CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208264Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	January 13, 2017
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 208264
Product Name and Strength:	Tepadina (thiotepa) for Injection 15 mg, 100 mg
Product Type:	Single-ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Adienne
Submission Date:	January 11, 2017
OSE RCM #:	2016-902-3
DMEPA Primary Reviewer:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMO

The Division of Hematology Products (DHP) requested that we review the revised carton labeling for Tepadina (Appendix A) to determine if they are acceptable from a medication error perspective. We reviewed the carton labeling in previous label and labeling reviews. [abc] The current revisions were made to align to the route of administration statement with the Prescribing Information and container labels.

2 CONCLUSION

The revised carton labeling for Tepadina is acceptable from a medication error perspective. We have no further recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Whaley E. Label and Labeling Review for Thiotepa for Injection (NDA 208264). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 JUN 8. 17 p. OSE RCM No.: 2016-902.

[b] Whaley E. Label and Labeling Memo for Thiotepa for Injection (NDA 208264). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 JUL 16. 4 p. OSE RCM No.: 2016-902-1.

[c] Whaley E. Label and Labeling Memo for Tepadina (NDA 208264). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 OCT 31. 5 p. OSE RCM No.: 2016-902-2.

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/s/

EBONY A WHALEY
01/13/2017

HINA S MEHTA
01/13/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 1/5/17

To: Charlene Wheeler, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Comments on draft labeling (Package Insert, Carton & Container Labeling) for Tepadina (thiotepa) for injection, for intravenous, intracavernous, or intravesical use
NDA 208264

In response to your labeling consult request dated April 14, 2016 we have reviewed the draft Package Insert and draft carton and container labeling for Tepadina (thiotepa) for injection, for intravenous, intracavernous, or intravesical use (Tepadina). This review is based upon the version of the draft PI accessed from the shared drive on January 5, 2016.

If you have any questions, please contact Rachael Conklin at (240) 402-8189 or Rachael.Conklin@fda.hhs.gov.

PI

Section	**Statement from Draft (if applicable)**	**OPDP Comment**
HIGHLIGHTS OF PRESCRIBING INFORMATION: WARNINGS AND PRECAUTIONS		OPDP notes that only two of the eight warnings from section 5 are reflected in the Warnings and Precautions in the Highlights. Would it be possible to revise this section to better reflect the serious warnings presented in section 5? We recognize that the Highlights does not need to include all of the topics included in section 5; however, given that some of these events can be severe or fatal (e.g., myelosuppression, central nervous toxicity) their inclusion in the Highlights may be informative for providers.

HIGHLIGHTS OF PRESCRIBING INFORMATION: ADVERSE REACTIONS	The most common adverse reactions (incidence greater than 10%) were neutropenia, anemia, thrombocytopenia, elevated alanine aminotransferase, elevated aspartate aminotransferase, elevated bilirubin, mucositis, cytomegalovirus infection, hemorrhage, diarrhea, hematuria and rash (6.1).	OPDP notes that hematuria and rash have been removed from the table in section 6.1. We recommend updating the AR portion of the highlights to reflect the changes made to section 6.1
17 Patient Counseling Information		OPDP recommends that information regarding sections 5.3 Cutaneous Toxicity, 5.4 Concomitant Use of Live and Attenuated Vaccines, and 5.6 Central Nervous System Toxicity be included here as they contain information that is pertinent to patients.

Carton/Container Labeling

OPDP acknowledges and concurs with the November 21, 2016, review of the carton and container labeling by the Division of Medication Error Prevention and Analysis (DMEPA) and has no additional comments on the carton and container labeling.

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/s/

RACHAEL E CONKLIN
01/05/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	November 21, 2016
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 208264
Product Name and Strength:	Tepadina (thiotepa) for Injection 15 mg, 100 mg
Product Type:	Single-ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Adienne
Submission Date:	October 31, 2016
OSE RCM #:	2016-902-2
DMEPA Primary Reviewer:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMO

The Division of Hematology Products (DHP) requested that we review the revised carton labeling and container labels for Thiotepa for Injection (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during previous label and labeling reviews.[1][2]

2 CONCLUSION

The revised carton labeling and container labels are unacceptable from a medication error perspective. We note that the Prescribing Information (PI) has been updated to include the intracavitary and intravesical routes of administration. As such, the carton labeling and container labels should be updated to include all intended routes of administration.

(b) (4)

3 RECOMMENDATIONS FOR ADIENNE

We recommend the following be implemented prior to approval of this NDA 208264:

A. Carton labeling
   1. 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.
   2. (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 to assure that the carton label will comply with 21 CFR 201.25(c)(ii) which states that the bar code must remain intact under normal conditions of use.

B. Container labels
   1. Revise the presentation of the route of administration (b) (4) (b) (4) to "For Intravenous, intracavitary, or intravesical use". We recommend this

[1] Whaley E. Label and Labeling Review for Thiotepa for Injection (NDA 208261). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 MAR 31. 18 p. OSE RCM No.: 2016-902.

[2] Whaley E. Label and Labeling Memo for Thiotepa for Injection (NDA 208261). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 JUL 14. 4 p. OSE RCM No.: 2016-902-1.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

EBONY A WHALEY
11/21/2016

HINA S MEHTA
11/22/2016

CLINICAL INSPECTION SUMMARY

Date	August 17, 2016
From	Anthony Orencia M.D., F.A.C.P., GCPAB Medical Officer Susan D. Thompson, M.D., Team Leader for Janice Pohlman M.D., M.P.H., GCPAB Team Leader and Kassa Ayalew, M.D., M.P.H., GCPAB Branch Chief
To	Rosanna Setse M.D., Ph.D. Medical Officer Donna Przepiorka , M.D., Ph.D. Clinical Team Leader Charlene Wheeler, Regulatory Project Manager
NDA	208264
Applicant	ADIENNE SA
Drug	thiotepa (Tepadina®)
NME	No
Therapeutic Classification/Review	Expedited Review
Proposed Indication	risk reduction of (b) (4) rejection in Class 3 Thalassema (b) (4) patients
Consultation Request Date	April 25, 2016
Summary Goal Date	August 30, 2016
Action Goal Date	September 30, 2016
PDUFA Date	September 30, 2016

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

For NDA 208264, two clinical sites (Drs. Gaziev and Ciceri) were selected for audit and inspection. The preliminary classification for the inspection of Drs. Gaziev and Ciceri is No Action Indicated (NAI). 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.

2. BACKGROUND

Rejection after allogeneic bone marrow transplant for thalassemia major is characterized by a return of the thalassemic clone with no erythropoiesis of donor origin, which usually can also be defined as relapse. In the case of rejection, a second allogeneic transplantation may be the only treatment option to offer a chance of prolonged survival.

However, the outcome of a second hematopoietic stem cell translplant has a low thalassemia free survival rate and high probability of graft failure. Thiotepa, a myelosuppressive agent in transplantation with a known safety profile, is proposed as a candidate agent in class 3 beta thalassemia patients prior to repeat allogeneic bone marrow transplant.

Adverse events after thiotepa administration may include the following: (a) neurotoxicity following high doses of thiotepa (> 1000 mg/m^2) with confusion, disorientation and irritability, (b) mild nausea and vomiting, and (c) hyperpigmentation dermatitis of the body folds, which may develop 4-14 days post-thiotepa administration.

ADIENNE SA submits this NDA for thiotepa to reduce 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. CDER DHP requested two foreign study sites for inspection, since the study was conducted only at these two sites. These sites enrolled exclusively in Italy. CDER designated this submission as an expedited priority review.

STUDY RETALCLASS3

RETALCLASS3 was an observational, retrospective, case-series, multi-center, historical-controlled clinical study, to assess the impact of Protocol 26M on graft rejection in Class 3 Thalassemia patients. The primary objective was to assess the incidence of graft rejection following allogeneic bone marrow transplantation from an HLA-identical sibling donor in class 3 thalassemia patients treated according to "Protocol 26M" (a chemotherapeutic conditioning regimen with busulfan, cyclophosphamide, and thiotepa, preceded by pre-conditional cytoreduction-immunosuppresion regimen with hydroxyurea, azathioprine and fludarabine), in comparison with a control group of patients treated with standard "Protocol 26" (a chemotherapeutic conditioning regimen with busulfan and cyclophosphamide, only, preceded by pre-conditioning with hyroxyurea, azathioprine, and fludarabine). The primary efficacy of interest was the number and proportion of patients with transplantation graft rejection.

There were 76 patients: 25 patients treated with Protocol 26M and 51 patients treated with Protocol 26. The study was solely conducted in Italy. The study centers were in the International Center for Transplantation in Thalassemia and Sickle Cell Anemia, Mediterranean Institute of Hematology, University of Rome Tor Vergata (Rome) and Hematology and Bone Marrow Transplant Unit at San Raffaele Hospital, IRCCS (Milan).

3. RESULTS (by site):

Name of CI, Address	Site #, Protocol #, and # of Subjects	Inspection Date	Classification
Javid Gaziev, M.D. Instituto Mediterraneo di Ematologia Centro Internazionale di trapianti nella Talassemia e Sickle Cell Anemia Policlinico Tor Vergata Viale Oxford 81 Torre 6, Rome, Italy 00133	Study RETALCLASS3 Site 01 51 enrolled subjects	7/11 – 7/20, 2016	Pending: Preliminary NAI

Name of CI, Address	Site #, Protocol #, and # of Subjects	Inspection Date	Classification
Fabio Ciceri, M.D. Ospedale San Faffaele U.O. Ematologia E Trapiano Di Midollo Osseo Via Olgettina Milan, Italy 60-20132	Study RETALCLASS3 Site 02 25 enrolled subjects	7/25-7/28, 2016	Pending: Preliminary NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Study Site Investigators

1. **Javid Gaziev, M.D./Study Protocol RETALCLASS3/ Site 01**
   Rome, Italy 00133

The inspection was conducted from July 11-20, 2016. A total of 51 subjects were screened, and 51 subjects enrolled. Fifty one subjects completed the study. An audit of 51 subjects' records was conducted.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued at the conclusion of the inspection.

Data submitted by this clinical site appear acceptable in support of this specific indication.

2. **Fabio Ciceri, M.D./Study Protocol RETALCLASS3/ Site 02**
   Milan, Italy 60-20132

The inspection was conducted from July 25 to 28, 2016. A total of 25 subjects were screened, and 25 subjects were enrolled. Twenty five subjects completed the study. An audit of all 25 subjects' records was conducted.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued at the conclusion of the inspection.

Data submitted by this clinical site appear acceptable in support of this specific indication.

{See appended electronic signature page}

Anthony Orencia, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D. for
Janice Pohlman, M.D., M.P.H., Team Leader and
Kassa Ayalew, M.D., M.P.H., Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:
Central Doc. Rm.
DHP/Division Director/Ann Farrell
DHP/Medical Team Leader/Donna Przepiorka
DHP/Medical Officer/Rosanna Setse, M.D., Ph.D.
DHP/Project Manager/Charlene Wheeler
Review Division/Medical Officer/Anthony Orencia

OSI/Office Director/David Burrow (Acting)
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Janice Pohlman/Susan D. Thompson
OSI/DCCE/GCP Reviewer/Anthony Orencia
OSI/ GCP Program Analyst/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

ANTHONY J ORENCIA
08/17/2016

SUSAN D THOMPSON
08/17/2016

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

IND or NDA	NDA 208264
Brand Name	TEPADINA®
Generic Name	Thiotepa
Sponsor	Adienne SA
Indication	To reduce the risk of graft rejection when used in conjunction with high-dose busulfan and cyclophosphamide as a preparative regimen for allogenic haematopoietic progenitor cell transplantation for patients with class 3 β-thalassemia.
Dosage Form	Solution for intravenous infusion (IV)
Drug Class	Cytotoxic agent
Therapeutic Dosing Regimen	6 to 10 mg/kg/day divided in two daily infusions every 12 hours
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	Not evaluated
Submission Number and Date	SDN 003; 31 Mar 2016
Review Division	DOP1

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

There are major limitations in this QT study which make the interpretation of the results of QT assessment unreliable.

- 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).

In this QT study, the largest mean changes from baseline in QTcL (ΔQTcL) for thiotepa (two IV infusions of 5 mg/kg each, 12 hours apart) was 15.2 ms with a 90% CI of 4.3 ms to 26.0 ms. In this two-center, open-label, phase IV clinical trial in pediatric patients undergoing allogeneic haematopoietic progenitor cell transplantation, 30 patients with different levels of hepatic function (Child-Pugh score A for normal liver function and score B for liver impairment) were planned but only 12 pediatric patients with normal hepatic function (Child-Pugh score A) were enrolled and received thiotepa (two IV infusions of 5 mg/kg each, 12 hours apart). Overall summary of findings is presented in Table 1.

Table 1: The Point Estimate and the 90% CI Corresponding to the Largest Upper Bound for Thiotepa 5 mg/kg IV (FDA Analysis)

	ΔQTcL (ms)			
Time (Hour)	**N**	**Mean**	**SE**	**90% CI**
3 Hours after the End of the 2nd Dose	11	15.2	6.0	(4.3, 26.0)

The Applicant is using the maximum recommended therapeutic dose of 10 mg/kg/day divided in two daily iv infusions for this study. There is no accumulation with the second dose over first dose. No information about the effect of hepatic and renal impairment or drug-drug interactions is known.

The ECG assessment was not conducted at the expected Tmax (i.e., around the time of end of infusion: 3 and 15 hours since the start of first infusion). Amongst the limited ECG samples, the observed increases in QTc interval following the second dose of thiotepa cannot be directly explained by plasma concentrations of thiotepa and its active metabolite (TEPA) because the similar increases in QTc interval after the first dose of thiotepa were not observed, even though the drug exposures are expected to be similar between the first and second dose. Therefore it is unclear whether the observed increases in QTc interval following the second dose was caused by the study procedure or the thiotepa treatment; conclusions regarding exposure-response relationship cannot be made.

1.2 QT-IRT'S COMMENTS TO REVIEW DIVISION

Given the major limitations of this QT study as mentioned in section 1.1, we cannot determine whether or not thiotepa has an effect on the QTc interval. Thiotepa has been approved in the US for more than 55 years and the decision whether the sponsor should perform additional QT assessment will depend on the clinical safety experience, available proarrhythmic and cardiac safety data from post-marketing reports, and whether the new product results in significantly higher exposure (i.e., C_{max} or AUC) than the approved product. We recommend that the sponsor summarizes these data for our further review.

2 PROPOSED LABEL

The following is the sponsor's proposed labeling language related to QT.

12.2 Pharmacodynamics

(b) (4)

Reviewer's Comment: Given the major limitations of this QT study as mentioned in section 1.1, we recommend no QT labeling to be included. We defer final labeling decisions to the Division.

3 BACKGROUND

3.1 PRODUCT INFORMATION

TEPADINA® (Thiotepa) is an ethylene imine-type compound, chemically and pharmacologically related to nitrogen mustard. A major active metabolite is triethylenephosphoramide (TEPA). Thiotepa is a versatile agent which can be used in the preparative regimen prior to haematopoietic progenitor cell transplantation (HPCT) for patients with a wide variety of disorders, from leukemia to solid tumors, from thalassemia to autoimmune disorders. The radiomimetic action of Thiotepa is believed to occur through the release of ethylene imine radicals that, as in the case of irradiation therapy, disrupt the bonds of deoxyribonucleic acid (DNA), e.g. by alkylation of guanine at the N-7, breaking the linkage between the purine base and the sugar and liberating alkylated guanine.

3.2 MARKET APPROVAL STATUS

TEPADINA® has been approved in Europe in 2010 and it is indicated, in combination with other chemotherapy medicinal products:

1) With or without TBI (total body irradiation), as conditioning treatment prior to allogeneic or autologous HPCT (haematopoietic progenitor cell transplantation) 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.

Thiotepa was originally approved in USA in 1959 and has been in use for treatment of neoplastic diseases.

3.3 PRECLINICAL INFORMATION

Not provided.

3.4 PREVIOUS CLINICAL EXPERIENCE

As alkylating agent, thiotepa produces the most profound inhibition of tumour cell growth in vitro with the smallest increase in medicinal product concentration. Due to its lack of extramedullary toxicity despite dose escalation beyond myelotoxic doses, thiotepa has been used for decades in combination with other chemotherapy medicinal products prior to autologous and allogeneic HPCT.

Regarding QT intervals, in the current study, none of the patients showed U-waves, arrhythmias, or other abnormalities. No syncopes, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de points and sudden deaths were recorded. One patient experienced non serious seizure which resolved.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of thiotepa's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT did not review the protocol prior to conducting this study. The sponsor submitted the study report ADN009 for thiotepa, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

Phase IV study to assess the effect of hepatic impairment on the pharmacokinetics of thiotepa and the potential of thiotepa to alter the QT interval, in pediatric patients undergoing allogeneic haematopoietic progenitor cell transplantation

4.2.2 Protocol Number

ADN009

4.2.3 Study Dates

14 May 2015 − 11 Oct 2015

4.2.4 Objectives

The primary objective of the study was to assess the effect of moderate hepatic impairment on the pharmacokinetics of thiotepa and its metabolite triethylenephosphoramide (TEPA) in pediatric patients undergoing allogeneic bone marrow transplantation (ABMT). The pharmacokinetic (PK) parameters of thiotepa and TEPA were originally planned to be compared in two pediatric populations characterized

by different levels of liver function as defined by Child-Pugh Score A (normal liver function) vs score B (liver impairment).

As a result of the premature study discontinuation, the main objective focused on patient's safety, which included:

- The assessment of the cardiac safety of thiotepa, in particular in relation to the ventricular repolarization (QT/QTc interval analysis), in pediatric patients,
- The general safety of thiotepa with the collection of treatment-emergent adverse events (TEAEs) and analysis of their possible association with thiotepa,
- Blood cell counts up to 30 days after transplantation.

4.2.5 Study Description

4.2.5.1 Design

This was a two-center, open-label, phase IV clinical trial in pediatric patients undergoing allogeneic haematopoietic progenitor cell transplantation (HPCT). The study was originally planned to enroll pediatric patients with different levels of hepatic function (Child-Pugh score A and score B). Due to the impossibility to enroll Child-Pugh B liver impairment patients, the study was prematurely terminated.

4.2.5.2 Controls

Neither placebo nor positive (moxifloxacin) controls were used.

4.2.5.3 Blinding

The study was open-label.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

There was one treatment in the study:

TEPADINA® (thiotepa) was administered intravenously through a central venous catheter with two infusions of 5 mg/kg each, 12 hours apart on the first day of the conditioning regimen. The duration of each infusion was 3 hours.

The impossibility of enrolling patients with Child-Pugh B (liver impairment) led to the conduction of the study in only the single arm with Child-Pugh score A (normal liver function).

4.2.6.2 Sponsor's Justification for Doses

Not provided.

Reviewer's Comment: The Applicant is using the maximum recommended therapeutic dose of 10 mg/kg/day divided in two daily iv infusions for this study. There is no accumulation with the second dose, with calculated accumulation ratio of 0.84. The maximum tolerated dose is not determined for this drug. Metabolism of thiotepa to TEPA

in human liver microsomes is the major mechanism of clearance of this compound. No information about the effect of hepatic and renal impairment or drug-drug interactions is known.

4.2.6.3 Instructions with Regard to Meals

Not applicable.

Reviewer's Comment: Because the drug will be administered intravenously, food is not likely to cause changes in drug exposure.

4.2.6.4 ECG and PK Assessments

ECG: 12-lead ECG tracings were collected before the first infusion of thiotepa, and at 6, 12 (time of start of second infusion), 18 and 36 hours since the start of the first infusion. In case of clinically relevant alterations observed in the ECGs, an additional ECG was collected also on day 7.

PK: Serial blood samples were taken for the PK analysis, prior to the start of the first infusion on day 1, and at 3 (end of first 3 hour infusion of thiotepa), 3.25, 3.5, 4, 6, 12 and 15 (end of the second 3 hour infusion of thiotepa) hours since the start of the first infusion of thiotepa.

Reviewer's Comment: The ECG assessment strategy is inadequate since for any of the two doses there was no ECG measurement around the time of end of infusion (3 and 15 hours since the start of first infusion), where maximum plasma concentration of thiotepa is expected.

4.2.6.5 Baseline

The QT/QTc value at screening visit was used as baseline.

4.2.7 ECG Collection

Standard 12-Lead ECGs were obtained while subjects were at rest.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 12 pediatric patients (4 females and 8 males) undergoing allogeneic haematopoietic progenitor cell transplantation enrolled in the study. The average age of the 12 patients was 5.5 years, ranging from 1.0 to 14.0 years. The 12 patients had normal liver function (Child-Pugh score A). All of the 12 patients received at least one dose of the study drug and thus were included in the safety population.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The following Table 2 from the sponsor's report shows the pre-post differences compared to the screening visit. No relevant changes of the assessed QT and QTc intervals were seen during this study.

Table 2: Pre-post Differences of ECG Parameters (Safety Set, N = 12) (Sponsor's Results)

Parameter Visit	Mean change from screening	SD
QT interval, single beat		
Day 1 (1st Thiotepa infusion)	-4.0	24.0
Day 1 (2nd Thiotepa infusion)	18.8	34.9
Day 2	7.4	33.7
QTcB interval, single beat		
Day 1 (1st Thiotepa infusion)	-6.0	21.9
Day 1 (2nd Thiotepa infusion)	-0.5	30.1
Day 2	-4.0	28.1
QTcF interval, single beat		
Day 1 (1st Thiotepa infusion)	0.0	0.0
Day 1 (2nd Thiotepa infusion)	22.8	20.6
Day 2	13.8	18.2
QTcL interval, single beat		
Day 1 (1st Thiotepa infusion)	0.0	0.0
Day 1 (2nd Thiotepa infusion)	18.0	17.5
Day 2	8.3	8.5

Source data: Table 14.3.4.1
QT = QT interval (time between the start of the Q wave and the end of the T wave in the heart's electrical cycle), QTc = corrected QC, QTcB = Bazett QT correction, QTcF = Fridericia QT correction, QTcL = Framingham QT correction, SD = standard deviation

Source: The sponsor's clinical study report, T-Table 12.5.1, page 48.

Reviewer's Comments: Please see the reviewer's analysis in section 5.2.

4.2.8.2.2 Assay Sensitivity

Not Applicable.

4.2.8.2.3 Categorical Analysis

Predominantly, 100.0% of patients with available data showed a QT/QTc interval less than 450 msec at the different visits. For 1 patient (8.3%), the QTcB interval (Bazett QT correction; single beat) exceeded the upper limit of 450 msec at day 1 (2nd Thiotepa infusion) and day 2, respectively. All patients with available data always had a QT/QTc interval less than 480 msec and 500 msec, respectively. The results indicate that the administration of Thiotepa generally did not lead to a marked prolongation of the QT/QTc interval.

QTc interval increases from baseline less than 30 msec were predominantly documented for the majority of patients with available data; all patients with available data had QTc interval increases from baseline less than 60 msec.

4.2.8.3 Safety Analysis

No patient died in the course of this study and no patient discontinued the study prematurely due to an AE.

In the course of this study, 10 patients (83.3%) experienced treatment emergent adverse events (TEAEs). The majority of patients (N = 8 [66. 7%]) suffered from TEAEs assessed to be related to the study treatment.

Serious TEAEs were recorded for 2 patients (16.7%). They occurred in patients [redacted] (b) (6) (life-threatening 'Sepsis') and [redacted] (b) (6) (severe 'Venoocclusive liver disease). Both non-fatal, serious TEAEs were assessed by the reporting investigators to be not related to the study treatment.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK parameters for drug (thiotepa) and its metabolite (TEPA), for the first iv infusion of 5 mg/kg dose of thiotepa is presented in Table 3. There was no supratherapeutic dose of thiotepa utilized in the study. The concentration-time profile for therapeutic dose of thiotepa (10 mg/kg/day divided into two iv infusions 12 hours apart) and associated concentration-time profile for its metabolite TEPA is illustrated in Figure 3 as a part of reviewers' assessment.

Table 3: Pharmacokinetic Parameters for Thiotepa (Drug) and TEPA (Metabolite) after 3-hour IV infusion of 5 mg/kg Thiotepa

Treatment		t_{max} (min)	C_{max} (ng/mL)	AUC_{0-12h} (ng•h/mL)	$AUC_{0-\infty}$ (ng•h/mL)
ThioTEPA	N	11	11	12	12
	Mean	**182,7**	**3640,27**	**10841,14**	**11437,94**
	SD	6,1	1780,83	5332,98	5782,95
	Median	**180,0**	**3112,92**	**10093,77**	**10890,08**
	Min	180,0	1475,86	3750,38	3564,60
	Max	195,0	6873,19	19750,41	20199,98
	CV%	3,3	48.9	49.19	50,56
TEPA	N	11	11	12	9
	Mean	**204,5**	**268,84**	**1723.31**	**2016.64**
	SD	24,4	97,10	675.65	899.31
	Median	**195,0**	**312,56**	**1719.46**	**2107.91**
	Min	180,0	50,25	327.92	429.94
	Max	240,0	373,14	2812.95	3858.01
	CV%	11,9	36,12	39.21	44.59

Source: Table III, page 10281 of 10320 in Applicant's Clinical Study Report.
Note: Commas are used instead of decimal point symbol in the Applicant's PK reporting as seen above.

4.2.8.4.2 Exposure-Response Analysis

Not provided by the Applicant.

Reviewer's Analysis: Amongst the limited ECG samples, the observed increases in QTc interval following the second dose of thiotepa cannot be directly explained by plasma concentrations of thiotepa and its active metabolite (TEPA) because the similar increases in QTc interval after the first dose of thiotepa were not observed, even though the drug exposures are expected to be similar between the first and second dose;therefore, further exposure-response analyses for QTc were not conducted.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We used predose baseline and generated ECG parameters based on available QT/RRs. The statistical analyses from the reviewers were based on the generated data. We evaluated the appropriateness of the correction methods (QTcB, QTcF, and QTcL).

Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

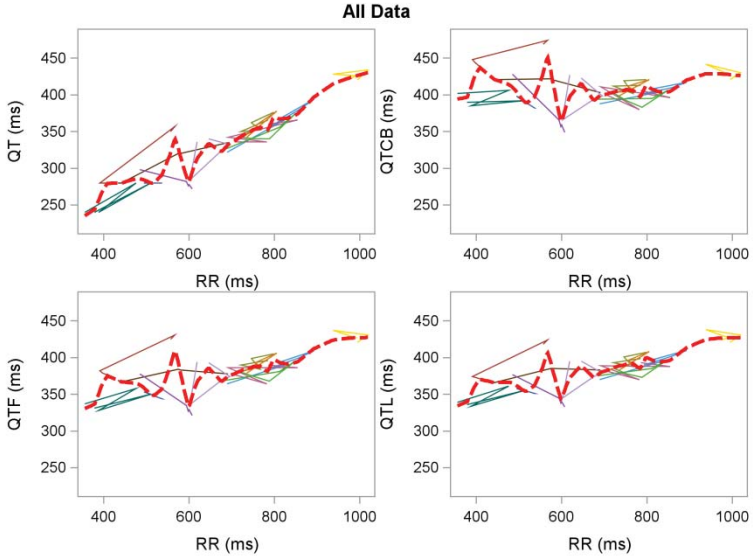
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 4, it appears that QTcL is the best correction method. Therefore, QTcL was used for the primary statistical analysis.

Table 4: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

	QTcB		QTcF		QTcL	
Treatment Group	**N**	**MSSS**	**N**	**MSSS**	**N**	**MSSS**
Thiotepa 5 mg/kg IV	12	0.17745	12	0.12743	12	0.09720

The relationship between different correction methods and RR is presented in Figure 1.

Figure 1: QT, QTcB, QTcF, and QTcL vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Thiotepa

The statistical reviewer used descriptive analysis to show the ΔQTcL effect. The analysis results are listed in the following table.

.

Table 5: Analysis Results of ΔQTcL for Thiotepa 5 mg/kg IV

	ΔQTcL (ms)			
Time (Hour)	**N**	**Mean**	**SE**	**90% CI**
3 Hours after the End of 1st Dose	11	3.4	3.6	(-3.1, 9.9)
Before the Admin. of the 2nd Dose	10	6.5	3.0	(1.0, 12.0)
3 Hours after the End of the 2nd Dose	11	15.2	6.0	(4.3, 26.0)
24 Hours after the Admin. of the 2nd Dose	11	9.2	6.2	(-2.1, 20.4)

The largest mean change from baseline in QTcL (ΔQTcL) was 15.2 ms with a 2-sided 90% CI of 4.3 ms to 26.0 ms, which occurred at 3 hours after the end of the 2nd dose. The result should be interpreted with caution as it is not powered to exclude large increases in QTc (>20 ms).

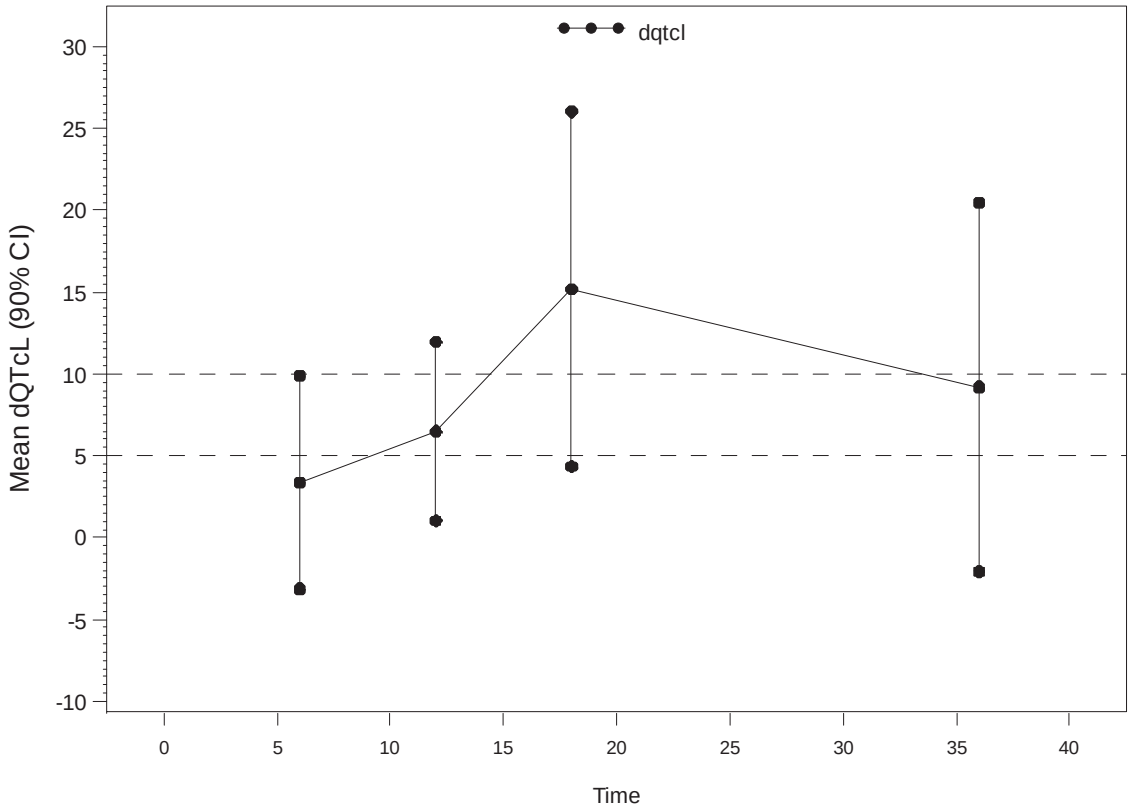
5.2.1.2 Assay Sensitivity Analysis

Not Applicable.

5.2.1.3 Graph of ΔQTcL Over Time

The following figure displays the time profile of ΔQTcL for thiotepa 5 mg/kg IV.

Figure 2: Mean and 90% CI ΔQTcL Timecourse



5.2.1.4 Categorical Analysis

Table 6 lists the number of subjects as well as the number of observations whose QTcL values were ≤ 450 ms and between 450 ms and 480 ms. No subject's QTcL was above 450 ms.

Table 6: Categorical Analysis for QTcL

	Total N		QTcL<=450 ms		450<QTcL<=480 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Day 1 Predose	11	11	11 (100%)	11 (100%)	0 (0.0%)	0 (0.0%)
Thiotepa 5 mg/kg IV	12	47	12 (100%)	47 (100%)	0 (0.0%)	0 (0.0%)

Table 7 lists the categorical analysis results for ΔQTcL. No subject's change from baseline in QTcL was above 60 ms.

Table 7: Categorical Analysis of ΔQTcL

	Total N		ΔQTcL<=30 ms		30<ΔQTcL<=60 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Thiotepa 5 mg/kg IV	11	43	9 (81.8%)	39 (90.7%)	2 (18.2%)	4 (9.3%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals for the mean changes from baseline in HR (ΔHR) are presented in Table 8. An HR decreasing effect was observed at 3 hours after the end of infusions; the result was not reliable due to small number of patients.

The outlier analysis results for HR are presented in Table 9.

Table 8: Analysis Results of ΔHR for Thiotepa 5 mg/kg IV

	ΔHR (bpm)			
Time (Hour)	**N**	**Mean**	**SE**	**90% CI**
3 Hours after the End of 1st Dose	12	-6.6	3.0	(-12.0, -1.2)
Before the Admin. of the 2nd Dose	11	-1.5	4.1	(-8.9, 6.0)
3 Hours after the End of the 2nd Dose	12	-11.6	3.1	(-17.1, -6.1)
24 Hours after the Admin. of the 2nd Dose	12	-1.6	5.2	(-10.9, 7.7)

Table 9: Categorical Analysis Results of HR

	Total N	HR<=100 bpm	HR>100 bpm	HR>45 bpm	HR<=45 bpm
Treatment Group	**Subj. #**	**Subj. #**	**Subj. #**	**Subj. #**	**Subj. #**
Day 1 Predose	12	6 (50.0%)	6 (50.0%)	12 (100%)	0 (0.0%)
Thiotepa 5 mg/kg IV	12	3 (25.0%)	9 (75.0%)	12 (100%)	0 (0.0%)

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals for the mean changes from baseline in PR (ΔPR) are presented in Table 10. No statistically significant PR effect was observed.

The outlier analysis results for PR are presented in Table 11.

Table 10: Analysis Results of ΔPR for Thiotepa 5 mg/kg IV

	ΔPR (ms)			
Time (Hour)	**N**	**Mean**	**SE**	**90% CI**
3 Hours after the End of 1st Dose	12	3.8	3.3	(-2.1, 9.8)
Before the Admin. of the 2nd Dose	11	6.2	6.8	(-6.1, 18.4)
3 Hours after the End of the 2nd Dose	12	1.5	4.3	(-6.1, 9.1)
24 Hours after the Admin. of the 2nd Dose	12	-1.2	2.2	(-5.1, 2.7)

Table 11: Categorical Analysis for PR

	Total N		PR<=200 ms		PR>200 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Day 1 Predose	12	12	12 (100%)	12 (100%)	0 (0.0%)	0 (0.0%)
Thiotepa 5 mg/kg IV	12	47	11 (91.7%)	46 (97.9%)	1 (8.3%)	1 (2.1%)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals for the mean changes from baseline in QRS (ΔQRS) are presented in Table 12. No statistically significant QRS effect was observed.

The outlier analysis results for QRS are presented in Table 13.

Table 12: Analysis Results of ΔQRS for Thiotepa 5 mg/kg IV

	ΔQRS (ms)			
Time (Hour)	**N**	**Mean**	**SE**	**90% CI**
3 Hours after the End of 1st Dose	12	0.2	1.4	(-2.3, 2.6)
Before the Admin. of the 2nd Dose	11	4.2	4.0	(-3.1, 11.5)
3 Hours after the End of the 2nd Dose	12	0.2	1.3	(-2.1, 2.6)
24 Hours after the Admin. of the 2nd Dose	12	1.5	2.2	(-2.4, 5.4)

Table 13: Categorical Analysis for QRS

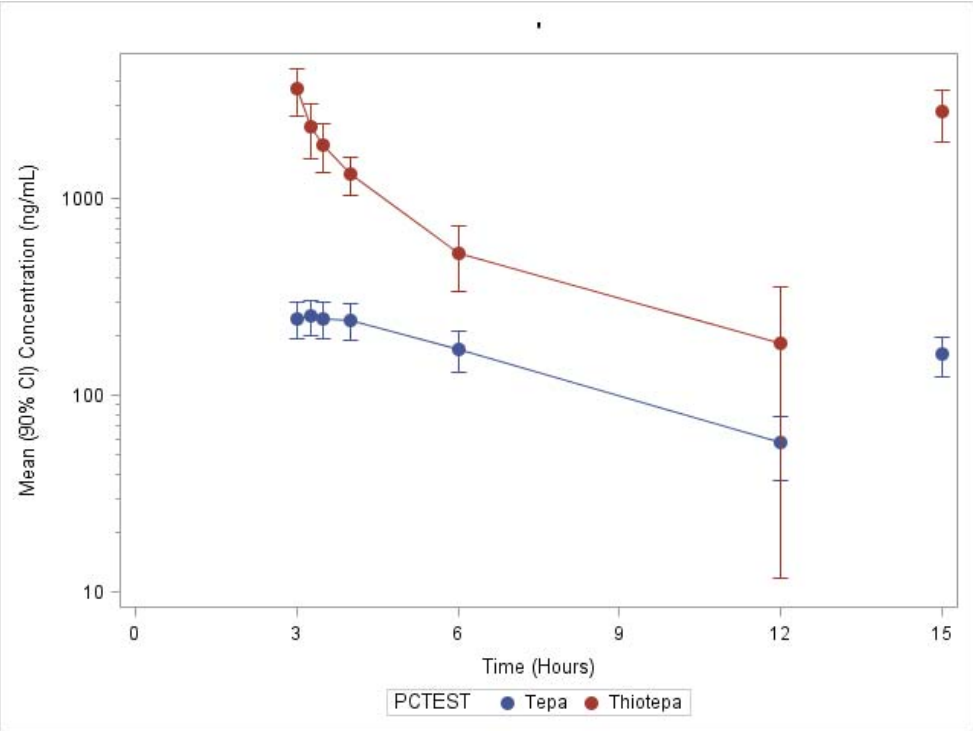
	Total N		QRS<=110 ms		QRS>110 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Day 1 Predose	12	12	12 (100%)	12 (100%)	0 (0.0%)	0 (0.0%)
Thiotepa 5 mg/kg IV	12	47	12 (100%)	47 (100%)	0 (0.0%)	0 (0.0%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean drug and metabolite concentration-time profile is illustrated in Figure 3.

The exploratory plots of the concentration-time course (Figure 3) and ΔQTcL-time course (Figure 2) show that the observed increases in QTc interval following the second dose of thiotepa cannot be directly explained by plasma concentrations of thiotepa and its active metabolite (TEPA) because the similar increases in QTc interval after the first dose of thiotepa were not observed, even though the drug exposures are expected to be similar between the first and second dose. Therefore it is unclear whether the observed increases in QTc interval following the second dose was caused by the study procedure or the thiotepa treatment; conclusions regarding exposure-response relationship cannot be made.

Figure 3: Mean drug (thiotepa; red line) and metabolite (TEPA; blue line) concentration-time profiles for 5 mg/kg thiotepa dose administered as 3-hour iv infusion at time 0 and 12 hours



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

Events identified to be of clinical importance per the ICH E14 guidelines, i.e., syncope, significant ventricular arrhythmias or sudden cardiac death, did not occur in this study.

One patient [redacted] (b) (6)) had a treatment-emergent seizure that was not considered to be a serious adverse event.

5.4.2 ECG assessments

Paper ECGs were submitted for review. Some ECG intervals in the clinical dataset were not the same as those in the paper ECGs. Therefore, the sponsor should revisit those ECG data.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose and exposure	Dosing regimen: 125 mg/m^2 every 12 hours for two doses Thiotepa: (*After the first dose*) $AUC_{0-\infty}$. Mean: 11437.94 μg.h/L (%CV: 50.6); Cmax. Mean: 3640.27 μg/L (%CV: 48.9); (*At the steady-state*) Cmax. Mean: 3417.91 μg/L (%CV: 53.7); Tepa*:* *(After the first dose*) $AUC_{0-\infty}$. Mean: 2016.64 μg.h/L (%CV: 44.6); Cmax. Mean: 268.84 μg/L (%CV: 36.1); (*At the steady-state*) Cmax. Mean: 161.62 μg/L (%CV: 44.3);	
Maximum tolerated dose	N.A.	
Principal adverse events	The most frequently documented adverse events were mucosal inflammation and pyrexia. No dose limiting adverse events, no adverse events leading to premature study discontinuation have been postponed.	
Maximum dose tested	Single Dose	125 mg/m^2
	Multiple Dose	125 mg/m^2 every 12 hours for two doses
Exposures Achieved at Maximum Tested Dose	Single Dose	Thiotepa: $AUC_{0-\infty}$. Mean: 11437.94 μg.h/L (%CV: 50.6); Cmax. Mean: 3640.27 μg/L (%CV: 48.9); Tepa*:* *(After the first dose*) $AUC_{0-\infty}$. Mean: 2016.64 μg.h/L (%CV: 44.6); Cmax. Mean: 268.84 μg/L (%CV: 36.1)
	Multiple Dose	Thiotepa*:*

		(*At the steady-state*) Cmax. Mean: 3417.91 µg/L (%CV: 53.7); <u>Tepa</u>*:* (*At the steady-state*) Cmax. Mean: 161.62 µg/L (%CV: 44.3);
Range of linear PK	50-300 mg/m^2	
Accumulation at steady state	Accumulation ratio R_{acc}=0.84 (%CV:39.2)	
Metabolites	Thiotepa is metabolized in human liver microsomes by CYP3A4 (major) and CYP2B6 (minor), to the pharmacologically active metabolite, Tepa. Pharmacokinetic variability of thiotepa may be related to expression of hepatic CYP isozymes. Tepa/Thiotepa exposure ratio (%): 23.4 % (%CV:70)	
Absorption	Absolute/Relative Bioavailability	*Not applicable*; the drug was administered as a 2-h intravenous infusion
	Tmax	*Not applicable*
Distribution	Vd	Mean: 29.7 L/m^2 (%CV: 44.4)
	% bound	N.A.
Elimination	Route	• Metabolism of thiotepa to tepa in human liver microsomes is the major mechanism of clearance of this compound • Other routes
	Terminal t½	• Thiotepa*:* 103.7 min (%CV: 64.3). • Tepa: 239.7 min (%CV: 28.6).
	CL	Mean: 0.23 L/min/m^2 (%CV: 51.5)
Intrinsic Factors	Age	The data currently available show an inverse relationship between pediatric age and the total body clearance of Thiotepa. *From 2 to 6 years (8 pts):* AUC= Mean: 9502.61 µg.h/L (%CV:37.9); Cmax= 3136.06 µg /L (%CV:44.4). *From 10 to 14 years (3 pts):* AUC= Mean: 19223 µg.h/L (%CV:6.9);

		Cmax= 4984.83 μg /L (%CV:46.4)
	Sex	N.A
	Race	N.A.
	Hepatic & Renal Impairment	N.A.
Extrinsic Factors	Drug interactions	N.A.-
	Food Effects	N.A.
Expected High Clinical Exposure Scenario	N.A.	
Preclinical Cardiac Safety	N.A.	
Clinical Cardiac Safety	Regarding QT intervals, none of the patients showed U-waves, arrhythmias, or other abnormalities. No syncopes, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de points and sudden deaths were recorded. One patient experienced non serious seizure which resolved.	

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/s/

DEVI KOZELI on behalf of HUIFANG CHEN
07/18/2016
Signing for Huifang because she is on leave

QIANYU DANG
07/18/2016

DHANANJAY D MARATHE
07/18/2016

JIANG LIU
07/18/2016

MICHAEL Y LI
07/18/2016

CHRISTINE E GARNETT
07/19/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	July 14, 2016
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 208264
Product Name and Strength:	Thiotepa for Injection 15 mg, 100 mg
Product Type:	Single-ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Adienne
Submission Date:	July 5, 2016
OSE RCM #:	2016-902-1
DMEPA Primary Reviewer:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader (Acting):	Hina Mehta, PharmD

1 PURPOSE OF MEMO

The Division of Hematology Products (DHP) requested that we review the revised carton labeling and container labels for Thiotepa for Injection (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

2 CONCLUSION

The revised container labels and carton labeling are unacceptable from a medication error perspective. The strength statement appears directly adjacent to the proprietary name on the carton labeling and container labels. We recommend that the display of this information is revised to ensure consistency with current labeling standards. Additionally, the display of the established name should be revised.

We continue to recommend that the Sponsor considers inclusion of the NDC number 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.

3 RECOMMENDATIONS FOR ADIENNE

We recommend the following be implemented prior to approval of this NDA 208264:

A. Carton labeling
    1. Revise the presentation of the established name as follows:

       (thiotepa) for injection

    2. Relocate the strength statement below the proprietary name, established name, and dosage form to ensure consistency with current labeling standards.[2]
    3. We recommend the inclusion of the NDC number 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.

B. Container label
    1. See recommendation A.1. through A.3. and revise accordingly.

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[1] Whaley E. Label and Labeling Review for Thiotepa for Injection (NDA 208261). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 MAR 31. 18 p. OSE RCM No.: 2016-902.

[2] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

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EBONY A WHALEY
07/14/2016

HINA S MEHTA
07/14/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 8, 2016
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 208264
Product Name and Strength:	Thiotepa for Injection 15 mg, 100 mg
Product Type:	Single-ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Adienne
Submission Date:	March 31, 2016
OSE RCM #:	2016-902
DMEPA Primary Reviewer:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Yelena Maslov, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed labels and labeling for Thiotepa for Injection (NDA 208264) for areas of vulnerability that could lead to medication errors. The Division of Hematology Products (DHP) requested this review as part of their evaluation of the 505(b)(2) submission for Thiotepa for Injection. The reference listed drug (Thioplex, NDA 022393) was approved on December 22, 1994 and was withdrawn federal register effective June 4, 2004.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We evaluated the proposed container labels, carton labeling, and Prescribing Information (PI) for Thiotepa for Injection, NDA 208264. Thiotepa for Injection is an antineoplastic agent indicated for use in conjunction with high-dose busulfan and cyclophosphamide as a preparative regimen for allogenic hematopoietic progenitor cell transplantation in patients with class 3 β-thalassemia. Because Thiotepa for Injection and the RLD Thioplex have different indications, the dosing for Thiotepa for Injection (b) (4) is higher than the dosing for Thioplex (0.3 to 0.4 mg/kg/dose). Additionally, Thiotepa for Injection can be administered intravenously, while Thioplex was approved for the intravenous, intracavitary, and intravesical routes of administration. We discussed the difference in dosing between Thioplex and Thiotepa for Injection with the Clinical review team and determined that adequate labeling can help mitigate confusion regarding Thiotepa for Injection dosing.

Additionally, Thiotepa for Injection is supplied as 15 mg and 100 mg vials requiring reconstitution and dilution prior to administration. This differs from RLD Thioplex which was only available as a 15 mg vial. However, because the dosing for Thiotepa for Injection is higher than the dosing for Thioplex, we find the addition of the 100 mg vial to be acceptable. Also, during a US shortage of thiotepa, the Agency temporary allowed importation non-US licensed Thiotepa for Injection; the shortage has since resolved and importation stopped in December 2015.[1,2] During the period in which non-US licensed Thiotepa for Injection was available in the US, the Agency did not receive medication error reports of confusion regarding the addition of the Thiotepa for Injection 100 mg vial to the marketplace.

Additionally, we note that the proposed 15 mg vial provides doses that are consistent with doses that would be required for a limited patient population. However, we note that the 15 mg vial strength may help limit the amount of excess product as compared to the 100 mg vial for certain doses.[3] For example, a pediatric patient weighing 20 kg may receive a dose (b) (4) every 12 hours (b) (4). The use of 15 mg vials to dispense a (b) (4) dose would have less product waste than if the 100 mg vial was used. Therefore, we find that the 15 mg vial is clinically useful.

We note that the Prescribing Information should be revised to provide clear instructions regarding the dosing and the maximum cumulative dose per conditioning regimen. Section 2 Dosage and Administration lists the dosing for Thiotepa for Injection as (b) (4) (b) (4) (b) (4); however, the information may appear confusing to some readers. Therefore, this section should be clarified to mitigate the risk of misinterpretation. Additionally, Section 16 How Supplied/Storage and Handling should be revised to inform health care provides of the special handling precautions necessary for Thiotepa for Injection, which is a cytotoxic drug.

Regarding the carton labeling and container label, we acknowledge the Applicant's use of unique color borders for the 15 mg and 100 mg vial strengths of Thiotepa for Injection. However, we recommend that the application of color is increased to provide clear differentiation and to prevent selection errors. For example, the unique color could be

[1] Dear Healthcare Professional Letter for Thiotepa. 25 JUL 2013. Available from http://www fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM251666.pdf.
[2] ASHP. Drug Shortages Bulletin for Thiotepa for Injection. Available from http://www.ashp.org/menu/DrugShortages/CurrentShortages/bulletin.aspx?id=589.

[3] Guidance for Industry: Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products. Food and Drug Administration. 2015 [cited 2016 MAY 6]. Available from http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm389069.pdf.

incorporated into the display of the proprietary name or the use of the color borders could be increased. Additionally, the display of key prescribing information, such as established name, dosage form, and strength, on the carton labeling and container label should be revised to reflect current labeling standards.

We searched the FAERS database to identify medication errors involving thiotepa. We identified two cases of accidental exposure and one case each of wrong dose, wrong drug, and wrong route errors (see Appendix E for detailed description of cases). To mitigate the potentially hazardous implications of accidental exposure to Thiotepa for Injection, the PI and carton labeling and container labeling should be revised to more clearly convey the special handling requirements. Additionally, we recommend revisions to the labeling to increase clarity of the dosing information listed in Section 2 Dosage and Administration of the PI.

4 CONCLUSION & RECOMMENDATIONS

We determined that there are areas within the Prescribing Information, container label, and carton labeling that can be improved upon to reduce the risk of medication errors and to increase clarity and prominence of key information.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Section 2 Dosage and Administration, 2.1 (b) (4)
    i. The dosing information should be revised to increase the clarity and to mitigate confusion regarding the maximum cumulative dose. Therefore, the second paragraph of this section should be revised to read:
2. (b) (4)

3. Section 16 How Supplied/Storage and Handling, 16.1 How Supplied
    i. The NDC numbers for both product strengths are denoted by a placeholder (e.g. XXXXX-XXXX-XX); please submit the actual NDC numbers for the Agency to review. Additionally, we recommend that the product codes in the NDC numbers are different for each product strength to mitigate the risk of wrong strength errors.[2]
4. Section 16 How Supplied/Storage and Handling, 16.2 Storage and Handling
    i. Thiotepa for Injection is a cytotoxic drug; however, the special handling requirements for Thiotepa for Injection are not provided in this section. Therefore, this section should be revised to include the statement below to convey the special handling requirements:

    "Thiotepa for Injection is a cytotoxic drug. Follow applicable special handling and disposal procedures.[x]"
    x = numerical citation to ""OSHA Hazardous Drugs." *OSHA*. *http://www.osha.gov/SLTC/hazardousdrugs/index.html*"

    ii. Revise "2°C -8°C" to "2°C to 8°C". We recommend this revision to mitigate the risk of misinterpretation of the storage information.

4.2 RECOMMENDATIONS FOR THE ADIENNE

We recommend the following be implemented prior to approval of NDA 208264:

A. Carton Labeling

1. Revise the presentation of the proprietary name, established name, and dosage form to correspond with one of the examples shown below.[4] Additionally, this revision will ensure consistency with USP requirements.[5]

Proprietary name (thiotepa for injection)	**OR**	Proprietary name (thiotepa) for injection	**OR**	Proprietary name (thiotepa) For Injection

2. Revise the presentation of the product strength to correspond with one of the examples show below. We recommend this revision to mitigate the risk of medication errors due to misinterpretation of total amount of drug per vial.[2]

XX mg/vial	**OR**	XX mg per vial

3. We note that for both strengths of Thiotepa for Injection, the majority of the label background is white with the limited application of a unique color border on the upper portion of the labeling. Thus, this scheme does not provide adequate differentiation among the two strengths of the product. As a result, selection errors may occur. Therefore, we recommend you revise the labels to increase utilization of color differentiation throughout the label (e.g., increase the application of the border or display each strength in unique colors). We recommend this revision to adequately differentiate the strengths and to mitigate the risk of wrong strength errors.
4. Consider revising the statement [redacted (b) (4)] [redacted (b) (4)] Additionally, increase the prominence of the statement, using boldface font or increased font size. We recommend these revisions to minimize the risk of administering the drug as an intravenous bolus.
5. Relocate the statement “Caution: Cytotoxic agent” to the principal display panel to increase the prominence of this important special handling statement.

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[4] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

[5] United States Pharmacopeia. USP General Chapter <1121> Nomenclature.

6. Revise the principal display panel (PDP) to include an “Rx Only” statement as this statement is required on the drug label by Section 503(b)(4)(A) of the Federal Food, Drug, and Cosmetic Act. Additionally, ensure that the “Rx Only” statement appears less prominent than other important information (e.g., proprietary name, strength, route of administration).
7. Consider bolding the statement “Store and transport refrigerated between 2°C to 8°C (36° to 46°F).” We recommend this revision to increase the prominence of this important information and minimize the risk of the storage information being overlooked.
8. Consider inclusion of the NDC number 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.

B. Container Label

1. See recommendations A.1. through A.3. and revise accordingly.
2. If space permits, consider revising the statement (b) (4) (b) (4) We recommend this to minimize the risk of administering the drug as an intravenous bolus.
3. If space permits, include the statement “Caution: Cytotoxic agent” to convey this important special handling statement to health care professionals.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Thiotepa for Injection that Adienne submitted on March 31, 2016, and the listed drug (LD).

Table 2. Relevant Product Information for Thiotepa for Injection and the Listed Drug

Product Name	**Thiotepa for Injection**	**Thioplex**
Initial Approval Date	N/A	December 22, 1994
Active Ingredient	thiotepa	thiotepa
Indication	Reducing the risk of graft rejection when used in conjunction with high-dose busulfan and cyclophosphamide as a preparative regimen for allogenic haematopoietic progenitor cell transplantation for patients with class 3 β-thalassemia.	Palliative therapy for a variety of neoplastic diseases including: adenocarcinoma of the breast, adenocarcinoma of the ovary, for controlling intracavitary effusions secondary to neoplastic disease of various serosal cavities, and for the treatment of superficial papillary carcinoma of the urinary bladder
Route of Administration	Intravenous	Intravenous, intracavitary, intravesical
Dosage Form	Lyophilized powder	Lyophilized powder
Strength	15 mg, 100 mg	15 mg
Dose and Frequency	6—10 mg/kg/day, divided in two daily infusions, administered in conjunction with high-dose busulfan and cyclophosphamide, without exceeding the total maximum cumulative dose of 10 mg/kg, during the entire conditioning treatment.	*Intravenous*: 0.3—0.4 mg/kg/dose every 1—4 weeks *Intracavitary*: 0.6—0.8 mg/kg/dose *Intravesical*: 60 mg instilled in the bladder
How Supplied	Single dose vial	Single use vial
Storage	Must be stored and transport refrigerated at 2°C to 8°C (36° to 46°F). DO NOT FREEZE. If not used immediately after reconstitution, the product is stable for 8 hours when stored at 2°C to 8°C (36° to 46°F). After dilution the product is stable for 24 hours when stored at 2°C to 8°C (36° to 46°F) and	Store in refrigerator at 2°C to 8°C (36° to 46°F). Protect from light.

	for 4 hours when stored at 25°C (77°F).	

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On April 27, 2016, we searched the L:drive and AIMS using the terms, Thioplex and thiotepa, to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identify any previous reviews

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On April 26, 2016, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care Community Nursing PA Patient Safety Joint Commission
Search Strategy and Terms	Match Any of the Words: Thiotepa Thioplex

D.2 Results

Our search did not identify any newsletter articles relevant to this review.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on April 26, 2016 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[6]

Table 3: FAERS Search Strategy	
Date Range	**Initial FDA Rcvd Date to:** 20160401
Product	**Thiotepa** [active ingredient] **Thioplex** [product name]
Event (MedDRA Terms)	**DMEPA Official FBIS Search Terms Event List:** Contraindicated Drug Administered (PT) Drug Administered to Patient of Inappropriate Age (PT) Inadequate Aseptic Technique in Use of Product (PT) Medication Errors (HLGT) Overdose (PT) Prescribed Overdose (PT) Prescribed Underdose (PT) Product Adhesion Issue (PT) Product Compounding Quality Issue (PT) Product Formulation Issue (PT) Product Label Issues (HLT) Product Packaging Issues (HLT) Product Use Issue (PT) Underdose (PT)
Country	USA

E.2 Results

Our search identified 27 cases, of which 5 described errors relevant for this review.

Accidental exposure (n = 2)

[6] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

Two cases (FAERS Case No. 5400656 and 5403150) described instances of long term occupational exposure to multiple neoplastic agents, including thiotepa. In the first case, the reporter stated that the patient was exposed to thiotepa while employed as a pharmacist. The patient died of non-Hodgkin's lymphoma. In the second case, the patient also experienced occupational exposure to Thiotepa and was later diagnosed with non-Hodgkin's lymphoma and chronic lymphocytic leukemia.

A review of the Prescribing Information indicates that Section 2 Dosage and Administration informs HCPs of the special handling requirements for Thiotepa for Injection; however, Section 16 How Supplied/Storage and Handling should be revised to more clearly convey this information. Additionally, the carton labeling and container label can be improved to inform HCPs to utilize special precautions during handling.

Wrong dose (n = 1)

One report (FAERS Case No. 3990081) described a case in which there was confusion regarding the dose of thiotepa used in a particular chemotherapy protocol; an actual medication error did not occur. The pharmacist reviewed the high dose chemotherapy orders, and the physician provided a copy of the protocol to clarify. The pharmacist was concerned because the protocol listed the dose in "total mg/m^2", with the intention that the dose would be given over four days. The pharmacist found this to be confusing and reported that "you had to assume from this protocol that 6000 mg/m^2 was to be administered over four days" instead of as one dose.

We note that the Thiotepa for Injection Prescribing Information does not reference specific chemotherapy protocols. However, a review of the Prescribing Information for Thiotepa for Injection indicates that Section 2 Dosage and Administration should be revised to increase clarity regarding the dosing and the maximum cumulative dose.

Wrong drug (n = 1)

One case (FAERS Case No. 4491865) reported that a patient was administered Thiotepa 30 mg intravenously instead of "IVF dye". The reporter indicated that the patient did not experience adverse events. Contributing factors were not reported.

Labeling revisions in response to this medication error are not necessary.

Wrong route (n = 1)

One case (FAERS Case No. 3996967) described a report of patient receiving Thiotepa intramuscularly instead of intravesically. The patient did not experience adverse events as a result. Contributing factors were not reported.

A review of the Prescribing Information and carton and container labeling for Thiotepa for Injection indicates that Thiotepa for Injection is for intravenous use only. Therefore, labeling mitigations are not needed in response to this error.

We excluded 22 cases because they described unrelated literature reports (n = 13), medication errors that did not involve thiotepa (n = 8), and product labeling confusion with Thioplex (n = 1).

E.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

FAERS Case Number	Manufacturer Control Number
5400656	96050007
5403150	09496022
3990081	Not reported
4491865	8500287
3996967	03-205-0186

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[7] along with postmarket medication error data, we reviewed the following Thiotepa for Injection labels and labeling submitted by Adienne on March 31, 2016.

- Container label
- Carton labeling
- Prescribing Information

G.2 Label and Labeling Images

- **Container Label**

(b) (4)

[7] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

EBONY A WHALEY
06/08/2016

YELENA L MASLOV
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