Office of Clinical Pharmacology Review

BLA Number/Supplement	021882 / S28; 206910 / S09; 207968 / S04
Link to EDR	\\CDSESUB1\evsprod\NDA021882\0250 (Exjade tablets) \\CDSESUB1\evsprod\NDA206910\0095 (Jadenu tablets) \\CDSESUB1\evsprod\NDA207968\0045 (Jadenu Sprinkle granules)
Submission Date	06/15/18
Submission Type	Priority
Brand Name	Jadenu, Exjade
Generic Name	Deferasirox
Dosage Forms and Strengths	Jadenu Tablets: 90 mg, 180 mg, 360 mg. Jadenu Sprinkle granules: 90 mg, 180 mg, 360 mg. Exjade Tablets: 125 mg, 250 mg, 500 mg
Route of Administration	Oral
Approved Indications	• 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 (Fe/g dw) and a serum ferritin greater than 300 mcg/L
Proposed Indications	None
Applicant	Novartis
OCP Review Team	Sriram Subramaniam, PhD; Junshan Qiu Ph.D., Lian Ma (TL), Ruby Leong, Pharm.D. (TL)
OCP Final Signatory	NAM Atiqur Rahman, PhD Director, Division of Clinical Pharmacology V Office of Clinical Pharmacology

1. Executive Summary

The Applicant submitted supplements to NDA 021882, 206910, 207968 with results from a pediatric trial of deferasirox for pediatric exclusivity determination [Written Request (WR) issued on May 29, 2018; Reference ID: 4269682]. The requirement for investigating deferasirox in <1 month of age was waived.

Deferasirox is an iron chelator approved for the treatment of chronic iron overload due to blood transfusions in patients ≥2 years of age, and in patients ≥10 years of age with non-transfusion-dependent thalassemia (NTDT) syndromes with a liver iron (Fe) concentration (LIC) of at least 5 mg Fe per gram of dry weight (Fe/g dw) and a serum ferritin > 300 mcg/L.

Exjade (deferasirox: NDA 021882) tablets for oral suspension (*i.e.*, dispersible tablets: DT: 125 mg, 250 mg and 500 mg) was approved on November 2, 2005. Jadenu (deferasirox: NDA 206910) film-coated oral tablets (90 mg, 180 mg, and 360 mg) and Jadenu Sprinkle (deferasirox: NDA 207968) oral granules (90 mg, 180 mg, and 360 mg) were approved on March 30, 2015 and July 18, 2017, respectively, which the Applicant stated would overcome the palatability issues with Exjade and increase compliance of deferasirox.

The purpose of Study CICL670F2202 was to investigate treatment compliance of the new Jadenu Sprinkle granule formulation compared to Exjade DT formulation in children and adolescents aged ≥ 2 and < 18 years with any transfusion-dependent anemia requiring chelation therapy due to iron overload. The primary objective was to evaluate patient compliance (using stick pack or tablet counts) and change in serum ferritin for both formulations, and secondary objectives included evaluation of pre-dose and post-dose pharmacokinetics (PK) to support patient compliance, and exploration of exposure-response (E-R) relationships for measures of safety and effectiveness. The supplement includes proposed language to update Sections 8.4 of the US prescribing information to describe the findings from the pediatric trial.

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.

1.1 Recommendations

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.

Signatures:

Junshan Qiu, Ph.D. Pharmacometrics Reviewer Division of Pharmacometrics II	**Lian Ma, Ph.D.** Pharmacometrics Team Leader Division of Pharmacometrics II
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DCPV: DDD – B Booth; DD – NA Rahman

2. Summary of Labeling Recommendations

- 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.

3. Overview of the Product and Regulatory Background

For brevity, only QBR questions related to the current submission are addressed below. For additional details, please refer to the clinical pharmacology review in DAARTS for original NDA 021882 (DARRTS 10/11/2005), NDA 206910 (DARRTS ID 3696818), and NDA 207968 (DARRTS ID 4083952).

PERTINENT REGULATORY HISTORY

- 12/17/14: WR (expired January 1, 2018) was issued for a randomized, open-label, two arm phase 2 study to evaluate treatment compliance of a deferasirox granule formulation and a deferasirox DT formulation in children and adolescents aged ≥ 2 and < 18 years at enrollment with any transfusion-dependent anemia requiring chelation therapy due to iron overload. Randomization will be stratified by age groups (2 to <10 years, 10 to <18 years). The study treatment duration will be up to 48 weeks
- 05/29/18: WR was issued and modified to include efficacy duration to 24 weeks, instead of 48 weeks.
- 06/15/18: In the original submission for this supplement, PK and PK/PD data, and bioanalytical report were not provided.
- 7/11/18: In response to the July 6, 2018 information request, PK information was provided, but PK/PD information and analyses were not included.
- 7/27/18: In response to the July 18, 2018 information request, PK/PD information and analyses were provided.
- 9/19/18: In response to the September 14, 2018 information request, renal function data re-estimated as eGFR was provided, including PK/PD analyses for eGFR.

4. Clinical Pharmacology Questions

4.1 What are the design features of the clinical pharmacology and clinical study used to support dosing or claims?

The design of the pediatric trial, Study CICL670F2202, study is summarized in **Table 1**. The study design and PK endpoints are consistent with the revised WR.

Table 1: Study design

Purpose	Parameters
Study Design	Randomized Multicenter, Open-Label, 2-arm
Primary Objectives	• Patient compliance (Q4W) up to 25 weeks and end of treatment • Change in serum ferritin from baseline at 24 weeks
Secondary Objectives	• Pre- and post-dose deferasirox concentrations • Explore PK-PD relationships

Study Population	71 pediatric patients with chelation naïve transfusion dependent anemia • 2 to < 10 years: n=32 for DT & n=30 for Granule • 10 to < 18 years: n=4 for DT & n=5 for Granule • White, Asian, and Black
Proposed Dose	Once daily 20 mg/kg DT or 14 mg/kg Granules. Dose adjustment based on serum ferritin
PK	• Pre-dose at Weeks 1, 3, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, and 45 • 3 hours post-dose at Weeks 5 and 9

4.2 What is the PK characteristics of the drug?

The mean steady-state pre-dose concentrations, which is surrogate for AUC_{tau}, were similar between the granule and DT formulations across visits (**Table 2**). Although the mean 3-hour post-dose concentrations, C_{max}, were higher for the DT formulation at 5 weeks and 9 weeks, there was considerable overlap in variability (**Figure 1**).

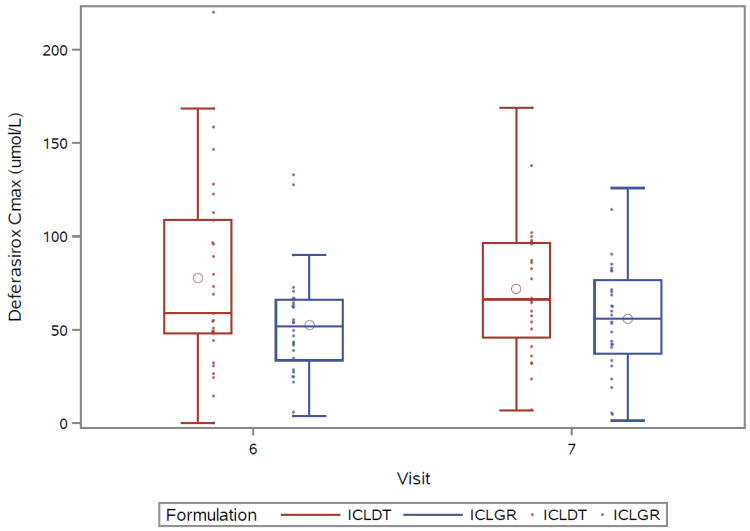
Table 2: Dose adjusted pre-dose deferasirox concentrations by visit for Exjade DT and Jadenu Sprinkle granule formulations

Week	Dose-adjusted Pre-dose Deferasirox Concentrations (µmol/L)*	
	Exjade DT	**Jadenu Sprinkle Granule**
1	1.4 (93)	1.2 (340)
3	14 (133)	12 (119)
5	14 (115)	12 (132)
9	19 (119)	12 (102)
13	19 (122)	14 (109)
17	17 (109)	14 (136)
21	19 (120)	13 (172)
25	17 (148)	17 (99)
29	24 (112)	13 (167)
33	20 (164)	14 (186)
37	19 (135)	15 (130)
41	20 (134)	17 (119)
45	28 (142)	20 (119)

*Geometric mean (%CV of geometric mean); Number of evaluable patients with non-zero concentrations (n) = 7 (for DT and Granule) at Week 1, and n=48-65 (DT) and n=49-71 (Sprinkle Granule) at Weeks 3 to 45. Zero concentrations are considered as missing in geometric mean and Geo-CV calculations.

Source: Table 14.2-6.2, Information Request for CICL670F2202: Exploratory PK/PD, SDN259

Figure 1: Dose adjusted 3-hour post-dose deferasirox concentrations by visit for Exjade DT and Jadenu Sprinkle granule formulations



Red plots correspond to Exjade DT and blue plots correspond to Jadenu Sprinkle granule formulations. Visit 6 and 7 correspond to Weeks 5 and 9, respectively
Source: Reviewer's Analysis

4.3 What are the characteristics of the exposure-response relationship for efficacy and safety?

E-R analyses were explored, consistent with the WR. E-R analyses were conducted for both efficacy endpoint of change in serum ferritin from baseline, and safety endpoints of change in serum creatinine, CLcr, eGFR, and UPCR. Deferasirox pre-dose concentrations (C_{trough}, surrogate for AUC) and renal laboratory parameters at Weeks 1, 3, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, and 45 were used for the analyses. Deferasirox 3-hour post-dose concentrations (C3h, C_{max}) at Weeks 5 and 9, were utilized for the analyses as well. The results show that the pre-dose concentrations appear to correlate with both efficacy and safety endpoints, which are generally consistent with findings from prior E-R analyses with Exjade. The E-R relationships were comparable for the two formulations across visits.

5. Bioanalytical Measurement of Deferasirox

As in the original NDA 207968, a validated liquid chromatography with tandem mass spectrometric detection was used to quantitate deferasirox concentrations in Study CICL670F2202, with a lowest limit of quantitation of 0.67 µmol/L.

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/

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