CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206910Orig1s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM

Date: January 20, 2015
From: Christopher Sheth, Ph.D.
Division of Hematology Oncology Toxicology (DHOT)
Office of Hematology and Oncology Products (OHOP)
Re: Approvability for Pharmacology and Toxicology
NDA: 206910
Drug: Jadenu (deferasirox) film-coated tablets
Applicant: Novartis Pharmaceuticals Corp
Indications: 1. Treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older.
2. 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.

NDA 206910 was submitted on May 30, 2014. The Applicant proposed Jadenu as a film-coated tablet formulation of deferasirox in three strengths of 90 mg, 180mg and 360 mg for oral administration for the treatment of patients with chronic iron overload. The proposed Jadenu tablets will contain deferasirox along with the excipients microcrystalline cellulose, crospovidone, povidone K30, magnesium stearate, colloidal silicon dioxide, and poloxamer 188 (all excipients will be referenced to National Formulary standards). Opadry blue will be used to film-coat the tablets.

Deferasirox is an orally active tridentate iron chelator approved on November 2, 2005 and marketed by the Applicant under the trade name Exjade (NDA 021882) as a dispersible tablet formulation in three strengths of 125 mg, 250 mg, and 500 mg for oral suspension. Exjade tablets contain deferasirox along with microcrystalline cellulose, crospovidone, povidone K30, magnesium stearate, silicon dioxide, lactose monohydrate, and sodium lauryl sulfate (all excipients are referenced to National Formulary standards). The newly proposed formulation of Jadenu is intended to address undesirable characteristics of Exjade that may impact compliance, especially in young children, such as the requirement for a fasting state, the chalky texture of the dispersion, and the volume of liquid for administration (100-250 ml). Jadenu film-coated tablets are to be swallowed once daily and may be taken on an empty stomach or with a low-fat breakfast (i.e., less than 7% fat content).

The Applicant is cross-referencing NDA 021882 for the nonclinical data needed to support product labeling. The nonclinical findings are summarized in the "Executive Summary" of Dr. Tamal Chakraborti's review of NDA 021882 and reflected in the Exjade label. In the current submission to NDA 206910, two pharmacokinetic studies in dogs testing six new tablet formulations to support the pediatric reformulation of deferasirox were reviewed by Dr. Ramadevi Gudi. The proposed tablet formulation was not actually tested in these dog studies, and the pharmacokinetics of the formulations that were studied in dogs were not comparable to the approved dispersible tablets. The Applicant studied the proposed film-coated tablet in humans in clinical pharmacology trials, a bioequivalence study and a food effect study

demonstrating fully equivalent exposure with an AUC_{last} ration of 100% compared to the reference formulation. The proposed nonclinical sections of the Jadenu label are similar to those for the Exjade label with the exception of a labeling format update to reflect the newly published Pregnancy Lactation and Labeling Rule in addition to having different trade names. The nonclinical sections of the Jadenu label were also updated to reflect the change in maximum recommended dose from 20 mg/kg for Exjade to 14 mg/kg for Jadenu. Dr. Chakraborti's review of NDA 021882 noted that $AUC_{0\text{-}24hr}$ for mice are unavailable, thus animal-to-human exposure multiples based on exposures were substituted by comparisons of dose based on body surface area. To maintain consistency the Jadenu label retains comparisons of dose based on body surface area.

Recommendation: I agree with Dr. Ramadevi Gudi, the pharmacology and toxicology reviewer for NDA 206910, that there are no nonclinical issues to preclude the approval of Jadenu for the proposed indications.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTOPHER M SHETH
01/21/2015

JOHN K LEIGHTON
01/21/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	206910
Supporting document/s:	SD 1
Applicant's letter date:	May 30, 2014
CDER stamp date:	May 30, 2014
Product:	Jadenu™ (deferasirox) Film-coated Tablets
Indication:	Chronic iron overload due to blood transfusions (transfusional hemosiderosis)
Applicant:	Novartis Pharmaceuticals Corporation
Review Division:	Division of Hematology Oncology Toxicology (DHOT) for Division of Hematology Products (DHP)
Reviewer:	Ramadevi Gudi, Ph.D.
Acting Team Leader:	Christopher Sheth, Ph.D.
Division Director:	John Leighton, Ph.D. Ann Farrell, M.D. (DHP)
Project Manager:	Linhua Tzeng

Disclaimer

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MEMORANDUM

MEMO DATE: 8/26/2014

TO: To the file for NDA 206910
FROM: Ramadevi Gudi, Ph.D., Pharmacologist; Division of Hematology Oncology Toxicology, DHP
THROUGH: Christopher Sheth, Ph.D., Acting Team Leader; Division of Hematology Oncology Toxicology, DHP

Background

Novartis Pharmaceuticals Corporation submitted a NDA for deferasirox film-coated tablets under a new tradename, Jadenu™, 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 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. Jadenu™ is a new film-coated tablet formulation of a currently approved Exjade® (Deferasirox, ICL670), dispersible tablets (DT) developed by Novartis for oral suspension for the same indication. The Applicant indicates that for some patients specifically children of 2-5 years old, some of the characteristics of the current deferasirox formulation are undesirable and may have an impact on compliance. Some aspects of the drug are reported to reduce adherence to treatment [Mednick et al 2010]. The requirement for a fasting state, the chalky texture of the dispersion, and the volume of liquid for administration (100-250 ml) may be inconvenient. The Applicant indicates that the proposed FCT formulation is expected to improve patient acceptance and compliance.

Nonclinical data:

The nonclinical studies for Exjade® were reviewed during this initial submission of NDA 021882. Studies reviewed included pharmacology; safety pharmacology; pharmacokinetics; general toxicology studies in mice, rats and marmoset monkeys; genetic toxicology; fertility, reproductive performance (Segment I) in rats, teratology (Segment II) in rats and rabbits and peri- and post-natal development (Segment III) in rats; local tolerance studies and carcinogenicity (p53 (+/-) transgenic mice and Wistar (b) (4) rats) studies. Exjade® was also tested orally in juvenile mice and rats to support its use in pediatric patients aged 2 years and above. There were no pharmacology/toxicology issues, and approval was recommended for Exjade by the pharmacology/toxicology review team (Dr. Tamal K. Chakraborti, Ph.D.). The Applicant is cross-referencing the nonclinical data in NDA 021882.

To support the new formulation development of deferasirox, two pharmacokinetic studies (0900739 and 1000323) were conducted in dogs using single oral administration of 375 mg of deferasirox. A total of six new formulations of deferasirox (non-enteric coated tablet, enteric-coated tablet I, enteric-coated tablet II, enteric-coated pellet, non-coated pellet I, and non-coated pellet II) were tested and compared with DT.

Study 0900739 (*Table 3-1 excerpted from Applicant's NDA*):

- Non-enteric coated tablets (Formulation 2) have comparable exposure to the reference DT formulation.
- The two enteric-coated tablet formulations (Formulation 3, and Formulation 4) showed delayed time to reach tmax and lower (<50%) exposure than DT.

Study 1000323 (*Table 3-2 excerpted from Applicant's NDA*)

- Enteric-coated pellet (Formulation B) resulted in comparable bioavailability to the DT formulation.
- The relative bioavailability of non-coated pellets I (Formulation C) or non-coated pellets II (Formulation D) was 52%, or 169%, respectively compared to DT.

Reviewer agrees with the Applicant's determination that these formulations are not comparable to the approved deferasirox (Exjade) dispersible tablet (DT) from these studies. The Applicant further modified the formulation of deferasirox to use in a pilot pharmacokinetic study in healthy volunteers. These studies will not be reviewed since the to-be marketed film-coated tablet formulation is modified and there are clinical data available in healthy volunteers. No additional pharmacology/toxicology studies were submitted to NDA 206910.

Table 3-1 Pharmacokinetic parameters of deferasirox in Study 0900739

PK parameter Formulation description	Formulation 1 DT	Formulation 2 Non-enteric coated tablet	Formulation 3 Enteric-coated tablet I	Formulation 4 Enteric-coated tablet II
Tmax (h)	1.75 (1 – 3)	1.75 (1 – 2)	4 (2 – 4)	2 (1 – 24)
Cmax (µmol/L)	92.6 ± 24.1	92.9 ± 18.6	32.7 ± 25.8	37.7 ± 24.7
AUC0-48h (h·µmol/L)	442 ± 164	454 ± 52.1	192 ± 101	210 ± 124
Relative bioavailability (%)	100	113 ± 35.3	47.7 ± 25.6	48.7 ± 30.1

Values are median (range) for Tmax, and mean ± SD for others (crossover, n= 8 except Formulation 3)

N=7 for Formulation 3 as one dog that had unexplainable high concentration at 24 hours post-dose was excluded from descriptive statistics

Source: [Study R0900739-Table 1.1]

Table 3-2 Pharmacokinetic parameters of deferasirox in Study 1000323

PK parameter Formulation description	Formulation A DT	Formulation B Enteric-coated Pellet	Formulation C Non-coated pellet I	Formulation D Non-coated pellet II
Tmax (h)	1.75 (1.5 – 3)	1.75 (1 – 4)	2 (1 – 4)	2 (1 – 3)
Cmax (µmol/L)	74.4 ± 15.7	80.4 ± 14.0	36.6 ± 18.0	117 ± 36.9
AUC0-48h (h·µmol/L)	311 ± 77.3	349 ± 126	149 ± 89.6	502 ± 134
Relative bioavailability (%)	100	115 ± 28.1	52.0 ± 22.4	169 ± 48.3

Values are median (range) for Tmax, and mean ± SD for others (n= 8, crossover)

Source: [Study R1000323-Table 1.1]

Clinical data:

Based on discussion with FDA at Type C meeting on February 27, 2012, clinical pharmacology trials with the film-coated tablets, [study F2102], a pivotal bioequivalence study and [study F2103], a food effect study were conducted. It is stated that these studies demonstrated fully equivalent exposure with an AUClast ratio of 100%, however, Cmax did not meet the standard bioequivalence criteria, showing an approximate 30% increase over the reference formulation. This topic was discussed with FDA at a Type C meeting on July 26, 2013 and it was agreed that a registration of the new formulation could be achieved despite these higher Cmax values.

Following clinical studies are included in this filing in support of the film coated tablet (FCT)

Table 1-1 Clinical studies included in the submission

Study no. / Type of study	Title	N	Deferasirox dose (form)	Food
[Study F2101] / pilot bioavailability study	A randomized, open-label, single-center, four-period, cross-over study evaluating the bioavailability of deferasirox (single dose) from three new formulations in comparison to the reference marketed deferasirox formulation in healthy subjects	20	1500mg (uncoated tablets) / 1500mg (DT)	fasted/ fasted
[Study F2102] / pivotal pharmacokinetic comparability study	A randomized, open-label, single-center, phase I, crossover study to evaluate the pharmacokinetic comparability of deferasirox new tablet formulation with the reference dispersible formulation in healthy subjects	32	1080mg (FCT) / 1500mg (DT)	fasted/ fasted
[Study F2103] / food effect study	A single-center, open-label, randomized, cross-over study to investigate the effect of food on the pharmacokinetics of new deferasirox tablet formulation in healthy subjects	25	1080mg (FCT)	fed/ fasted
(b) (4)				
[A2409 PK/PD analysis]	A one-year, open-label, single arm, multi-center trial evaluating the efficacy and safety of oral ICL670 (20 mg/kg/day) in patients diagnosed with transfusion-dependent iron overload: PK/PD analysis.	1744	20 mg/kg body weight/day (dispersible tablet formulation)	

DT= dispersible tablets (current formulation); FCT= film-coated tablets; (b) (4) N= number of subjects exposed to deferasirox; PK/PD: pharmacokinetic/pharmacodynamic

Labeling changes:

Novartis is seeking marketing approval for the film-coated tablets as 90 mg, 180 mg and 360 mg strengths for oral administration for the treatment of patients with chronic iron overload. It is intended to be used for all currently approved deferasirox indications.

According to the dosage and administration section of the label, the recommended dosage is 14 mg/kg body weight once daily in patients with transfusional iron overload. In patients with NTDT syndromes, the recommended initial daily dose is 7 mg per kg body weight once daily. The drug name was changed from (b) (4) to the proposed proprietary name “Jadenu” throughout the label. However, the proposed proprietary name, Jadenu was denied by OPDP (see proprietary name review by Neal Vora Dated August 22, 2014 in DARRTS under NDA 206910). There are no other changes made to the nonclinical sections (8.1 Pregnancy, (b) (4), 12.1 Mechanism of Action and 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility).

Impurities/heavy metals

The drug substance of deferasirox contains residual solvent [redacted] (see below for the levels of residual solvents present in the drug substance, excerpted from the Applicant NDA).

Impurities					
35601.01	Residual solvents by GC ▪ [redacted] ▪ ▪ ▪ ▪	 Not more than [redacted] % Not more than [redacted] % Not more than [redacted] ppm Not more than [redacted] ppm Not more than [redacted] %	-	+ 2)	+ 3)
35661.01	Residual solvents by on-line NIR ▪ [redacted]	 Not more than [redacted] %	+ 6)	-	-

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.

Residual Solvent	Level of residual solvent (mg) per deferasirox dose of 840 mg	ICH Q3C PDE (mg/ppm/day)
[redacted]	NMT [redacted] mg	[redacted] mg
	NMT [redacted] mg	[redacted] mg
	NMT [redacted] PM	[redacted] ppm
	NMT [redacted] PM	[redacted] PM
	NMT [redacted] mg	[redacted] mg

NMT = No More Than

The drug substance of deferasirox contains heavy metals [redacted].

36911.01	Heavy metals by ICP-OES (b) (4)	Not more than (b) (4) ppm Not more than pm each Not more than ppm	+ 5)	+ 5)	-
36941.01	Heavy metals by X-ray fluorescence (b) (4)	Not more than (b) (4) pm Not more than pm each Not more than ppm	+ 5)	+ 5)	-
38061.01	Specific impurity by HPLC (b) (4)	Not more than (b) (4) ppm	-	+ 2)	+ 3)
54001.01	Impurities by HPLC Any unspecified impurity Total impurities	(b) (4) Not more than % Not more than %	+	+	+

2) = These alternate methods may be used for batch release in certain conditions (e.g. equipment failure or legal restrictions such as pharmacopoeias) and contingent on final QA review and approval.
3) = Performed at 0-time only during Stability Testing.
5) = Test 36911.01 "Heavy metals by ICP-OES" is an alternate method to test 36941.01 "Heavy metals by X-ray fluorescence". Only one test must be performed.

For each heavy metal, the proposed drug substance acceptance criteria, the level of each heavy metal for the maximum dose of 840 mg, and the permitted daily exposure (PDE) recommended in the USP and EMA guidelines are shown in the table below.

Heavy metal	Level of heavy metal (µg) per deferasirox dose of 840 mg*	EMA/USP Oral Daily Dose PDE (µg/day)
(b) (4)	(b) (4) µg	(b) (4)
	µg	(b) (4) SP
	µg	USP

*Maximum dose based on 60 kg person.

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.

USP:
http://www.usp.org/sites/default/files/usp_pdf/EN/hottopics/232_ElementalImpuritiesLimits.pdf
EMA:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003587.pdf

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/s/

RAMADEVI GUDI
11/20/2014

CHRISTOPHER M SHETH
11/20/2014