CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206910Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA # Supplement #	206910
Applicant Name	Novartis Pharmaceuticals, Inc.
Date of Submission	05/30/14
PDUFA Goal Date	3/30/15
Proprietary Name / Established (USAN) Name	Jadenu/deferasirox
Dosage Forms / Strength	Film-coated oral Tablets/90 mg, 180 mg, and 360 mg
Proposed Indication(s)	Same as Exjade
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Andrew Dmytrijuk, M.D./Kathy Robie-Suh, M.D., Ph.D.
Statistical Review	
Pharmacology Toxicology Review	Ramadevi Gudi, Ph.D./Christopher Sheth, Ph.D.
CMC Review/OBP Review	Josephine Jee, Ph.D./Banu Sizanli Zolnik, Ph.D./Angelica Dorantes, Ph.D./Paul Seo,Ph.D.
Microbiology Review	Bryan S. Riley, Ph.D./Stephen Metcalfe, Ph.D.
Clinical Pharmacology Review	Wenchi Hsu, Ph.D., Lian Ma Ph.D., Nitin Mehrotra, Ph.D., Sara Schrieber, Pharm.D.
OPDP	James Dvorsky/Katie Davis
OSI	Jyoti Patel, Ph.D./Sam H. Haidar, Ph.D., R. Ph. William Taylor, Ph.D.
CDTL Reviews	Kathy Robie-Suh, M.D., Ph.D.
OSE/DMEPA	Neil Vora, Pharm, D.,M.B.A./Yelena Maslov, Pharm.D./Lubna Merchant, Pharm.D., M.S.

Signatory Authority Review Template

1. Introduction

Deferasirox is an iron chelating agent approved. On November 2, 2005, Exjade (deferasirox) was initially approved under the accelerated approval regulations for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older. On January 23, 2013, Novartis was granted approval for the treatment of chronic iron overload in patients with non-transfusion-dependent thalassemia syndromes. This application is for a new formulation of deferasirox that the applicant proposes will address the palatability issues.

Currently Exjade has accelerated approval.

On May 30, 2014, Novartis submitted this NDA for Jadenu (deferasirox, new film-coated tablets: 90 mg, 180 mg, and 360 mg). This application contains clinical pharmacology trials, a bioequivalence study and a food effect study demonstrating fully equivalent exposure with respect to AUC; however, not with respect to Cmax.

2. Background

This application is for a new formulation of deferasirox. Other iron chelators are currently approved: Desferal (deferoxamine mesylate) and Ferriprox (deferiprone).

3. CMC/Device

Dr. Jee reviewed this application. In her review she states the following:

From CMC perspective, this application is approvable pending recommendation from Biopharmaceutics. EES has an overall "Acceptable" recommendation for this NDA.
Review of the package insert labeling and container and carton labels are found adequate by DMEPA and CMC.
An expiration dating period of 24-month is granted for Deferasirox Film-Coated Tablets (30 tablets bottle) when stored at 25oC (77 oF); excursions permitted between 15oC to 30oC (59oF to 86oF). Protect from moisture. An expiration dating period of 6 months is granted for Deferasirox Film-Coated, Physician Samples (4 tablets bottle).

No microbiology issues exist that would preclude approval.

4. Nonclinical Pharmacology/Toxicology

No issues exist that would preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

No issues exist that would preclude approval.

The following text is from the Clinical Pharmacology review:
A food-effect study involving administration of Jadenu to healthy subjects under fasting conditions and with a low-fat (fat content <7% of total calories) or high-fat (fat content >50% of total calories) meal indicated that the AUC and Cmax were slightly decreased after a low-fat meal (by 11% and 16%, respectively). After a high-fat meal, AUC and Cmax were increased by 18% and 29%, respectively. The increases in Cmax 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.

The Office of Clinical Pharmacology recommends approval and Division of Biopharmaceutics secondary review recommends approval.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

No issues arose that would preclude approval.

8. Safety

No new issues were identified.

9. Advisory Committee Meeting

N/A

10. Pediatrics

The applicant will be required to develop this formulation for use in the pediatric patient population. This application will have the same PMRs as those established for Exjade.

11. Other Relevant Regulatory Issues

Office of Scientific Investigation (DSI)
The recommendation from this Office was approval.

There are no other unresolved relevant regulatory issues.

12. Labeling

The labeling was reviewed by all disciplines and consultant staff.

13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action

Accelerated Approval based on the accelerated approval status for Exjade. All unfulfilled PMR/PMCs for Exjade will also be required for Jadenu.

- Risk Benefit Assessment – Jadenu is a 505 b1 application relying on the studies and nonclinical data submitted for Exjade in addition to a few clinical pharmacology studies necessary to establish a scientific bridge for the Jadenu formulation.

- Recommendation for Post marketing Risk Management Activities- Routine pharmacovigilance

- Recommendation for other Post marketing Study Requirements (PMR)/ Commitments (PMC)- (see letter for final language)

  Accelerated Approval PMRs

  Establish a registry for children aged 2 to < 6 years to enroll approximately 200 patients receiving deferasirox and follow them for 5 years. Data collection will be at least monthly for renal function and blood pressure and yearly for growth and development. Submit your monitoring scheme for our review and comment.

  Conduct a trial to assess the long-term efficacy 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.

  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.

  Conduct a prospective, randomized trial in at least 210 patients with low to intermediate risk myelodysplastic syndromes (MDS) receiving deferasirox for transfusional iron overload (approximately 140) or placebo (approximately 70) to determine the efficacy and safety of (b) (4)

(deferasirox) in this population. The trial will continue for 3 years from the date the last patient is enrolled.

PMRs under 505 (o)

Establish a registry of children (aged 10 to <18 years old at enrollment) with NTDT and treated with deferasirox for documented iron overload. (b) (4) follow at least 40 children for up to 5 years to assess and analyze the long-term safety of treatment with (b) (4) (deferasirox), including an assessment of growth, compared to children on a regular transfusion program receiving (b) (4) (deferasirox) (based on historical data). Provide annual interim reports on enrollment and outcomes. 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 all 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. (b) (4) This study does not replace monitoring and reporting as required by regulations.

Complete 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.

Conduct (b) (4) 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 2 years of follow-up.

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/s/

ANN T FARRELL
03/30/2015