

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208264Orig1s000**

**CHEMISTRY REVIEW(S)**

**Recommendation: APPROVAL** from the CMC perspective.

**NDA 208264  
Review #1**

Drug Name/Dosage Form	Tepadina, Lyophilized powder
Strength	15 mg and 100 mg
Route of Administration	Intravenous infusion, intracavitary, or intravesicle use after reconstitution and dilution
Rx/OTC Dispensed	Rx
Applicant	Adienne SA
US agent, if applicable	Mr. Bruce Thompson, Regulance LLC

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0000	<i>February 26, 2015</i>	<i>CMC information (Rolling Submission)</i>
0007	<i>October 31, 2016</i>	<i>Drug Product, Process</i>

**Quality Review Team**

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Haripada Sarker, Ph.D.	CDER/OPQ/ONDP/DNDAPI
Drug Product	Rajiv Agarwal, Ph.D.	OMPT/CDER/OPQ/ONDP/D NDPI/NDPBII
Process	Kumar Janoria	CDER/OPQ/OPF/DPAIII
Microbiology	Yuansha Chen	CDER/OPQ/OPF/DMA
Facility	Steven Hertz	CDER/OPQ/OPF/DPAIII
Biopharmaceutics	Om Anand	CDER/OPQ/ONDP/DB
Regulatory Business Process Manager	Rabiya Laiq	CDER/OPQ/OPRO/B1
Application Technical Lead	Anamitro Banerjee	CDER/OPQ/ONDP/DNDPI/N DPBII
Laboratory (OTR)	NA	
ORA Lead	Paul Perdue Jr.	
Environmental Analysis (EA)	N/A	

## Quality Review Data Sheet

**1. RELATED/SUPPORTING DOCUMENTS**

**A. DMFs:**

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	(b) (4)	Active	August 29, 2016	Adequate
	Type III			Active	Information is in NDA	Adequate
	Type III			Active	Information is in NDA	Adequate
	Type III			Active	Information is in NDA	Adequate

**B. Other Documents: *IND, RLD, or sister applications***

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20058	Thioplex (LD)

**2. CONSULTS**

None

## Executive Summary

### I. Recommendations and Conclusion on Approvability

This NDA is recommended for APPROVAL from the CMC perspective.

### II. Summary of Quality Assessments

#### A. Product Overview

*FDA granted the orphan drug designation #07-2378 for TEPADINA (Thiotepa) on April 02, 2007 for “conditioning treatment prior to hematopoietic stem cell transplantation” pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 USC 360bb). TEPADINA is manufactured as a lyophilized powder for injection in strengths of 15 mg/vial and 100 mg/vial. TEPADINA is intended to reduce the risk of graft rejection when used in conjunction with high-dose busulfan (BU) and cyclophosphamide (CY) as a preparative regimen for allogeneic haematopoietic progenitor cell transplantation (HPCT) for patients with class 3  $\beta$ -thalassemia.*

<p><b>Proposed Indication(s) including Intended Patient Population</b></p>	<ul style="list-style-type: none"> <li>• To reduce the risk of graft rejection when used in conjunction with high-dose busulfan and cyclophosphamide as a preparative regimen for allogeneic hematopoietic progenitor (stem) cell transplantation (HSCT) for pediatric patients with class 3 <math>\beta</math>-thalassemia.</li> <li>• For treatment of adenocarcinoma of the breast or ovary.</li> <li>• For controlling intracavitary effusions secondary to diffuse or localized neoplastic diseases of various serosal cavities.</li> </ul> <p>For treatment of superficial papillary carcinoma of the urinary bladder.</p>
<p><b>Duration of Treatment</b></p>	<p>NA</p>
<p><b>Maximum Daily Dose</b></p>	<p>5 mg/kg in pediatric patients intravenously twice approximately 12 hours apart on Day -6 before allogeneic HSCT</p>
<p><b>Alternative Methods of Administration</b></p>	<p>NA</p>

## B. Quality Assessment Overview

Tiotepa USP is manufactured (b) (4) and is supplied to be used in the manufacture of Thiotepa for Intravenous infusion, intracavitary, or intravesicle use. Thiotepa USP manufactured by (b) (4) follows CMC information used in the (b) (4) (b) (4) process and approved under NDA 020058. The analytical methodology was originally developed to meet the requirements of the monograph for Thiotepa USP. It also contained in-house testing for critical quality attributes (Assay, related substances, clarity, particle count, and residual solvents). The applicant provided comparative impurity profile of the Thiotepa USP drug substance used in this NDA and the drug substance used for the approved NDA as well as the USP reference standard lot H. All the CMC information for the manufacture of the drug substance is provided in the Type II DMF (b) (4). DMF (b) (4) was last reviewed by Dr. Haripada Sarkar on August 29, 2016 and found to be adequate. The DMF holder submitted updated stability information on September 21, 2016 which is adequate. The applicant is proposing a retest period of (b) (4) when stored under refrigerated conditions (b) (4) based on real time stability data. The retest period was found acceptable by the Drug substance reviewer.

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

Drug product is a white lyophilisate. The formulation does not contain any excipient.

(b) (4)

The applicant provided validation data for container closure integrity tests, however, batch data were not provided in the submission. Based on risk assessment of the available data, the microbiology review team found the container closure system acceptable from the microbiology perspective.

The manufacturing process for the the proposed drug product involves (b) (4) (b) (4). This process is typical for lyophilized products. (b) (4)

(b) (4)

The (b) (4) controls were found to be adequate. (b) (4) (b) (4), the applicant proposed an overfill of (b) (4) for the 15 mg presentation. (b) (4)

(b) (4)

(b) (4)

In response to an IR comment, the applicant reported that studies are currently being conducted (b) (4). The results of these studies are expected in early 2017. The time-frame for reporting the results of these studies to the agency is acceptable to the process reviewer. Based on the risk assessment, the process reviewer did not see a need to request a post marketing commitment (PMC) from the applicant.

The applicant requested a waiver of the in-vivo study of the proposed drug product. Since the formulation does not contain any excipient, same as the listed drug Thioplex, the Biopharmaceuticals review team granted the applicant's waiver request.

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

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

**C. Special Product Quality Labeling Recommendations (NDA only)**

None

**D. Final Risk Assessment (see Attachment)**

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Agarwal**

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**Anamitro  
Banerjee**

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LABELING

## R Regional Information

## 1.14 Labeling

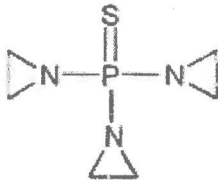
*Labeling & Package Insert*DESCRIPTION section:**11 DESCRIPTION**

TEPADINA (thiotepa) is an alkylating agent. <sup>(b)</sup> is supplied as a non-pyrogenic, sterile lyophilized powder for intravenous use after reconstitution and dilution. <sup>(4)</sup>

TEPADINA is available in a single-dose vial containing:

- 15 mg thiotepa. After reconstitution with 1.5 ml of water for injection, each ml contains 10 mg thiotepa.
- 100 mg thiotepa. After reconstitution with 10 ml of water for injection, each ml contains 10 mg thiotepa.

Thiotepa is a synthetic product with antitumor activity. The chemical name for thiotepa is Tris(1-aziridinyl)phosphine sulfide. Thiotepa has the following structural formula:



Thiotepa has the molecular formula  $C_6H_{12}N_3PS$ , and a molecular weight of 189.23, and it appears as fine, white crystalline flakes, with a melting range of 52°C to 57°C. It is soluble in water and organic solvents. When reconstituted with sterile water for injection, the resulting solution has a pH of approximately 5.5 to 7.5. Thiotepa is unstable in acid medium.

Is the information accurate?  Yes  No

If "No," explain.

Is the drug product subject of a USP monograph?  Yes  No

If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.



**HOW SUPPLIED section:**

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**16.1 How supplied**

TEPADINA is supplied as Unit carton with one single-dose Type I clear glass vial with a bromobutyl stopper.

**TEPADINA 15 mg**

One vial contains 15 mg thiotepa. (NDC5396400101).

**TEPADINA 100 mg**

One vial contains 100 mg thiotepa.(NDC5396400202).

**16.2 Storage and Handling**

TEPADINA vials must be stored and transport refrigerated at 2°C to 8°C (36° to 46°F). DO NOT FREEZE.

(b) (4)

i) Is the information accurate?  Yes  No

If "No," explain.

ii) Are the storage conditions acceptable?  Yes  No

If "No," explain.

**DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:**

**2 DOSAGE AND ADMINISTRATION**

**2.1 Recommended Dosage**

Class 3  $\beta$ -Thalassemia

The recommended dose of TEPADINA in pediatric patients is 5 mg/kg (twice) approximately 12 hours apart on Day -6 before allogeneic HSCT in conjunction with high-dose busulfan and cyclophosphamide, as outlined in Table 1.

**Table 1: Dosage Regimen For Allogeneic HSCT In Pediatric Patients With Class 3  $\beta$ -Thalassemia**

Treatment	Day prior to transplantation										
	Day -10	Day -9	Day -8	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0
Busulfan IV weight-based dose *	▲	▲	▲	▲							
TEPADINA IV 5 mg/kg twice					▲						
Cyclophosphamide IV 40 mg/kg/day						▲	▲	▲	▲		
Stem cell infusion											▲

\*Busulfan IV dose (weight based):

- <9 kg: 1.0 mg/kg every 6 hours
- >9 and <16 kg: 1.2 mg/kg every 6 hours
- >16 and <23 kg: 1.1 mg/kg every 6 hours
- >23 and <34 kg: 0.95 mg/kg every 6 hours
- >34 kg: 0.8 mg/kg every 6 hours

APPEARS THIS WAY ON ORIGINAL

Infuse via a central venous catheter. Prior to and following each infusion

(b) (4)

(b) (4)  
(b) (4)

Adenocarcinoma of the Breast or Ovary

The recommended dose of TEPADINA for treatment of adenocarcinoma of the breast or ovary is 0.3 to 0.4 mg/kg intravenously. Doses should be given at 1 to 4 week intervals. Initially the higher dose in the given range is commonly administered. The maintenance dose should be adjusted weekly on the basis of pretreatment control blood counts and subsequent blood counts. Maintenance doses should not be administered more frequently than weekly.

Malignant Effusions

The recommended dose of TEPADINA for treatment of malignant effusions is 0.6 to 0.8 mg/kg intracavitary. Administration is usually effected through the same tubing which is used to remove the fluid from the cavity involved. Doses should be given at 1 to 4 week intervals. Initially the higher dose in the given range is commonly administered. The maintenance dose should be adjusted weekly on the basis of pretreatment control blood counts and subsequent blood counts. Maintenance doses should not be administered more frequently than weekly.

Superficial Papillary Carcinoma of the Urinary Bladder

The recommended dose of TEPADINA for treatment of superficial papillary carcinoma of the urinary bladder is 60 mg in 30 to 60 mL of Sodium Chloride Injection into the bladder by catheter. The solution should be retained for 2 hours. If the patient finds it impossible to retain 60 mL for 2 hours, the dose may be given in a volume of 30 mL. The patient may be repositioned every 15 minutes for maximum area contact. The usual course of treatment is once a week for 4 weeks. The course may be repeated if necessary, but second and third courses must be given with caution since bone-marrow depression may be increased.



Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)?

Yes  No  N/A

If "No," explain.

**R Regional Information**

**1.14 Labeling**

***Immediate Container Label (15 and 100 mg)***



(b) (4)



**Reviewer's Assessment:** *The applicant responded to deficiencies and revised the label as recommended. Adequate.*



(b) (4)

**Reviewer's Assessment:** *According to CFR 207.35(b)(3)(i), the NDC number should be on the top third of the principle display panel, unless it is continuous to the bar code and in a prominent place (not the bottom of the container). It appears that the NDC/bar code fulfills that requirement.*

(b) (4)  
(b) (4)

*This concern was communicated to the DMEPA. An information request was sent to the applicant and a revised container/closure was received on 25-NOV-2016.*

(b) (4)

*DMEPA also requested that the presentation of the route of administration should be revised*

(b) (4),

*(b) (4) to ensure that all intended routes of administration are labeled. These labels were amended with this information on 25-NOV-2016.*

(b) (4)

(b) (4)

**Note:** *The applicant also asked within the communication on whether they can use the same NDC number that they have used when the product was an unapproved, marketed product. From the reading of CFR 207.35(b)(4)(i), this would be acceptable because it is still a prescription product.*

*The deficiencies (under list of deficiencies) were identified and communicated to the applicant at various times. The applicant responded satisfactorily to the deficiencies on 25-NOV-2016.*

*The container labeling is now adequate.*

**List of Deficiencies:**

- 1) The proposed container labels list the proprietary name, established name, and dosage form on the same line. Revise the presentation of the proprietary name, established name, and dosage form to correspond with one of the examples shown below. Additionally, this revision will ensure consistency with USP requirements.

Tepadina	<b>OR</b>	Tepadina
(thiotepa) for injection		(thiotepa)
		For Injection

- 2) Consider inclusion of NDC numbers on the carton labeling and container labels to facilitate product identification since the NDC number is often used as an

additional verification prior to drug dispensing in the pharmacy. Additionally, ensure that the product code (middle 3-4 digits) is different for each strength.

- 3) 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.
- 4) (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.
- 5) Revise the presentation of the route of administration (b) (4)  
to "For Intravenous, intracavitary, or intravesical use". We recommend this revision to the container labels to ensure that all intended routes of administration are labeled.

**Conclusion:** *Labels and Labeling are adequate from a CMC stand point.*

**Primary Labeling Reviewer Name and Date:** *Rajiv Agarwal, 28-NOV-2016*

**Secondary Reviewer Name and Date (and Secondary Summary, as needed):**



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Agarwal**

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PROCESS

**Product Background:** TEPADINA is a sterile, lyophilized product for intravenous (IV) infusion that contains thiotepa. Thiotepa is a synthetic product with antitumor activity. TEPADINA is indicated in 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  $\beta$ -thalassemia

**NDA:** 208264

**Drug Product Name / Strength** TEPADINA® (thiotepa) 15 and 100 mg for Injection

**Route of Administration:** Intravenous

**Applicant Name:** ADIENNE SA

**Review Summary:**

List Submissions being reviewed (table):

➤ Document(s) Reviewed (SD-#)	➤ Date Received
Email Communication from Sponsor (14 Attachments)	11/28/2016
8	10/31/2016
Email Communication from Sponsor (2 Attachments)	10/17/2016
1	02/26/2015

**High level Summary:**

Drug Product manufacturing involves (b) (4). Firm has submitted manufacturing development reports for both the presentations. The manufacturing process development for 15mg/vial presentation was started back in 1970 which was modified and updated to include 100mg presentation at another manufacturing site. The development of TEPADINA (the current product application) for the US market was again associated with a change of the manufacturing process with change in manufacturer. (b) (4)

**Highlight Key Outstanding Issues from Last Cycle:** N/A

**Concise Description Outstanding Issues Remaining:**

- Outstanding issues include: none

**Additional Background Information:**

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**FACILITIES**

**Product Background**

**NDA:** 208264

**Drug Product Name / Strength:** Thiotepa 15mg/vial and 100 mg/vial

**Route of Administration:** Lyophilized powder for injection

**Applicant Name:** Adienne SA

**Review Summary**

All facilities in NDA 208264 are acceptable for the listed responsibilities.

**List Submissions being reviewed:** NDA-208264-ORIG-1

**Highlight Key Outstanding Issues from Last Cycle:** N/A

**Concise Description Outstanding Issues Remaining:** None

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## CHAPTER VII: Biopharmaceutics

**NDA: 208264**

**Drug Product Name: Tepadina® (Thiotepa)**

**Strength(s): 15 mg/vial and 100 mg/vial**

**Route of Administration: Intravenous (IV)**

**Applicant Name: Adienne Sa**

### **Executive Summary:**

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

The NDA submission is also supported with the published literature references to support the labeling information. From a Biopharmaceutics perspective, the formulations used in Heideman et al 1989; Jacobson et al, 2002, Van Maanen et al, 1999, Henner et al, 1987, Ng et al, 1991, Terenzi et al 1990, Down et al 1998, Henner et al 1987, Huitema et al 2001 and Rae et al, 2002 publications are adequately bridged to the proposed drug product.

From the Biopharmaceutics perspective, NDA 208264 for Tepadina® (thiotepa) 15 mg/vial and 100 mg/vial, is recommended for **APPROVAL**.

**Submission:**

NDA 208264 (Tepadina<sup>®</sup>, Thiotepa for Injection) was received by the FDA on March 31, 2016 for Tepadina<sup>®</sup> (Thiotepa) 15 mg/vial and 100 mg/vial under 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The Quality section (m3) was submitted to the agency on February 26, 2015. The biowaiver request was submitted on March 31, 2016. In a submission dated, July 14, 2016, the Applicant provided additional information supporting the biowaiver request.

**Background:**

Thiotepa for injection (NDA 011-683) was approved on March 9, 1959 by the FDA. The marketing Application for Thiotepa was subsequently withdrawn. A second formulation of thiotepa was developed as Thioplex and approved under NDA 020058 on December 22, 1994. The Thioplex NDA was also withdrawn by the Applicant and appears in the Orange Book, under Discontinued Drug Products list. There is also an Abbreviated New Drug Application (ANDA) for thiotepa (ANDA 075547) approved in the U.S. on April 2, 2001 that used Thioplex NDA 020058 as the Reference Listed Drug; this product is marketed in the US at a strength of 15 mg/vial for injection.

This 505 (b)(2) application relies for approval on the previous findings of safety and effectiveness from the previously listed drug Thioplex (thiotepa for injection), NDA 020058; a new indication is being sought in this Application.

*The proposed new indication for Tepadina<sup>®</sup> is to reduce the risk of graft rejection when used in conjunction with high-dose busulfan and cyclophosphamide as a preparative regimen for allogeneic haematopoietic progenitor cell transplantation (HPCT) for patients with class 3  $\beta$ -thalassemia.*

On April 2<sup>nd</sup> 2007, FDA granted the orphan drug designation #07-2378 for Tepadina<sup>®</sup> (Thiotepa) for “conditioning treatment prior to hematopoietic stem cell transplantation”. The Applicant requested a biowaiver of in vivo bioavailability study [21 CFR 320.22(b)(1)].

**Biopharmaceutics:**

Tepadina<sup>®</sup> is manufactured as a lyophilized powder for injection in strengths of 15 mg/vial and 100 mg/vial, and is intended to be administered by intravenous route. The intended clinical duration of Tepadina<sup>®</sup> treatment consist of infusions every 12 or 24 hours.

Tepadina<sup>®</sup> is a lyophilized powder for solution, intended solely for intravenous administration after reconstitution and dilution and its absolute bioavailability is considered to be 100 per

cent. No excipients are included in the drug product; therefore, there is no concern about potential disposition kinetics changes due to excipients.

#### Biowaiver Request:

The NDA submission included a biowaiver request for Tepadina® (thiotepa), lyophilized powder for solution intended solely for intravenous administration citing 21 C.F.R. 320.22(b) (1). NDA 020058, Thioplex (thiotepa for injection) was identified as the listed drug product as the basis for the submission. However, no comparative information between the proposed product and the listed drug product could be located in the submission dated March 31, 2016. In the submission dated, July 14, 2016, the Applicant provided the following information:

**Table 1: Comparison of the Thioplex NDA 020058 and Tepadina formulations before reconstitution and dilution**

Product	Dosage form	Active Ingredient/Quan	Excipients
Thioplex 15 mg	Lyophilized powder for injection	15 mg thiotepa*	None
Tepadina 15 mg	Lyophilized powder for injection	15 mg thiotepa*	None
Tepadina 100 mg	Lyophilized powder for injection	100 mg thiotepa	None

\*Quantity stated

(b) (4)

The Applicant stated that Tepadina and Thioplex NDA 020058 lyophilized powder for solution are intended solely for intravenous administration after reconstitution at the same solution concentration of 10 mg/ml and the same pH range, as detailed in Table 2.

**Table 2: Comparison of the Thioplex NDA 020058 and Tepadina after reconstitution (with Sterile Water for Injection)**

Product	Concentration (active ingredient) of the reconstituted solution	pH of the reconstituted solution
Thioplex 15 mg	10 mg/ml	5.5 – 7.5 at 25°C
Tepadina 15 mg	10 mg/ml	5.5 – 7.5 at 25°C
Tepadina 100 mg	10 mg/ml	5.5 – 7.5 at 25°C

Physicochemical data for Tepadina and Thioplex NDA 020058 diluted solution in 0.9 % sodium chloride injection are presented in Table 3. The Applicant stated that, as presented in Table 3, below, the administered diluted solutions are comparable in terms of pH and final concentration of thiotepa.

**Table 3: Comparison of Thioplex NDA 020058 and Tepadina after reconstitution and dilution with 0.9 % sodium chloride injection at 25°C and 2-8°C**

Product	Nominal thiotepa Concentration (active ingredient) of the diluted solution	Actual initial thiotepa concentration (mg/ml)	% Initial thiotepa concentration remaining	pH of the reconstituted and diluted solution	Temperature	Reference
Thioplex 15 mg	1 mg/ml	(b) (4)	(b) (4)	5.5 – 7.5	25°C	Murray et al. 1997
Tepadina 15 mg	1 mg/ml			5.5 – 7.5	25°C	Compatibility study AA-178-R-V01
Tepadina 100 mg	1 mg/ml			5.5 – 7.5	25°C	Compatibility study AA-178-R-V01
Thioplex 15 mg	1 mg/ml			5.5 – 7.5	2-8°C	Murray et al. 1997
Tepadina 15 mg	1 mg/ml			5.5 – 7.5	2-8°C	Compatibility study AA-178-R-V01
Tepadina 100 mg	1 mg/ml			5.5 – 7.5	2-8°C	Compatibility study AA-016-R-V01

**Reviewer’s Assessment:**

Tepadina<sup>®</sup> is a lyophilized powder for solution with no additional excipients. The pH of the Applicant’s 1% solution of the proposed drug product is (b) (4) [Specification range is pH (b) (4)]. The pH range [pH 5.5 to 7.5] of Thioplex and Tepadina after reconstitution (with Sterile Water for Injection and 0.9 % sodium chloride injection, 1 mg/ml), is similar. The Applicant reported that the Osmolality (mOsm/kg) of 1 mg/ml solution of thiotepa in 0.9% Sodium Chloride is between 264 to 273 mOsm/kg. Since the formulation of Thioplex and Tepadina are identical [only the active drug substance and no excipient], disposition kinetics of Thiotepa should be similar from these two products.

**Bridging of Formulations:**

The current NDA submission is also supported with published literature references to support the labeling information. Therefore, in support of the scientific bridge between the drug product(s) used in the literature studies and the proposed drug product to support the acceptance of the scientific literature the Applicant provided the following information:

The drug product Tepadina and the listed drug Thioplex NDA 020058 show the same formulation since they are given as a lyophilized powder for solution which contains the active ingredient thiotepa only. A 100 mg formulation, whose composition is comparable with the 15 mg, was also developed by Adienne Sa. The Tepadina lyophilized powder is intended solely for intravenous administration after reconstitution at the same solution concentration of 10 mg/ml.

A sterile injectable dosage form of Thiotepa was first developed by American Cyanamid Company in the early 1950's. (b) (4)

(b) (4)

(b) (4) In this formulation Thiotepa was also introduced into the EU market under the name "Thiotepa Lederle" by Cyanamid Corporation and in the US market by IMMUNEX under the name "Thiotepa" in 1971.

The

(b) (4)

(b) (4)

(b) (4) reconstituted solutions of Thiotepa Lederle and Tepadina diluted in the same saline solution volume (500 ml), they can be considered comparable in terms of physico-chemical properties of the solution administered to patients. Therefore, the clinical response from the administration of Thiotepa Lederle Laboratories can be considered similar to that from Tepadina (thiotepa) administration.

After US registration of Thioplex NDA 020058 in 1994, the same 15 mg drug product was registered worldwide (e. g. Australia, EU), therefore where no thiotepa brand name is reported after this period, the Applicant believes that it is referred to the sole Thioplex formulation available on the market since 1994.

**Reviewer's Assessment:**

In support of the scientific bridge between drug product(s) used in the literature studies and the proposed drug product, the Applicant provided a tabular compilation of the literature [Appendix 1 provides the truncated compilation] and formulation information provided in the literature. The provided literature used thiotepa which was provided by



Lederle Laboratories, Wyeth Lederle, or the USP(Rockville, MD.). In some cases of literature references submitted, the information on thiotepa product brand could not be provided.

This Reviewer agrees with the Applicant that Thiotepa Lederle and Tepadina diluted in the same saline solution, are comparable in terms of physico-chemical properties of the solution administered to patients; in a diluted infusion, sodium chloride and sodium bicarbonate are not likely to affect the disposition kinetics of thiotepa.

This Reviewer also notes that the USP<sup>1</sup> provides only the drug substance thiotepa and not the formulation with any added excipients. Since the proposed product also contains only thiotepa and no added excipients, the information in the scientific literature which used thiotepa obtained from USP can also be used for labelling purposes, where applicable.

Some of the literature references do not provide details of the composition of the formulation or any comparative chemical and physical measurements. However, the formulations used in Heideman et al 1989; Jacobson et al, 2002, Van Maanen et al, 1999, Henner et al, 1987, Ng et al, 1991, Terenzi et al 1990, Down et al 1998, Henner et al 1987, Huitema et al 2001 and Rae et al, 2002 publications are adequately bridged to the proposed drug product.

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<sup>1</sup> <http://static.usp.org/pdf/EN/referenceStandards/certificates/1664000-R046R0.pdf>

**Reviewer's Final Assessment: Adequate**

This 505 (b)(2) Application relies, for its approval, on FDA's findings of safety and effectiveness for the listed drug. In addition, this Application is supported with data obtained from the scientific literature. This NDA includes a biowaiver request for the conduct of bioavailability/bioequivalence study(ies). According to 21 CFR 320.22(b)(1), a drug product's in vivo bioavailability or bioequivalence may be considered self-evident and a waiver of in vivo studies may be granted if the drug product meets the following criteria:

"It is a parenteral solution intended solely for administration by injection, and contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application."

The proposed drug product is a parenteral solution for administration by injection, and the proposed drug product has the same active ingredient (thiotepa), and has the same dosage form, route of administration and indication as the LD. In addition, there are no inactive ingredients in the proposed product and the Listed Drug product. As discussed above, disposition kinetics of thiotepa should be similar from these two products [Thioplex and Tepadina]. Therefore, the Applicant's request for a waiver of the in vivo study for their proposed product, Tepadina® (thiotepa) for Injection (15 mg/vial and 100 mg/vial, is granted.

In addition, from a Biopharmaceutics perspective, the formulations used in Heideman et al 1989; Jacobson et al, 2002, Van Maanen et al, 1999, Henner et al, 1987, Ng et al, 1991, Terenzi et al 1990, Down et al 1998, Henner et al 1987, Huitema et al 2001 and Rae et al, 2002 publications are adequately bridged to the proposed drug product.

**RECOMMENDATION**

A waiver of the in vivo bioequivalence study requirement is granted.

From the Biopharmaceutics perspective, NDA 208264 for Tepadina® (Thiotepa) for Injection (15 mg/vial and 100 mg/vial, is recommended for **APPROVAL**.

Om Anand, Ph.D. [Date: 11/30/2016]

Biopharmaceutics Reviewer  
Division of Biopharmaceutics  
Office of New Drug Products/OPQ

I concur with Dr. Om Anand's assessment and recommendation.

Okpo Eradiri, Ph.D. [Date: 11/30/2016]

Acting Biopharmaceutics Lead  
Division of Biopharmaceutics  
Office of New Drug Products/OPQ

**Appendix 1:**

Information provided in published literature

Specific sections of the 505(b)(2) NDA – Module 4 and Module 5	Source of information	Annotated labelling section
	<ul style="list-style-type: none"> <li>- Reliance on FDA’s previous finding of safety and efficacy for listed drug Thioplex NDA 020058</li> <li>- Reliance on published literature (supporting information on thiotepa product/administration)</li> </ul>	
<b>MODULE 4 – Non Clinical</b>		
Pharmacology	<u>Published Literature</u> Terenzi 1990 Enhancement of T cell-depleted bone marrow allografts in mice by thiotepa - <b>Thiotepa was provided by Lederle Laboratories (Pearl River, NY)</b>	13.2 Animal Pharmacology
	Down 1998 Thiotepa improves allogeneic bone marrow engraftment without enhancing stem cell depletion in irradiated mice - <b>Thiotepa was provided by Wyeth Lederle (Pearl River, NY)</b>	13.2 Animal Pharmacology
Pharmacokinetics, Toxicology	<u>Thioplex NDA 020058</u>	13 Nonclinical Toxicology 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
<b>MODULE 5 Clinical</b>		
Pharmacokinetic Absorption	<u>Thioplex NDA 020058</u>	12.3 Pharmacokinetics Absorption
Pharmacokinetic Distribution	<u>Published Literature</u> Przepiorka 1995 Dosing of Thiotepa for myeloablative therapy – <b>No information on thiotepa product brand.</b>	12.3 Pharmacokinetics Distribution Volume of distribution
	Huitema 2001 Population pharmacokinetics of thioTEPA and its active metabolite TEPA in patients undergoing high-dose chemotherapy - <b>No information on thiotepa product brand.</b>	12.3 Pharmacokinetics Distribution Protein binding
	Heideman 1989 Phase I and Pharmacokinetic Evaluation of Thiotepa in the Cerebrospinal Fluid and Plasma of Pediatric Patients: Evidence for Dose- dependent Plasma Clearance of Thiotepa - <b>Thiotepa was provided by Lederle Laboratories (Pearl River, NY) in 15-mg sterile glass vials containing 80 mg of NaCl and 50 mg of NaHCO<sub>3</sub>.</b>	12.3 Pharmacokinetics Distribution CSF:plasma ratio

Pharmacokinetic Metabolism	<p><u>Published Literature</u></p> <p>Jacobson 2002 Cytochrome P450 isozymes 3A4 and 2B6 are involved in the in vitro human metabolism of thiotepa to TEPA - <b>Thiotepa was obtained from USP(Rockville, Md.) for in vitro study</b></p>	12.3 Pharmacokinetics Elimination  Hepatic metabolism, cytochrome P450-mediated metabolism
	<p>Van Maanen 1999 A Search for New Metabolites of N,N<sup>I</sup>,N<sup>II</sup>-triethylenethiophosphoramidate - ThioTEPA was obtained from Cyanamid Benelux (Etten-Leur, the Netherlands). Administration of three 4-day courses of thioTEPA 40 mg/m<sup>2</sup>, twice daily</p>	12.3 Pharmacokinetics Elimination  Conjugation
Pharmacokinetic Elimination	<p><u>Published Literature</u></p> <p>Van Maanen 2001 Urinary excretion of thioTEPA and its metabolites in patients treated with high-dose cyclophosphamide, thioTEPA and carboplatin - <b>No information on thiotepa product brand.</b></p>	12.3 Pharmacokinetics Elimination  Urinary excretion
	<p>Henner 1987 Pharmacokinetics of continuous-infusion high-dose thiotepa – Thiotepa was obtained as a sterile powder from <b>Lederle Laboratories in vials containing 15-mg of thiotepa, 80 mg of NaCl, and 50 mg of NaHCO<sub>3</sub>.</b></p>	12.3 Pharmacokinetics Elimination  Clearance
	<p>Huitema 2001 Population pharmacokinetics of thioTEPA and its active metabolite TEPA in patients undergoing high-dose chemotherapy - <b>No information on thiotepa product brand.</b></p>	12.3 Pharmacokinetics Elimination  Elimination half life
Potential drug interaction with phenytoin	<p><u>Published Literature</u></p> <p>De Jonge 2005 Significant induction of cyclophosphamide and thiotepa metabolism by phenytoin – <b>No information on thiotepa product brand.</b></p>	7.2 Concomitant use not recommended
Thiotepa metabolism via CYP2B6 and CYP3A4	<p><u>Published Literature</u></p> <p>Jacobson 2002 Cytochrome P450 isozymes 3A4 and 2B6 are involved in the in vitro human metabolism of thiotepa to TEPA - <b>Thiotepa was obtained from USP(Rockville, Md.) for in vitro study</b></p>	7.3 Interactions with drugs metabolised using the Cytochrome P450 system

<p>Effect of the co-administration of CYP2B6 and CYP3A4 inhibitors on the pharmacokinetics of thiotepa and TEPA</p>	<p><u>Published Literature</u> Eckhart 2008 Relations between polymorphisms in drug-metabolising enzymes and toxicity of chemotherapy with cyclophosphamide, thiotepa and carboplatin – <b>No information on thiotepa product brand.</b></p>	<p>7.3 Interactions with drugs metabolised using the Cytochrome P450 system</p>
<p>Effect of the co-administration of cytochrome P450 inducers on the pharmacokinetics of thiotepa and TEPA</p>	<p><u>Published Literature</u> Ng 1991 N,N',N"-triethylenethiophosphoramidate (thio-TEPA) oxygenation by constitutive hepatic P450 enzymes and modulation of drug metabolism and clearance in vivo by P450- inducing agents – <b>Thiotepa was obtained from Lederle Laboratories Division, American Cyanamid Co., Pearl River, NY</b></p>	<p>7.3 Interactions with drugs metabolised using the Cytochrome P450 system</p>
<p>Effect of thiotepa on the metabolism and pharmacokinetics of CYP2B6 substrates</p>	<p><u>Published Literature</u> Rae 2002 Triethylenethiophosphoramidate is a specific inhibitor of cytochrome P450 2B6: implications for cyclophosphamide metabolism – <b>Thiotepa was obtained from USP for in vitro study</b></p>	<p>7.3 Interactions with drugs metabolised using the Cytochrome P450 system</p>
<p>Thiotepa must not be administered with cyclophosphamide</p>	<p><u>Published Literature</u> De Jonge 2004 Integrated Population Pharmacokinetic Model of both cyclophosphamide and Thiotepa suggesting a mutual drug-drug interaction – <b>No information on thiotepa product brand.</b></p>	<p>7.3 Interactions with drugs metabolised using the Cytochrome P450 system</p>
<p>Effect of thiotepa on plasma pseudochoolinesterase and succinyl-coline</p>	<p><u>Published Literature</u> Viby-Mogensen 1985 Interaction of Other Drugs With Muscle Relaxants – <b>No information on thiotepa product brand.</b></p>	<p>7.4 Other drug interactions</p>
<p>Effect of thiotepa on cyclosporine, tacrolimus and myelosuppressive or myelotoxic drugs.</p>	<p><u>Published Literature</u> Pession 1996 Phase I study of high-dose thiotepa with busulfan, etoposide, and autologous stem cell support in children with disseminated solid tumors – <b>No information on thiotepa product brand.</b></p>	<p>7.4 Other drug interactions</p>

Special Population: renal impairment, hepatic impairment	<u>Published Literature</u> Ekhart 2009 Altered cyclophosphamide and thiotepa pharmacokinetics in a patient with moderate renal insufficiency – <b>No information on thiotepa product brand.</b>	12.3 Pharmacokinetics Special populations Renal impairment
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Anand

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**MICROBIOLOGY**

**Product Background:**

**NDA:** 208264

**Drug Product Name / Strength:** TEPADINA (Thiotepa), 15 mg/vial and 100 mg/vial

**Route of Administration:** IV injection

**Applicant Name:** ADIENNE SA

**Manufacturing Site:**

(b) (4)

**Method of Sterilization:** (b) (4)

**Review Summary:**

**List Submissions being reviewed (table):**

Submit	Received	Review Request	Assigned to Reviewer
2/25/2015	2/26/2015	N/A	4/13/2015
7/14/2016	7/14/2016	N/A	N/A
11/23/2016	11/23/2016	N/A	N/A

\*IR response submitted electronically

**Highlight Key Outstanding Issues from Last Cycle:**

Container closure integrity test results

**Concise Description Outstanding Issues Remaining:** N/A

**P DRUG PRODUCT**

**P.1 Description of the Composition of the Drug Product**

- Description of drug product – White lyophilisate

- Drug product composition –

Configuration	Ingredient	Content per vial
100 mg/vial	Thiotepa	100 mg
15 mg/vial	Thiotepa	15 mg

- Description of container closure system –

Configuration	Component	Description	Manufacturer
100 mg/vial	Tube	(b) (4) glass vial Type I	(b) (4)
	Stopper	(b) (4) bromobutyl stopper	
15 mg/vial	Tube	(b) (4) glass vial Type I	
	Stopper	(b) (4) bromobutyl stopper	

**Acceptable**

**P.2 Pharmaceutical Development**

**P.2.5 Microbiological Attributes**

- Container-Closure and Package integrity - (3.2.P.2.5. pharmaceutical-development-p25-100mg.pdf and pharmaceutical-development-p25-(b) (4)mg.pdf)

**Note to reviewer:** It is not clear if the container/closure system used for validation was the same as for the drug product and clarification will be requested.

Study/Report # and date: 15 mg container closures: (b) (4) reference (b) (4), dated (b) (4). 100 mg container closures: (b) (4) reference (b) (4), dated (b) (4).

Test method: microbial immersion

Brief description: Twenty test vials filled with TSB were immersed into bacterial culture for 24 hours, and then disinfected by vaporization of Ipasept 70. Ten vials were left on the bench as negative control. Growth promotion was performed on 10 vials. The vials were incubated at 30-35°C for 7 days.

Challenge organism: *Pseudomonas aeruginosa*

Challenge level: (b) (4)

Results:

Vials	Sample	# Positive/ # Tested
(b) (4)		

*Information Request: The following comments were sent to the sponsor in an IR letter dated 5/3/2016. The sponsor submitted the response in 5/20/2016. The original comments followed by the sponsor's response are included below in italics.*

*Comments: Regarding the container closure integrity test:*

- a) Please clarify if the vials and stoppers tested in the microbial ingress were the same as the ones proposed for production of TEPADINA.
- b) Please clarify if (b) (4) the vials were immersed in the bacterial culture. If not, please provide new testing data.
- c) Please clarify if breached vials were included as positive control and subjected to the same microbial immersion test. If so, please provide results from these positive controls.
- d) In both reports of container closure integrity test, it was stated in the method sections (e.g. page 6 of the document pharmaceutical-development-p25-15mg.pdf) that 10 vials were spiked with the micro-organism for positive control (growth promotion). However, in the conclusion section (e.g. page 8 of the document pharmaceutical-development-p25-15mg.pdf), it is stated that growth from 20 positive control vials were observed. Please clarify the discrepancy.

*Response: a-c) The sponsor confirmed that the vials and stoppers used in microbial ingress test were the same as the ones proposed for the production of TEPADINA. (b) (4)*

*(b) (4) There was no breached vial included as positive control. New CCIT data will be submitted.*

*d) The sponsor clarified that 10 positive control vials were used in the test. The discrepancy was a typo.*

*2<sup>nd</sup> Information Request: The following comments were sent to the sponsor in an IR letter dated 11/8/2016. The sponsor submitted the response in 11/23/2016 via email. The original comments followed by the sponsor's response are included below in italics.*

**Comment:** It is stated in the submission dated July 14, 2016 (ADIENNE Responses to FDA CMC Information Request dated 03<sup>rd</sup> May 2016) that new container/closure integrity test would be performed (b) (4)

(b) (4) Please submit the new integrity testing data for the drug product container/closure (b) (4).

**Note to reviewer:** The applicant sent an email to the Agency in 10/3/2016, asking if CCIT can be performed with dye ingress method instead of microbial immersion method. We agree that dye ingress method can be used for CCIT.

**Response:** The following method validation report was provided:

Report #: AA-320-R-V01

Title: Tepadina 15 mg & 100 mg Drug Product Analytical method Validation: Container Closure Integrity Testing (CCIT)

Date: 11/23/2016

**Testing method:** Dye ingress.

Drug product vials are used for the CCIT. Positive control vial is prepared by puncturing the vial with a 2  $\mu$ m internal diameter capillary needle. Twenty drug product vials and the positive control vial are submerged into a beaker filled with 1 mg/mL solution of methylene blue dye. The beaker is placed in a vacuum oven. Vacuum (b) (4) is applied for 30 minutes. The vacuum is released and the vials are kept in the methylene blue solution for another 30 minutes. Vials are cleaned. Drug products in the vials are reconstituted to 10 mg/mL. (b) (4) (b) (4) mL of the reconstituted solution is scanned for absorbance in a spectrophotometer from (b) (4) nm to (b) (4) nm. Absorbance of the sample vials is compared to that of the sensitivity solution, which contains (b) (4)  $\mu$ g/mL methylene blue solution.

Detection sensitivity is equivalent to the intrusion of (b) (4) (b) (4) methylene blue solution.

Results of the test were not provided.

**Note to reviewer:** The applicant initially provided the CCIT test results with microbial ingress method without (b) (4). In the IR response dated 11/23/2016, the applicant agreed to (b) (4) on the CCIT performed with dye ingress method.

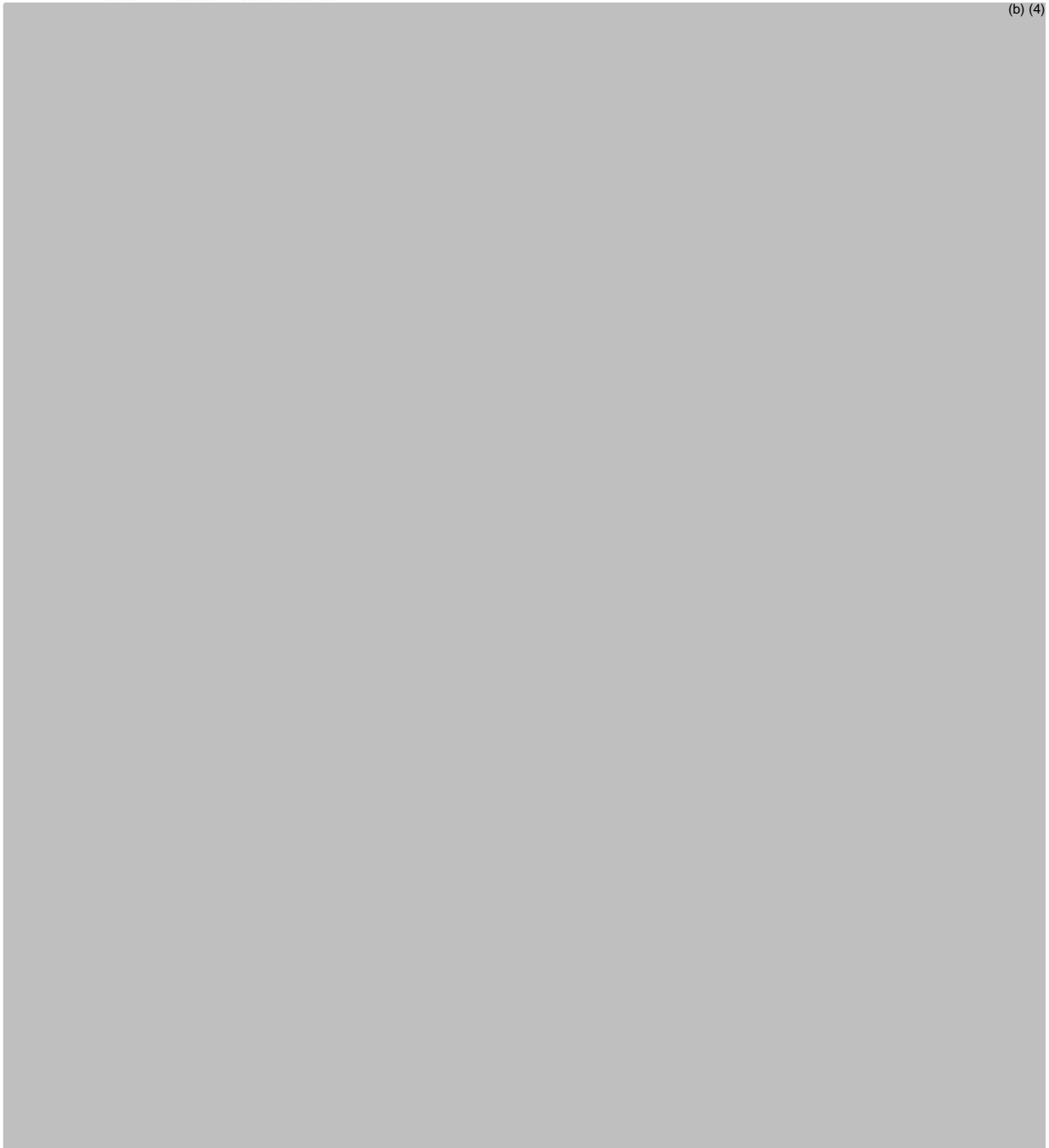
### Acceptable

- Antimicrobial Effectiveness Testing - (2.3. introduction-100mg.pdf, p. 44 of 70)

The drug products are sterile lyophilized powders (b) (4). They are packaged in single dose vials. It is indicated that the reconstituted solution in WFI is stable up to 24 hours at 5±3°C. At 25°C, the diluted solution has to be used within 4 hours. Antimicrobial effectiveness testing is not required.

Acceptable

**P.3 Manufacture**  
**P.3.1 Manufacturers**



(b) (4)

**P.7 Container Closure System - See P.1.**

**P.8 Stability**

**P.8.1 Stability Summary and Conclusion**  
(3.2.P.8.1. stability-summary-100mg.pdf)

Proposed Expiry: 18-months at 2 °C - 8°C

(b) (4)

**Acceptable**

**P.8.3 Stability Data**

Stability data is provided for three batches of Thiotepa 100 mg: 09A16, 09A22 and 09A30, and three batches for Thiotepa 15 mg: 11KG12, 11K14 and 11K30. Bacteria endotoxin and sterility for the above batches comply with the specification at 0 month, 18 month and 24 month.

**Acceptable**

**R REGIONAL INFORMATION**

**R.1 Executed Batch Record**

Executed lot #(s): 09A22, 11K14

The batch records confirm that validated sterilization/depyrogenation and manufacturing processes were used for the manufacture of the exhibit batch. (b) (4)

**Acceptable**

R.2 Comparability Protocol – No CP was included in the application.

**2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1**

**A. PACKAGE INSERT (1.14)**

Storage temperature: 2°C-8°C; Route of administration: IV; Container: Single dose

Reconstituted/Further Diluted Drug Product

Pre-use storage: 2°C-8°C

Reconstitution: Reconstitute the 15mg/vial product with 1.5 mL WFI, or the 100 mg/vial with 10 mL WFI. If not used immediately after reconstitution the product is stable for 8 hours when stored at 2°C -8°C.

Further product dilution: Reconstituted drug solution must be further diluted with 500 mL of 0.9% Sodium Chloride (1000 mL if the dose is higher than 500 mg), or with an appropriate volume to obtain a final TEPADINA concentration between 0.5 and 1mg/mL. After dilution the product is stable for 24 hours when stored at 2°C -8°C and for 4 hours when stored at 25°C.

It is stated that “From a microbiological point of view, the product should be used immediately”.

**Acceptable**

***List of Deficiencies:***

None

***Conclusion/Recommendation:***

Recommended for approval on the basis of sterility assurance.

***Primary Microbiology Reviewer Name and Date:***



Yuansha Chen, Ph.D, CDER/OPQ/OPF/DMA/Brach II  
12/5/2016

***Secondary Reviewer Name and Date (and Secondary Summary, as needed):***

Neal J. Sweeney, PhD.

Quality Assessment Lead (acting)

CDER/OPQ/OPF/DMA/Brach II

12/5/2016





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Yuansha  
Chen

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## ATTACHMENT I: Final Risk Assessment

### A. Final Risk Assessment - NDA

#### a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Sterility	<ul style="list-style-type: none"> <li>Formulation</li> <li>Container closure</li> <li>Process parameters</li> <li>Scale/equipments</li> <li>Site</li> </ul>	H	(b) (4)	Acceptable to microbiologist	Controls are in place and continue stability monitoring post approval
Endotoxin Pyrogen	<ul style="list-style-type: none"> <li>Formulation</li> <li>Container closure</li> <li>Process parameters</li> <li>Scale/equipments</li> <li>Site</li> </ul>	M		Acceptable to microbiologist	Controls are in place and continue stability monitoring post approval
Assay (API), stability	<ul style="list-style-type: none"> <li>Formulation</li> <li>Container closure</li> <li>Raw materials</li> <li>Process parameters</li> <li>Scale/equipment</li> <li>Site</li> </ul>	L		Acceptable	Controls are in place, continue stability monitoring post approval
Physical stability (solid state)	<ul style="list-style-type: none"> <li>Formulation</li> <li>Container closure</li> <li>Raw materials</li> <li>Process parameters</li> <li>Scale/equipment</li> <li>Site</li> </ul>	L		Acceptable	Controls are in place, continue stability monitoring post approval
Osmolality	<ul style="list-style-type: none"> <li>Formulation</li> <li>Raw materials</li> <li>Process parameters</li> <li>Scale/equipment</li> <li>Site</li> </ul>	L		-----	-----
Uniformity of Dose (Fill volume/deliverable volume)	<ul style="list-style-type: none"> <li>Formulation</li> <li>Container closure</li> <li>Process parameters</li> <li>Scale/equipment</li> <li>Site</li> </ul>	L		Acceptable	(b) (4)
pH (High)	<ul style="list-style-type: none"> <li>Formulation</li> <li>Container closure</li> <li>Raw materials</li> <li>Process parameters</li> <li>Scale/equipment</li> </ul>	L		Acceptable	Controls are in place during stability testing. Continue stability monitoring

	• Site		(b) (4)		post approval
pH (Low)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	L		Acceptable	Controls are in place. Continue stability monitoring post approval
Particulate Matter	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	M		Acceptable	Controls are in place. Continue stability monitoring post approval
Leachables extractables	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	L		Acceptable	Controlled via DMF
Redispersability/ Reconstitution time	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	M		Acceptable	Controls are in place. Continue stability monitoring post approval
Moisture content	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	L		Acceptable	Controls are in place. Continue stability monitoring post approval
Appearance (b) (4)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	L		Acceptable	Controls are in place. Continue stability monitoring post approval
Appearance (color/turbidity)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	L		Acceptable	Controls are in place. Continue stability monitoring post approval
Microbial Limits	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> </ul>	L			

b)



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Agarwal

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Anamitro  
Banerjee

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**OVERALL ASSESSMENT AND SIGNATURES:**

***Application Technical Lead Name and Date:***

***This application is recommended for APPROVAL from the CMC perspective.***

***Anamitro Banerjee, Ph.D.***

***December 10, 2016***



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Banerjee

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## MEMORANDUM

### NDA 208264: TEPADINA® Thiotepa for Injection

Date: June 01, 2016  
Reviewer: Anamitro Banerjee  
Applicant: 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  $\beta$ -thalassemia.

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#### Background

NDA 208264 (TEPADINA® Thiotepa for Injection) was received by the FDA on March 31, 2016. The CMC section (m3) was submitted to the agency on February 26, 2015. In the original February 26, 2015 submission, the applicant provided a letter of authorization (LOA) for the DMF (b) (4) (DMF holder: (b) (4)). Subsequently, on August 27, 2015, the DMF was administratively closed as the DMF holder did not respond to the Overdue Notification Letter (ONL) dated March 18, 2015.

The applicant was notified of the DMF status via an IR letter dated May 13, 2016 and during a teleconference on May 18, 2016. The NDA applicant indicated that a new DMF (DMF (b) (4)) was submitted for (b) (4) by the same DMF holder. The applicant indicated that they will provide an LOA for the new DMF. The new DMF was received by the agency on April 25, 2016 and was deemed active on May 26, 2016. In response to an IR, the applicant indicated that they will provide the LOA as soon as the DMF holder provides them the LOA upon receipt of an official notification on the status of this DMF from the agency. The applicant anticipates that they will submit the LOA to the agency during the week of May 30, 2016.

#### Comments:

The applicant provided the LOA for the DMF at the time of submission of the CMC section. The DMF was administratively closed *after* the NDA submission; and the applicant has committed to provide LOA for the replacement DMF from the same DMF holder. ONDP recommends filing this NDA from the CMC perspective.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ANAMITRO BANERJEE  
06/01/2016