CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207968Orig1s000

NON-CLINICAL REVIEW(S)

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:	NDA 207968
Supporting document/s:	0001
Applicant's letter date:	July 16, 2016
CDER stamp date:	July 21, 2016
Product:	JADENU® Sprinkle (deferasirox) granules
Indication:	Treatment of chronic iron overload
Applicant:	Novartis Pharmaceuticals Corporation
Review Division:	Division of Hematology Oncology Toxicology (DHOT)
Reviewers:	Ramadevi Gudi, PhD
Supervisor/Team Leader:	Christopher M. Sheth, PhD
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Project Manager:	Suria Yesmin

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Executive Summary

Novartis Pharmaceuticals Corporation submitted a NDA 207968 for deferasirox (ICL670) granules under the proposed tradename, JADENU® Sprinkle, 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.

The new formulation JADENU® Sprinkle for oral administration is presented as two different dosage forms: granules packaged in sachets and a film-coated tablet (FCT).

The Applicant submitted nonclinical pharmacokinetic studies (Study No.: dmpk-r1000323 and Study No. dmpk-r0900739) in dogs with various formulations of ICL670 (Exjade). According to the Applicant, ICL670 Formulation D (b) (4), Exjade Batch number: TRD-2692-014 from study no. dmpk-r1000323 and ICL670 Formulation 2, Batch no. TRD-2648-68 from study no. dmpk-r0900739 was the most functionally similar to the new JADENU Sprinkle product.

Brief Discussion of Nonclinical Findings:

The plasma pharmacokinetics of newly developed formulation variants of ICL670 in comparison to commercial Exjade dispersible tablets was investigated in male Beagle dogs. The dogs were administered with single oral doses of 375 mg as four different formulations in a crossover design of 4 periods, with 7-day washout between treatments. The plasma concentrations analysis with ICL670 formulation D (Batch TRD-2692-014) resulted in higher exposure and higher relative bioavailability in comparison with Exjade dispersible tablets. Similar exposure (AUC_{0-48h} and C_{max}) values and concentration-time curves were observed with ICL670 Formulation 2, Batch no. TRD-2648-68 in comparison with Exjade dispersible tablets.

Recommendations

This NDA is approvable from a pharmacology toxicology perspective.

Drug Information

Drug

CAS Registry Number: 201530-41-8

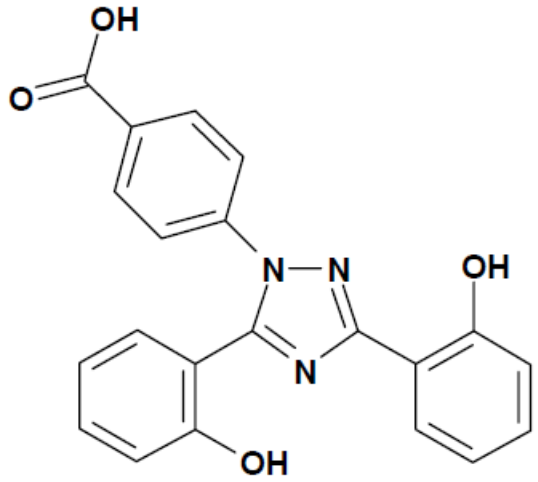
USAN: Deferasirox

Code Name: ICL670, ICL670-NXA, ICL670-NXB, CGP72670

Chemical Name: 4-[3,5-Bis(2-hydroxyphenyl)-[1,2,4]-triazol-1-yl]benzoic acid
Commercial name: Exjade® dispersible tablets

Molecular Formula/Molecular Weight: C21H15N3O4/ 373.36

Structure or Biochemical Description



Pharmacologic Class: Iron Chelator

Regulatory Background

An Information Request was sent to the Applicant on December 14, 2016 as follows:

In reference to the two DMPK dog studies (1.Study # dmpk-r1000323 and 2.Study # dmpk-r0900739), please clarify which formulation given to dogs is most similar to the New formulation JADENU® Sprinkle (deferasirox) granules.

The Applicant's response was received on 12/16/2016

In study DMPK-r1000323 formulation TRD-2692-014, and in study DMPK-r0900739 formulation TRD-2648-68, were functionally the most similar to the new JADENU® Sprinkle drug product.

Pharmacokinetics

Study title: A crossover pharmacokinetic study of ICL670 following single oral administration to Pentagastrin-pretreated nonnaïve male Beagle dogs
Study No.: dmpk-r1000323

Key Findings:

ICL670 formulation D (Batch TRD-2692-014) which is the most similar to the new JADENU® Sprinkle drug product (according to the Sponsor) (b) (4) resulted in a higher exposure and higher relative bioavailability in dogs in comparison with Exjade Tablets.

Methods:
Eight male Beagle dogs of age 6 months to 2 years old, weighing 8-10 kg were pretreated with pentagastrin intramuscularly at 6 µg/kg and I h later received 375 mg dose via oral gavage of formulations as shown in the table below.

Table -1: Treatment of dose groups

Group/ Period	Date of Administration	Test Article	Formulation	Batch N.	Nominal Dose (mg/dog)	Dose Route
1/1	Jul-08-2010	ICL670	Suspension	2008-0846 for 125mg tablet and 2007-0628 for 250mg tablet	375	p.o.
1/2	Jul-15-2010	ICL670	(b) (4)	TRD-2648-110	375	p.o.
1/3	Jul-22-2010	ICL670		TRD-2692-012	375	p.o.
1/4	Jul-29-2010	ICL670		TRD-2692-014	375	p.o.

Plasma pharmacokinetics of ICL670 was studied after oral administration in a crossover design of 4 periods, with 7-day washout between treatments of the newly developed formulation variants in comparison to commercial Exjade dispersible tablets.

Test article used:

1. Formulation A: **Exjade dispersible tablets** Batch number: VLMK/2008-0846 for 125 mg tablet and VMLK/2007-0628 for 250 mg tablet
2. Formulation B: (b) (4) form B Exjade LCM minitablets Batch number: TRD-2648-110
3. Formulation C: (b) (4) form C Exjade LCM multiparticulates Batch number: TRD-2692-012
4. Formulation D: (b) (4) form D Exjade LCM multiparticulates Batch number: TRD-2692-014

Blood samples were collected at pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24 and 48 hrs post-dose.

Results

Clinical signs: Loose feces were observed in one animal in Period 2, dosed with [redacted] (b) (4) (Batch TRD-2648-110). Loose feces mixed with white and colorless jelly-like excretion was found in one dog dosed in Period 4 [redacted] (b) (4) (Batch TRD-2692-014).

Plasma Analysis:

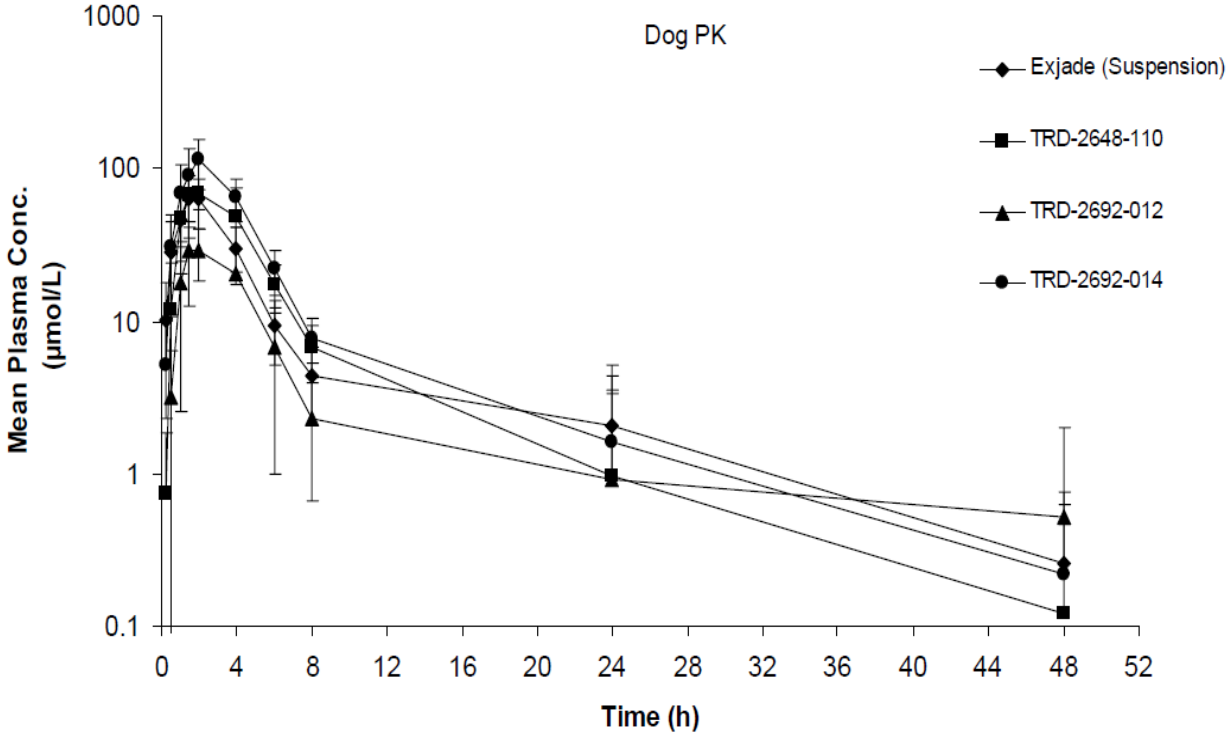
- The mean Cmax reached at approximately 2 h post dose after administration of 375 mg ICL670 in different formulations.
- Exposure (Cmax and AUC0-48h) was the highest after dosing [redacted] (b) (4) in Period 4 followed by [redacted] (b) (4) in Period 2, exjade tablets in Period 1 and [redacted] (b) (4) in Period 3.
- Similar pattern was observed with the relative bioavailability. It was the highest after dosing with [redacted] (b) (4) in Period 4 followed by [redacted] (b) (4) in Period 2, exjade tablets in Period 1 and [redacted] (b) (4) in Period 3.

Table-2: Mean Plasma Pharmacokinetic Parameters of ICL670

Parameter	Period 1 (mean ± SD)	Period 2 (mean ± SD)	Period 3 (mean ± SD)	Period 4 (mean ± SD)
Compound form:	Suspension of Exjade tablets, formulation A	[redacted] (b) (4) formulation B	formulation C	formulation D
Batch number	2008-0846 and 2007-0628	TRD-2648-110	TRD-2692-012	TRD-2692-014
Actual ICL670 dose (mg/dog):	375	375	375	375
Cmax (µmol/L)[c]:	74.4 ± 15.7	80.4 ± 14.0	36.6 ± 18.0	117 ± 36.9
Tmax (h)[a]:	1.75	1.75	2	2
Tlast (h)[a]:	24	8	8	8
AUC0-48h (µmol/L *h)[c]:	311 ± 77.3	349 ± 126	149 ± 89.6	502 ± 134
AUCinf (µmol/L *h)[c]:	315 ± 93.3	321 ± 135	122 ± 69.7	474 ± 148
Relative bioavailability[b]:	1.00 ± 0.00	1.15 ± 0.281	0.520± 0.224	1.69 ± 0.483

[a] median
[b] Calculated as: AUC0-48h Period x/AUC0-48h period 1
[c] Geometric mean

Figure-1: Mean (± SD) plasma concentration profiles of ICL670 following oral administration (375 mg/dog) in male Beagle dogs



Study Title: Pharmacokinetics of ICL670 after oral administration of 375 mg as four formulations in dogs.
Study No. dmpk-r0900739:

The pharmacokinetics of ICL670 (Exjade) after single oral doses of 375 mg as four different formulations in Pentagastrin® pre-treated male Beagle dogs was studied.

Key Findings:

- The exposure (AUC0-48h and Cmax) for the [redacted] (b) (4) tablet (form 2) which is the most similar to the new JADENU® Sprinkle drug product (according to the Sponsor) and the commercial Exjade dispersible tablets (form 1) showed similar values and concentration-time curves to ICL670.
- The two [redacted] (b) (4) tablet forms (Form 3 and Form 4) exhibited delayed time to reach maximum concentration and lower plasma exposure and showed about 2-fold lower relative bioavailability

Methods:

Eight male beagle dogs of 6 months to 2 years old, weighing 6.36 to 8.50 kg were pre-treated with pentagastrin followed by the administration of ICL670 after one hour.

Treatment of Dosing Groups

Formulation	Dose (mg)	Characteristics
1	375 (one 125 mg and one 250 mg tablet per dog)	Form 1: Commercial Exjade dispersible tablets. 125 mg and 250 mg dose strengths. Batch #: S0002 for 125 mg tablet and S0010 for 250 mg tablets as suspension in 50 mL water
2	375	Form 2: [redacted] tablet, HPMC as binder, 375 mg dose strength. Batch #: TRD-2648-68
3	375	Form 3: [redacted] tablet, HPMC as binder. 375 mg dose strength. Batch #: TRD-2648-73
4	375	Form 4: [redacted] tablets, WG, PVP as binder, 375 mg dose strength. Batch #: TRD-2692-001

Dogs were dosed as described below:

Treatment group	Treatment 1	Treatment 2	Treatment 3	Treatment 4
Dosing date	17-Nov-2009	24-Nov-2009	2-Dec-2009	9-Dec-2009
Form	1	2	3	4

Blood samples were collected at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24 and 48 h post dose.

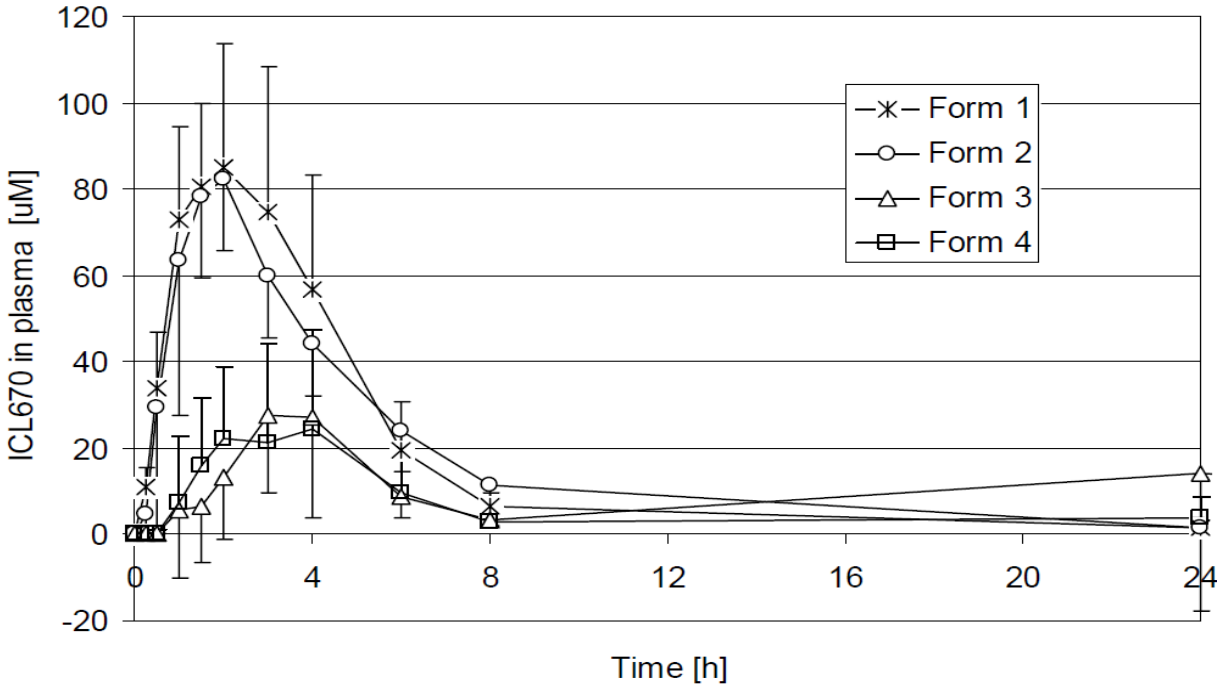
Results

Table 3: Pharmacokinetic parameters of ICL670 in plasma

PK parameter	Form 1	Form 2	Form 3 [c]	Form 4
Tmax (h)[a]	1.75 [1 - 3]	1.75 [1 - 2]	4 [2 - 24]	2 [1 - 24]
Cmax (µM)	92.6 ± 24.1	92.9 ± 18.6	40.2 ± 32.0	37.7 ± 24.7
AUC0-48h (h·µM)	442 ± 164	454 ± 52.1	423 ± 659	210 ± 124
Relative bioavailability (%) [b]	100	113 ± 35.3	101 ± 151	48.7 ± 30.1

a: median [range]; b: bioavailability relative to form 1; c: When excluding dog 103 for descriptive statistics, PK parameters were 4 [2 - 4], 32.7 ± 25.8, 192 ± 101 and 47.7 ± 25.6 for Tmax (h), Cmax (µM), AUC0-48h (h·µM) and relative bioavailability (%), respectively.

Figure 2: Mean plasma concentrations



Labeling

There are no new labelling changes to the nonclinical sections.

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/s/

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05/02/2017

CHRISTOPHER M SHETH
05/02/2017