CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203856Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review (2)

Date	September 6, 2013
From	Ali Al-Hakim, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA #	203856
Applicant	Roxane Laboratories
Date of Original Submission **Date of Resubmission**	December 21, 2011 July 17, 2013
PDUFA Goal Date	September, 17, 3013
Proprietary Name / **Established Name**	N/A Cyclophosphamide
Dosage forms / Strength	Immediate release capsules 25mg and 50 mg
Proposed Indication(s)	Cyclophosphamide drug product is an alkylating agent indicated for the treatment of malignant diseases such as certain types of lymphomas and leukemias, neuroblastoma and carcinoma of the breast.
Recommended	Approval

1. Introduction

NDA 203856 was originally submitted on December 21, 2011 with insufficient drug product stability data (6 months). Therefore, based on the insufficient drug product stability data, a Refusal to File Letter (RTF) was issued on 17-FEB-2012. Roxane, the sponsor of the NDA, resubmitted the NDA on July 03, 2012 with 12 months of stability data. The Agency granted a standard review with an initial PDUFA goal date of May 03, 2013. However, there were outstanding CMC issues related to dissolution and impurities. The reported stability results of one lot of 25 mg and one lot of 50 mg capsules (b) (4) did not meet acceptance criteria for dissolution and degradation products (unspecified degradation products) testing. Based on the preliminary studies and in response to an FDA information request letter dated 25-MAR-2013, the sponsor agreed to provide results of a study to address these issues at the end of April 2013. The results of the above study were provided, as an amendment to the NDA, on April 26, 2013. Initial assessment of the information submitted by the sponsor did not provide adequate and complete response to address the issue concerning that one out of three NDA registration batches did not meet the proposed NDA specification. Therefore, a CR letter was issued on May 03, 2013. In response to this CR letter, the applicant submitted CMC information (2 new batches with appropriate stability data) on July 17, 2013. The submitted CMC information was reviewed and found acceptable by

the CMC reviewer, Josephine Jee. Refer to CMC review dated September 04, 2013 and final approval recommendation.
24 months of expiry dated for the drug product was granted
Storage Conditions:
Store at 20°C to 25°C (68°F to 77°F), excursion permitted between 15°C and 30°C (between 59°F and 86°F).
Additional CMC related information is discussed in **section 3 below.**

2. Background

This NDA is a 505(b)(2) referencing Cytoxan® NDA 012141 tablets 25 mg and 50 mg. However, this NDA is no longer listed in the Orange Book. Cyclophosphamide, the active ingredient in both NDAs, is an Alkylating Agent (nitrogen mustard) with antineoplastic and immunosuppressant properties.
The applicant has provided justification for introducing the new dosage form, capsules and discontinuation of the tablets. The justification includes exposure protection to end-users, the development of a more stable product and the closing of the tablets' current manufacturing site.

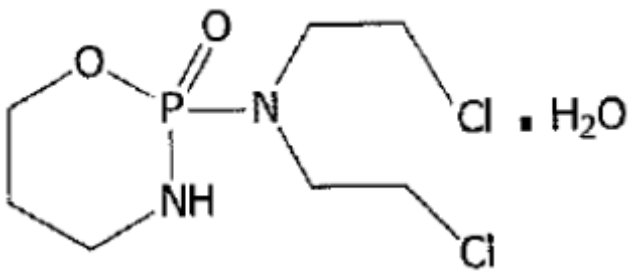
The listed drug for this application, Cytoxan (Cyclophosphamide) Tablets (NDA 012141), was approved November 16, 1959; however, Baxter no longer markets the tablets. The Applicant for this NDA (Roxane) currently markets Cyclophosphamide tablets (25 mg and 50 mg) under ANDA 040032. On December 21, 2011, the Applicant submitted this 505(b)2 NDA for approval of Cyclophosphamide Capsules with the identical characteristics (indication, dosage, and strength) as the tablet formulation.

Cyclophosphamide, the active ingredient in all NDAs, is an Alkylating Agent (nitrogen mustard), with antineoplastic and immunosuppressant properties.

Dosing Regimen and Administration
Treatment of Malignant Diseases: 1 mg per kg to 5 mg per kg per day for both initial and maintenance dosing.
Treatment of Nonmalignant Disease: (b) (4)

3. Chemistry, Manufacturing and Control (CMC)

The active pharmaceutical ingredient is Cyclophosphamide, which is an Alkylating Agent (nitrogen mustard) and possesses antineoplastic and immunosuppressant properties. Chemical Structure, Chemical Name and Molecular Weight are provided below.



Chemical Name:
(+)-2-[Bis (2-chloroethyl) amino] tetrahydro-2H-1,3,2,-oxazaphosphorine 2-oxide, monohydrate
Empirical formula is: C7H15Cl2N2O2P • H2O Molecular weight: 279.1

The drug substance is manufactured/chemically synthesized by (b) (4) (b) (4) (b) (4). Cyclophosphamide is included in the current USP. Cyclophosphamide is a synthetic antineoplastic drug chemically related to the nitrogen mustards.

The drug product capsules are an immediate release formulation and the capsules are formulated in two different strengths: 25 mg and 50 mg. Cyclophosphamide Capsule, 25 mg, is described as a blue/blue opaque capsule with "54 006" printed in black ink on the capsule body, containing a white to off-white powder. Cyclophosphamide Capsule, 50 mg, is described as blue/blue opaque capsule with "54 881" printed in black ink on the capsule body, containing a white to off-white powder. They are packaged in HDPE bottles. The inactive ingredients are USP/NF materials, Pregelatinized Starch, NF, and Sodium Steryl Fumarate, NF, and (b) (4)

CMC related quality reviews:

- Facilities review/inspection
  An Establishment Evaluation Request (EER) was submitted to the Office of Compliance and an overall acceptable recommendation was issued for the application on July 25, 2013.

ONDQA Biopharm reviewer, Dr. Z. Dong has granted in-vivo bioequivalence (BE) request and recommended approval for this NDA from the Biopharmaceutics perspective. The request for a BE waiver is submitted with respect to a human bioequivalence study to support the bridge in formulation from a tablet to a capsule. The biowaiver is based on the data submitted in IND 112,446 to support the approval of a BCS-Class 1 classification for cyclophosphamide. ONDQA

Biopharmaceutical Review dated August 20, 2013, reported that "with respect to the resubmission of the NDA 203-856 for Cyclophosphamide Capsules, approval is recommended in this review cycle from the Biopharmaceutics perspective".

- Microbiology is not applicable for the proposed drug product dosage form.

As indicated above, the resubmission/responses to the CR letter which were mainly CMC issues which were reviewed and evaluated by the CMC reviewer, Josephine Jee, who concluded in her review dated September 04, 2013 that the CMC response are adequate and the NDA is recommended for approval.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology reviewer, Dr. Ching-Jey Chang, concluded in first review cycle dated April 26, 2013 that there are no outstanding issues that would preclude approval of this NDA from a Pharmacology/Toxicology perspective and therefore, the nonclinical discipline recommends approval of the NDA.
Memo dated August 23, 2013 reported that 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 and recommended approval.

5. Clinical Pharmacology

The clinical pharmacology reviewer, Sarah J Schrieber, reported in her review dated August 28, 2913 that "a biowaiver was requested by the sponsor for Cyclophosphamide capsules under IND 112446 on March 03, 2012 based on the Biopharmaceutics Classification System (BCS). Permeability of cyclophosphamide was evaluated using an *in vitro* monolayer model. Based on the data submitted, the clinical pharmacology reviewer concluded that cyclophosphamide is a highly permeable drug". There are no Clinical Pharmacology deficiencies that preclude an approval recommendation for this NDA.
Review dated August 26, 2013, reported that "the clinical pharmacology review was completed during the first review cycle with no pending issues (Sarah Schrieber reviewer). With respect to the resubmission of the NDA 203-856 for Cyclophosphamide Capsules, approval is recommended in this review cycle from the clinical pharmacology perspective".

6. Microbiology

Not Applicable

7. Clinical/Efficacy

No new clinical data were provided for this submission.

8. Safety

No new clinical data were provided for this submission.

8. Postmarket Experience

Not Applicable

9. Advisory Committee Meeting

This product was not discussed at an Advisory Committee meeting.

10. Pediatrics

Not Applicable

11. Other Relevant Regulatory Issues

- Application Integrity Policy (AIP): This was not raised during the pre-approval inspections for this NDA.

- The primary stability batches submitted were manufactured at the proposed commercial manufacturing located at (b) (4). Additional batches were also manufactured new commercial facility located at 1809 Wilson Road, Columbus, Ohio. Office of Compliance issued an overall acceptable recommendation for all sites associated with this NDA.
- Exclusivity or patent issues of concern: No issues were noted for this NDA.
- Financial disclosures: Not applicable
- Other GCP issues: None
- DSI audits: Not applicable
- Other discipline consults: None
- Any other outstanding regulatory issues: None

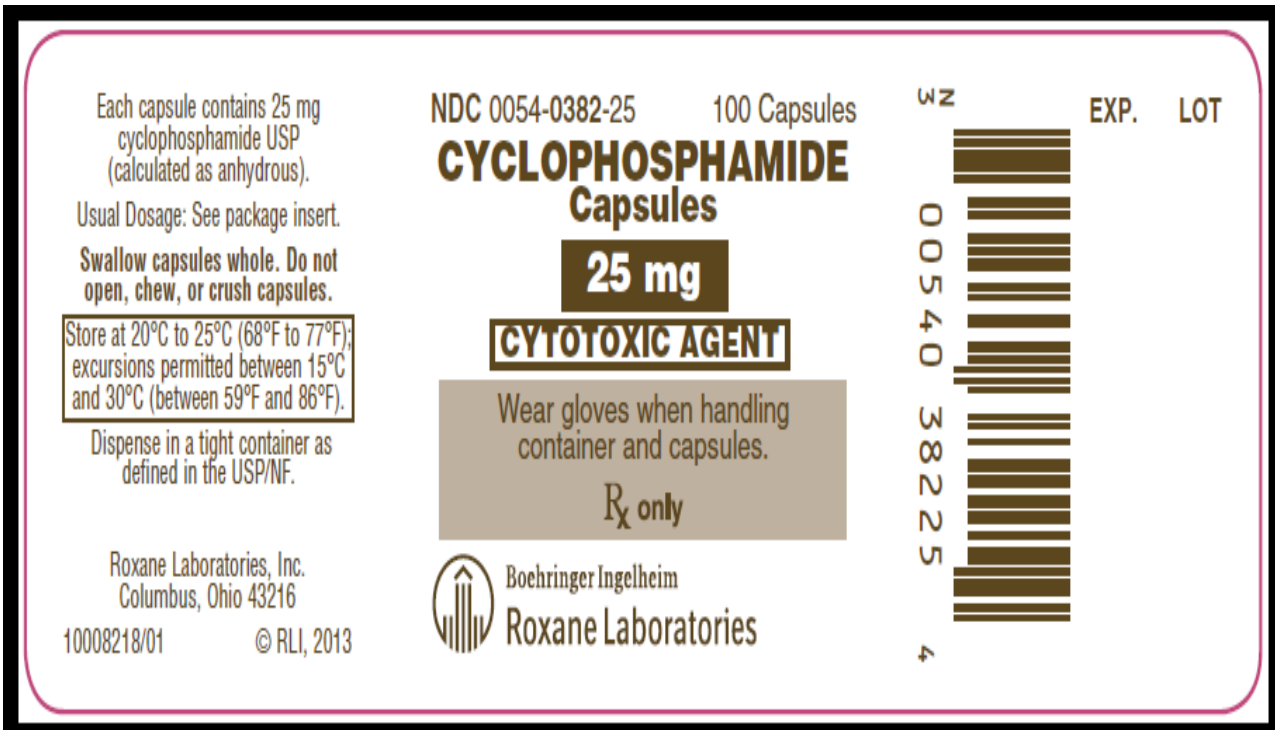
12. Labeling

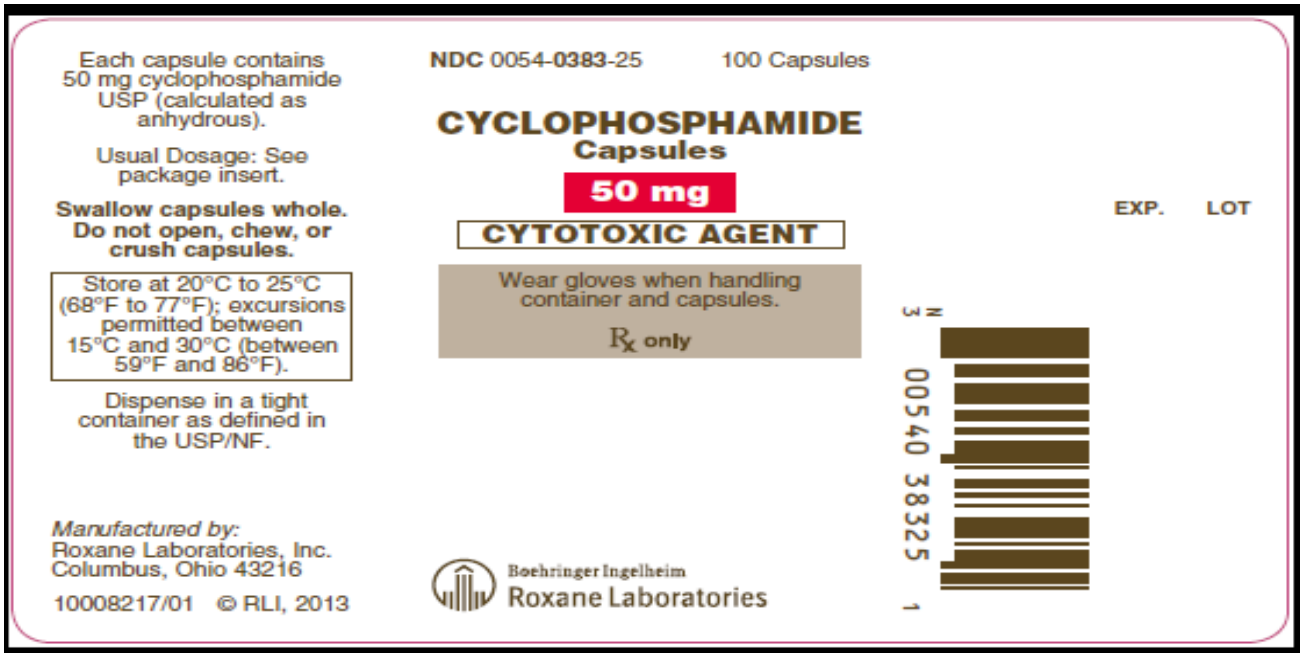
General:

Proprietary name:
There was no proprietary name proposed for this product.

DMEPA review dated September 05, 2013, by Jibril Abds-Samad, reported that "DMEPA previously reviewed Cyclophosphamide Capsules in OSE Reviews 2012-2531 and 2013-1745, and we looked at the reviews to ensure all our recommendations were implemented. All the revisions to the labels and labeling were implemented". The reviewer concluded that DMEPA finds all Applicant's revisions to the container labels and insert labeling are acceptable.

Copies of the package labels for the 25 mg and 50 mg tablets are provided below.





Patient labeling/Medication guide:
This is not required for this product.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

- Risk Benefit Assessment
  The review of this NDA is based primarily on chemistry, manufacturing and controls data.

- Recommendation for Postmarketing Risk Management Activities
  This does not apply to this NDA.

- Recommendation for other Postmarketing Study Commitments
  None

- Recommended Comments to Applicant
  None

Overall Conclusion
The NDA is recommended for approval.

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Office of New Drug Quality Assessment

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/s/

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09/06/2013