CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206910Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	March 27, 2015
From	Kathy M. Robie Suh, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA	206910
Applicant	Novartis Pharmaceuticals Corp
Date of Submission	May 30, 2014
PDUFA Goal Date	March 30, 2015
Proprietary Name / Established (USAN) names	Jadenu (deferasirox)
Dosage forms / Strength	Tablets for oral administration; 90 mg, 180 mg, and 360 mg
Proposed Indication(s)	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
Recommended:	Approval

1. Introduction

Exjade (deferasirox) is 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. The currently approved formulation is a dispersible tablet which must be dispersed in water (or orange juice or apple juice) and the liquid swallowed.

Exjade was approved under Accelerated Approval regulations [redacted (b) (4)].

The current application provides for a new tablet formulation of deferasirox which can be swallowed whole. In addition, for the new formulation the sponsor has proposed a lower tablet strength (compared to the dispersible tablet) based on results of the bioavailability study comparing the two formulations.

2. CMC/Device

In this NDA the sponsor is seeking approval of a new formulation of deferasirox. The chemistry, manufacturing and controls (CMC) review was conducted by J Jee, Office of New Drug Quality and Assessment (reviews finalized 12/3/2014 and 3/18/2015).

Regarding the drug substance, the review states deferasirox is manufactured by [redacted (b) (4)] and comments complete CMC information regarding deferasirox drug substance has been submitted in NDA 21882 (Exjade) which was approved on 02-NOV-2005. Regarding stability the review comments: "Stability studies on three (3) prototype batches (commercial scale) and four (4) supportive batches at accelerated storage conditions 40°C/75% RH, six (6) months), and at long-term storage conditions (25°C/60% RH), up to 60 months were submitted to support the stability of the drug substance. The assay of one of the three batches was found out of specification at the [redacted (b) (4)] months period; however, the assay results at the 60 month period met the drug substance specification. In addition, photostability, forced degradation, heat stability and hygroscopicity were studied [redacted (b) (4)]. The retest date requested for deferasirox is [redacted (b) (4)] months ("Do not store [redacted (b) (4)] C") and it is based on accumulated ICH stability data. Based on the data submitted, the stability data supports the retest period of 36 [redacted (b) (4)] and it is granted." The drug product is described as immediate release, film-coated tablets with strengths: 90 mg, 180 mg, and 360 mg of deferasirox. The review states excipients used in the formulation are USP/NF ingredients: microcrystalline cellulose [redacted (b) (4)], and [redacted (b) (4)], crospovidone, povidone K30, magnesium stearate, colloidal silicon dioxide, poloxamer, and opadry blue, a common pharmaceutical colorant.

The Chemistry Review concluded, "From a CMC perspective, Novartis Pharmaceuticals Corp. has submitted sufficient CMC information to support approval of the drug. There are no outstanding deficiencies with the application. The referenced NDA 21882 for defesiranox *[sic]* drug substance has been reviewed and found to be adequate to support the NDA. An overall "Acceptable" recommendation was made by the Office of Compliance for the pre-approval inspection of the NDA. However, this application is approvable pending recommendation from Biopharmaceutics recommendation." The CMC Review Memo by J Jee dated 3/18/2015 provided review of the update of the Drug Specification submitted by Novartis dated 12-MAR-2015. That review memo concluded:

> The proposed final dissolution specification is acceptable to B. S. Zolnik, Ph.D., Biopharmaceutics Reviewer, Division of Biopharmaceutics, Office of New Drug Products.
>
> The remaining tests, analytical methods, and acceptance criteria remain the same as in the original submission and reviewed by this reviewer on 24-NOV-2014; see below for updated drug product specifications.
>
> From the CMC perspective, NDA 206910 for Jadenu™Film-Coated Tablets (deferasirox) is recommended for Approval.

The CMC Review (12/3/2014) stated the container labels, sample, physician sample carton labeling, and physician sample container labeling and the package insert submitted in the application are acceptable from the CMC perspective.

The CMC Review provides the following discussion regarding the Environmental Assessment and concludes that the sponsor's request for categorical exclusion is acceptable and no further action is necessary.

> As set forth in 21 CFR Part 25.31(a), action on a New Drug Application is categorically excluded from the requirement to prepare an Environmental Assessment or an Environmental Impact Statement if the action does not increases the use of the active moiety. "Increased use", as defined in 21 CFR Part 25.5(a), will occur if the drug is "administered at higher dosage levels, for longer duration or for different indications than were previously in effect, or if the drug is a new molecular entity."
> Novartis Pharmaceuticals Corporation has filed a New Drug Application for a new film-coated tablet formulation of deferasirox. Currently the recommended starting dose of deferasirox as Exjade tablets for oral suspension is 20 mg per kg and is available as 125, 250 and 500 mg dispersible tablets. The new strength-adjusted film-coated tablet will be dosed at a starting dose of 14 mg per kg and will be made available as 90, 180 and 360 mg tablet.
> Novartis Pharmaceuticals Corporation certifies that this submission for deferasirox film coated tablets qualifies for a categorical exclusion in accordance with 21 CFR Part 25.31(a) as the concentration of the active moiety, deferasirox, will be not be increased.
> Further, Novartis Pharmaceuticals Corporation states that, to the best of its knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment and would thus require the preparation of at least an Environmental Assessment

ONDQA Review Memo evaluating the proposed manufacturing process and design space for drug production by D Ghosh, PhD (11/20/2014) describes that the sponsor's product development employed Quality by Design (QbD) and Quality Risk Management (QRM)

principles in the manufacturing process development in line with ICHQ8, Q9, and Q10 guidances. The manufacturing process development plan follows classical QbD approach:

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

The review noted that the process incorporated a non-critical process parameter (b) (4) but that this was justified "due to its potential impact on product quality when combined with another variable (b) (4) The review found the proposed control strategy and manufacturing settings for critical process parameters (CPPs) and non-CPPs to be adequate and found the proposed plan for continual verification of the manufacturing process during the life cycle of the product to be adequate.

3. Nonclinical Pharmacology/Toxicology

The non-clinical Pharmacology/Toxicology primary review of this application was conducted by R Gudi, Ph.D. (final signature, 11/20/2014). No additional non-clinical pharmacology/toxicology studies for deferasirox were submitted in this application.

The Pharmacology/Toxicology review identified that the drug substance of deferasirox contains residual solvents (b) (4) The review commented that, "For each residual solvent, the proposed drug substance acceptance criteria and the level of each residual solvent for the maximum dose of 840 mg and permitted daily exposure (PDE) according to ICH Q3C are shown in the table below. The specifications are below the ICHQ3C PDE limits. Therefore, there are no pharmacology/toxicology issues." Similarly, the review found that with regard to heavy metals, "The amounts of heavy metals are less than the permitted daily exposure (PDE) for oral deferasirox at a maximum dose of 840 mg/day based on 14 mg/kg/day, according to USP<231> and the European Guideline on the Specification Limits for Residues of Metal Catalysts." The Supervisory Pharmacology/Toxicology Review (CM Sheth, PhD., final signature 1/21/2015) agrees with Dr. Gudi's review that there are no nonclinical issues to preclude approval of the deferasirox tablet formulation for the proposed indications.

4. Clinical Pharmacology/Biopharmaceutics

The Division of Biopharmaceutics review was completed by BS Zolnik (2/23/2015 and 3/13/2015).

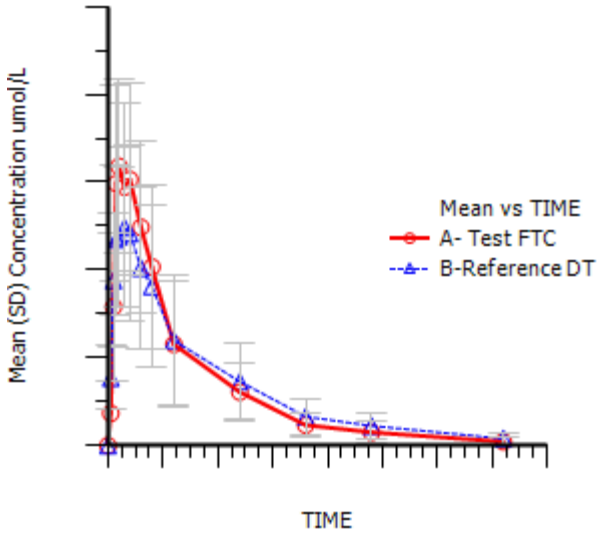
As listed in the Biopharmaceutics Review (2/23/2015), five clinical studies were submitted in the Jadenu application:

- **Study F2101**, a pilot relative bioavailability study comparing the pharmacokinetics of the three uncoated tablet formulations of deferasirox to the currently available marketed DT formulation at 1500 mg dose to select a formulation for further development
- **Study F2102**, a pivotal single-dose fasted bioequivalence study conducted to evaluate the pharmacokinetics of the proposed deferasirox drug product (FCT, 1080 mg) to those of the listed drug product, Exjade tablets for oral suspension (DT, 1500 mg) using bioequivalence criteria
- **Study F2103**, a food effect study to assess the pharmacokinetics of deferasirox FCT when administered under fasting or fed conditions (low fat or high fat meal).
- (b) (4)
- **Study A2409 PK/PD analysis**, a post-hoc PK/PD analysis of a clinical study for the currently approved dispersible tablet (DT) formulation to determine the relative contributions of AUC and Cmax to the safety and efficacy profiles of deferasirox.

Bioequivalence (BE) Study F2102 was evaluated in the Biopharmaceutics Review. Study F2102 was designed to compare the proposed Jadenu film-coated formulation (FTC) versus the reference Exjade tablets for oral suspension (aka dispersible tablet formulation, DT) in healthy subjects under fasted conditions. The sponsor's analysis of the study results found that AUC0-last, AUCinf fell within the 80-125% criteria for bioequivalence, but Cmax failed these criteria (90% CI 120-140%), indicating that the reference Exjade and the proposed Jadenu products are not bioequivalent. The Biopharmaceutics Review confirmed the sponsor's findings and gave the following results for the statistical analysis for the bioequivalence metrics, $AUC_{0\text{-last}}$, AUC_{inf} and C_{max} comparing the Jadenu film-coated tablet (FCT) and Exjade dispersible tablet (DT; DP).

Studies F2101 and (b) (4) were not considered critical to the evaluation and were not covered in the Biopharmaceutics review.

The mean plasma deferasirox concentration-time profile after single dose 1080 mg (360 mg X 3) FTC vs single dose 1500 mg (500 mg X 3) DT



PK variable	Unit	Treatment	N	Geometric mean	Geometric mean ratio (% Ref)	90 % CI
Ln(Cmax)	umol/L	FTC (test)	32	105.83	1.30	120.28-140.05
		DP (ref)	32	81.54		
Ln(AUClast)	umol x h/L	FTC (test)	32	1273.44	1.00	93.17-107.77
		DP (ref)	32	1270.86		
Ln(AUCinf)	umol x h/L	FTC (test)	32	1306.69	0.98	91.57-105.87
		DP (ref)	32	1327.10		

The review also noted that, "Since the biowaiver's requirement of an acceptable bioequivalence study for the highest strength was NOT met, the Applicant's biowaiver request is not fully supported and the biowaiver for the lower 90 and 180 mg strengths of Jadenu (deferasirox) film coated tablets is NOT granted."

Based on the failed bioequivalence results with respect to Cmax a complete response recommendation for the application was made by Biopharmaceutics in the 2/23/2015 review. Following discussion of possible clinical implications of the out-of-range Cmax with the clinical review team, Biopharmaceutics completed an addendum to the review (3/13/2015) stating, "The Clinical Reviewer, Dr. Andrew Dmytrijuk responded that from the clinical perspective, there were no additional safety concerns with 30% higher Cmax values and reiterated that the higher Cmax values observed with Jadenu were within the overall range of those observed with Exjade in healthy subjects and patients. Also, Dr. Dmytrijuk mentioned that the provided exposure-response data for renal laboratory values were sufficient to support

the overall safety of the product. Refer to Dr. Dmytrijuk's clinical review for specific details." The Addendum concludes, "From the Biopharmaceutics perspective, NDA 206910 for Jadenu (deferasirox) tablets is recommended for **APPROVAL.**"

To address the deviation from the FDA's 80-125% criteria for bioequivalence, the sponsor submitted a post-hoc PK/PD analysis (Study A2409) in support of the safety of their proposed product. The Clinical Pharmacology Review (W Hsu and L Ma, 2/3/2015) summarized the results of the bioavailability comparison of Exjade to Jadenu as follows:

> The bioavailability (based on AUC) of Jadenu was 36% greater than with deferasirox tablets for oral suspension. After strength-adjustment, Jadenu (i.e., 360 mg strength) was equivalent to deferasirox tablets for oral suspension (i.e., 500 mg strength) with respect to the mean AUC under fasting conditions, however the mean C_{max} was increased by 30% (90% CI: 1.2, 1.4).
>
> The exposure-response analysis for safety using data from clinical trials with deferasirox tablets for oral suspension indicated that 30% increase in Jadenu C_{max} is not clinically meaningful;
>
> - Exposure-response analyses using tablets for oral suspension clinical trial data in patients showed that renal laboratory abnormalities are not strongly associated with the deferasirox C_{max}..
> - Only minor safety observations such as nausea and headaches were reported at C_{max} in historical deferasirox tablets for oral suspension trials.
> - Despite the 30% increase in mean C_{max} with Jadenu compared to the tablet for oral suspension, the C_{max} values with Jadenu were still within the overall range of those observed with the tablet for oral suspension formulation in healthy subjects and patients.

Regarding the food effect study the Clinical Pharmacology review indicated that, "the AUC and C_{max} were slightly decreased after a low-fat meal (by 11% and 16%, respectively). After a high-fat meal, AUC and C_{max} were increased by 18% and 29%, respectively. The increases in C_{max} due to the change in formulation and due to the effect of a high-fat meal may be additive. Therefore, it is recommended that Jadenu should be taken on an empty stomach or with a low-fat meal."

5. Clinical Microbiology

The Office of Pharmaceutical Science (OPS)/New Drug Microbiology Staff review of the application (BS Riley, 8/1/2014) commented, "The NDA for JADENU does not include a Microbial Limits specification for drug product release or stability; however, the applicant provides a suitable rationale for the exclusion of this testing." The review considered factors including (b) (4) , manufacturing environment, and evaluation of microbial limits for 30 batches of the drug product. The review concluded that the microbiological quality of

the drug product is suitably controlled and recommended the application for approval from the standpoint of product quality microbiology.

6. Clinical/Statistical- Efficacy

The Clinical Review of this application was conducted by A Dmytrijuk, M.D., (final signature 3/17/2015). No new clinical efficacy studies were conducted for this application. Dr. Dmytrijuk's Clinical Review discusses that the current application for Jadenu cross-references the safety and efficacy findings for Exjade in NDA 21882. Exjade is 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 Dr. George Shashaty and Dr. Donna Przepiorka (10/26/2005 and 1/9/2013, respectively).

Dr. Dmytrijuk's review notes that because the bioavailability of the Jadenu product (based on AUC) is greater than that of Exjade as described under section 4 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 finds that the proposal appears to be reasonable and also notes that, similar to Exjade, the Jadenu dose adjustment during treatment for the indicated patient populations is based on serum ferritin level and LIC which limits potential overexposure to Jadenu.

7. Safety

The Clinical Review of the safety aspects of this application was conducted by A Dmytrijuk, M.D., (final signature 3/17/2015).

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

Regarding safety of Jadenu the Clinical Review comments, "Review of safety in the studies supporting the Jadenu application NDA 206910, i.e., studies F2101, F2102 and F2103, does not raise new or additional safety concerns for Jadenu compared to the marketed Exjade product. These studies were conducted in normal healthy male and female subjects. The safety labeling described in the Exjade product label is the same the safety labeling for the proposed Jadenu product label." Dr. Dmytrijuk states further that review of the most recent Annual

Report for Exjade NDA 21882 (submitted December 19, 2014 and covering period November 2, 2013 to November 1, 2014) did not identify any new safety issues.

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 Dr. Dmytrijuk's Clinical Review (3/17/2015) the sponsor requested a waiver of requirement for pediatric studies under PREA for the current application. The sponsor cited previous communication with the Agency under IND 58554 regarding the proposed Pediatric Study Plan (PSP) (b) (4)

(b) (4)

10. Other Relevant Regulatory Issues

Initial review of the proposed proprietary name Jadenu by the Division of Medication Error Prevention and Analysis (DMEPA) (NH Vora, 8/22/2014) found the name acceptable from a safety perspective but concluded that it was unacceptable from a promotional perspective citing concern that the name "Jadenu" implies that Jadenu (deferasirox) is a new drug (rather than a new formulation of deferasirox). Review of a request from the sponsor for reconsideration of the proposed proprietary name which included marketing research data provided by the sponsor found the additional information sufficiently convincing and concluded the name Jadenu is acceptable (NH Vora, final signature 12/2/2014). A letter to the sponsor (12/3/2014) informed the sponsor that the name Jadenu was "conditionally acceptable" and stated that, "if any of the proposed product characteristics as stated in your October 22, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review."

The Office of Scientific Investigtions declined to inspect the clinical site and analytical site for Study F2102 stating that these sites have been inspected on other occasions during recent years with no significant observations identified.findings (JB Patel, 10.22.2014).

11. Labeling

The sponsor included proposed labeling in the submission.

Final wording for the labeling for the (b) (4) 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) (J Dvorsky, 2/25/2015). Recommendations included clarifications under Dosage and Administration regarding taking with food and recommendation for consistency of drug name use (Jadenu or deferasirox) within the Warnings and Precautions section. See the OPDP review for detailed recommendations.

Division of Medication Error Prevention and Analysis (DMEPA) review was done by NH Vora (final signature 9/24/2014). The review found the container labels, sample carton labeling, sample container labeling and prescribing information acceptable from the medication error perspective. The review recommended that the sponsor consider providing and education campaign for health care providers to provide clear information on differences between Jadenu and Exjade.

12. Recommendations/Risk Benefit Assessment

Regarding benefit/risk for approval of Jadenu the Clinical Review (A Dmytrijuk, 3/17/2015) states the following.

> The recommendation for the approval of Jadenu is based on the safety and efficacy of the marketed Exjade (deferasirox) product and the available Jadenu supportive safety information from the pharmacokinetic (PK) and bioavailability studies F2101, F2102, F2103. No new or additional safety concerns were identified in this Clinical Review of NDA 206910 for Jadenu or in the review of the Exjade Annual Report NDA 21882 supporting document 982 letter date December 19, 2014 (covering the reporting period from November 2, 2013 to November 1, 2014) completed by Dr. Andrew Dmytrijuk final signature date March 1, 2015. Overall, the risk benefit assessment favors the approval of Jadenu for the same indications as that of Exjade. Jadenu provides a swallowable tablet option of deferasirox for patients with transfusional iron overload and NTDT syndromes.
>
> Jadenu is a film coated tablet 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. Patients who can't swallow tablets still would have the option of receiving Exjade. Because the bioavailability (based on AUC) of Jadenu was 36% greater compared to Exjade, the sponsor proposes an equivalent 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 compared to Exjade, 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 Exjade the Jadenu dose adjustment during treatment for the indicated patient populations is based on serum ferritin level and LIC which limits potential overexposure to Jadenu.

The Clinical Review recommended that the outstanding post-marketing requirements/commitments for Exjade should apply as well to Jadenu. For studies to fulfill these remaining post-marketing requirements patients may receive either Exjade or Jadenu. The postmarketing requirements include the following:

1

Establish a registry for children aged 2 to < 6 years to enroll approximately 200 patients (b) (4) deferasirox and follow them for 5 years. Collect data at least monthly for renal function and blood pressure and yearly for growth and development. Submit your monitoring scheme for our review and comment.

2

Conduct a trial to assess the long-term efficacy and safety of deferasirox in patients with NTDT and high LIC. The trial should assess response rates in the subset of patients with baseline LIC values >15 mg Fe/g dw (proportion of patients achieving an LIC <5 mg Fe/g dw and time to achieving an LIC <5 mg Fe/g dw). Follow-up of all subjects for up to 5 years is necessary.

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.

4

Conduct a prospective, randomized trial in 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.

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.

6

Conduct an enhanced pharmacovigilance study (including proactive surveillance and follow-up of spontaneous reports) to characterize the frequency and severity of adverse events of special interest (ESIs), defined as deaths, and severe or serious events of kidney or liver toxicity, in adults receiving deferasirox for documented iron overload related to multiple transfusions for myelodysplastic syndrome with anemia requiring transfusions. This study does not replace monitoring and reporting as required by regulations.

7

Complete a study of long-term follow-up (3 years) in 150 patients with myelodysplastic syndromes (MDS) receiving deferasirox to evaluate safety (including cardiac, hepatic, endocrine and renal) and hematologic and clinical benefit of deferasirox in these patients.

8

Conduct a trial to assess ocular toxicity in patients receiving deferasirox. Examinations should include distance visual acuity, applanation tonometry, lens photography, and wide angle fundus photography of retina and optic nerve and should be done at baseline (prior to deferasirox initiation) and at six month intervals. At least 60 patients should complete 2years of follow-up.

9

Conduct a trial to assess the long term safety of deferasirox in patients with NTDT by conducting a trial of deferasirox for the treatment of iron overload (LIC ≥5 mg Fe/g dw) in non-transfusion dependent thalassemia (NTDT) in patients aged 10 years and greater with up to 5 years total follow-up.

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 should also be under Accelerated Approval regulations.

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/s/

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03/31/2015