

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 21-882	Submission Date(s): 12/23/2011
Brand Name	Exjade
Generic Name	deferasirox
Reviewer	Joseph Grillo, Pharm.D.
Team Leader	Julie Bullock, Pharm.D.
OCPB Division	DCP-5
ORM division	OND/ OHOP/DHP
Sponsor	Novartis
Relevant IND(s)	58,554
Submission Type; Code	Efficacy supplement (SDN# 678)
Formulation; Strength(s)	Tablets for oral suspension: 125 mg, 250 mg, 500 mg
Indication	The treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older

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1 EXECUTIVE SUMMARY

Exjade (deferasirox) is an orally active chelator that is selective for iron and is indicated for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. The applicant is now seeking approval for the treatment of chronic iron overload in patients with non-transfusion-dependent thalassemia syndromes (NTDT) aged 10 years and older.

The safety and efficacy of deferasirox in the treatment of patients with NTDT and iron overload is based on a prospective, randomized, double-blind, placebo-controlled, phase II Trial (Trial A2209). Since pharmacokinetic samples were not obtained in this trial formal exposure-response and exposure-safety analyses in the NTDT population were not conducted. The incidence of certain AE's (i.e., headache, rash, fatigue, rhinitis, and dyspepsia), severe AE's, and increases in serum creatinine were higher in the 10 mg/kg/day dose compared to 5 mg/kg/day.

Trial A2202/E was conducted in the hereditary hemochromatosis (HH) population and was also submitted in this application to provide additional safety data. A descriptive analysis of trough concentrations was conducted in this trial. (b) (4)

1.1 Recommendation

From a clinical pharmacology perspective, this efficacy supplement is ACCEPTABLE provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert.

1.2 Post Marketing Requirements

None

1.3 Post Marketing Commitments

None

1.4 Comments to the Applicants

None

1.5 Summary of Important Clinical Pharmacology Findings

Exjade (deferasirox) is an orally active chelator that is selective for iron and is indicated for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. The applicant is now seeking approval for the treatment of chronic iron overload in patients with non-transfusion-dependent thalassemia syndromes (NTDT) aged 10 years and older. The safety and efficacy of deferasirox in the treatment of patients with NTDT and iron overload is based on a prospective, randomized, double-blind, placebo-controlled, phase II trial (Trial A2209). A phase I/II open-label, dose escalation trial in hereditary hemochromatosis (HH) patients (Trial A2202/E), was also submitted to provide additional safety and pharmacokinetic data.

Since pharmacokinetic samples were not obtained in Trial A2209, formal exposure-response and exposure-safety analyses in the NTDT population were not conducted. The applicant reports that a dose- response effect was observed in the NTDT population, with change in LIC from baseline to Week 52 favoring the 10 mg/kg/day group compared to

the 5 mg/kg/day group (p=0.009). In addition, the incidence of certain AE's (i.e., headache, rash, fatigue, rhinitis, and dyspepsia), severe AE's, and increases in serum creatinine were higher in the 10 mg/kg/day dose compared to 5 mg/kg/day. The reviewer find's the high intersubject variability for exposure and clearance of both deferasirox and the Fe-[ICL670]2 chelate reported in the original NDA limits the usefulness of these dose-response and dose-safety data to estimate true exposure-response and exposure-safety in the NTDT population.

Trough concentrations were obtained in the HH population (Trial A2202/E). The descriptive analysis of these data report that trough levels in patients with HH were higher than those reported in a historical trial of patients with transfusion-dependent iron overload. (b) (4)

Signatures

Joseph Grillo, Pharm.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 5

Julie Bullock, Pharm.D.
Clinical Pharmacology Team Leader
Division of Clinical Pharmacology 5

2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review? (Do not include full details of formulation here. Details go in Biopharmaceutics section.)

Not applicable to this submission.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Exjade (deferasirox) is an orally active chelator that is selective for iron (as Fe³⁺) and is indicated for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. The applicant is now seeking approval for the treatment of chronic iron overload in patients with non-transfusion-dependent thalassemia syndromes (b) (4) aged 10 years and older.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

- Transfusional Iron Overload: Initial oral daily dose is 20 mg/kg body weight. Doses of up to 40 mg/kg may be considered dependant on clinical response. [approved]
- Non-transfusion-dependent Thalassemia Syndromes (NTDT): Initial oral daily dose is 10 mg/kg body weight. Doses of up to 20 mg/kg may be considered dependant on clinical response. [under review]

2.2 General Clinical Pharmacology

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

The safety and efficacy of deferasirox in the treatment of patients with NTDT and iron overload is based on Trial A2209, a prospective, randomized, double-blind, placebo-controlled, phase II trial. Patients enrolled in Trial A2209 were males or females, at least 10 years old, with NTDT syndromes and iron overload. Two deferasirox starting dose regimens (5 and 10 mg/kg/day) were evaluated. Each deferasirox regimen had a matching placebo. The change in LIC from baseline to Week 52 was the primary efficacy endpoint. Pharmacokinetics (PK) was not evaluated in this trial.

A phase I/II open-label, dose escalation trial in hereditary hemochromatosis (HH) patients (Trial A2202/E), was also submitted to provide additional safety data. Patients received one of four planned deferasirox dose levels: dose level 1 (5 mg/kg/day), dose level 2 (10 mg/kg/day), dose level 3 (15 mg/kg/day) and dose level 4 (20 mg/kg/day). All patients received treatment for 24 weeks in the core trial and an additional 6 months in the extension phase. Out of the 37 patients completing the core trial, 26 chose to continue with the extension and 23 completed the extension trial. The applicant also submitted PK trough data from this trial.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

Defer to the Clinical reviewer regarding the adequacy of the efficacy and safety endpoints used in trial A2209.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships? (If yes, refer to 2.6, Analytical Section; if no, describe the reasons.)

Not applicable to this submission.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

A formal exposure-response analysis in the NTDI population was not conducted; however, the applicant reports that a dose response effect was observed, with change in LIC from baseline to Week 52 being in favor of the 10 mg/kg/day group compared to the 5 mg/kg/day group (p=0.009). In addition, the effect of dose escalation appeared more pronounced in patients whose starting dose was 10 mg/kg/day. These patients achieved the greatest reduction in LIC at Week 52 (-4.02 mg Fe/g dry weight [dw]) after being dose escalated to 20 mg/kg/day. In contrast, patients who were treated with 10 mg/kg/day throughout the trial showed a smaller decrease in LIC (-3.57 mg Fe/g dw). Patients treated with 5 mg/kg/day throughout the trial and those who started at 5 mg/kg/day and then were dose escalated to 10 mg/kg/day achieved a comparable reduction in LIC (-1.88 and -1.82 mg Fe/g dw, respectively). While these results may be useful in determining the efficacy of deferasirox in NTDI, the reviewer finds the high intersubject variability for exposure and clearance of both deferasirox and the Fe-[ICL670]2 chelate, noted in the original NDA (See OCP review by Dr.'s Al-Fayoumi and John 10/11/2005), limits the usefulness of these dose-response data to estimate exposure-response.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

A formal exposure-safety analysis in the NTDI population was not conducted; however, the applicant reports that headache, rash, fatigue, rhinitis, and dyspepsia were more frequent (at least 5% difference) in the 10 mg/kg/day deferasirox group than the 5 mg/kg/day deferasirox group. The incidence of severe AEs were also higher in the 10 mg/kg/day dose than the 5 mg/kg/day dose groups. In addition, mean creatinine levels increased slightly over time in both deferasirox- and placebo treated patients (median increase ranging from 12.1 to 7.4%), with the highest increase observed in patients treated with 10 mg/kg/day deferasirox. The proportion of patients with more than one gastrointestinal event was also higher in the 10 mg/kg/day deferasirox group. The reviewer finds the high intersubject variability for exposure and clearance of both

deferasirox and the Fe-[ICL670]₂ chelate, as discussed above, limits the usefulness of these data to estimate exposure-safety.

2.2.4.3 Does this drug prolong the QT or QTc interval? (You must answer this question, unless this is addressed in the question above.)

Not applicable to this submission.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

See Sections 2.2.4.1 and 2.2.4.2. The dose of Exjade proposed by the applicant is within the range currently approved. Since exposure-response and safety-response were not determined we defer to the Clinical reviewer regarding the appropriateness of the dose in NTDT in light of the reported efficacy and safety analysis.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters? (Provide tables to refer to in subsequent questions in this section.)

Trough concentrations, for a descriptive pharmacokinetic analysis, were obtained in patients with iron overload resulting from HH [Trial A2202]. The reported increase in mean trough levels of deferasirox appeared dose-proportional in the dose range of 5 to 15 mg/kg/day at week 4, but the trend of dose-proportionality was not apparent thereafter (Table 1). There was minor fluctuation in the trough concentrations at the presumed steady-state trough levels of deferasirox on repeated dosing for 24 weeks. Overall the reviewer finds the reported trough concentrations limited by the high variability.

Table 1: Mean (CV) trough levels of deferasirox by dose

		Exjade Dose		
		5 mg/kg (N=11)	10 mg/kg (N=15)	15 mg/kg (N=22)
Week 4	N	10	14	17
	Trough (µmol/L)	9.6 (91.2)	19.6 (48.4)	30.5(66.3)
Week 8	N	10	12	17
	Trough (µmol/L)	8.9 (65.8)	23.9(95.4)	27.1(80.2)
Week 12	N	10	12	13
	Trough (µmol/L)	10.6 (111.1)	28.7 (83.1)	23.4(48.7)
Week 16	N	10	11	11
	Trough (µmol/L)	12.4 (93.9)	21.6 (76.5)	21.8 (85.8)
Week 20	N	9	10	8
	Trough (µmol/L)	11.7 (88.1)	26.5(67.7)	27.6(91.8)
Week 24	N	10	9	6
	Trough (µmol/L)	14.6 (83.6)	21.3 (102.4)	26.8 (41.7)

The overall deferasirox trough levels in patients with HH were higher than those reported previously in patients with transfusion-dependent iron overload.¹ While the baseline serum ferritin levels reported in HH patients (676 to 849ng/mL) were much lower than previously

¹ In Trial A0105, conducted in patients with transfusion-dependent iron overload, deferasirox trough levels on Days 15 to 360 ranged from 10.1 to 14.5 µmol/L at 10 mg/kg, and from 13.8 to 20.6 µmol/L at 20 mg/kg.

reported in patients with transfusion-dependent iron overload (serum ferritin levels >2000 ng/mL), the possible impact of this finding on the reported exposure difference between the HH and the transfusion-dependent iron overload populations is unknown.

(b) (4)

2.3 Intrinsic Factors

Not applicable to this submission.

2.4 Extrinsic Factors

Not applicable to this submission.

2.5 General Biopharmaceutics

Not applicable to this submission

2.6 Analytical Section

Not applicable to this submission

3 DETAILED LABELING RECOMMENDATIONS

No Clinical Pharmacology related labeling issues

4 APPENDIX

4.1 Filing Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

NDA/BLA Number	021882	Brand Name	Exjade
OCP Division (I, II, III, IV, V)	5	Generic Name	deferasirox
Medical Division	DHP	Drug Class	Iron Chelator
OCP Reviewer	Joseph Grillo, Pharm.D.	Indication(s)	<ul style="list-style-type: none"> The treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. (Approved) The treatment of chronic iron overload in patients with non-transfusion-dependent thalassemia syndromes (b) (4) aged 10 years and older. (under review)
OCP Team Leader	Julie Bullock, Pharm.D.		
Pharmacometrics Reviewer	N/A		
Date of Submission	12/23/2011		
Estimated Due Date of OCP Review	9/12/12		
Medical Division Due Date	9/18/12		
PDUFA Due Date	10/23/12		
Dosage Form	Tablets for oral suspension: 125 mg, 250 mg, 500 mg.		
Dosing Regimen	<ul style="list-style-type: none"> Transfusional Iron Overload: Initial daily dose is 20 mg/kg body weight. Doses of up to 40 mg/kg may be considered dependant on clinical response. (approved) Non-transfusion-dependent Thalassemia Syndromes (NTDT): Initial daily dose is 10 mg/kg body weight. Doses of up to 20 mg/kg may be considered dependant on clinical response. (under review) 		
Route of Administration	Oral		
Sponsor	Novartis		
Priority Classification	Standard		

Clin. Pharm. and Biopharm. Information

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			For patients with hereditary hemochromatosis (HH) not NTDT
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	1		Troughs in patients with HH not NTDT
Dose proportionality -				

fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 1:				
Phase 2/3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	1		NTDT population. No exposure or PK. Analysis based on different doses
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	X			Waiver requested
Literature References				
ECG Monitoring				
Biomarkers				
Immunogenicity Testing				
Total Number of Studies		2		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	

	Content Parameter	Yes	No	N/A	Comment
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	PK for HH population only
5	Has a rationale for dose selection been submitted?	X			Multiple doses studied
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
11	Is the appropriate pharmacokinetic information submitted?		X		Purpose of HH exposure for NTDT indication unclear
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X		Analysis for NTDT based on dose and response/safety. No exposure information collected.
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Requested waiver
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	Requested waiver
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and			X	

	Content Parameter	Yes	No	N/A	Comment
	provided in this submission?				

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

No ___ Yes X

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

- N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- None

Reviewing Clinical Pharmacologist

Date

Team Leader/Supervisor

Date

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

/s/

JOSEPH A GRILLO
12/04/2012

JULIE M BULLOCK
12/05/2012