CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208264Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	208264
Link to EDR	\\CDSESUB1\evsprod\NDA208264\0002
Submission Date	March 31, 2016
Submission Type	Priority
Brand Name	Tepadina
Generic Name	Thiotepa
Dosage Form and Strength	Lyophilized powder for Injection, 15 mg/vial and 100 mg/vial
Route of Administration	Intravenous
Proposed 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
Applicant	Adienne SA
Associated Applications	NDA 020058 (Thioplex; Immunex), ANDA 075547 (thiotepa; West-Ward Pharmaceutical International Ltd.)
OCP Review Team	Sriram Subramaniam, PhD; Stacy Shord, PharmD (TL)
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1. EXECUTIVE SUMMARY

Thioplex (thiotepa) for Injection, 15 mg/vial (as lyophilized powder) was approved in 1994 for palliation of a variety of neoplastic diseases. In 2001, three generic drug products of Thioplex were approved. Thioplex has since been discontinued. Only one thiotepa drug product (ANDA 075547) is currently available and listed as the reference drug. The recommended doses (routes of administration) are 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).

This review includes evaluation of a 505(b)(2) NDA submission for Tepadina (thiotepa). In addition to the indications for Thioplex, Tepadina is proposed for reducing the risk of graft rejection with high-dose busulfan and cyclophosphamide as a preparative regimen for allogenic hematopoietic progenitor (stem) cell transplantation (HSCT) for patients with class 3 β-thalassemia. The proposed dosing regimen for the graft rejection indication is (b) (4) (b) (4).

Adienne submitted three studies: a retrospective study (ADN010) in pediatric patients (2-12 years) with class 3 β-thalassemia undergoing HSCT, and two clinical pharmacology studies including a study to evaluate the effect of mild hepatic impairment on thiotepa pharmacokinetics (PK) and QT/QTc prolongation in patients (ADN009) and an in vitro study to evaluate the effect on cytochrome P450 (CYP) enzymes on thiotepa metabolism (ADI/REP/01). In addition, Adienne referenced clinical pharmacology information for thiotepa from literature and the Thioplex labeling.

No exploratory exposure-response analyses for efficacy endpoints and toxicities could be conducted, because no PK samples were collected in the registration trial (ADN010). The proposed dose was based on the efficacy and toxicity of Tepadina in the registration trial and meta-analysis of literature data.

The key review questions focused on the appropriateness of dose recommendations for Tepadina use in patients taking concomitant CYP3A modulators, and in patients with hepatic impairment and renal impairment.

1.1 Recommendations

This NDA is acceptable from a clinical pharmacology perspective, provided that the Applicant and the Agency come to an agreement regarding the labeling language. The Office of Clinical Pharmacology recommends approval of this NDA.

Review Issues	Recommendations and Comments
Supportive evidence of effectiveness	A retrospective, historical-controlled study provides primary evidence. A meta-analysis of literature data provides secondary evidence.
General dosing instructions	A dose of (b) (4) 5 mg/kg, twice daily via intravenous infusion for a total to two doses appears to be effective and safe, given the limited data available.

Dosing in patient subgroups (intrinsic and extrinsic factors)	• Avoid concomitant use of strong CYP3A4 inhibitors and inducers. If cannot be avoided, closely monitor for adverse reactions. • No dose adjustment for patients with mild hepatic impairment and mild renal impairment. • Monitor for toxicity in patients with moderate and severe renal impairment and moderate and severe hepatic impairment following prolonged treatment.
Bridge between the "to-be-marketed" and clinical trial formulations	A bioequivalence trial to compare the approved thiotepa formulations and Tepadina was not necessary, as thiotepa is an intravenous drug product with no excipients. A scientific bridge exists between thiotepa products used in the literature and Tepadina to support the acceptance of the scientific

1.2 Post-Marketing Requirements and Commitment

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Thiotepa is an alklylating agent which disrupts the DNA bonds, and thereby causes cytotoxicity by interrupting crucial cellular processes, such as the biosynthesis of nucleic acids and protein. The following is a summary of the clinical pharmacokinetics (PK) of thiotepa. The following PK parameters for pediatric population are from Study ADN009 and for adult population are from literature (Appendix 4.1, 4.3, and 4.4). The metabolism and excretion data are from the current thiotepa labeling and literature. Information from thiotepa labeling is identified where applicable:

Absorption: Not applicable as thiotepa is administered intravenously (IV).

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 thioetpa 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.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

For the graft rejection indication, the applicant proposes a dosing regimen of (b) (4) (b) (4) (b) (4) The proposed thiotepa dose is based on the dose administered in the retrospective Study ADN010-RETALCLASS3 (hereafter will be referred as ADN010) and the published literature.

For the solid tumor indications, the following doses (routes of administration) are recommended based on Thioplex labeling: 0.3-0.4 mg/kg at 1 to 4 week intervals (IV), 0.6-0.8 mg/kg (intracavity), and 60 mg as 30-60 mL (intravesical).

2.2.2 Therapeutic individualization

- Avoid coadministration of strong CYP3A4 inhibitors and strong CYP3A4 inducers. If the modulators cannot be avoided, closely monitor for adverse drug reactions.
- No dose adjustments when coadministered CYP2B6 substrates.
- No dose adjustment for patients with mild hepatic impairment (HI) and mild renal impairment (RI).
- Monitor for toxicity in patients with moderate and severe RI and moderate and severe HI following prolonged treatment.

2.3 Outstanding Issues

No outstanding issues.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling concepts to be included in the final package insert:

- 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.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Thiotepa for Injection, 15 mg/vial, was approved in 1959, with sodium chloride and sodium bicarbonate as excipients. In 1994, Thioplex (thiotepa) for Injection, 15 mg/vial, was approved for the treatment of a variety of tumors, including adenocarcinoma of the breast or ovary, malignant effusions, and superficial papillary carcinoma of the urinary bladder. Thioplex did not contain any inactive ingredients. Both products were lyophilized powder for injection. In 2001, three generic drug products of Thioplex were approved. Only one thiotepa drug product (ANDA 075547) is currently available and is listed as the reference drug. Thiotepa (ANDA 075547) is marketed as single use vials containing 15 mg of lyophilized powder with no inactive ingredients. The labeling recommends that thiotepa be administered as initial and maintenance doses, with an initial higher dose followed by a lower maintenance dose adjusted weekly based on complete blood counts. The recommended thiotepa doses (route of administration) include rapid infusion of 0.3-0.4 mg/kg at 1 to 4 week intervals (IV), 0.6-0.8 mg/kg (intracavity), and 60 mg as 30-60 mL (intravesical)[1].

In the current NDA, the applicant is seeking approval of Tepadina (thiotepa), 15 mg/vial and 100 mg/vial, via the 505(b)(2) approval pathway, for reducing the risk of graft rejection with high-dose busulfan and CP as a preparative regimen for allogenic hematopoietic progenitor (stem) cell transplantation (HSCT) for pediatric patients with class 3 β-thalassemia. In addition, Tepadina will also be indicated for the indications listed in the Thioplex labeling. Tepadina was granted an Orphan Drug Designation by FDA on April 2, 2007 (#07-2378).

The applicant proposes a Tepadina dosing regimen of (b) (4) (b) (4). The Tepadina dose is based on a retrospective study (ADN010) and literature data from thalassemia / ß-thalassemia patients undergoing HSCT. No PK sampling was collected in Study ADN010. The results from Study ADN010 showed that no graft rejection occurred in patients with class 3 β-thalassemia (n=25) conditioned with busulfan, Tepadina, and CP compared to 25.5% graft rejection in patients (n=51) conditioned with busulfan and CP (p=0.0036).

3.2 General Pharmacological and Pharmacokinetic Characteristics

The PK parameters listed below for pediatric patients are from Study ADN009 and for adult patients from the literature (Appendix 4.3).

[1] Thiotepa labeling dated February 2015. Drugs@FDA.

Pharmacology	
Mechanism of Action	Alkylating agent that disrupts DNA bonds resulting in cytotoxicity.
Active Moieties	The major active metabolite of thiotepa is TEPA (triethylenephosphoramide).
QT Prolongation	In 12 patients administered 10 mg/kg/day, the QTc interval was < 500 ms. QTc interval increases from baseline were < 60 ms. However, data are not conclusive (refer to Appendix 4.2).
General Information	
Bioanalysis	Measured by LC/MS/MS following protein precipitation.
Healthy Volunteers vs. Patients	No information.
Drug exposure at single dose following the therapeutic dosing regimen	With 5 mg/kg IV infusion (mean± SD) in 12 pediatrics: **AUC_{0-inf}**: 11437 ± 5782 ng.h/mL (Thiotepa) and 2017 ± 899 ng.h/mL (TEPA). **C_{max}**: 3640 ± 1781 ng/mL (Thiotepa) and 269 ± 97 ng/mL (TEPA). **Median T_{max}**: 180 minutes (thiotepa) and 195 minutes (TEPA). **C_{max} at the end of 2nd dose infusion**: 2756 ± 1573 ng/mL (Thiotepa) and 162 ± 72 ng/mL (TEPA) With 20 mg IV bolus to 250 mg/m^2 IV infusion (mean± SD) in adults: **AUC_{0-inf}**: 822 ± 83 ng.hr/mL to 15800 ng.hr/mL (Thiotepa) and 1084 ± 234 ng.hr/mL to 18200 ± 2000 ng.hr/mL (TEPA) **C_{max}**: 1591 ± 239 ng/mL to 2080 ± 130 ng/mL (Thiotepa) and 75 ± 14 ng/mL to 1880 ± 150 ng/mL (TEPA)
Minimal effective dose or exposure	Not provided.
Maximal tolerated dose or exposure	Not Provided.
Dose Proportionality	Not studied. Literature data not clear.
Accumulation	Pediatric: 0.84 (thiotepa) and 0.66 (TEPA) (60 mg to 225 mg) Adult: 1.01 (thiotepa) (20 mg)
Variability	With 5 mg/kg IV infusion (mean± SD) in 12 pediatrics: CV% for Cmax: 49% and AUC_{0-12}: 49% (Thiotepa) CV% for Cmax: 36% and AUC_{0-12}: 39% (TEPA) With 20 mg IV bolus to 250 mg/m^2 IV infusion (mean± SD) in adults: CV% for Cmax: 6-74% and AUC_{0-t}: 10-25% (Thiotepa) CV% for Cmax: 8-19% and AUC_{0-t}: 11-22% (TEPA)
Absorption	
Bioavailability [oral]	Not applicable.
T_{max} [IV]	With 5 mg/kg IV infusion (median) in 12 pediatrics: 180 minutes (Thiotepa) and 195 minutes (TEPA) With 20 mg IV bolus to 250 mg/m^2 IV infusion (median) in adults: 2 (50%) min to 2.2 hours (thiotepa), and 3 (42%) hours (TEPA)

Distribution	
Volume of Distribution	With 5 mg/kg IV infusion (median) in 12 pediatrics: The mean estimated volume of distribution is 30 L/m^2 (17.19-54.86 L/m^2) after a single infusion, and appears to be independent of dose. With 20 mg IV bolus to 250 mg/m^2 IV infusion (median) in adults: The mean volume of distribution ranged from 1.0 L/kg (30%) to 1.9 L/kg (17%).
Plasma Protein Binding	≤ 20%
Blood to Plasma Ratio	0.7-0.8
Substrate transporter systems [*in vitro*]	Not provided.
Elimination	
Mean Terminal Elimination half-life	With 5 mg/kg IV infusion (mean) in 12 pediatrics: 1.7 (64%) hours (Thiotepa) and 4 (29%) hours (TEPA). With 20 mg IV bolus -6 mg/kg IV infusion (mean) in adults: 1.4 (7%)to 3.7 (14%) hours (Thiotepa), and 4.9 to 17.6 (20%) hours (TEPA)
Metabolism (Appendix 4.4)	
Primary metabolic pathway [*in vitro*]	Literature data indicates thiotepa is metabolized by CYP3A and CYP2B6 to its major active metabolite TEPA. See Figure 1.
Inhibitor/Inducer	No clinical studies have been conducted to evaluate the effect of CYP3A4 or CYP2B6 modulators on the PK of thiotepa. In vitro data suggests that CYP3A4 and CYP2B6 inhibitors may decrease metabolism of thiotepa.
Excretion (Appendix 4.1)	
Primary excretion Pathways (% dose) ±SD	Urinary excretion of thiotepa is less 2% of the dose. Urinary excretion of TEPA is about 2% to 11% of the thiotepa dose.

Metabolic Pathway of ThioTEPA:

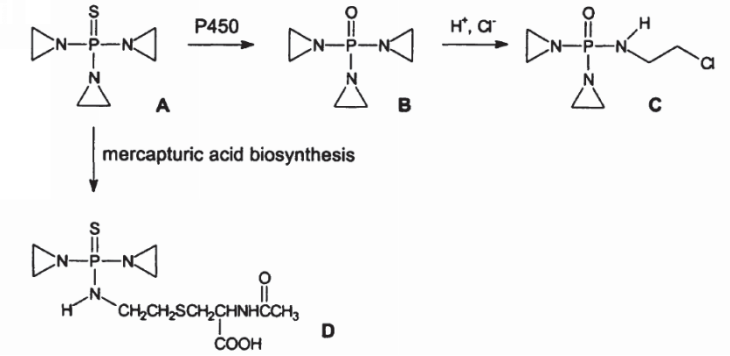


Figure 1: ThioTEPA (A), TEPA (B), monochloroTEPA (C) and thioTEPA-mercapturate (D).
Source: van Maanen et al. (2001). Anticancer Drugs; 12(6): 519-24.

TEPA (B) is formed in the liver after oxidative desulfuration of thiotepa; in vitro data suggests that CYP2B6 and CYP3A4 are responsible for the metabolism of thiotepa to TEPA. The conversion of TEPA to monochloroTEPA (C) is influenced by the pH and the chloride concentration. Also, thiotepa is converted to thioTEPA-mercapturate (D) after glutathione

conjugation, followed by the removal of the glutamate moiety by glutathionase and subsequent removal of glycine by a peptidase. Finally, the amino group of cysteine is acetylated by a hepatic N-acetylase, resulting in the mercapturic acid conjugate[2].

3.3 Clinical Pharmacology Questions

3.3.1 Does the clinical pharmacology information provide supportive evidence of effectiveness?

No clinical pharmacology information was provided to support the proposed dose. The proposed dose of [redacted] (b) (4) to minimize graft rejection is based on a retrospective study (ADN010) and literature data from patients with thalassemia / ß-thalassemia. No PK sampling was collected in Study ADN010 to permit exposure-response analysis for efficacy or safety endpoints. No dose-exposure relationship can be explored with limited dose range.

Per Thioplex labeling, the recommended thiotepa dose is rapid infusion of 0.3-0.4 mg/kg at 1 to 4 week intervals (IV), 0.6-0.8 mg/kg (intracavity), and 60 mg as 30-60 mL (intravesical).

3.3.2 Is the proposed general dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dosing regimen for pediatrics with class 3 ß-thalassemia appears appropriate based on the available efficacy and safety data.

The results from the retrospective, historical-controlled study (ADN010) identified no graft rejection in pediatric (4-16 years old) patients with class 3 β-thalassemia (n=25) conditioned with busulfan (weight-based dose) for 4 consecutive days followed by Tepadina (2 doses x 5 mg/kg IV, 12 hours apart) and then CP (40 mg/kg/day) for 4 consecutive days compared to 25.5% graft rejection in patients (n=51) conditioned with busulfan followed by CP (p=0.0036).

The incidence of Grade 2 to 4 acute graft-versus-host disease (GvHD) was similar in the Tepadina and control groups (28% vs. 26%), but the incidence of any chronic GvHD was higher in Tepadina group versus control group (35% vs. 14%). The overall incidence of adverse events (AE) related to treatment during 30 day post-transplant period were higher in Tepadina group compared to control group (84% vs 8%), with the most common AEs observed with Tepadina being stomatitis, diarrhea, abnormal hepatic function, viral infection, hematuria, and skin disorders; however, the incidence of serious AEs during 30-day post-transplant period was lower with Tepadina compared to control group (32% vs 51%). The most common serious AEs in the Tepadina group included stomatitis, abnormal hepatic function, and mucosal inflammation.

In addition, Adienne provided a meta-analysis of efficacy and safety data collected during the conduct of nine clinical trials from literature in patients with thalassemia / ß-thalassemia (0.6 - 37 yrs) (n=408) treated with thiotepa (total dose of 6 mg/kg to 10 mg/kg IV) and antithymocyte globulin, CP, busulfan, fludarabine, or treosulfan. The results of the meta-analysis showed a higher graft rejection rate (9.6%) with thiotepa compared to ADN010; however, per Adienne,

[2] van Maanen et al. (2001). Anticancer Drugs; 12(6): 519-24.

the studies with comparative data showed that regimens containing thiotepa produced a better outcome than regimens that did not include thiotepa, and secondary efficacy endpoint results were comparable to those in Study ADN010. Also, the incidence of acute GvHD (18%) and chronic GvHD (6%) with thiotepa in the meta-analysis was lower compared to the incidence reported in ADN010. The Applicant attributes these differences to a larger (n=286) and more varied (includes adults) patient population in the meta-analysis.

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

Yes. A management strategy is required for patients with moderate and severe organ impairment.

Hepatic impairment (HI):

No dose adjustment is recommended for patients with mild HI based on the data from Study ADN009. Although patients with normal hepatic function were not included in the study, the CL of patients with mild HI in Study ADN009 was similar to that of patients with normal hepatic function to mild HI based on literature data (Appendices 4.2 and 4.3). 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 (Appendix 4.3: Ackland et al., 1988[15]). Therefore, patients with moderate and severe should be monitored for signs and symptoms of toxicity following treatment with Tepadina for an extended period of time.

Renal Impairment (RI):

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. The existing thiotepa labeling and literature data indicates that the fraction of thiotepa dose excreted unchanged in urine is low (< 2%) in patients with cancer (Van Maanen et al., 1999 & 2001; Hagen et al., 1990)[2, 4, 10], 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 (Appendix 4.3: Eckart et al., 2009[16]). The patient experienced Grade 3 mucositis and diarrhea, and Grade 2 AST and bilirubin toxicity. Therefore, patients with moderate and severe RI should be carefully monitored for signs and symptoms of toxicity following treatment with Tepadina for an extended period of time.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Yes. A management strategy is required for the coadministration of CYP3A4 modulators. A description of possible interaction with CYP2B6 substrates will be included in the labeling, as well.

It is recommended that the concomitant use of strong CYP3A4 inhibitors and inducers be avoided, due to the potential for an increase in exposure to thiotepa or TEPA. Alternative medications with no or minimal potential to inhibit or induce CYP3A4 should be considered. If coadministration of a strong CYP3A4 modulator cannot be avoided, patients should be closely monitored for adverse reactions. No clinical drug-drug interaction (DDI) studies have been

conducted to evaluate the effect of CYP2B6 and CYP3A4 modulators on thiotepa PK, but in vitro data from the literature suggests that thiotepa is a substrate of CYP2B6 and CYP3A4 (Appendix 4.4: Jacobson et. al., 2002[17]). No recommendations are proposed for the use of strong CYP2B6 modulators as there are no reported exclusive strong CYP2B6 modulators (FDA DDI guidance[3]).

Literature data suggest that thiotepa is an inhibitor of CYP2B6 in vitro (Appendix 4.4: Rae 2002[18]). However, no dose recommendation is proposed as the clinical relevance of this *in vitro* interaction is unknown. Nonetheless, the in vitro findings are described in the labeling.

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 (Appendix 4.5). No recommendations are proposed for the use of Tepadina with CP; however, the findings are described in the labeling, including the sequence dependent effect on the metabolism of CP.

3.3.5 Does this drug prolong the QT or QTc interval?

The available data suggests that thiotepa is unlikely to prolong the QT/QTc interval.

Although all patients had a QTc interval < 500 ms, and QTc interval increases from baseline < 60 ms in Study ADN009 following administration of two doses of 5 mg/kg 12 hours apart of Tepadina, the interpretation of the results is confounded by study design issues: no control arm, no ECGs collected at the expected Tmax (~ 3 hr) and limited sample size (See QT-IRT review, DARRTS ID 3959533). FDA requested that Adienne present available post-marketing arrhythmia and cardiac safety data to confirm the study results (for details refer to QT-IRT review, DARRTS ID 3959533). In response, Adienne reported 13 cases of Grade 1/2 ECG abnormalities in patients (22-67 years old) dosed with thiotepa (30 mg/m^2 to 20 mg/kg) along with multiple drugs (e.g., etoposide, melphalan, CP, rituximab, cytabarine) based on search of post-marketing reports for Tepadina and Thioplex (Module 5.3.6, SDN 8). Of the 13 cases, there was one instance of Grade 2 QT prolongation in a 63 year old patient, two weeks following 340 mg BID of thiotepa. This patient had a history of cardiac disorders; however, the contribution of thiotepa could not be ruled out. In addition, Adienne reported that a literature search of cardiac disorders and thiotepa revealed 39 results, none of which included cases of arrhythmias or QT prolongation from Tepadina or Thioplex or thiotepa.

Nonetheless, considering that thiotepa has been in use for a long time and the proposed dose (b) (4) is only for a single day administration, a post marketing requirement for QTc prolongation study for Tepadina to determine the effects of thiotepa on the QTc interval will not be issued.

3.3.6 Has a scientific bridge has been established between drug product(s) used in the literature studies and the proposed drug product to support the acceptance of the scientific literature?

Yes. A scientific bridge has been established between the listed drug and the drug products listed in the literature supporting the labeling recommendations and Tepadina.

[3]CDER Guidance for Industry Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (2012). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

Thiotepa, 15 mg/vial, approved in 1959 in the US (approved in EU in 1971 as Thiotepa Lederle per Adienne) included sodium chloride and sodium bicarbonate as inactive ingredients, while 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.

4. APPENDICES

4.1 Urinary Excretion of Thiotepa

Per the current thiotepa labeingl[1], thiotepa and TEPA in urine each account for less than 2% of the administered dose. The available literature data supports the inclusion of this statement in the Tepadina labeling.

Literature Data

Urine was collected on days 1-4 from a patient receiving 80 mg/m^2/day IV thiotepa and 265 mg/m^2/day IV carboplatin (van Maanen et al., 1999)[4]. Thiotepa was obtained from Cyanamid Beneluz (Etten-Leur, Netherlands). Less than 1% of total dose was excreted as thiotepa. The total excretion of TEPA was ~8 times that of thiotepa. Thiotepa-mercapturate in urine accounted for 12% of the administered dose.

In another study in 8 patients receiving a single 4-day CTC course (1500 mg/m^2 IV CP → 400 mg/m^2/day IV carboplatin→ 120 mg/m^2/day IV thiotepa) (van Maanen et al., 2001)[2], the mean percent of the administered dose (%CV) in urine was 0.5% (60%) for thiotepa, 11 % (55%) for TEPA, 0.5% for monochloroTEPA, and 11% (40%) for thiotepa-mercapturate. The thiotepa formulation used in this study was not provided.

In another study, urine collected from 6 patients administered thiotepa (20 mg bolus IV) , showed that urinary excretion of thiotepa and TEPA each accounted for less than 2% of the administered dose (Hagen et al., 1990)[10]. The thiotepa formulation used in the study was not provided.

4.2 Hepatic Impairment and QT/QTc Assessments

The available literature and safety data supports caution in patients with moderate or severe HI and suggests that thiotepa is unlikely to prolong the QT/QTc interval.

[4] Van Maanen MJ, et al. (1999). Cancer Res.;59: 4720-24.

The current thiotepa labeling[1] states that the PK of thiotepa in patients with RI and HI has not been evaluated, and recommends against administering thiotepa in such patients and if absolutely necessary, thiotepa may be used in low dosage in such patients.

Adienne conducted a two-center Study ADN009 to evaluate the effect of HI on the PK of thiotepa and its metabolite, and assess the effect of thiotepa on the QT/QTc interval. The study was originally designed to compare the PK of thiotepa and TEPA in patients with mild and moderate (Child-Pugh A and B) HI to that of patients with normal hepatic function; however, due to the difficulty in enrolling patients with moderate HI, the study was modified to a single arm study in patients with mild HI and the PK evaluation was reduced to descriptive analyses. In the study report, Adienne referred to Child-Pugh A as normal hepatic function, but confirmed that the patients enrolled were mild HI in their response dated May 24, 2016 (SDN 6) to the information request.

Purpose	Parameters
Study Design	Two-center, single-arm study. The study included a screening phase (within 14 days prior to dosing), a treatment phase (on Day 1), and a 30-day follow-up period.
Primary Objectives	• Evaluate the effect of HI on the PK of thiotepa and TEPA • Assess the QT/QTc prolongation potential of thiotepa
Study Population	Twelve pediatric patients (1-14 yrs: 10-45 kg) with mild HI (Child-Pugh A) and undergoing allogenic HCPT were enrolled.
Eligibility Criteria	*Inclusion*: • Patients >1 and <18 years • Patients with Child-Pugh score A or B. *Exclusion* • For patients with organ dysfunction: o Total bilirubin > 10 x ULN. o AST and ALT > 10 x ULN. o Creatinine clearance < 40 mL/min. • Received CYP2B6 or 3A4 inhibitors or CYP inducers within 10 days prior to thiotepa dose. • Patients with significant ECG abnormalities.
Proposed Dose	Two 5 mg/kg Tepadina IV infusions (over 3 hours each), 12 hours apart.
PK Sampling Schedule	**First Infusion**: Prior to start of infusion, and at 180 (end of infusion), 195, 210, 240, 360, and 720 min after infusion. **Second Infusion**: 180 min after infusion.
ECG Monitoring Schedule	Before first infusion, 180 min after the end of first infusion (i.e., 360 min after start of infusion), and 24 hours after the second infusion (and on Day 7 if clinically indicated).

PK Results:

The available PK data is summarized in Table 1.

Table 1: PK Parameters of Thiotepa & TEPA in Study ADN009 [arithmetic mean (%CV) & Min., Max.)

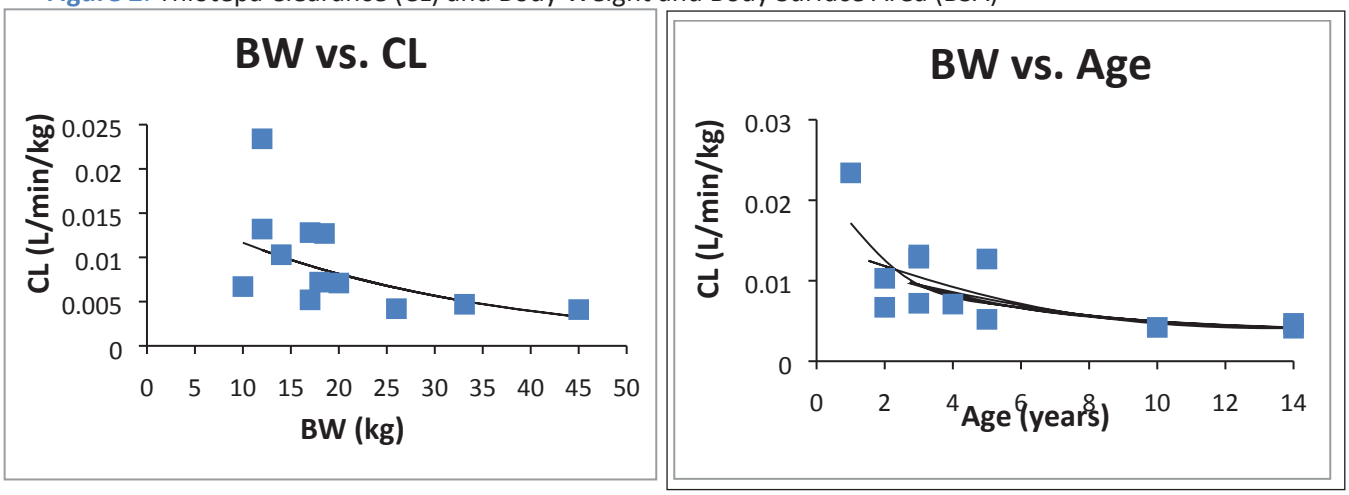
Analyte	$AUC_{0\text{-}12h}$	$AUC_{0\text{-}inf}$	$AUC_{0\text{-}inf}$	C_{max}	T_{max}	$T_{1/2}$	CL	Vd

	ng*hr/mL	ng*hr/mL	**Ratio % TEPA/TT**	ng/mL	min	min	L/min/m^2	L/m^2
Thiotepa	10841 (49%) 3750, 19750	11438 (51%) 3564, 20199	23.34 (70%) 3.4, 61	3640 (49%) 1475, 6873	180 180, 195	104 (64%) 52, 304	0.23 (52%) 0.11, 0.50	30 (44%) 17, 55
TEPA	1723 (39%) 328, 2813	2017 (45%) 430, 3858		269 (36%) 50, 373	195 180, 240	240 (29%) 168, 341		

Analyte	**C180 1st dose**	**C180 2nd Dose**	**Ratio**
Thiotepa	3417 (54%) 1354, 6873	2757 (517%) 268, 4525	0.84 (39%) 0.18, 1.35
TEPA	162 (44%) 33, 279	162 (44%) 32, 278	0.66 (25%) 0.41, 0.93

TT=thiotepa, C180= concentration at 3 hour post-dose, CL=clearance, Vd=volume of distribution, T½ = elimination half-life

Figure 2: Thiotepa Clearance (CL) and Body Weight and Body Surface Area (BSA)



The CL and V_d observed in patients with mild HI were comparable to literature data from pediatric patients with normal hepatic function and in adults with normal hepatic function (Appendix 4.3). Although the CL shows a trend to decrease with increase in body weight, and age, the sample size is small and the variability is high. Also, the results are mixed in literature: Kletzel et al. (1992)[7] (Appendix 4.3) did not find any statistically significant relationship between age and CL in 2-12 year old patients dosed at 300 mg/m^2 as 2 hour IV infusions, daily for 3 days.

Safety:

All patients with available data had a QTc interval < 500 ms, and QTc interval increases from baseline < 60 ms; however, interpretation of the results is confounded by study design issues, as no control arm was included, ECG was not collected at the expected Tmax (~ 3 hr), and sample size was small (for details refer to QT-IRT review, DARRTS ID 3959533).

Two patients (17%) reported acute GVHD (affecting the skin), of which one was drug-related. Ten of the 12 (83%) patients experienced AEs following treatment, mostly mucosal inflammation and pyrexia (50%). Eight patients experienced treatment-related AEs mostly Grade ≥2 mucositis. In the study by Huitema et al. (2002)[11], a relationship between TEPA AUC of the first course and severe (Grade ≥2) mucositis after multiple courses was observed (a course = 60 or 40 mg/m^2 BID for 4 days as part of CTC). No patients were discontinued prematurely due to AEs. Two patients experienced serious but non-fatal AEs: life-threatening sepsis and severe veno-occlusive disease. Per study report, both events were not related to thiotepa.

In the study of Przepiorka et al. [1995][5], a significant association in any toxicity Grades ≥ 2 and combined thiotepa and TEPA AUC > 30 mg.h/L or TEPA C_{max} levels > 1750 ng/mL were found at thiotepa dose of 150 mg/m^2 to 250 mg/m^2. However, in Study ADN 009, the mean combined thiotepa and TEPA AUC (~15 mg.h/L) and TEPA C_{max} (~170 ng/mL) were 2- to 10-fold lower. In the study by Huitema et al. (2002) [11], a significant relationship between thiotepa AUC of the first course and AST elevation after first course, were identified. Also, thiotepa AUC was found to correlate with neutrophil toxicity at thiotepa multiple doses of 30 mg/m^2 to 75 mg/m^2 (O'Dwyer et al., 1991)[14]. However, no hematological abnormalities were reported in Study ADN009.

4.3 Tabular Summary of PK Data from Literature

The following PK data was available from literature and the application, and supported the PK data included in the Tepadina labeling and the management strategy for organ impairment.

Reference	Dose (mg/m^2)	Route-Time	n	CL (L/hr/m^2) Mean ± SD or Range	Vd (L/m^2) Mean ± SD or (Range)	T1/2 (hr) Mean ± SD
Pediatrics						
Heideman 1989[6, a] (1-21 years)	25	IV bolus	3	28.6 (17-53)	18.4 (16-25)	1.7
	50	IV bolus	4	15.7 (12-20)	29.6 (21-41)	1.8
	65	IV bolus	4	15.4 (11-29)	22 (15-38)	1.3
	75	IV bolus	5	11.9 (7-29)	25 (17-29)	2
	50	IV - 8hr	3	12.8 (9.7-16.4)	17.4 (13.4-25)	1.2
	65	IV - 8hr	2	13.5 (11-17)	18.6 (16-33)	1.5
Kletzel 1989[7, b]	300	IV - 2hr	10	11.3 ± 1.7	19.4 ± 2.6	1.5 ± 0.6
ADN009	**5 mg/kg**	**IV - 3hr**	**12**	**13.8** ± 7.2	**29.7** ± 13.1	**1.7** ± 1.1

[5] Przepiorka D, *et al.* (1995). Cancer Chemother. Pharmacol.; **37**: 155-60.
[6] Heideman RL, *et al.* (1989). Cancer Res.; **49**:736-41
[7] Kletzel M, *et al.* (1992). Bone Marrow Transplant.; **10**:171-75.

Adults						
Hagen 1987[8]	20 mg	IV bolus	6	25.3 ± 4.0 L/hr	48 ±8 L	1.37 ± 0.09
Hagen 1991[9, c]	60 mg	IV bolus	13	16.7[e] (26.8 ± 3.8 L/hr)	--	2.4 ± 0.3
	80 mg			15.7[e](25.1 ± 3.3 L/hr)	--	2.3 ± 0.3
Hagen 1990[10, d]	20 mg	IV bolus	6	14.6 ± 3.3[f]	--	1.6 ± 0.13
Huitema 2002[11, h]	60	IV - 0.5 hr	46	20.0* (34.5 ± 9.8 L/hr)	26.5* (45.8 ± 7.2 L)	
De Jonge 2004[12, j]	40-60	IV - 0.5 hr	49	9.4		
Lazarus, 1987[13]	135	IV bolus	16	27.9 ± 19.2	1.0 ± 0.3 L/kg	2.6 ± 1.5
Przepiorka, 1995[5, k]	150-250	IV – 4 hr	15	18.1 ± 1.3	47.4 ± 4.7	3.7 ± 0.5
O-Dwyer[14]	30-75	IV bolus	21	18.9 ± 2.8 - 46.7 ± 13.6	47.3 (42%) – 72 (16%)	1.3 – 2.2
	1.8-6 mg/kg		14	0.45 L/hr/kg (0.25-0.76)	1.6 L/kg (0.9-2.3)	2.7 ± 1.2 (1.33-4.8)
Ackland 1988[15]	1.8	IV - 0.5 hr	3	12.4* (0.36 ± 0.08 L/h/kg)	50.7* (1.46 ± 0.57 L/kg)	2.3 ± 0.4
	3.6		3	12.7*(0.37 ±0.09 L/hr/kg)	59.2* (1.71 ± 0.39 L/kg)	2.3 ± 0.8
	4.8		5	19.8* (0.57± 0.16 L/hr/kg)	65.0* (1.88 ± 0.31 L/kg)	2.3 ± 1.3
	6		2	14.1* (0.30, 0.51 L/h/Kg)	54.1* (1.5, 1.6 L/kg)	2.6 (3.1, 2.1)

[a]Tumor patients (1-21 years of age) with bilirubin < 2 mg/dL, AST/ALT < 1.5 x normal, & CLcr > 60 mL/min/1.73 m^2. Thiotepa from Lederle Laboratories (NY).

[b] Tumor patients (2-12 years of age) with bilirubin, AST/ALT & CLcr > 2SD above ULN. Thiotepa from Lederle Laboratories (NY).

[c] Tumor patients (45-84 years of age) with bilirubin 4-12 µmol/L & serum creatinine 90-102 µmol/L. Thiotepa from Lederle Laboratories.

[d] Tumor patients (62-85 years of age) with bilirubin 3-13 µmol/L & serum creatinine 56-314 µmol/L. Thiotepa formulation not provided.

[e] Reviewer estimated mean CL based on mean BSA=1.6 m^2

[f] Reviewer estimated mean CL =Dose/(AUC *BSA)

[h] Tumor patients (< 60 years of age) with bilirubin <20 µmol/L, ALT/AST < 1.5 x ULN, & CLcr > 60 mL/min. Thiotepa formulation not provided

[j]Tumor patients (16-59 years of age) with bilirubin 3-21 µM, ALT 8-117 U/L, AST 7-59 U/L, & Serum creatinine 40-88 µM. Thiotepa formulation not provided

Tumor patients (< 60 years of age) with bilirubin <6 mg/dL, serum creatinine < 2.5 mg/dL, & CLcr > 50 mL/min. Thiotepa formulation not provided.

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[8] Hagen B *et al.* (1987). Cancer Chemother. Pharmacol.; **19**:143-48

[9] Hagen B, *et al*. (1991). Cancer Chemother. Pharmacol.; **27**:373-78.

[10] Hagen B, *et al*. (1990). Cancer Chemother. Pharmacol.; **25**:257-62.

[11] Huitema ADR *et al.* (2002). Ann. Oncol.; **13**:374-84.

[12] De Jonge ME *et al*. (2004). J Pharmacokinet. Pharmacodyn.; **31**(2):135-56.

[13] Lazarus HM *et al.* (1987). Cancer Treat. Rep.; **71**: 689-95

[14] O'Dwyer PJ *et al.* (1991). Cancer Res.; **51**: 3171-76

[15] Ackland SP *et al.* (1988). J. Clin. Oncol.; **6**(7): 1192-96.

*converted to L/hr/m2 or L/m2 using BSA = 1.73 m2 and BW=60 kg
[k]16-54 years, with busulfan & CP. TT IV daily for 3 days[4].

Renal Impairment (Eckart et al., 2009)[16]:
In a patient with moderate RI (CLcr = 38 mL/min) receiving 4-day high dose CTC [CP 1500 mg/m^2/day IV for 1 hr → carboplatin AUC= 5 mg min/mL/day → 400 mg/m^2/day IV for 1 hr → thioTEPA 120 mg/m^2 IV 30 min], exposures of thiotepa and TEPA were increased by 43% and 157%, respectively, compared to patients with normal renal function (n=24). The patient experienced Grade 3 mucositis and diarrhea, and Grade 2 AST and bilirubin toxicity. The patient died on Day 43 post-transplantation due to acute respiratory syndrome. In the patients with normal renal function, 13% had Grade 3 mucositis, no patients had diarrhea, 25% had Grade 2 AST, and 4% had Grade 2 bilirubin toxicity. The thiotepa formulation was not provided.

Hepatic Impairment (Ackland et al., 1988)[15]:
In 2 patients with moderate HI and liver metastases receiving 7 mg/kg thioTEPA IV for 30 min, exposures of thiotepa increased by 1.7-fold compared to one patient with normal hepatic function receiving the same dose. One of these two patients died of progressive tumor before marrow reinfusion. No other safety information is available from these patients. The thiotepa formulation was not provided.

4.4 In Vitro DDI Studies

The available data suggest the thiotepa undergoes metabolism by CYP3A4 and CYP2B6 to its active metabolite TEPA and that thiotepa inhibits CYP2B6 activity in vitro. Additional data show that thiotepa inhibits the metabolism of CP to one of its active metabolites.

Study ADI/REP/01
Adienne evaluated the potential for DDI between thiotepa and inhibitors of CYP3A4 in hepatocytes and human liver microsomes (HLM).

Thiotepa and TEPA (1 µM or 10 µM test compound) stability was tested in hepatocytes and HLM (0.5 mg microsomal protein/ml). Test compound was incubated for up to 90 minutes in hepatocytes, and 40 minutes in HLM. Midazolam, testosterone, 4-methylumbelliferone or dextromethorphan were used as controls. Both thioTEPA and TEPA were stable in human hepatocytes (0.5 and 1 million cells/ml), and in HLM (0.5 mg protein/mL).

Thiotepa concentrations of 30 µM were used to generate the inhibition profiles. CYP3A4 Inhibitors were tested at six concentrations (n=2) and incubated for 40 minutes in HLM (1 mg/mL) with thiotepa and cofactor NADPH. The positive control inhibitor ketoconazole and the negative control compound sulfaphenazole were routinely used with the CYP3A4 substrates midazolam and testosterone. Solvent control samples with no NADPH added were also incubated to define the minimum TEPA production expected.

[16] Eckhart C *et al.* (2009). Cancer Chemother. Pharmacol.; **63**: 375-79.

Table 2: Results of Study ADI/REP/01

Inhibitors and concentrations

Inhibitor	Concentration range (µM)
Ketoconazole	10 – 0.003
Voriconazole	500 – 0.16
Posaconazole	10 – 0.003
Fludaribine phosphate	100 – 0.032
Treosulfan	100 – 0.032
Busulfan	500 – 0.16
Carboplatin	500 – 0.16
Sulfaphenazole	100 – 0.032

IC50 (µM) Results for Inhibition of Thiotepa Metabolism

Compound ID	Mean IC_{50} (µM)	Approximate Ki (µM)	Concentration of compound giving R=1.1 (µM)
Ketoconazole	>10	>5	>0.5
Voriconazole	244	122	12
Posaconazole	>10	>5	>0.5
Fludaribine	>100	>50	>5
Treosulfan	>100	>50	>5
Busulfan	>500	>250	>25
Carboplatin	>500	>250	>25
Sulfaphenazole	>100	>50	>5

The study reported limited inhibition for the compounds tested. The most significant effect was for voriconazole, with IC_{50} of 244 µM (the 95% confidence intervals were 46 µM and 1.3 mM). No other compound inhibited TEPA production sufficiently to report an $IC_{50;}$ however, the results are not conclusive. The interpretation of the results is confounded by problems with the study: several data from ketoconazole and voriconazole were excluded for contamination and ketoconazole and posaconazole concentrations used were < Km.

Literature Studies

Effect of CYP3A4 and CYP2B6 on Thiotepa Metabolism (Jacobson *et al.,* 2002)[17]

Pooled HLM (0.5 mg protein/mL) were incubated with CYP inhibitors for CYP1A2 (furafylline), 2A6 (coumarin), 2C19 (omeprazole), 2D6 (quinidine), 3A4 (ketoconazole, troleandomycin), 2C9 (sulfaphenazole), or 2E1 (4-methylpyrazole, disulfiram) with 100 µg/mL thiotepa. Thiotepa was obtained from USP. With 1 µM to 50 µM ketoconazole, TEPA formation was reduced 20% to 60%. Inhibition with CYP2E1 inhibitors was inconsistent. All other inhibitors produced minimal or no reduction in TEPA. Studies with cloned expressed (CE) CYP microsomes, indicated that CE CYP2B6 and CYP3A4 microsomes catalyzed TEPA formation about 4-fold compared to controls, but not CE CYP2A6 and CYP2E1 microsomes. Incubation of thiotepa with anti-CYP2B6 antibody and CE CYP2B6 microsomes resulted in 69% reductions in the formation of TEPA, but no change in TEPA formation occurred in HLM.

Effect of Thiotepa on CYP2B6 (Rae et al, 2002)[18]:

Using HLM, CYP2B6 activity was reduced by 78 ± 0.2% by 50 µM thiotepa, using 200 µM S-mephenytoin as a probe for CYP2B6 activity. However, thiotepa at 100 µM demonstrated <20% inhibition of the microsomal activity of CYP1A2, 2C9, 2C19, 2D6, 2E1, and 3A4. Isoform-specific substrate reaction probes were used at their ~Km. Effect of thiotepa on recombinant CYP

[17] Jacobson PA *et al.* (2002). Cancer Chemother. Pharmacol.; 49(6):461-67.

[18] Rae JM *et al*. (2002). Drug Metab. Dispos.; **30**(5):525-30.

enzymes showed that thiotepa (50 µM) inhibited the activity of recombinant human CYP2B6 by 42.5 ± 2.4%, but had ≤ 15% inhibitory on activity of recombinant enzymes CYP2C8, 2C9, 2C19, 2E1 and 3A4. Dose response of thiotepa (0-100 µM) on inhibition of CYP activity, showed that thiotepa is an inhibitor of CYP2B6 activity in HLM (Ki = 4.8 ± 0.3 µM), and recombinant CYP2B6 (6.2 ± 0.7 µM). These Ki values are within the plasma concentration range of thiotepa (1-20 µM). Thiotepa was obtained from USP.

Interaction of Thiotepa and CP (Huitema ADR et al., 2000)[19]:
Interaction of thiotepa and CP was investigated in HLM. The Km for the conversion of CP to its metabolite 4-OH-CP was 40 µg/mL (149 µM). Thiotepa inhibited the conversion of CP to 4-OH-CP with an IC_{50} of 4.4 µg/mL (23 µM). Per the authors, the thiotepa concentrations in vivo are ~1.5 µg/mL to 3 µg/mL at 60 mg/m^2/day. However, CP did not inhibit the conversion of thiotepa to TEPA (refer to Appendix 4.5). The thiotepa that was used in the study was LederleTEPA (AHP Pharma, The Netherlands).

4.5 In Vivo DDI Studies

No clinical DDI studies were conducted by Adienne to determine the effects of CYP3A4 and CYP2B6 inhibitors on thiotepa, and the effect of thiotepa on drugs that are substrates of CYP2B6. The current thiotepa labeling[1] states that the potential PK interaction of thiotepa with any concomitantly administered medications has not been formally investigated, and does not recommend combining thiotepa with other alkylating agents (e.g., CP) or with irradiation to avoid severe toxicity.

The following literature information was provided by Adienne and supported the current labeling recommendations regarding potential interaction with CYP2B6 substrates and CP:

Drug interaction between thiotepa and CP (Huitema ADR et al., 2000)[19]:
CP shows autoinduction, which causes a decreased exposure to CP and an increased exposure to 4-OH-CP during treatment. Twenty patients underwent 31 courses of CTC (CP 1500 mg/m^2/day IV for 1 hr → carboplatin 400 mg/m^2/day IV for 1 hr → thioTEPA 60 mg/m^2 BID as 0.5 hr IV) or multiple courses of reduced dose CTC (two-third dose) for 4 consecutive days. A sharp decrease in 4-OH-CP concentrations was observed immediately after the start of the thioTEPA infusions (2 hours after the start of CP infusion). Further, altering the sequence of CTC infusion schemes (Scheme A: CP→ carboplatin → thiotepa, or Scheme B: thiotepa→ carboplatin→ CP) on Day 1 and Day 2 in three patients showed that administration of thiotepa prior to CP (Scheme B) resulted in 62% reduction in C_{max} and 26% reduction in AUC of 4-OH-CP compared to thiotepa after CP (Scheme A). Thiotepa was used in the study was LederleTEPA (AHP Pharma, The Netherlands).

Effect of concomitant administration of thiotepa and CP (De Jonge et al., 2004)[12]:
Based on plasma concentrations of CP, 4-OH-CP, thiotepa, and TEPA on two separate days from 49 patients receiving high-dose CTC [CP (1000 or 1500 mg/m^2/day IV), thiotepa (80 or 120 mg/m^2/day as 0.5 hr IV) and carboplatin (266 or 400 mg/m^2/day IV)] given in short infusions during four consecutive days], the authors developed a population PK model describing the

[19] Huitema ADR, *et al*. (2000). Cancer Chemother. Pharmacol.; **46**: 119-27.

mutual drug-drug interaction of CP and thiotepa at the level of enzyme kinetics. The model described the PK of CP, 4-OH-CP, thiotepa, and TEPA adequately. According to the model, total thiotepa CL increased only by 10% to 25% during a course, while CP CL increased by 50% during a course. The thiotepa formulation used in the study was not provided; however, based on the date of publication and the available marketed thiotepa formulation at that time (1994-2004), the thiotepa formulation is likely to be Thioplex.

The above results may not be applicable for the proposed dosing regimen for Tepadina, as CP will be administered 12 hours after the last thiotepa dose and thiotepa has a short half-life (1 hr to 4 hrs).

Effect of CP Exposure and Safety (Ayash et al., 1992)[20]:
An inverse relationship between exposure (AUC) of CP and durable duration of tumor response and cardiac toxicity has been observed. Increased rate of conversion of CP may enhance both tumor cytotoxicity and end-organ toxicity.

Effect of Phenytoin on Thiotepa (De Jonge *et al*. 2005)[21]
One patient was administered two 4-day courses of CTC (1500 mg/m^2/day IV CP followed by IV carboplatin and 60 mg/m^2 BID IV thiotepa) with a 28-day holiday period between the courses. Five days prior to the second CTC course, the patient received phenytoin. The PK samples were collected on Day 1 of both courses and analyzed for CP, 4-OH-CP, thiotepa and TEPA. Compared to the first CTC course, the AUC in the second CTC course with phenytoin was reduced by 67% for CP and 29% for thiotepa, and increased by 115% for TEPA and 51% for 4-OH-CP. C_{max} increased by 600% for 4-OH-CP and 300% for TEPA. The thiotepa formulation used in the study was not provided, however, based on the date of publication and the available marketed thiotepa formulation at that time (1994-2004), the thiotepa formulation is likely to be Thioplex.

However, the usefulness of this study is limited as it represents only one patient.

4.6 QT-IRT Review

Refer to QT-IRT review dated July 19, 2016 (DARRTS ID 3959533).

4.7 Bioanalytical Method Report

Plasma samples in the Study ADN009 were analyzed for thiotepa and TEPA concentrations using a validated liquid chromatography method with tandem mass spectrometric detection (LC/MS/MS) following protein precipitation. Hexamethylphosphoramide was used as the internal standard.

Calibration range for thiotepa and TEPA was between 10 ng/mL and 2500 ng/mL. Quality controls were at 10 ng/mL (LLOQ), 20 ng/mL (QCL), 200 ng/mL (QCM), and 2000 (QCH) ng/mL. Selectivity, and matrix effect was validated. The intra-assay and inter-assay accuracy (97% to 107% of the nominal concentration) and precision (2% to 12% CV) were within acceptable limits. The short term (21 hours at -80^{o}C and 6 hours at room temperature), freeze-thaw (3

[20] Ayash LJ *et al.* (1992). J. Clin. Oncol.; **10**: 995-1000.
[21] De Jonge *et al*. (2005). Cancer Chemother. Pharmacol.; **55**: 507-10.

cycles), and long-term (4 months and 10 days at -80°C) matrix stability, and dilution integrity (10x) was validated.

Study samples were analyzed across seven analytical runs for thiotepa and TEPA. The in-study between-day assay accuracy and precision were acceptable for thiotepa and TEPA. The study samples at the C_{max} range > ULOQ were reanalyzed following dilution. Incurred sample reanalysis (ISR) of 13 study samples for thiotepa and TEPA analyzed showed relative differences (*i.e.*, normalized to their mean value) <20% between original and repeat values for 77% of the samples. The storage period prior to analysis for all the samples from Study ADN009 was within the validated long-term stability period.

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SRIRAM SUBRAMANIAM
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