associated with iron overload requiring iron chelation therapy and with a history of transfusion of at least 20 packed red blood cell (PRBC) units, and a treatment goal of reduction, not maintenance of iron burden as measured by serum ferritin.
- Serum ferritin > 1000 ng/mL, measured at screening Visit 1 and screening Visit 2 (the mean value will be used for eligibility criteria).

Randomized study treatment duration was to be 48 weeks, with an optional extension phase where all patients received the granules up to 5 years.

The co-primary efficacy endpoints were:

- Compliance measured by stick pack/tablet count pediatric ICT naïve patients with iron overload after 24 weeks of treatment. Compliance will be measured by stick pack/tablet count: it will be performed by study personnel every 4 weeks (week 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45 and end of treatment) based on the amount of medication dispensed, returned and reported as lost/wasted by the patient / caregiver
- Change from baseline in serum ferritin at 24 weeks of treatment. Serum ferritin testing will be performed at Screening Visits 1 and 2 and every 4 weeks from week 5 till end of treatment visit. Compliance will be measured by stick pack/tablet count every 4 weeks. The change in serum ferritin will be assessed at weeks 24 and 48 weeks.

As described in the Statistical Review:

> An interim analysis plan was added in the 8 December 2017 SAP to conduct descriptive analyses on safety and efficacy on all randomized iron chelation naïve patients (ICT naïve based on either in IRT or CHY eCRF page) who have completed a minimum of 12 weeks (≥84 days) of treatment exposure or discontinued from treatment core phase at the time of the cut-off date. The primary endpoints, i.e. serum ferritin change from baseline and overall compliance measured by stick pack /tablet count, and key safety data will be summarized descriptively. In addition, two supportive analyses were performed:
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> - Descriptive summary of serum ferritin change from baseline will be provided after imputing missing values using multiple imputation method.
> - Predictive probability of success of the primary analysis for serum ferritin change from baseline will be assessed using normal approximation based on observed interim analysis data.

As described in the Clinical Review, as of the data cut-off (November 16, 2017), 206 of planned 216 subjects were enrolled which included 90 ICT naive subjects and 116 ICT pre-treated subjects. In accordance with the requirement of the Written Request the iron chelation therapy (ICT) naive subjects, the data submitted in this supplement for the study report for Study F2202 requesting Pediatric Exclusivity focuses on all randomized ICT naive subjects, who have completed a minimum of 12 weeks (≥ 84 days) of treatment exposure or discontinued from treatment prior to week 48 of deferasirox therapy at the time of the cut-off date.

Among the 71 randomized ICT-naïve patients (35 granules; 36 DT) all except 1 (randomized to granules) received treatment. Mean age of patients was 4.4 years in the granule group and 3.7 years in the DT group with 30/35 (86%) patients in the granule group and 33/36 (92%) of patients in the age 2 to <10 years age cohort. The Statistical Review noted that, "Some of the baseline characteristics were different across treatment groups. The proportion of male subjects was higher in the deferasirox DT arm (61% vs. 49%). The baseline SF values were numerically higher in the deferasirox DT arm as compared to the deferasirox granule arm (2068.4 ng/mL vs. 1717.1 ng/mL in mean, respectively)." The primary efficacy results are summarized in the following table from the Statistical Review:

Table 3: Summary and Analysis of the Compliance and Efficacy results over 24-weeks

Endpoints	DFX Granule N=35	DFX DT N=36
Compliance at Week 25		
n	29	32
Mean (SD)	91(18)	91(11)
95% CI	(84, 97)	(87, 95)
Median	94	94
Min - Max	41 – 133	57 – 125
Q1 – Q3	86 – 96	91 – 97
Serum Ferritin Change (ng/ml) at week 25 from baseline		
n	27	27
Mean (SD)	288.2(682.4)	349.3(670.0)
95% CI	(18.3, 558.1)	(84.3, 614.3)
Median	241.0	348.0
Min – Max	-855 – 1645	-1304 – 1923
Q1 – Q3	-270.0 – 901.0	-106.0 – 774.0

[Source: FDA review and CSR by the sponsor]

The Statistical Reviewer comments summarized:

> *This descriptive analysis shows similar compliance rates and numerically different SF changes between the two arms (more decrease in SF seen in DXF granules arm). However, the interim analysis was added to the SAP and conducted after the study database lock. This is considered post-hoc analysis. Results from the analysis are considered inconclusive. To claim similarity in labeling, an equivalence study with a pre-specified margin of equivalence and planned sample size according to the margin need to be conducted.*
>
> *In addition, the reviewer conducted the planned primary analyses using the reported data and found that the power to detect significant compliance difference and SF change from the baseline given the observed data were about 56% and 6%, respectively.*

The Statistical Review also found that "*Results from the analyses for secondary efficacy endpoints were consistent with that for primary efficacy endpoints"* but noted, *"However all the analyses are exploratory in nature."*

The efficacy conclusions and labeling recommendations from the Statistical Review are as follows:

> **5.2 Conclusions and Recommendations**
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> The applicant submitted data and an interim report of a prospective, randomized, open-label, multicenter, two-arm, Phase II study to evaluate treatment compliance and change in serum ferritin (SF) from baseline of the deferasirox granule formulation and a deferasirox DT formulation (1:1 randomization) in children and adolescents aged ≥ 2 and <18 years at enrollment with any transfusion-dependent anemia requiring chelation therapy due to iron overload.
>
> The protocol pre-specified final primary efficacy analysis at the EOT was not performed. Instead, a descriptive interim analysis was conducted. *This descriptive analysis shows similar compliance rates and numerically different SF changes between the two arms (more decrease in SF seen in DXF granules arm). However,* the interim analysis was added to the SAP and conducted after the study database lock. This is considered post-hoc analysis. Results from the analysis are considered inconclusive.
>
> **5.3 Labeling Recommendations**
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> The interim efficacy analyses were descriptive in nature. Therefore, all the efficacy results are inclusive and should not be included in the labeling. For an attempt to show similar efficacy or compliance ratesin labeling, an equivalence study with a pre-specified margin of equivalence and planned sample size according to the margin need to be conducted.

Regarding change in serum ferritin, the Clinical Review commented, "It is not expected that a statistically significant change in serum ferritin would be observed between the treatment groups, assuming similar compliance between the study drugs, because the active ingredient, i.e., deferasirox, is the same in each treatment arm. A larger study would need to be performed to observe any differences in serum ferritin between the two treatment arms." The Clinical Review recommended that the sponsor should complete enrollment of all 96 ICT-naïve patients into Study F2202.

8. Safety

The review of safety data for this application was conducted by Andrew Dmytrijuk, M.D., (Clinical Review, final signature 12/06/2018).

At the time of the interim analysis treatment was ongoing for 17/35 (48.6%) and 17/36 (47.2%) patients in the granule and dispersible tablet (DT) treatment groups, respectively. Of these, 15 (42.9%) in the granule group and 13 (36.1%) in the DT group had completed the core treatment phase of 48 weeks.

Patient disposition is summarized in the following table from the Statistical Review (Haiyan Chen, final signature 11/30/2018):

Table 1 : Patient Disposition during the Core Phase (FAS-1)

	DFX Granule N=35 n (%)	DFX DT N=36 n (%)
Treated with study drug	34 (97.1)	36 (100.0)
Not treated	1 (2.9)	0 (0.0)
Treatment ongoing	17(48.6)	17(47.2)
Completed treatment core phase	15(42.9)	13(36.1)
Discontinued from treatment core phase	3 (8.6)	6 (16.7)
Adverse event(s)	1 (2.9)	2 (5.6)
Protocol deviation	1 (2.9)	0 (0.0)
Recovery	1 (2.9)	0 (0.0)
Withdrawl by subject/parent/guardian	0 (0.0)	2 (5.6)
Lack of efficacy	0 (0.0)	1 (2.8)
Physician decision	0 (0.0)	1 (2.8)

Source: Applicant's Clinical Study Report Table 10-1

As summarized in the Clinical Review SAEs were reported in 7 patients in the DT treatment group and 9 patients in the granule treatment group. SAEs reported in ≥ 2 patients were sickle cell crisis in 2 patients each in the DT and granule treatment groups (4 total) and 2 reported cases of pyrexia in the granule treatment group compared to 1 in the DT treatment group (3 total). There were no deaths. No patients showed worsening of renal function from creatinine clearance >60 mL/min to <60 mL/min after deferasirox therapy. Generally, a similar proportion of patients in each treatment group had an increase from baseline in ALT or AST. There were two patients in the DT treatment group and 0 patients in the granule treatment group with the AE increased serum total bilirubin defined as > 2mg/dL.

No ECG/echocardiography data from the cardiac safety substudy was provided by the sponsor in the interim analysis of Study F2202.

In Study F2202 specific ophthalmologic safety evaluations were to be conducted because of concerns raised in the original adult studies for deferasirox. The ophthalmologic adverse reactions included lens opacities, cataracts, elevations in intraocular pressure, and retinal

disorders that were reported at a frequency of less than 1% among subjects treated with deferasirox. Ophthalmologic examination included distance visual acuity testing, applanation tonometry, lens photography and wide angle fundus photography of the retina and optic nerve. In the interim report, there were 56 patients, i.e., 29 patients in the dispersible treatment (DT) arm and 27 patients in the granule treatment arm, who completed all ocular examination tests at baseline. There were only 23 patients, i.e., 13 patients in the DT arm and 10 patients in the granule treatment arm who completed all ophthalmologic examination tests as per protocol (ophthalmologic examinations performed at baseline, after 24 weeks of therapy and at the end of therapy).

9. Advisory Committee Meeting

There was no Advisory Committee Meeting for this supplement.

10. Pediatrics

Currently Exjade, Jadenu and Jadenu Sprinkle are labeled for use in patients ≥2 years of age with chronic iron overload due to blood transfusions and in patients ≥10 years of age with non-transfusion-dependent thalassemia (NTDT) syndromes and with a liver iron concentration ≥5mg iron/ g dry weight and serum ferritin >300 mcg/L. This supplement does not propose to expand the indications or age range for deferasirox use. Review of the pediatric data for the submission is provided under sections 7 Efficacy and 8 Safety above.

Labeling recommendations from Division of Pediatric and Maternal Health were provided and are summarized under section 12 Labeling below.

11. Other Relevant Regulatory Issues

The Statistical Review (Haiyan Chen, 11/30/2018) also provided a summary and comments for the Pediatric Exclusivity Determination for deferasirox.

12. Labeling

The sponsor included proposed labeling in the submission incorporating results of Study F2202 under section 8.4 Pediatric Use. Recommendations for labeling were provided by the several review disciplines discussed above and in discussions with the entire review team.

The proposed labeling was reviewed by the Division of Pediatric and Maternal Health (DPMH) (Elizabeth Durmowicz, 11/14/2018). The following DPMH discussion and recommendations for the proposed labeling were provided in the review:

DPMH Discussion of Proposed Labeling Recommendations:

Because these pediatric data are submitted in response to a WR, the deferasirox labeling (i.e., labeling for Exjade (NDA 021882) and Jadenu (NDA 206910, NDA 207968)) must be updated to include information about the results of Study CICL670F2202.[9]

DPMH agrees with the applicant that information from this trial should be included in the Pediatric Use subsection at the end of the current information underneath the "Transfusional Iron Overload" heading because this information is related to the safe and effective pediatric use of the drug for this indication, and the data from this trial do not provide interpretable safety or efficacy data that would support inclusion of information in other sections of labeling.[10] DPMH does not recommend inclusion of information from this trial in the Clinical Studies section (because the trial was not conducted to establish efficacy or support a new indication)[11] or in the Adverse Reactions, Clinical Studies section (because the adverse reactions identified are consistent with current labeling).[12]

DPMH considered that comparative PK data from the two granule and DT formulations would not be helpful in the label for prescribers, but deferred to Clinical Pharmacology and Clinical. DPMH recommended the following wording for the labeling:

DPMH Labeling Recommendations:

DPMH recommended information to be added to the applicant's proposed labeling for subsection 8.4 for the deferasirox products is underlined. Information to be deleted has a ~~strikethrough~~.

(b) (4)

[redacted]

Clinical and Statistical Reviews of the submission found the interim analysis of data from the iron chelation (ICT) naïve patients was adequate for descriptive analysis only and should be considered exploratory. Based on discussion and recommendations from the Division of Pediatric and Maternal Health (DPMH) the Clinical Review recommends the following wording under 8.4 Pediatric Use to describe these Study F2202 study results:

- A trial conducted in treatment naïve pediatric patients, ages 2 years < 18 years with transfusional iron overload did not include a sufficient number of patients to provide additional meaningful information about the safety or compliance of the deferasirox oral tablets for suspension dosage form (Exjade) compared to the deferasirox granules dosage form (Jadenu Sprinkle).

  Overall safety profiles were also similar between the two formulations.

Labeling recommendations were provided by the Office of Prescription Drug Promotion (OPDP) (Robert Nguyen, final signature 11/27/2018). The recommendations were considered in discussions labeling with the entire review team.

The Patient Labeling Review of the patient package insert (PPI) was completed by Sharon R. Mills (Division of Medical Policy Programs (DMPP)) and Robert Nguyen (OPDP) (final signature 11/29/2018). The review recommended that the PPI be converted to a Medication Guide (MG) for patients to ensure that the information is provided to patients and caregivers. This was conveyed to the Applicant and the Applicant agreed. The review included detailed recommendations to simplify wording and clarify concepts where possible, ensure consistency with the Prescribing Information (PI) information, remove unnecessary or redundant information, ensure that the MG is free of promotional language and to ensure that the MG meets the Regulations as specified in 21 CFR 208.20 and the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

Final wording of the labeling is being developed in discussion with all involved review disciplines and negotiations with the Applicant.

13. Recommendations/Risk Benefit Assessment

The Applicant has submitted a Pediatric Supplement to respond to a Written Request for deferasirox issued on May 29, 2018. The submission is an interim report for a study comparing compliance and change in ferritin levels from baseline between the granule formulation (Jadenu Sprinkle) and the dispersible tablet (DT) formulation (Exjade) of deferasirox in iron-chelation therapy (ICT)-naïve pediatric patients age ≥2 years to <18 years.

The Clinical Review stated that Study F2202 showed that for deferasirox administered as a DT or granule formulation the two formulations have similar compliance and comparable effects on serum ferritin change from baseline at 24 and 48 weeks. Deferasirox administered either as a DT or granule appears to be able to slow down the rise of SF. Also, generally, the safety of the granule formulation of deferasirox appeared comparable to that of the DT formulation of deferasirox in pediatric patients based on available interim data from study F2202. However,

Clinical and Statistical Reviews of the submission found the interim analysis of data from the iron chelation (ICT) naïve patients was adequate for descriptive analysis only and should be considered exploratory.

Based on reviews and discussion with the review team including Division of Pediatric and Maternal Health input final wording recommended for inclusion in the labeling under section 8.4 Pediatric Use is as follows:

- A trial conducted in treatment naïve pediatric patients, ages 2 years < 18 years with transfusional iron overload did not include a sufficient number of patients to provide additional meaningful information about the safety or compliance of the deferasirox oral tablets for suspension dosage form (Exjade) compared to the deferasirox granules dosage form (Jadenu Sprinkle).

  Overall safety profiles were also similar between the two formulations.

Also, as recommended in the Clinical Review the sponsor should complete the full enrollment of planned 96 iron-chelation naïve patients into Study F2202 and carry the study to completion.

In addition, the Patient Labeling Review of the patient package insert (PPI) recommended that the PPI be converted to a Medication Guide (MG) for patients to ensure that the information is provided to patients and caregivers.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KATHY M ROBIE SUH
12/11/2018