CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208264Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann T. Farrell, M.D.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	208264 (505 b2)
Applicant	Addienne
Date of Submission	March 31, 2016
PDUFA Goal Date	January 31, 2017
Proprietary Name / **Non-Proprietary Name**	Tepadina/thiotepa
Dosage Form(s) / Strength(s)	15 mg and (b) (4) mg (b) (4)
Applicant Proposed Indication(s)/Population(s)	To reduce the risk of graft rejection when used in conjunction with high-dose busulfan and cyclophosphamide as a preparative regimen for allogeneic hematopoietic progenitor cell transplantation for patients with class 3 thalassemia plus other indications listed in existing thiotepa label
Action/Recommended Action for NME:	Approval
Approved/Recommended Indication/Population(s) (if applicable)	*To reduce the risk of graft rejection when used in conjunction with high-dose busulfan and cyclophosphamide as a preparative regimen for allogeneic hematopoietic progenitor (stem) cell transplantation (HSCT) for pediatric patients with class 3 beta-thalassemia*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**

Regulatory Project Health Manager	**Charlene Wheeler**
Medical Officer Review	**Rosanna Setse, M.D., Ph.D.**
Statistical Review	**Che Smith, Ph.D./Yuan Li Shen, Dr.P.H./Thomas Gwise, Ph.D.**
Pharmacology Toxicology Review	**Natalie Simpson, Ph.D./Christopher Sheth, Ph.D.**
OPQ Review	**Haripada Sarker, Ph.D./Rajiv Agarwal, Ph.D./ Kumar Janoria/ Yuansha Chen/Steven Hertz/Om Anand/Rabiya Laiq/Anamitro Banerjee, Ph.D./Paul Perdue**
Microbiology Review	**N/A**
Clinical Pharmacology Review	**Sriram Subramaniam, PhD; Stacy Shord, PharmD**
OPDP	**Rachael Conklin**
OSI	**Anthony Orencia M.D., F.A.C.P./Susan D. Thompson, M.D./Janice Pohlman M.D., M.P.H./ Kassa Ayalew, M.D., M.P.H.**
CDTL Review	**Donna Przepiorka, M.D., Ph.D.**
OSE/DEPI	**N/A**
OSE/DMEPA	**Leeza Rahimi, Pharm.D./Hina Mehta, Pharm.D./ Lubna Merchant, PharmD, MS**
OSE/DRISK	**N/A**
RPM	**Charlene Wheeler**

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Reference ID: 4046182

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Drs. Przepiorka and Setse have expertly summarized the benefit risk in their reviews and some text is excerpted here. The basis for approval is the results from Protocol 26M, a single-arm trial of Tepadina in combination with busulfan and cyclophosphamide. The results from 26M were compared to a historical control cohort.

From the primary clinical review:
Thalassemia major is a hereditary hemolytic anemia caused by genetic defects in globin genes (Cao and Galanello 2010). ..ß-thalassemia major is the most severe form of thalassemia and results from reduced or absent production of the beta-globin gene that leads to ineffective erythropoiesis and hemolytic anemia. Chronic anemia in thalassemic patients is managed conventionally with blood transfusion, iron chelation, and splenectomy in cases of hypersplenism. Despite these measures, progressive disease with major complications related to the disease and treatment still remain, resulting in poor clinical outcomes for these patients. Bone marrow transplantation (BMT) is the only known cure for thalassemia (Thomas, Buckner et al. 1982, Lucarelli, Galimberti et al. 1987). Graft rejection following HSCT is a major challenge and is highly predictive of thalassemia-free survival (TFS) (Angelucci 2010), a key parameter for measuring treatment efficacy in thalassemia patients. Clinically, ß-thalassemia major is classified into risk groups (Class 1, 2 & 3) based on the number of risk factors (hepatomegaly >2 cm, hepatic fibrosis at liver biopsy, and a history of irregular chelation) present at diagnosis; each of which have a negative effect on transplant outcome (Lucarelli, Galimberti et al. 1990). Although excellent transplantation outcomes have been achieved in class 1 to 2 patients, class 3 patients have had much poorer outcomes and transplant-related mortality (TRM) mainly due to toxicity (Lucarelli, Clift et al. 1996).

Study ADN010 (RETALCLASS3) was a retrospective, observational, multi-center study which assessed the impact of a myeloablative conditioning treatment (Protocol 26M) consisting of preconditioning cytoreduction with hydroxyurea, azathioprine and fludarabine followed by

conditioning regimen with IV busulfan (weight based dose), Tepadina (10 mg/kg total dose) and cyclophosphamide (160 mg/kg total dose) in class 3 thalassemia major patients undergoing allogenic HSCT.
The efficacy of Tepadina was based on the number and proportion of patients with primary or late graft rejection after conditioning treatment with Protocol 26M prior to HPCT. This endpoint was considered reasonably likely to predict clinical benefit. Primary graft rejection was defined as the presence of <15% donor cells or failure to achieve an absolute neutrophil count (ANC) >500 mm3 by day 28 post-transplant. Late graft rejection was defined as a loss of donor derived hematopoietic cells in bone marrow and peripheral blood (<15%) after initial graft function and return to erythrocyte transfusion dependence.
Twenty-five consecutive patients with class 3 thalassemia underwent first allogeneic transplantation from an HLA-identical donor and were treated according to Protocol 26M at 2 international study sites from February 2007 through November 2012. Overall, no patient treated with Tepadina experienced primary or late graft rejection (the incidence of graft rejection was 0/25 (0% (95% CI: [0, 0.12]). Among a historical control group of 51 patients who received the same preparative conditioning regimen but without Tepadina, the incidence of graft rejection was 13/51 (25.5% (95% CI: [0.13, 0.37]). Overall survival for patients who received Tepadina was 85.4% at 12 months….
The most common (> 10%) TEAE among patients who received Tepadina were stomatitis, diarrhea, gastrointestinal hemorrhage, hepatic function abnormalities, cytomegalovirus infection and hematuria.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• ß-thalassemia is the most severe form of thalassemia and results from reduced or absent production of beta-globin gene that leads to ineffective erythropoiesis and hemolytic anemia. • The current conventional treatment for thalassemia major consists of chronic transfusion and iron chelation therapy throughout life.	Patients with thalassemia require chronic transfusions and iron chelation therapy. Besides an allogeneic stem cell transplant, there are limited treatment options for these patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Despite the use of chronic transfusions and development of newer chelating agents, thalassemia remains a progressive disease with major complications related to the disease and treatment associated with early death.	
Current Treatment Options	• No drugs are approved for the prevention of graft rejection after allogeneic hematopoietic stem cell transplant. • Bone marrow transplantation is the only treatment option that can lead to cure of thalassemia. • Patients in class 3 thalassemia are considered at high risk for graft rejection and for transplant-related mortality (TRM).	There is a need for development of effective conditioning regimens to prevent graft failure and reduce transplant-related mortality in patients with class 3 thalassemia.
Benefit	• RETALCLASS 3 was a retrospective, multicenter, study to assess the incidence of primary or late graft rejection following allogeneic hematopoietic stem cell transplantation (HSCT) allogeneic hematopoietic stem cell transplantation in patients with class 3 thalassemia treated with a conditioning regimen including Tepadina. • Overall, no patient (0.0%) treated with Tepadina experienced graft rejection. In comparison, graft rejection occurred in 13 patients (25.5%) treated historically with a standard conditioning regimen without Tepadina. • The limited sample size (n=25) did not permit an analysis of efficacy outcomes across subgroups. • Findings from a systematic literature review of studies evaluating Tepadina as conditioning treatment prior to allogeneic HSCT were consistent with findings from RETALCLASS3.	Tepadina is effective for reducing the incidence of graft rejection in patients with class 3 thalassemia undergoing allogeneic HSCT.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	• In patients with class 3 thalassemia who received 5 mg/kg of IV Tepadina twice on day -6 pretransplant, the most common (> 10%) TEAE were stomatitis, diarrhea, gastrointestinal hemorrhage, hepatic function abnormalities, cytomegalovirus infection and hematuria. • Grades 2-4 acute GvHD occurred in 7/25 (28.0%) of patients treated with Tepadina and 13/51 (25.5%) of patients in the historical group without Tepadina from Day 30 to Day 90. • Chronic GvHD occurred in 8/23 (34.8 %) patients treated with Tepadina and 7/49 (14.3%) of patients treated without Tepadina in the historical group. • Transplant related mortality at Day 100 and 1 year post transplant was 4% and 12% for patients treated with the Tepadina containing regimen. • Abnormalities in hematology and chemistry laboratory results were as expected in hematopoietic transplant recipients within the first 30 days posttransplant. • No life threatening (grade 4) serum chemistry abnormalities and no abnormalities in serum creatinine occurred in the 30 day post- transplant observation period in the Tepadina group. • No differences in safety by demographic subgroup were identified.	• Tepadina causes myelosuppression.
Risk Management	Myelosuppression	• To minimize risks, Tepadina should only be administered in controlled inpatient settings. • Labeling should include clear dosing instructions, and a boxed warning about severe bone marrow suppression, as well as warnings and precautions for other serious risks.

2. Background

No products are approved for use in the proposed specific indication. Please see section 1 for an analysis of condition and benefit and risks.

This application is a 505 b2 with clinical data mostly from pediatric patients undergoing bone marrow transplant. Allogeneic stem cell transplant for thalassemia major is typically performed during the pediatric age.

The Applicant references Thioplex NDA 020058 as the RLD.

3. Product Quality

From the CMC review:
This NDA is recommended for APPROVAL from the CMC perspective.

Drug product is a white lyophilisate.

The 24-months pivotal stability program comprises three commercial production scale batches (09A16, 09A22 and 09A30) for 100 mg strength and batches (11G12, 11K14, 11K30) for 15 mg strength. Stability studies were performed in accordance with the "ICH
Harmonised Tripartite Guideline, Stability Testing of new Drug Substances and Products
(Q1A(R2))". The applicant proposed 18 month (at 2°C to 8°C (36°F to 46°F)) of expiration dating is proposed (and granted).

The facility reviewer found (b) (4) *the drug substance manufacturing, packaging, and testing site acceptable based on profile.*

The facility reviewer found the (b) (4) *the drug product manufacturing, packaging, and testing site acceptable based on profile.*

4. Nonclinical Pharmacology/Toxicology

No issues arose during the review which precluded approval. New non-clinical information from publications were reviewed which noted "neurotoxicity/degenerative effects and impaired neurogenesis with cognitive effects in animals treated with thiotepa."

5. Clinical Pharmacology

No issues arose during the review which precluded approval.

From the primary clinical pharmacology review:
Adienne submitted three studies: a retrospective study (ADN010) in pediatric patients (2-12 years) with class 3 β-thalassemia undergoing HSCT, and two clinical pharmacology studies including a study to evaluate the effect of mild hepatic impairment on thiotepa pharmacokinetics (PK) and QT/QTc prolongation in patients (ADN009) and an in vitro study to evaluate the effect on cytochrome P450 (CYP) enzymes on thiotepa metabolism (ADI/REP/01).
In addition, Adienne referenced clinical pharmacology information for thiotepa from literature and the Thioplex labeling.
No exploratory exposure-response analyses for efficacy endpoints and toxicities could be conducted, because no PK samples were collected in the registration trial (ADN010). The proposed dose was based on the efficacy and toxicity of Tepadina in the registration trial and meta-analysis of literature data.

6. Clinical Microbiology –N/A

7. Clinical/Statistical-Efficacy

From the primary clinical review:

In the retrospective study of patients with class 3 thalassemia treated with a conditioning regimen including Tepadina prior to allogenic HSCT, the incidence of primary or late graft rejection was 0% (95% CI: [0, 0.12]). In a historical group of 51 patients who received the same preparative conditioning regimen, without Tepadina, the incidence of graft rejection was 13/51 (25.5% (95% CI: [0.13, 0.37]). These findings taken together provide substantial evidence of clinical benefit and support approval of Tepadina for this serious condition with a significant unmet need.

The safety review revealed mild to moderate TEAE in class 3 thalassemia patients at a total Tepadina dose of 10 mg/kg during conditioning prior to allogeneic HSCT. As expected from myeloablative treatment, profound myelosuppression occurred in all patients; however, all patients treated with Tepadina engrafted, and by 30 days post-transplant, most hematological parameters had normalized. Majority of treatment-emergent chemistry laboratory were mild –moderate (Grades 1-2) in severity. The occurrence of grades 2 to 4 acute GVHD was comparable in patients treated with Tepadina (28.0%) and in the historical control group (25.5%). Likewise, a similar proportion of patients in both groups developed chronic GVHD at 1-year posttransplantation. These risks can be moderated in part by the cautious administration of Tepadina in controlled hospital settings that will allow for appropriate intervention as needed should a serious adverse reaction occur. Appropriate warnings, contraindications and instructions for dosing will be provided in the Prescribing Information. With the recommended mitigation strategies in place, the potential benefit from treatment with Tepadina should outweigh the risks for pediatric patients with class 3 thalassemia undergoing allogeneic HSCT.

From the primary clinical review:

This reviewer recommends regular approval of Tepadina for the indication "to reduce the risk of graft rejection when used in conjunction with high-dose busulfan and cyclophosphamide as a preparative regimen for allogeneic hematopoietic progenitor (stem) cell transplantation (HSCT) for pediatric patients with class 3 β-thalassemia". Approval is based on the finding of 0% incidence of graft rejection in Class 3 thalassemia patients treated with a Tepadina containing regimen for conditioning prior to undergoing HLA-identical, sibling allogenic HSCT.

This conclusion is strengthened by the finding of comparable safety outcomes (transplant related mortality, treatment emergent adverse reactions and graft-versus-host disease rates) in patients treated with Tepadina compared to a historical group of patients treated with the same conditioning regimen but without Tepadina. Efficacy and safety results from a systematic review of the published literature were also consistent with the findings from the pivotal study supporting this application.

I concur with the primary reviewer's findings and the clinical team leader's assessment. I agree that the Applicant has provided substantial evidence of effectiveness required by law 21 CFR 314.126(a)(b) to support approval.

8. Safety

See section 7. Dr. Setse's safety review included analyses of death, SAEs, transplant-related mortality at Day 100 and one year post-transplant.

From Dr. Przepiroka's review:
Following review of all available data, myelosuppression, infection, hypersensitivity, cutaneous toxicity, veno-occlusive disease, central nervous system toxicity, carcinogenicity and embryo-fetal toxicity were identified as potentially life-threatening or fatal risks of Tepadina that warranted a warning. Since thiotepa is also immunoablative, an additional precaution against concomitant use with live or attenuated vaccines is also warranted.

9. Advisory Committee Meeting

This application was not taken to an AC as neither efficacy nor safety issues arose necessitating a public discussion.

10. Pediatrics

This application included pediatric patient data.

11. Other Relevant Regulatory Issues

- *Application Integrity Policy (AIP)*- None
- *Exclusivity or patent issues of concern*- None
- *Office of Scientific Investigations (OSI) Audits*

  From the OSI review:

  Based on results of the inspections, the data submitted by the sponsor in support of the requested indication appear acceptable and the study appears to have been conducted adequately.

- *Financial Disclosure*

No financial concerns arose during the review.

- *Other Good Clinical Practice (GCP) issues* - None

12. Labeling

INDICATIONS AND USAGE section:

(b) (4)

This Application provided for the conversion of a decades old label to the newer format incorporating PLR and PLLR.

All disciplines participated in labeling.

13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

None

- Other Postmarketing Requirements and Commitments

None

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/s/

CHARLENE N WHEELER
01/25/2017

ANN T FARRELL
01/25/2017