CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208264Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	January 10, 2017
From	Donna Przepiorka, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA #	NDA 208264 (Original)
Applicant	Adienne SA
Date of Submission	March 31, 2016
PDUFA Goal Date	January 31, 2017
Proprietary Name	Tepadina
Non-Proprietary Name	Thiotepa
Dosage form(s) / Strength(s)	Lyophilized powder, 15 mg and 100 mg
Recommendation on Regulatory Action	Regular approval

Recommended Indications

- 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
- For treatment of adenocarcinoma of the breast or ovary
- For controlling intracavitary effusions secondary to diffuse or localized neoplastic diseases of various serosal cavities
- For treatment of superficial papillary carcinoma of the urinary bladder

Additional Material Reviewed/Consulted	**Primary Reviewer(s)**
Product Quality Assessment (12/10/2016)	- Anamitro Banerjee, PhD, Rajiv Agarwal, PhD, Haripada Sarker, PhD, Kumar Janoria, PhD, Yuansha Chen, PhD, Steven Hertz, Om Anand, PhD
Nonclinical Review (12/28/2016)	- Natalie Simpson, PhD
Office of Clinical Pharmacology Review (12/22/2016)	- Sriram Subramaniam, PhD
Interdisciplinary Review Team Consult (7/19/2016)	- Huifang Chen, MS
Clinical Review (12/27/2016)	- Rosanna Setse, MD, PhD
Statistical Review (12/20/2017)	- Che Smith, PhD
Division of Oncology Products 1 Consult (8/31/2016)	- Gwynn Ison, MD
Division of Oncology Products 1 Consult (10/18/2016)	- James X. Xu, MD
Office of Scientific Integrity Consult (8/17/2016)	- Anthony Orencia, MD
Proprietary Name Review (10/12/2016)	- Leeza Rahimi, Pharm.D.
Labeling Review (6/8/2016, 11/21/2016, 1/5/2017)	- Ebony Whaley, PharmD, Rachel Conklin

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1. Benefit-Risk Assessment

1.1 Recommendation on Regulatory Action

NDA 208264 for Tepadina was submitted as a 505(b)(2) application. Based on the drug product information provided in the NDA, the identity, purity, quality, strength and container/closure integrity of drug product can be established. The Biopharmaceutics and Clinical Pharmacology reviewers agreed that there was sufficient information to establish a bridge to the listed drug in order to rely on the information in Thioplex and Thiotepa for Injection labeling. Therefore, I recommend regular approval of Tepadina for the following indications from the listed drug:

- "For treatment of adenocarcinoma of the breast or ovary"
- "For controlling intracavitary effusions secondary to diffuse or localized neoplastic diseases of various serosal cavities"
- "For treatment of superficial papillary carcinoma of the urinary bladder"

I also recommend regular approval of Tepadina for the new 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 beta-thalassemia."

The recommendation for the additional indication is based on the results of Protocol 26M, a single-arm trial of Tepadina in combination with busulfan and cyclophosphamide which showed a much lower than expected rate of graft rejection and a manageable safety profile for patients undergoing HSCT for class 3 beta-thalassemia. The benefit-risk assessment below is limited to the new indication.

1.2 Benefit-Risk Framework

Table 1. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Beta-thalassemia major is a fatal disease. • Allogeneic HSCT is a potentially curative therapy. • Patients with class 3 beta-thalassemia have a reported 16% rate of graft rejection using tolerable doses of busulfan and cyclophosphamide. • Graft rejection reduces long-term thalassemia-free survival.	Graft rejection is a serious disorder that impairs long-term outcomes for patients transplanted for beta-thalassemia.

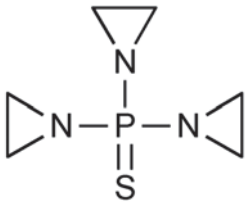
Table 1. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• There are no drugs approved for prevention of graft rejection after allogeneic HSCT. • Intensifying the preparative regimen reduced graft rejection for patients with class 1 or 2 beta-thalassemia. • Use of an intensified preparative regimen resulted in greater treatment-related mortality (TRM) for patients transplanted for class 3 beta-thalassemia who have pre-existing disease-related liver dysfunction.	There is a need for new drugs to prevent graft rejection without increasing TRM in patients with class 3 beta-thalassemia undergoing HSCT.
Benefit	• Protocol 26M was a single-arm trial of Tepadina 5 mg/kg given twice on day -6 in combination with busulfan and cyclophosphamide for patients with class 3 beta-thalassemia undergoing marrow transplantation (BMT) from an HLA-identical sibling donor. • In Protocol 26M, none (0%) of the 25 patients treated had primary or late graft rejection. By contrast, 13 (25.5%) of 51 patients transplanted similarly but without using Tepadina had graft rejection. • The 1-yr TRM was not substantially increased in the patients in Protocol 26M.	Use of Tepadina in the preparative regimen was associated with a very low risk of graft rejection without a substantial increase in TRM.
Risk	• Myelosuppression, infection, hypersensitivity, cutaneous toxicity, veno-occlusive disease, central nervous system toxicity, carcinogenicity and embryo-fetal toxicity are known potential serious adverse reactions for Tepadina. • For the patients treated on Protocol 26M, the most common adverse reactions were mucositis, cytomegalovirus infection, hemorrhage, diarrhea, hematuria and rash. • For the patients treated on Protocol 26M, clinically significant laboratory abnormalities included neutropenia, anemia, thrombocytopenia, elevated alanine aminotransferase, elevated aspartate aminotransferase, and elevated bilirubin.	High-dose Tepadina may cause serious or fatal adverse reactions.
Risk Management	• The risk of serious adverse reactions was minimized in the clinical trial by treatment under the care of a qualified transplant physician.	Monitoring for and managing the adverse reactions attributed to Tepadina should be within the standard of care for transplant physicians. Labeling should include warnings to highlight the most serious potential adverse reactions.

2. Background

2.1 Product Information

Established Name:	Thiotepa
Proposed Trade Name:	Tepadina
Dosage Forms:	Lyophilized powder for injection, 15 mg and 100 mg
Chemical Class:	Aziridine (CAS 52-24-4)
Chemical Name (IUPAC):	1,1′,1″-Phosphorothioyltriaziridine
Therapeutic Class:	Antineoplastic drug
Pharmacological Class:	Alkylating agent
Mechanism of Action:	Thiotepa is a cell cycle-phase independent, DNA-directed, polyfunctional alkylating agent. It is believed to exert its activity through induction of S-phase cell cycle arrest and cell death as a result of DNA cross-links or adduct S formation.
Proposed Indication:	To reduce the risk of graft rejection when used in conjunction with high-dose busulfan and cyclophosphamide as a preparative regimen for allogenic hematopoietic progenitor cell transplantation for patients with class 3 beta-thalassemia.
Proposed Dose-Schedule:	(b) (4)



Thiotepa for Injection, 15 mg/vial, was approved in 1959 (NDA 011683) with sodium chloride and sodium bicarbonate as excipients. Thioplex (thiotepa) for Injection, 15 mg/vial, was approved in 1994 (NDA 020058) with no excipients. In 2001, three generic thiotepa drug products were approved using Thioplex as the reference listed drug. Only one thiotepa drug product (ANDA 075547, West-Ward Pharmaceuticals Corp.) is available in the US currently.

2.2 Therapeutic Context

Beta-thalassemia major is an hereditary disorder marked by homozygous beta-globin gene mutations that result in a lack of functional beta-globin protein and subsequent ineffective erythropoiesis due to the toxic imbalance of globin chains. If left untreated, the disorder may be fatal in childhood. With regular red blood cell transfusions, median survival was extended to 20-25 years of age (Zurlo et al., 1989). With both regular transfusions and chelation therapy,

median survival was extended further but with reduced quality of life (Modell et al., 2000). The causes of death included complications of anemia and iron overload. Allogeneic HSCT is the only curative therapy for beta-thalassemia. In the US, beta-thalassemia major is a rare disease; fewer than 50 patients with beta-thalassemia major undergo allogeneic HSCT annually in the US (CIBMTR 2015).

The combination of busulfan and cyclophosphamide is an accepted allogeneic HSCT preparative regimen for patients with beta-thalassemia major who have HLA-identical donors (Lucarelli et al., 1990), and marrow (BMT) is the preferred source of stem cells (Gavamzadeh et al, 2008). Using this approach, however, there was substantial treatment-related toxicity and graft rejection specifically for the small subgroup of patients with Class 3 disease (hepatomegaly, portal fibrosis and ineffective chelation therapy), resulting at 3 years posttransplant in 16% graft rejection, 53% event-free survival, and only 61% overall survival (Lucarelli et al., 1990). Lowering the cyclophosphamide dose reduced the treatment-related mortality but also led to an increase in graft rejection (Lucarelli et al., 1996), which was only partially offset by the subsequent addition of a precytoreduction combination therapy to eradicate erythropoiesis prior to initiation of the preparative regimen (Sodani et al., 2004). Hence, there continues to be a need to develop approaches to reduce graft rejection without increasing treatment-related complications for patients with Class 3 beta-thalassemia major undergoing allogeneic BMT.

2.3 Regulatory Background

FDA provided the Applicant with verbal or written advice regarding the clinical development program on eight occasions from 9/2010 to 4/2014. (b) (4) (b) (4) (b) (4) FDA recommended that Adienne plan for a 505(b)(2) submission for Tepadina, and further advised that "Adienne will need to conduct or obtain the results of adequate and well-controlled clinical trials" to support the application, advice that was re-iterated at several meetings. Subsequent discussions between FDA and the Applicant from 7/2012 on addressed the design of a single-arm study of Tepadina to reduce the incidence of graft rejection with a comparison to a multicenter historical control as the pivotal trial for an NDA, with emphasis that such a study be designed to be compliant with the requirements of 21 CFR 314.126.

Key regulatory milestones achieved by the Applicant for Tepadina in the presubmission period included Orphan Designation for "conditioning treatment prior to hematopoietic stem cell transplantation" on 4/2/2007, Fast Track Designation "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 β-thalassemia" on 7/28/2014, and acceptance of a plan for submission of parts of the NDA on 1/15/2015. The submission of parts of NDA 208264 commenced on 2/26/2015 and was complete 3/31/2016.

Tepadina was approved by EMA in 3/15/2010 "in combination with other chemotherapy medicinal products 1) with or without total body irradiation (TBI), as conditioning treatment prior to allogeneic or autologous hematopoietic progenitor cell transplantation (HPCT) in hematological diseases in adult and pediatric patients; 2) when high dose chemotherapy with HPCT support is appropriate for the treatment of solid tumors in adult and pediatric patients." Due to a critical shortage of thiotepa for injection in the US, FDA allowed Adienne SA to temporarily import Tepadina into the US market from 2011 through 2015.

3. Product Quality

3.1 Manufacturing

The drug substance is Thiotepa USP manufactured according to the (b) (4) process as approved under the NDA 020058 for Thioplex, the listed drug. The Applicant cross-referenced the Type II DMF (b) (4) for all drug substance manufacturing information. The Drug Substance reviewer identified no deficiencies in the DMF. The Applicant proposed a retest period of (b) (4) with storage at 2°C to 8°C. The Drug Substance reviewer found this proposal to be acceptable.

The drug product is a lyophilized powder for injection formulated in strengths of 15 mg/vial and 100 mg/vial without excipients. The Process reviewer noted that the manufacturing process was typical for a lyophilized product and considered the (b) (4) controls to be adequate. Vials and stoppers conformed to the USP (current edition). The 100 mg presentation has (b) (4), but the 15 mg presentation has a (b) (4) to meet assay specifications. The Applicant is pursuing studies to optimize the process and (b) (4) in the 15 mg/vial strength product with a target completion of 1Q2017. The Process reviewer reported that the planned protocol was adequate. The Drug Product reviewer did not consider the risk of (b) (4) (b) (4) sufficient to warrant a postmarketing commitment to eliminate the overall.

Degradation reportedly resulted in the formation of (b) (4) degradation products as well as (b) (4). The main impurities in the drug product are (b) (4). The Drug Product reviewer noted that the specified limits for the impurities were justified.

Stability studies were performed in accordance with the “ICH Harmonised Tripartite Guideline, Stability Testing of New Drug Substances and Products (Q1A(R2)).” Three commercial production scale batches were used in the 24-months pivotal stability program. (b) (4) (b) (4) only 18 months (at 2°C to 8°C (36°F to 46°F) of expiration dating was proposed by the Applicant, and this was acceptable to the Drug Product reviewer.

The Applicant proposed that the drug product be reconstituted in sterile water for injection and diluted in normal saline. On the basis of the results of the compatibility studies, the Drug Product reviewer agreed with the Applicant that, if refrigerated, the reconstituted product should be used within 8 hours, and the diluted product should be used within 24 hours.

The Drug Product reviewer reported that (b) (4) was observed during storage, resulting in haziness of the reconstituted solution. The Applicant proposed to instruct users to (b) (4) utilize a 0.2 (b) (4) micron in-line filter (b) (4) (b) (4) The Drug Product reviewer found the proposal to utilize an in-line filter to be acceptable.

The Applicant claimed a categorical exclusion from the requirement for an environmental assessment under 21 CFR 25.31(b). The Drug Product reviewer accepted the claim.

3.2 Microbiology

The Microbiology reviewer identified no outstanding process deficiencies, found the container closure system to be adequate, and noted that the proposed instructions for preparation and storage were acceptable.

3.3 Biopharmaceutics

The Biopharmaceutics reviewer indicated that "Tepadina® (thiotepa) 15 mg/vial and 100 mg/vial, is a lyophilized powder for solution, for intravenous administration after reconstitution and dilution that contains the same active ingredient (thiotepa), is the same dosage form, for the same route of administration [IV use only] as the listed drug (LD), Thioplex® (thiotepa for injection, NDA 020058). There are no inactive ingredients in the proposed product and the listed product. As the formulation of Thioplex and Tepadina are identical [only the active drug substance and no excipient], disposition kinetics and the bioavailability of Thiotepa should be similar from these two products [Thioplex and Tepadina]. Therefore, the Applicant's request for a waiver of the in vivo study for their proposed product, Tepadina® (thiotepa) 15 mg/vial and 100 mg/vial, is granted."

3.4 Facilities

Drug substance is manufactured (b) (4). A PAI was performed on (b) (4), and the initial field recommendation was NAI. The Facilities reviewer recommended approval of the facility for the functions listed in the application.

Drug product is manufactured [redacted] (b) (4)
A routine surveillance GMP inspection was performed on [redacted] (b) (4). A Form 483 was issued for four items [redacted] (b) (4) [redacted] (b) (4) OPQ/OS/DQSA reviewed the firm's response and concurred with the VAI classification. The Facilities reviewer recommended approval of the facility for the functions listed in the application.

The Product Quality review team recommended approval of this NDA.

4. Nonclinical Pharmacology/Toxicology

4.1 Mechanism of Action

The Applicant described thiotepa as "a cell cycle-phase independent, DNA directed, polyfunctional alkylating agent, related chemically and pharmaceutically to nitrogen mustard. It is believed to exert its pharmacological activity through induction of S-phase cell cycle arrest and cell death as a result of DNA cross-links or adduct S formation" (Module 2.4, Section 2.4.2.1).

The Nonclinical reviewer indicated that "The radiomimetic action of thiotepa is believed to occur through the release of ethyleneimine radicals which, like irradiation, disrupt the bonds of DNA. One of the principle bond disruptions is initiated by alkylation of guanine at the N-7 position, which severs the linkage between the purine base and the sugar and liberates alkylated guanines."

4.2 Toxicology

The nonclinical data for the listed drug showed that thiotepa was mutagenic and carcinogenic, and it impaired futility. New nonclinical information from publications reported by the Nonclinical reviewer included "neurotoxicity/ degenerative effects and impaired neurogenesis with cognitive effects in animals treated with thiotepa."

Based on the bridge described by the Biopharmaceutics reviewer (Section 3.3 above), the Nonclinical reviewer accepted the Applicant's proposal to rely on the nonclinical data for the listed drug for labeling.

5. Clinical Pharmacology

The following includes information excerpted from Office of Clinical Pharmacology Review and the Interdisciplinary Review Team (IRT) for QT Studies Consultation:

5.1 Clinical Pharmacology Program

The Clinical Pharmacology reviewers assessed data from 2 clinical studies and 1 nonclinical study; these included a retrospective study (ADN010) in pediatric patients with class 3 beta-thalassemia undergoing BMT, a prospective study (ADN009) to evaluate the effect of mild hepatic impairment on thiotepa pharmacokinetics (PK) and QT/QTc prolongation in patients, and an in vitro study to evaluate the effect on cytochrome P450 (CYP) enzymes on thiotepa metabolism (ADI/REP/01).

In addition, the primary Clinical Pharmacology reviewer determined that the scientific bridge proposed by the applicant between Tepadina and thiotepa products used in publications since 1994 was adequate. Specifically, the reviewer indicated "Thioplex, 15 mg/vial and the subsequent generics (15 mg/vial) had no inactive ingredients similar to Tepadina. Adienne stated that since thiotepa (or Thiotepa Lederle) and Tepadina are reconstituted in the same volume (500 mL), they can be considered comparable in terms of physico-chemical properties of the solution administered to patients. Therefore, the clinical exposure after administration of thiotepa or Tepadina can be considered similar. In addition, per Adienne, following approval of Thioplex in 1994, the same drug product was registered worldwide (e. g., Australia, EU). Therefore, Adienne states that the thiotepa formulation used after 1994 refers to Thioplex. FDA concurs with Adienne's rationale. Therefore, a scientific bridge exists between thiotepa product used in the literature studies and the proposed drug product to support the acceptance of the scientific literature." On the basis of this bridge, the reviewer also used information for thiotepa from the published literature and the Thioplex labeling for the review.

5.2 Pharmacokinetics

The summary of the main pharmacokinetic (PK) parameters included:

"Distribution - The mean estimated volume of distribution is 30 L/m^2 following single IV dose in pediatric patients, and 1 L/kg to 1.9 L/kg for doses of 20 mg to 250 mg/m^2 as an IV bolus or up to 4 hour infusion, and appears to be independent of dose. Protein binding is less than 20%.

Metabolism - Thiotepa undergoes hepatic metabolism. In vitro data from literature suggests that thiotepa is metabolized by CYP3A4 and CYP2B6. The major active metabolite of thiotepa is TEPA (triethylenephosphoramide) per thiotepa labeling.

Elimination - The mean elimination half-life was 1.7 hours (thiotepa) and 4 hours (TEPA) in pediatric population, and from 1.4 hours to 3.7 hours for thiotepa and from 4.9 hours to 17.6 hours for TEPA in adult population. The total clearance of thiotepa ranged from 0.58 L/hr/kg or

13.8 L/h/m^2 in pediatric patients following a dose of 5 mg/kg, and from 14.6 L/hr/m^2 to 27.9 L/hr/m^2 adult patients between 20 mg to 250 mg/m^2.

Excretion - The identified metabolites of thiotepa are all excreted in the urine. Urinary excretion of thiotepa and TEPA is complete by 6 hours and 8 hours, respectively. The mean urinary recovery (as fraction of dose administered) of thiotepa and its metabolites is 0.5% for the thiotepa, and 2% to 11% for TEPA."

Hepatic Impairment - "No dose adjustment is recommended for patients with mild HI based on the data from Study ADN009... No clinical studies have been conducted to evaluate the effect of moderate and severe HI on thiotepa PK; however, two patients with moderate HI had increased plasma levels following multiple doses of thiotepa."

Renal Impairment - "No dose adjustment is necessary for mild renal impairment. No clinical studies have been conducted to evaluate the effect of RI on PK of thiotepa...however, the available literature describes a patient with moderate RI who had increased thiotepa and TEPA exposure following multiple doses of thiotepa compared to patients with normal renal function."

Drug-Drug Interactions - "No clinical drug-drug interaction (DDI) studies have been conducted to evaluate the effect of CYP2B6 and CYP3A4 modulators on thiotepa PK." "Literature data suggest that thiotepa is an inhibitor of CYP2B6 in vitro." "Thiotepa reduces the metabolism of CP to its active metabolite 4-hydroxycyclophosphamide (4-OH-CP) which may potentially affect the efficacy of chemotherapy including CP."

5.3 Pharmacodynamics

The IRT reviewed ADN009 (two intravenous infusions of Tepadina 5 mg/kg each 12 hours apart), including electronic datasets and waveforms submitted to the ECG warehouse. They identified the following limitations in the study results:

- "There are some discrepancies between the ECG intervals in the clinical dataset and those in the paper ECGs.
- Control arm and time-matched baseline ECGs were not included in this study; therefore, it is unclear whether the increase in QTc interval following the second dose was caused by study procedures or the thiotepa treatment.
- The ECG assessment strategy was inadequate in this study because there were no ECG measurements around the time of the end of infusion (3 and 15 hours from the start of first infusion) for the two doses, where maximum plasma concentrations of thiotepa and its active metabolite, TEPA, are expected.
- Only 11 pediatric patients had ECG measurements; the sample size is small and not powered to exclude large increases in QTc (>20 ms)."

Although they found that the mean largest change from baseline in QTcL (ΔQTcL) for thiotepa was only 15.2 ms with a 90% CI of 4.3 ms to 26.0 ms, due to the limitations noted above, they indicated that the study was not sufficient to determine whether Tepadina had an effect on the QT interval. They also recommended that given the extensive use of thiotepa, safety data from post-marketing reports should be assessed to determine whether further study is needed.

The Clinical Pharmacology reviewer assessed the reports of ECG abnormalities submitted by the applicant based on a search of the literature and post-marketing reports for Tepadina and Thioplex (Module 5.3.6, SDN 8). They found one instance of Grade 2 QT prolongation in the postmarketing reports and no cases of arrhythmias or QT prolongation from Tepadina, Thioplex or thiotepa in the literature. Given the apparent low risk, the reviewer recommended that a postmarketing requirement for QTc prolongation study for Tepadina to determine the effects of thiotepa on the QTc interval not be issued.

I agree that given the totality of the evidence presented above, further study of the effects of Tepadina on the QTc interval is not warranted.

5.4 Pharmacometrics

"No exploratory exposure-response analyses for efficacy endpoints and toxicities could be conducted, because no PK samples were collected in the registration trial (ADN010)."

5.4 Assessment of the Proposed Dose

On the basis of the information available from the clinical studies, literature review and Thioplex label, the Clinical Pharmacology reviewer concluded that Tepadina (b) (4) via intravenous infusion for a total to two doses appeared to be effective and safe for the graft rejection indication, and the reviewer indicated that for the solid tumor indications, Tepadina doses of 0.3-0.4 mg/kg at 1 to 4 week intervals (intravenous), 0.6-0.8 mg/kg (intracavity), and 60 mg as 30-60 mL (intravesical) were recommended. Additionally, concomitant use with strong CYP3A4 inhibitors and inducers should be avoided, no dose adjustment was needed for patients with mild hepatic or renal impairment, and patients with moderate or severe hepatic or renal impairment should be monitored for toxicity following prolonged treatment.

The Office of Clinical Pharmacology review team recommended approval of this NDA.

6. Clinical Microbiology

Not applicable.

7. Clinical Efficacy

7.1 Prevention of Graft Rejection

Proposed Indication: To reduce the risk of graft rejection when used in conjunction with high-dose busulfan and cyclophosphamide as a preparative regimen for allogenic hematopoietic progenitor cell transplantation for patients with class 3 beta-thalassemia.

7.1.1 Issues Related to the Clinical Development Program

Table 2: Table of Clinical Trials/Studies

Trials / Status	Design	Population	Primary Endpoint
ADN009	Prospective PK study	Patients <18 yrs old with planned allogeneic HSCT using thiotepa 5 mg/kg dose	PK parameters with or without hepatic impairment
ADN010 (RETALCLASS3)	Retrospective, multicenter comparative study	Patients <18 yrs old with class 3 thalassemia who underwent BMT from an HLA-identical donor on Protocols 26 or 26M	Number and proportion of patients with graft rejection.

The Applicant submitted the results of one prospective, single-arm PK study (ADN009), one retrospective multicenter study (ADN010), and a meta-analysis of the literature. ADN009 does not address efficacy with regard to the proposed indication, so it is not considered further in this review of efficacy. Regarding the meta-analysis, Dr. Smith concluded that "While the meta-analysis provides useful historical information about the incidence of posttransplant graft rejection and other transplant-related outcomes in beta-thalassemia and thalassemia major patients who were treated on conditioning regimens with and without thiotepa, some differences in study characteristics, patient populations, and follow up times make it difficult to make statistical inferences in comparison to the corresponding efficacy results of Study 01" (ADN010), and I agree with this conclusion. Therefore, only ADN010 is used to assess the efficacy of Tepadina.

Although it is uncommon to use a retrospective study as the basis of a regulatory submission, there were several issues that made this NDA acceptable for review, including a) in the US, there are so few patients with class 3 beta-thalassemia undergoing BMT from an HLA-identical donor that a randomized trial would be highly impracticable, b) the endpoint is a serious aspect of the disease and the treatment effect is large, so a randomized trial might be considered unethical, c) Protocol 26M was a prospective trial in the intended population, d) ADN010 is a prespecified retrospective analysis, and e) the safety and efficacy of thiotepa have been subject to FDA review in prior approvals.

I would also not regard the intended population as a small artificial subset devised to circumvent performing a traditional adequate and well-controlled trial. The Pesaro classification is a well-established risk schema with objective criteria, and the need to minimize regimen-related toxicity in the face of pre-existing disease-related organ dysfunction while avoiding graft rejection with a reduced intensity preparative regimen is unique to this population. Further study of graft rejection would not be warranted for the overall population of patients undergoing BMT from an HLA-identical donor using a standard tolerable preparative regimen, since the risk of graft rejection in the overall population is relatively low.

Nonetheless, the unusual nature of the clinical development program warranted additional safeguards against bias, including a 100% verification of the efficacy endpoints. On the basis of the inspections of the clinical sites in July, 2016, Dr. Orencia concluded that the data submitted appeared acceptable. Remaining issues regarding elements of the study design are discussed below.

7.1.2 Issues Related to Individual Clinical Trials/Studies

Study ADN010 (RETALCLASS3) was a retrospective historical-control study of the outcomes of patients transplanted on Protocol 26M to those treated according to Protocol 26. Eligible cases included children with class 3 beta-thalassemia who were $\leq$ 17 years old at BMT and who were undergoing first transplantation from an HLA-identical sibling donor. The treatment plan included precytoreduction, the preparative regimen, infusion of donor marrow, and GVHD prophylaxis. For Protocol 26M, the preparative regimen consisted of weight-based iv busulfan days -10, -9, -8 and -7, Tepadina 5 mg/kg iv twice on day -6, cyclophosphamide 40 mg/kg iv on days -5, -4, -3 and -2. For Protocol 26, the preparative regimen consisted of iv busulfan days -9, -8, -7 and -6, and cyclophosphamide 40 mg/kg iv on days -5, -4, -3 and -2.

Although the description of the preparative regimens suggests that the comparison would isolate the treatment effect of Tepadina, Dr. Che indicated that "It is difficult to determine if subjects from the treatment cohort and the historical control cohort come from the same underlying patient population due to insufficient data collection [and] lack of a pre-planned matching strategy," and as such chose to view ADN010 as a single-arm trial. The Applicant's 10/31/2016 response to an Information Request described the method for selection of the controls at the two clinical sites, and confirmed that the controls were not concurrent. Therefore, Dr. Che's decision to not make statistical inferences is reasonable.

The primary objective of ADN010 was to assess the incidence of graft rejection (primary or late). For the purposes of this study, primary graft rejection was defined as the presence of <15% donor cells or failure to achieve an ANC > 0.5 Gi/L by 28 days post-transplant, and 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. Unfortunately, such an endpoint may be confounded by death as a competing risk,

so the preferred endpoint would be thalassemia-free survival. However, since the statistician chose to assess the outcome of the Protocol 26M cohort as a single arm, the time-to-event endpoint would not be interpretable, and the binary endpoint of graft rejection would need to be used as planned in the protocol for the determination of efficacy.

Lastly, the Division also asked the Applicant to ensure that the protocol included a sample size calculation. No formal sample size calculation was provided, but the analysis did include 95% confidence intervals for the primary endpoint to assist in determining whether the results are clinically meaningful.

7.1.3 Integrated Assessment of Effectiveness

The outcomes were reviewed for 76 patients in ADN010. The baseline demographics are shown in Table 3.

Table 3: Baseline Demographics

Variable	Protocol 26 (N = 51)	Protocol 26M (N = 25)
Age, in years		
Mean (SD)	10.1 (3.37)	10.4 (2.74)
Median [Min, Max]	10 [4 – 16]	10 [5 – 16]
Gender [%, (N)]		
Female	56.9 (29)	40.0 (10)
Male	43.1 (22)	60.0 (15)
Height, in cm [Mean (SD)]	130.1 (12.58)	131.5 (14.25)
Weight, in kg [Mean (SD)]	26.9 (8.04)	29.2 (8.39)
Study Site [%, (N)]		
IT01	51.0 (26)	100 (25)
IT02	49.0 (25)	0 (0)

Source: Dr. Che's review

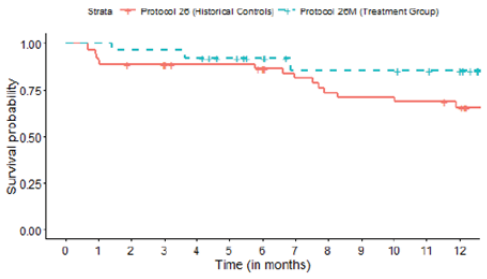
The results of the analysis of the primary efficacy endpoints is shown in Table 4. The upper limit of the 95% confidence interval for the incidence of graft rejection is 14%, which is lower than the expected incidence reported for the historical controls. The 1-year thalassemia-free survival of 85% suggests that the graft rejection results are not impacted by a high rate of death as a competing risk.

Table 4: Efficacy Results

Protocol Type	N	%	Clopper-Pearson 95% CI	
			Lower	Upper
Protocol 26 (N = 51)	13	25.5	0.143	0.396
Protocol 26M (N = 25)	0	0	0	0.137

Source: Dr. Che's review

Thalassemia-free survival by treatment cohort



(Blue dashed line= 26M; red solid line=26)

There were too few patients treated in the Protocol 26M cohort for any subgroup analyses of efficacy in ADN10 to be reliable. Of interest, no patient in the Protocol 26M cohort received ATG, but there were 15 subjects in the Protocol 26 cohort who received ATG during administration of the preparative regimen. Graft rejection was reported for 4 of the 15 patients in the Protocol 26 cohort who received ATG vs 9 of the 36 patients who did not, so the rate of graft rejection in the Protocol 26 cohort was not falsely elevated by the use of ATG.

Tepadina 5 mg/kg iv twice on day -6 was the only dose studied, and the Applicant did not provide any scientific justification for the dose used. Locatelli et al. (2003) reported on a series from the Eurocord Registry that included 26 children with thalassemia who underwent related-donor umbilical cord blood transplantation using busulfan and cyclophosphamide with or without thiotepa as the preparative regimen. The thiotepa dose was not indicated. Graft rejection was reported for 6 (38%) of 16 patients transplanted using busulfan plus cyclophosphamide and in 1 (11%) of 9 when the preparative regimen include thiotepa. Overall, the data suggest that adding Tepadina would reduce the risk of graft rejection when used in combination with busulfan plus cyclophosphamide as a preparative regimen for children with thalassemia, but whether the dose is optimal has not been determined.

7.2 Other Indications

7.2.1 Adenocarcinoma of the Breast or Ovary

The established bridge supports approval of the indication treatment of adenocarcinoma of the breast or ovary. Dr. Ison noted that although thiotepa is not current standard practice, the stated indication and instructions for intravenous use are not negated by any safety issues.

7.2.2 Malignant Effusions

The established bridge supports approval of the indication for controlling intracavitary effusions secondary to diffuse or localized neoplastic diseases of various serosal cavities. Dr. Ison noted that thiotepa still in use for treatment of malignant effusions albeit rarely, and there are no data in the literature to negate the current instructions for intracavitary use.

7.2.3 Superficial Papillary Carcinoma of the Urinary Bladder

The established bridge supports approval of the indication for treatment of superficial papillary carcinoma of the urinary bladder. Dr. Xu noted that thiotepa is still used in the treatment of urothelial cancer and that there was not sufficient information to warrant modification of the current recommended instructions for intravesical administration.

8. Clinical Safety

8.1 Adequacy of the Drug Exposure Experience

The population for assessment of safety of Tepadina consisted of 25 children treated in the Protocol 26M cohort of ADN010 and 12 children treated on ADN009. All children received Tepadina at 5 mg/kg twice on one day. There were also 51 children in the Protocol 26 cohort in ADN010 for comparisons without Tepadina. The demographics for ADN010 are shown above. The children participating in ADN009 had a median age of 3.5 years (range, 1-14 years); 8 were male and 4 were female. The total of 37 children treated with Tepadina is quite small for a safety database, but there is extensive experience with thiotepa outside the intended indication that can inform the safety review. Dr. Setse indicated that because the total treatment plan and the schedule of assessments differed for ADN010 and ADN 009, safety data could not be pooled.

8.2 Adequacy of the Clinical Safety Assessments

For ADN010, safety assessments were scheduled from the first Tepadina infusion through day 365 after transplantation. Since the majority of regimen-related toxicities occur during administration or within 30 days of transplantation, the duration of the schedule of assessments was acceptable. For ADN009, there were 8 scheduled study visits from screening through day 30 after transplantation. This would provide adequate for supporting data.

8.3 Integrated Analysis of Safety

Dr. Setse reported that for Study ADN010, the safety review showed:

- "Overall 8 deaths occurred: 3 deaths occurred in patients treated with Protocol 26M and 5 deaths were in the historical control group treated without Tepadina (Protocol 26). Transplant related mortality (TRM) at Day 100 post-transplant was 4% and 12% for Protocol 26M and Protocol 26 respectively. At 1 year post-transplant, TRM was 0.0% and 7.8% for the two groups respectively.

- Nine patients (11.8%) discontinued the study before the end of follow-up period. Eight (88.9%) of these discontinuations were due to death. One patient (11.1%) from Protocol 26 was lost to follow up. There were no early withdrawals due to adverse events.

- The most common (> 10%) TEAE among patients who received Tepadina were stomatitis, diarrhea, gastrointestinal hemorrhage, hepatic function abnormalities, cytomegalovirus infection and hematuria.

- SAEs occurred in 12 patients (23.5%) in the Protocol 26 group and 4 patients (16.0%) in the Protocol 26M group. Most SAEs were considered unrelated to Tepadina treatment. SAEs considered to be at least possibly related to Tepadina treated were gastrointestinal hemorrhage, seizure, subarachnoid hemorrhage and veno-occlusive disease.

- Subgroup analyses of adverse events by age and gender showed no safety signal.

- As expected from myeloablative treatment, profound myelosuppression occurred in all patients."

The most common adverse reactions occurring through 30 days after transplantation are shown in Table 5, and the rates of worse laboratory abnormalities through 30 days after transplantation are shown in Table 6.

Table 5: Study ADN010: Common Adverse Reactions

	Protocol 26M n=25 (%)		Protocol 26 n=51 (%)	
Adverse Reaction	**Any Grade**	**Grade 3-5[1]**	**Any Grade**	**Grade 3-5[1]**
Mucositis[2]	16 (64%)	4 (16%)	22 (43%)	1 (2%)
Cytomegalovirus Infection	12 (48%)	0	15 (29%)	0
Hemorrhage[3]	7 (28%)	2 (8%)	12 (24%)	3 (6%)
Diarrhea	6 (24%)	0	7 (14%)	2 (4%)
Hematuria[4]	5 (20%)	0	10 (20%)	3 (6%)
Rash[5]	3 (12%)	0	11 (22%)	0
Intracranial Hemorrhage[6]	2 (8%)	1 (4%)	0	0
Pseudomonas Infection	2 (8%)	0	0	0

[1]CTCAE v4
[2]Mucositis includes mouth hemorrhage, mucosal inflammation and stomatitis
[3]Hemorrhage includes all hemorrhage terms
[4]Hematuria includes cystitis hemorrhagic and hematuria
[5]Rash includes dermatitis exfoliative, palmar erythema, rash, rash maculo-papular, rash pruritic and skin toxicity
[6]Hemorrhage Intracranial includes hemorrhage intracranial and subarachnoid hemorrhage

Table 6: Study ADN010: Selected Laboratory Abnormalities

	Protocol 26M n=25 (%)		Protocol 26 n=51 (%)	
Adverse Reaction	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Elevated alanine aminotransferase	22 (88%)	6 (24%)	49 (96%)	14 (27%)
Elevated aspartate aminotransferase	20 (80%)	4 (16%)	45 (88%)	9 (18%)
Elevated total bilirubin	20 (80%)	4 (16%)	39 (77%)	2 (4%)
Elevated creatinine	0	0	2 (4%)	1 (2%)

The increases in the rates of mucositis and diarrhea are consistent with the known toxicity profile of thiotepa, and the rates of grades 3-5 events are expected for allogeneic HSCT. As shown in Table 6, there was no apparent increase in hepatic or renal toxicity.

Additional clinical outcomes related to safety are shown in Table 7. The addition of Tepadina did not delay neutrophil recovery. There was a numerical increase in the rates of acute and chronic GVHD as might be expected in a population with less graft rejection. TRM at 1 year was also slightly higher, but the survival curves were comparable.

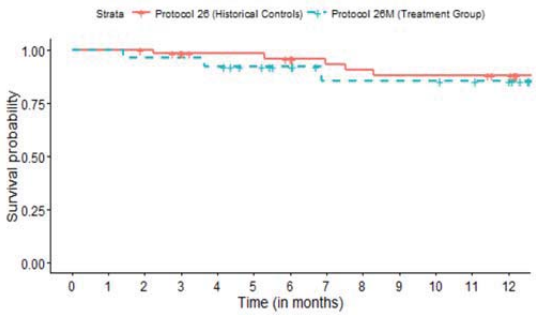
Table 7: Study ADN010: Additional Clinical Outcomes

Outcome	Protocol 26 M (n=25)	Protocol 26 (n=51)
Days to ANC recovery[a]	21 (16 - 23)	21 (14-42)
Days to PLT recovery[a]	52 (26-101)	23 (12-320)
Day-90 acute GVHD[b]	28% (13, 50)	25% (15, 40)
1-yr chronic GVHD[b]	32% (16, 54)	14% (6, 27)
1-yr OS[b]	85% (71, 100)	88% (78, 99)
1-yr TRM[b]	12% (0, 30)	8% (0, 20)

Source: Dr. Che's review and Dr. Setse's review

[a] Median, range
[b] %, (95% CI)

Overall survival by treatment cohort



(Blue dashed line= 26M; red solid line=26)

No additional safety issues were identified in Study ADN009.

No dose-toxicity evaluation could be performed, since the only Tepadina dose studied was two administrations of 5 mg/kg iv on day -6. Wolff et al. (1990) reported that with autologous marrow support, the maximal tolerated dose of thiotepa was 900 mg/m^2 (~22 mg/kg). Central nervous system toxicity was dose-limiting. Other dose-dependent toxicities included mucositis, esophagitis, nausea, vomiting, enterocolitis, cutaneous reactions and delayed hematopoietic recovery. In a Phase 1 study of combination therapy for allogeneic marrow transplantation, the maximal tolerated dose-schedule was thiotepa 250 mg/m^2 (~6 mg/kg) iv on days -9, -8 and -7 (total ~18 mg/kg), busulfan 1 mg/kg orally every 6 hours on days -6, -5, and -4, and cyclophosphamide 60 mg/kg iv on days -3 and -2; stomatitis and hepatotoxicity were dose-limiting (Przepiorka et al. 1994). The proposed dose of Tepadina (total 10 mg/kg) is within the reported maximal tolerated dose.

In their review of the postmarket experience (Tepadina 6th Periodic Safety Update Report, dated 6/25/2015), the Applicant noted the following "Important Identified Risks": myelosuppression, cardiac failure, mucositis, pediatric hepatic failure, veno-occlusive liver disease, hypersensitivity, graft versus host disease, infection, treatment related secondary malignancy, nervous system disorders, confusion, delirium, hallucination, renal failure, infertility, pulmonary toxicity, embolism and hemorrhage. Some of these were considered common toxicities of other drugs

used in high-dose combinations as preparative regimens, and this confounded confirming the relationship to Tepadina specifically. 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 viruses is also warranted.

9. Advisory Committee Meeting

This application was not discussed by an advisory committee.

10. Pediatrics

Since Tepadina has orphan designation for "conditioning treatment prior to hematopoietic stem cell transplantation," and this broad orphan designation encompasses the new indication for use of Tepadina in the preparative regimen to prevent graft rejection, this new indication is exempt from the requirements of the Pediatric Research Equity Act (PREA).

The indications treatment of adenocarcinoma of the breast or ovary, controlling intracavitary effusions secondary to diffuse or localized neoplastic diseases of various serosal cavities, and treatment of superficial papillary carcinoma of the urinary bladder are not new, and there is no associated new active ingredient, new dosage form, new dosing regimen, or new route of administration, so PREA does not apply.

11. Other Relevant Regulatory Issues

None.

12. Labeling

12.1 Proprietary Name

The Division of Medication Error Prevention and Analysis did not identify any other safety or misbranding concerns with the proposed proprietary name, Tepadina, and they determined that the proposed proprietary name, Tepadina, was acceptable.

12.2 Carton and Container Labeling

Major recommendations by the Drug Product reviewer included:

- The proposed container labels list the proprietary name, established name, and dosage form on the same line. Revise the presentation of the proprietary name, established name, and dosage form to correspond with one of the examples shown below. (Tepadina (thiotepa) for injection or Tepadina (thiotepa) For Injection). Additionally, this revision will ensure consistency with USP requirements.
- Consider inclusion of NDC numbers on the carton labeling and container labels to facilitate product identification since the NDC number is often used as an additional verification prior to drug dispensing in the pharmacy. Additionally, ensure that the product code (middle 3-4 digits) is different for each strength.
- Revise the presentation of the route of administration (b) (4) (b) (4) (b) (4). We recommend this revision to the carton labeling to ensure that all intended routes of administration are labeled.
- (b) (4) (b) (4). We recommend that the display of the barcode and NDC number is revised to be permanently printed on the carton labeling.
- Revise the presentation of the route of administration from (b) (4) to "For Intravenous, intracavitary, or intravesical use". We recommend this revision to the container labels to ensure that all intended routes of administration are labeled.

12.3 Prescribing Information

Major recommendations by the Clinical Pharmacology reviewer included:

- "In Section 12 (b) (4) describe the PK of thiotepa in pediatric and adult populations (volume of distribution, terminal half-lives, clearance) after IV bolus or infusion.
- In Section 12 (b) (4) include that CYP3A4 and CYP2B6 may be responsible for the metabolism of thiotepa, and urinary excretion information for thiotepa and TEPA.
- In Section 12. (b) (4) state that thiotepa clearance is not affected by mild HI and thiotepa AUC is increased with moderate HI and moderate RI.
- In Section 7.1, include recommendation to avoid concomitant use of strong CYP3A4 inhibitors and inducers due to the potential for an increase in exposure to thiotepa or TEPA, and consider an alternate medication with no or minimal potential to inhibit or induce CYP3A4. If coadministration of a strong CYP3A4 modulator cannot be avoided, closely monitor for adverse reactions.
- In Section 7.2, include that thiotepa may increase the exposure of drugs that are substrates of CYP2B6, and that thiotepa reduces the metabolism of cyclophosphamide (CP) to its active metabolite which may potentially affect its efficacy.
- In Sections 8.6 and 8.7, state that no dose adjustment is necessary for patients with mild RI and mild HI. Monitor for toxicity in patients with moderate and severe RI and moderate and severe HI following prolonged treatment with Tepadina."

Major recommendations by the Clinical reviewer included:

- "Include a Boxed Warning for the risk of severe bone marrow suppression or ablation with Tepadina use.
- The recommended dose of Tepadina in Section 2.1 should be the exact dose of Tepadina evaluated in clinical studies.
- Include a table showing the recommended dosage regimen for Tepadina, Busulfan, and Cyclophosphamide in the Section 2.1.
- Since efficacy was based on results in patients treated with Tepadina only, delete the table (b) (4)
- Include summary demographic data on patients treated with Tepadina in Section 14.
- Provide the data on the occurrence of acute and chronic GVHD in RETALCLASS3 in section 6.1.
- Include a table showing the worst key chemistry abnormalities in patients treated with Tepadina through 30 days post-transplant.
- (b) (4)
- Add more detailed information to section 6.2 on the safety signals identified from Post marketing experience of Tepadina."

Major recommendations by the Statistical reviewer included:

- "The reviewer recommends that no formal statistical comparisons are made between the cohorts (i.e., p-values).
- Additionally, the reviewer recommends that all results from the literature meta-analysis be excluded from the label since some study specifications do not allow for comparison with Protocol 26M and since efficacy outcomes were evaluated at different time points from Protocol 26M.
- Finally, the reviewer recommends exclusion of secondary endpoint results due to insufficient source data collection supporting results."

13. Postmarketing Recommendations

13.1 Risk Evaluation and Management Strategies (REMS)

A REMS is not recommended.

13.2 Postmarketing Requirements (PMRs) and Commitments (PMCs)

There are no recommended postmarketing requirements or postmarketing commitments.

14. Recommended Comments to the Applicant

There are no recommended comments to the applicant.

15. References

Center for International Blood and Marrow Transplant (CIBMTR), a contractor for the C.W. Bill Young Cell Transplantation Program operated through the U. S. Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau (2015). "Number of Transplants Reported for IEA - Beta Thalassemia Major From 2010 - 2014." U.S. Transplant Data by Disease Report. Last Updated: January 20, 2015.

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DONNA PRZEPIORKA
01/10/2017