CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205582Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

CDTL Review

Date	January 6, 2014
From	Albert Deisseroth, MD, PhD
Subject	CDTL Review
NDA Number	NDA 205582
Applicant	Sun Pharma Global FZE
Date of Submission	March 25, 2013
PDUFA Goal Date	January 27, 2014
Established Name	Decitabine for Injection
Dosage forms/Strength	Lyophilized powder containing 50 mg of decitabine in a 20 mL glass vial
Applicant's Proposed Indication	Treatment of patients with myelodysplastic syndromes (MDS)
Recommended:	Approval

Material Reviewed/Consulted	Reviewer/Author
Medical Officer Review	Thomas Herndon, MD
Pharmacology/Toxicology	Pedro L. Del Valle, PhD
CMC	William M. Adams, PhD
Regulatory Program Manager	Lara Akinsanya

TABLE OF CONTENTS

1. INTRODUCTION (This section was excerpted in part from the review of Dr. Tom Herndon):

On December March 25, 2013, Sun Pharmaceuticals Global FZE submitted a NDA under the Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, and as such, relies on publically available information. Three sources of safety information were presented in the application: the approved label for Dacogen, published reports and adverse events reported to the FDA post approval of Dacogen.

The proposed indication is the same as that for Dacogen: Treatment of patients with myelodysplastic syndrome (MDS).

Decitabine for Injection is a new formulation that differs from that of Dacogen. The drug product is the same (lyophilized powder containing 50 mg of decitabine in a 20 mL glass vial). However, in contrast to Dacogen, in which the drug product contains monobasic potassium phosphate and sodium hydroxide (b) (4) in the glass vial which contains the drug product, De ug product without the monobasic potassium phosphate and sodium hydroxide, which is provided in a separate diluent vial containing 10 mL of Water for Injection. Dacogen is reconstituted in 10 mL of USP water, while Decitabine for Injection is reconstituted in the diluent containing potassium phosphate and sodium hydroxide. Once reconstituted, both Dacogen and Decitabine for Injection result in a solution of the same composition.

Benefit Risk Discussion (This section is excerpted in part from the clinical review of Dr. Tom Herndon):

Efficacy: There are no new efficacy data provided with the application.

CMC: There were two impurities found in Decitabine for Injection: (b) (4) Sun proposed limits of (b) (4) as release criteria respectively for these two impurities.

Non-Clinical: The applicant performed a GLP repeat-dose toxicity study in CD-1 mice to compare the toxicity profile of Decitabine for Injection with that of Dacogen. These studies showed that the adverse event profiles of Decitibine for Injection and Dacogen were identical.

Safety: The Safety Summary, which showed that decitabine is without significant new risks when administered to patients with MDS, included:

a. A review of the most recent label (March 2010) which included information on one randomized trial and three open-label single arm studies; two schedules of administration were reviewed: the first regimen which consisted of 15 mg/m^2 infused over 3 hours every 8 hours for 3 days for one cycle, repeated every 6 weeks, and a second regimen consisting of 20 mg/m^2 infused over a 1 hour period on Days 1-5 of Week 1 every 4 weeks (one cycle);

b. An updated review of the worldwide literature since the most recent version of the Dacogen label (March 2010) which revealed no new safety signal;
c. A review of the AERS data from 2010 through August 2012 which detected no new safety signal.

CTDL Recommendation for Regulatory Action: On the basis of the above, this reviewer recommends approval.

2. BACKGROUND

2.a. Regulatory History (This section was excerpted from the review of Dr. Tom Herndon):

A pre-NDA Meeting was held on February 6, 2012. At the meeting, the Division of Hematology Products (DHP) expressed concern regarding the presence of levels of an impurity in the drug product, designated by its relative retention time, (b) (4), which exceeded ICH qualification standard limits. The impurity was identified as (b) (4). The applicant proposed one single specification for this impurity. (b) (4) Since the meeting, the applicant identified another impurity, (b) (4), in the drug product that also exceeds ICH qualification thresholds. The impurity was identified as (b) (4) The applicant proposed a limit of (b) (4) for the release and stability specifications.

The applicant performed a good laboratory practice (GLP) repeat-dose toxicity study in CD-1 mice to compare the toxicity profile of Decitabine for Injection with that of Dacogen to qualify the two impurities, (b) (4) and (b) (4). The results showed that, when dosed at 0.6 mg/kg/day, the toxicity profiles of both products were comparable.

During the pre-NDA meeting, the applicant and FDA agreed that no clinical studies of Decitabine for Injection were needed to be conducted if a biowaiver was granted. The applicant is requesting a waiver of the need to conduct in vivo bioequivalence studies, as outlined in 21 CFR 320.22(b)(1). A Biowaiver Request is included in this submission in Module 1.

The approved label for Dacogen (March 2010), together with publications describing new safety information identified in search of the literature since the most recent revision, serves as the basis for the Integrated Summary of Safety in this NDA. The applicant and FDA agreed that a summary of clinical efficacy is not needed for this submission.

2.b. MDS (This section was excerpted from the review of Dr. Tom Herndon):

There are three broad categories of available treatments for patients with MDS. These are supportive care, chemotherapy, and stem cell transplant. Commonly used supportive care treatments for patients with MDS include transfusions to treat anemia and thrombocytopenia, the use of erythropoiesis-stimulating agents (ESAs) such as epoetin alfa (Epogen®, Procrit®) and

darbepoetin alfa (Aranesp®) and granulocyte colony-stimulating factors such as filgrastim. Antibiotics may be given for infection(s).

The commonly used chemotherapy agents for the treatment of patients with MDS are azacitidine, decitabine, and lenalidomide. Both azacitidine and decitabine are approved by the FDA to treat all types of MDS, although they are used most often for patients with higher IPSS scores. Lenalidomide is approved for patients with transfusion-dependent anemia due to low- or intermediate-1-risk MDS associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities. These three agents are summarized in **Table 1**.

Table 1: Commonly used chemotherapy agents for the treatment of patients with MDS

Drug	Class	Approval Date
Azacitidine (Vidaza)	Nucleoside analog	19 MAY 2004
Decitabine (Dacogen)	Nucleoside analog	02 MAY 2006
Lenalidomide (Revlimid)	IMiD*	27 DEC 2005

*Immunomodulatory drug (IMiD)

Some patients with MDS receive immunosuppressive therapy with anti-thymocyte globulin (ATG) which may decrease the need for red blood cell transfusions.

Patients with high-risk subtypes of MDS with an increased risk of developing acute myelogenous leukemia (AML) may receive chemotherapy used to treat AML, such as cytarabine, idarubicin or daunorubicin.

High-dose chemotherapy with allogeneic stem cell transplantation is the only current treatment that can produce a long-term remission. However, transplantation may not be suitable for many patients with MDS.

3. CMC: Please see above Benefit-Risk discussion and CMC Review of Dr. William Adams for details. Dr. Adams recommended approval.

4.NON-CLINICAL: Please see above Benefit-Risk discussion and the Pharmcology/Toxicology Review of Dr. Pedro L. Del Valle for details. Dr. Del Valle recommended approval.

5. EFFICACY: No new efficacy data was submitted with the application.

6. SAFETY (This section is excerpted from the review of Dr. Tom Herndon): A search of the published literature was conducted on January 16, 2013. A summary of the AERS Database covering 2006 to 2012. No new safety information was found that should be added to the label. Dr. Herndon recommends approval.

7. ADVISORY COMMITTEE MEETING: No Advisory Committee meeting.

8. OTHER RELEVANT REGULATORY ISSUES: None

9. LABELING: The labeling is currently under negotiation.

10. CDTL RECOMMENDATIONS/RISK BENEFIT ASSESSMENT: The CDTL reviewer recommends approval.

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

/s/

ALBERT B DEISSEROTH
01/06/2014