

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203856Orig1s000**

**PHARMACOLOGY REVIEW(S)**

# Memorandum

**To:** NDA 203856 File

**CC:** Todd Palmby, Supervisory Toxicologist, CDER/OND/OHOP/DHOT

**From:** C.J. George Chang, Pharmacologist, CDER/OND/OHOP/DHOT

**Date:** 8/23/2013

**Re:** Nonclinical review/recommendation of July 17, 2013 resubmission (SDN#24; proposed product label)

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## Nonclinical Review and Recommendation

### Background:

On December 21, 2011, Roxane Laboratories (the Applicant) submitted this 505(b)(2) NDA (SDN#1) for Cyclophosphamide Capsules with the identical indication, dosage, and strength as the listed drug (tablet formulation previously approved under NDA 012141 of Baxter Healthcare and ANDA 040032 of Roxane). A refusal-to-file (RTF) decision was made by the Agency on February 17, 2012.

The Applicant resubmitted this NDA on July 3, 2012 (SDN#8), which was followed by a Complete Response letter issued by the Agency on May 3, 2013, due to CMC deficiencies. During that review cycle, a Pharmacology/Toxicology review was uploaded to DARRTS on April 26, 2013.<sup>1</sup>

A Class 1 resubmission was received on July 17, 2013 (SDN#24), which is the focus of this memorandum.

### Pharmacology/Toxicology Review:

There were no unresolved nonclinical issues following the previous review cycle or any changes to the package insert included in the Applicant's July 17, 2013 resubmission.

**Recommendation:** Approval

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<sup>1</sup> Chang CJG and Palmby T. Rev-NONCLINICAL-21 (Primary Review), NDA 203856, CDER DARRTS database, April 26, 2013.

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/s/  
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CHING-JEY G CHANG  
08/23/2013

TODD R PALMBY  
08/23/2013

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: 203856  
Supporting document/s: SD 8, 16  
Applicant's letter date: 7/3/2012  
CDER stamp date: 7/3/2012  
Product: Cyclophosphamide capsule  
Indication: Treatment of malignant disease such as certain types of lymphomas and leukemias, neuroblastoma and carcinoma of the breast and is often used in combination with other neoplastic drugs. It is also indicated for carefully selected cases of biopsy proven "minimal change" nephritic syndrome in children.  
Applicant: Roxane Laboratories, Inc.  
Review Division: Division of Hematology Oncology Toxicology  
(Division of Oncology Products 1)  
Reviewer: C.J. George Chang, DVM, MS, PhD, DABT  
Supervisor: Todd R. Palmby, PhD  
Division Director: John K. Leighton, PhD, DABT (acting)  
(Robert Justice, MD, MS)  
Project Manager: Lisa Skarupa, RN, MSN, AOCN

**Disclaimer**

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 203856 are owned by Roxane Laboratories or are data for which Roxane Laboratories has obtained a written right of reference. Any information or data necessary for approval of NDA 203856 that Roxane Laboratories does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 203856.

# 1 Executive Summary

## 1.1 Introduction

Roxane Laboratories (the Applicant) resubmitted a 505(b)(2) New Drug Application (NDA 203856) for cyclophosphamide capsule on July 3, 2012, following a previous determination of refuse to file.

## 1.2 Brief Discussion of Nonclinical Findings

There were no nonclinical study reports submitted with this NDA. However, input from the Pharmacology/Toxicology review team was requested by the CMC reviewer on two specifications for the drug product. The Applicant provided responses to information requests that were sent from FDA during the review of this NDA regarding the specification for (b) (4) in the drug product and the drug product degradant specifications. These responses were deemed acceptable from a Pharmacology/Toxicology perspective. See a more detailed review of these CMC issues in section 2.5 below.

## 1.3 Recommendations

### 1.3.1 Approvability

There are no outstanding issues that would preclude approval of this NDA from a Pharmacology/Toxicology perspective. The nonclinical discipline recommends approval of NDA 203856.

# 2 Drug Information

## 2.1 Drug

CAS Registry Number

6055-19-2

Generic Name

cyclophosphamide

Chemical Name

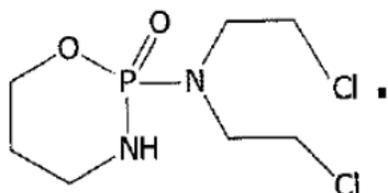
(+)-2-[Bis(2-chloroethyl)amino]-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide, monohydrate

2H-1,3,2-Oxazaphosphorin-2-amine, N,N-bis(2-chloroethyl)tetrahydro-, 2-oxide, monohydrate, (±)

Molecular Formula/Molecular Weight

$C_7H_{15}Cl_2N_2O_2P \cdot H_2O$  / 279.10

Structure



Pharmacologic Class

Alkylating drug

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 012141 (Cytosan) is named as the listed drug product for the basis of this 505(b)(2) submission.

## 2.3 Drug Formulation

The Applicant has formulated this drug product as 25 and 50 mg capsules, which is the primary basis for the 505(b)(2) application rather than an ANDA. The currently approved cyclophosphamide tablets are the same 25 and 50 mg strengths.

Cyclop			(b) (4)
Pregela	(b) (4)		(b) (4)
Sodium S			(b) (4)
(b) (4)			

*(excerpted from the Applicant's submission)*

## 2.5 Comments on Impurities/Degradants of Concern

During the review of this NDA, the CMC reviewer requested input from the Pharmacology/Toxicology team on the acceptability of a number of drug product specifications.

(b) (4)  
The CMC reviewer inquired about the specifications in the drug product for residual solvents. Upon review of the Applicant's justification for these specifications, all were found to be acceptable except that for (b) (4). The Applicant's justification for the specification of (b) (4) was that it meets the limits for (b) (4).

(b) (4)  
An information request was sent to the Applicant to provide an adequate justification for the (b) (4) specification of (b) (4). The Applicant responded by providing a summary of compiled toxicology data on (b) (4) from the literature and publically available sources. The Applicant provided a calculation of a permitted daily exposure (PDE) for oral (b) (4) based on a 13-week inhalation study in rats conducted by the National Toxicology Program. The study described did not identify an NOAEL, which is the preferred method to calculate a PDE. However, a LOEL was identified, which is acceptable if an appropriate safety factor is included. An additional concern was that these studies were conducted with (b) (4) administered via the inhalation route, rather than the oral route as cyclophosphamide is administered. However, it is assumed for these calculations that bioavailability by all routes of administration is 100%.

The Applicant provided the following calculation of a PDE for oral (b) (4) based on the 13-week repeat-dose toxicity study in rats with inhalation of (b) (4):

(b) (4)



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

The Applicant’s calculation of the (b) (4) PDE of (b) (4) is acceptable from a Pharmacology/Toxicology perspective. The maximum amount of (b) (4) that would be administered to a patient receiving 5 mg/kg/day of cyclophosphamide capsules would be (b) (4), based on the specification of (b) (4), which is lower than the proposed PDE. Therefore, the Applicant’s proposed specification (b) (4) in the cyclophosphamide drug product is acceptable from a Pharmacology/Toxicology perspective.

**(b) (4) and Single Largest Unspecified Degradant:**

The CMC reviewer requested Pharmacology/Toxicology input on the acceptability of the specifications for (b) (4) and Single Largest Unspecified Degradant in the drug product. The Applicant submitted two sets of drug product specifications: 1) Release Acceptance Criteria and 2) Stability Acceptance Criteria.

The specifications for the above drug product degradants that were originally submitted in the NDA were as follows:

Test	Release Acceptance Criteria	Stability Acceptance Criteria
Degradation Products	Degradation Products: (b) (4) : NMT: (b) (4) Single Largest Unspecified Degradant: NMT (b) (4) Total Degradants: NMT (b) (4)	Degradation Products: (b) (4) : NMT: (b) (4) Single Largest Unspecified Degradant: NMT (b) (4) Total Degradants: NMT (b) (4)

The proposed stability acceptance criteria of (b) (4) were not acceptable as they are above the qualification threshold in ICH Q3B of 0.2%. As the Applicant did not provide a justification for these specifications, and no nonclinical studies were submitted to this NDA that would have qualified these degradants to the proposed levels, an information request was sent to the Applicant to provide a single set of specifications for degradants at release and during stability.

The Applicant submitted a revised set of acceptance criteria for degradants in the drug product in response to the information request, which is as follows:

Test	Release Acceptance Criteria	Stability Acceptance Criteria
Degradation Products	Degradation Products: (b) (4) NMT: (b) (4) Single Largest Unspecified Degradant: NMT (b) (4) Total Degradants: NMT (b) (4)	Degradation Products: (b) (4) NMT: (b) (4) Single Largest Unspecified Degradant: NMT (b) (4) Total Degradants: NMT (b) (4)

As the Applicant’s revised drug product acceptance criteria for degradants do not exceed the qualification threshold of 0.2% in ICH Q3B, they are acceptable from a Pharmacology/Toxicology perspective.

### 2.6 Proposed Clinical Population and Dosing Regimen

The Applicant proposed the following same indications and dose for Cyclophosphamide capsules as for the listed drug, Cytoxan.

Indications:

Treatment of malignant disease such as certain types of lymphomas and leukemias, neuroblastoma and carcinoma of the breast and is often used in combination with other neoplastic drugs. It is also indicated for carefully selected cases of biopsy proven “minimal change” nephritic syndrome in children.

Doses:

Adult and pediatric doses for malignant diseases: 1 to 5 mg/kg/day for initial and maintenance dosing.  
 Dose for “minimal change” nephrotic syndrome: (b) (4)  
 (b) (4).

### 3 Studies Submitted

No new nonclinical studies were submitted with this NDA.

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/s/  
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CHING-JEY G CHANG  
04/26/2013

TODD R PALMBY  
04/26/2013

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number: 203856    Applicant: Roxane Laboratories Inc.    Stamp Date: 12/21/2011**

**Drug Name: Cyclophosphamide    NDA/BLA Type: 505(b)(2)**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			NA
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			NA
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			NA
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			NA
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?			NA
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			NA
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			NA

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement  
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA/BLA or Supplement**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		No impurity issues have been identified at this time; this will be a review issue.
11	Has the applicant addressed any abuse potential issues in the submission?	X		
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			NA

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE?** Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

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Reviewing Pharmacologist Date

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Team Leader/Supervisor Date

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement 010908

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/s/  
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WHITNEY S HELMS  
02/03/2012

ANNE M PILARO  
02/03/2012

I concur with the reviewer's conclusions regarding the information submitted with this NDA, and the recommendation from the nonclinical discipline that this NDA is fileable.