CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203856Orig1s000

MEDICAL REVIEW(S)
Clinical Summary
Division of Oncology Products

<table>
<thead>
<tr>
<th>Date</th>
<th>9/13/13</th>
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</thead>
<tbody>
<tr>
<td>Reviewer</td>
<td>Gwynn Ison, MD</td>
</tr>
<tr>
<td>Team Leader</td>
<td>Patricia Cortazar, MD</td>
</tr>
<tr>
<td>NDA/BLA#</td>
<td>203856</td>
</tr>
<tr>
<td>Applicant Name</td>
<td>Roxane Laboratories</td>
</tr>
<tr>
<td>Date of Submission</td>
<td>July 17, 2013</td>
</tr>
<tr>
<td>PDUFA Date</td>
<td>September 17, 2013</td>
</tr>
<tr>
<td>Propietary Name/ Established (USAN) Name</td>
<td>None/Cyclophosphamide</td>
</tr>
<tr>
<td>Dosage Forms/ Strength</td>
<td>Capsule</td>
</tr>
<tr>
<td>Proposed Indication</td>
<td>Cyclophosphamide drug product is an alkylating agent indicated for treatment of malignant diseases such as certain types of lymphomas and leukemias, neuroblastoma and carcinoma of the breast</td>
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Action
Approval

Summary
NDA 203856 is a 505(b)(2) referencing Cytoxan® NDA 012141 tablets 25 mg and 50 mg. The reference drug product for this application is Cytoxan (cyclophosphamide) Tablets (NDA 012141), originally approved on 11/16/59. The NDA Sponsor, Baxter, no longer markets the tablets. The applicant for the current NDA, Roxane, markets cyclophosphamide tablets (25mg and 50 mg) under ANDA 040032.

NDA 203856 was originally submitted 12/21/11 with insufficient drug product stability data (6 month), and the Applicant was issued a Refusal to File Letter (RTF) on 2/17/12 by FDA. The NDA was resubmitted on 7/3/12 with 12 months of stability data. During that review cycle, there were outstanding CMC issues related to dissolution and impurities. As a result, a Complete Response (CR Letter) was issued on 5/3/13.

The Applicant then re-submitted the NDA on 7/17/13, with the requested CMC information, including 2 new batches with appropriate stability data. Therefore, this is the 3rd review cycle for this application. During this review cycle, the submitted CMC information was reviewed and found to be acceptable by the CMC reviewer, Josephine Jee (review dated 9/4/13). Therefore, the review team is recommending approval of the current NDA, with 24 months of expiry dated for the drug product.

No new clinical data were provided with this submission, as no clinical studies were done for this 505(b)(2) application.

Labeling
DMEPA reviewed the submitted label (review dated 9/5/13 by Jibril Abd-Samad). According to the review, the Applicant implemented all revisions recommended by FDA,
and it was concluded that the revisions to the container labels and package insert are acceptable.

**Recommendation**
The review team is recommending approval of the current NDA submission. The review team has agreed to labeling.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GWYNN ISON
09/16/2013

PATRICIA CORTAZAR
09/16/2013
## Summary Review for Regulatory Action

<table>
<thead>
<tr>
<th>Date</th>
<th>5/3/2013</th>
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<tr>
<td>From</td>
<td>Anna Ibrahim MD</td>
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<tr>
<td>Subject</td>
<td>Division Director Summary Review</td>
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<tr>
<td>NDA/BLA #</td>
<td>203856</td>
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<tr>
<td>Applicant Name</td>
<td>Roxane Laboratories</td>
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<td>07/03/2012</td>
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<td>PDUFA Goal Date</td>
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<td>Proprietary Name / Established (USAN) Name</td>
<td>None/ Cyclophosphamide</td>
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<tr>
<td>Dosage Forms / Strength</td>
<td>Capsule/ 25 mg and 50 mg</td>
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<tr>
<td>Proposed Indication(s)</td>
<td>Cyclophosphamide 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 and is often used in combination with other neoplastic drugs. It is also indicated for carefully selected cases of biopsy proven “minimal change” nephrotic syndrome in children.</td>
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<td>Action/Recommended Action for NME:</td>
<td>Complete Response</td>
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### Material Reviewed/Consulted

<table>
<thead>
<tr>
<th>Material Reviewed/Consulted</th>
<th>Names of discipline reviewers</th>
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<tbody>
<tr>
<td>OND Action Package, including:</td>
<td>George Chang</td>
</tr>
<tr>
<td>Pharmacology Toxicology Review</td>
<td>Josephine Jee/ Zedong Dong</td>
</tr>
<tr>
<td>CMC Review/OBP Review</td>
<td>Ali Al-HAkim</td>
</tr>
<tr>
<td>CDTL Review</td>
<td>Jibril Abdus-Samadi</td>
</tr>
</tbody>
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OND=Office of New Drugs
DMEPA=Division of Medication Error Prevention and Analysis
CDTL=Cross-Discipline Team Leader
1. Introduction
This is the second cycle submission for a 505b2 NDA for cyclophosphamide by Roxane Laboratories. The applicant references the “original Cytoxan tablets NDA” in the cover letter made by Bristol-Myers Squibb. CMC information has been submitted in support of this NDA. This NDA received a “Refuse-to-File” action on 2/17/2012 in the initial cycle because of insufficient stability data.

2. Background
Per CDTL Dr Al-Hakim, “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.” The action on this NDA will be a Complete Response due to insufficient stability data.

3. CMC/Device
CMC reviewer, Josephine Jee stated in her review that “The recommendation for the application is Complete Response (CR) from a Chemistry, Manufacturing, and Controls (CMC) perspective until the following issues are addressed adequately:

- Acceptable stability results for Dissolution and Largest Unspecified Degradant that meet the proposed drug product specification for Lots 4000591 (25 mg) and Lot 4000592 (50 mg). The Applicant has committed to provide justifications and corrective measures for out of specification (OOS) results of Dissolution and degradants at the end of April 2013, as per their 25-MAR-2013 Communication.

- Revise the storage statements as they appeared in the containers and package insert labeling to “Store at 20°C - 25°C (68°F to 77°F). [See USP controlled room temperature].” Remove the statement (b)(4)

In the review amendment dated 4/30/2013, Josephine Jee states that “The above submission did not adequately address the CMC outstanding issues discussed with the sponsor on 25-MAR-2013. These issues are related to one NDA batch that did not pass the proposed specifications. Therefore, the CMC conclusion remains the same (NDA is not recommended for approval).”

Zedong Dong PhD stated that “From the Biopharmaceutics perspective, NDA 203-856 for Cyclophosphamide Capsules is recommended for approval.” He also stated that under IND
112,446 the BCS Committee at CDER/FDA approved the BCS Class-1 classification for cyclophosphamide capsules. Also the request for a BCS-based biowaiver for cyclophosphamide capsules (25 mg and 50 mg) in reference to cyclophosphamide tablets (25 mg and 50 mg) was granted.

CDTL Ali Al-Hakim PhD states that “The reported stability results of one lot of 25 mg and one lot of 50 mg capsules 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. However, 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”.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable.

4. Nonclinical Pharmacology/Toxicology

Per the non clinical reviewer C J George Change DVM, MS, PhD, DABT, “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 in the drug product and the drug product degradant specifications. These responses were deemed acceptable from a Pharmacology/ Toxicology perspective.” There were no outstanding issues that would preclude approval of this NDA from a Pharmacology/Toxicology perspective. The nonclinical discipline recommends approval of NDA 203856.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Sarah J. Schrieber, Pharm.D. in her review stated that a biowaiver was requested by the sponsor for Cyclophosphamid capsules under IND 112446 on 3/12/12 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. The biowaiver was granted (see Dr Dong’s review).

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.
6. Clinical Microbiology
Not applicable

7. Clinical/Statistical-Efficacy
No data was submitted. Not applicable

8. Safety
Not applicable

9. Advisory Committee Meeting
Not applicable

10. Pediatrics
Not applicable

11. Other Relevant Regulatory Issues
Includes but is not limited to:
- DSI Audits: none
- Financial Disclosure: Not applicable
- Other consults- a consult was requested from DMEPA. Due to the CR action, the label has not been finalized

There are no other unresolved relevant regulatory issues

12. Labeling
Due to the CR action, the label has not been finalized.

13. Decision/Action/Risk Benefit Assessment
- Regulatory Action: A Complete Response action will be taken.
• Risk Benefit Assessment. The applicant has not submitted sufficient stability data. As the CDTL stated “The NDA can not be approved from the CMC perspective, at this time, because of the outstanding CMC issues…”

• Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies: Not applicable

• Recommendation for other Postmarketing Requirements and Commitments Not applicable

Amna Ibrahim MD
Deputy Division Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
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/s/

AMNA IBRAHIM
05/03/2013
### Cross-Discipline Team Leader Review

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<tr>
<th>Date</th>
<th>April 30, 2013</th>
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<tbody>
<tr>
<td>From</td>
<td>Ali Al-Hakim, Ph.D.</td>
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<tr>
<td>Subject</td>
<td>Cross-Discipline Team Leader Review</td>
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<tr>
<td>NDA #</td>
<td>203856</td>
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<tr>
<td>Applicant</td>
<td>Roxane Laboratories</td>
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<tr>
<td>Date of Submission</td>
<td>December 21, 2011</td>
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<td>PDUFA Goal Date</td>
<td>May 03, 2013</td>
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<td>Proprietary Name/ Established Name</td>
<td>N/A Cyclophosphamide</td>
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<td>Dosage forms/ Strength</td>
<td>Immediate release capsules 25mg and 50mg</td>
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<tr>
<td>Proposed Indication(s)</td>
<td>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.</td>
</tr>
<tr>
<td>Recommended</td>
<td>Complete Response</td>
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1. **Introduction**

   NDA 203856 was originally submitted on December 21, 2012 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 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. However, 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.

   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\(^{(0)(4)}\). The justification includes exposure protection to end-users, the development of a more stable product and the closing of the tablets’ current manufacturing site.

2. **Background**

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: 

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 Structure of Cyclophosphamide](attachment:chemical_structure.png)

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 [Redacted]. 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

The chemistry reviewer, Ms. Josephine Jee, reported in her review dated April 02, 2013 that “The reported stability results of one lot of 25 mg and one lot of 50 mg capsules did not meet acceptance criteria for dissolution and degradation products (unspecified degradation products) testing. Based on the preliminary studies, BIRLI stated on 25-MAR-2013 that these results were observed in only two batches out of a total of six batches tested and the root cause appears to be the lot of API used. Further results to address this deficiency will be provided as an amendment to the NDA at the end of April 2013. Regarding expiry dating, this issue is pending result of the above study and subsequent NDA amendment. The sponsor submitted amendment to the NDA on April 29, 2013. However, the submission did not adequately address the CMC outstanding issues discussed with the sponsor on 25-MAR-2013. These issues are related to one NDA registration batch that did not pass the proposed specifications.

This is the basis for the recommended Complete Response Action for this NDA from a CMC perspective.

CMC related quality reviews:

- Facilities review/inspection
An Establishment Evaluation Request (EER) was submitted to the Office of Compliance on January 26, 2012. An overall acceptable recommendation was issued for the application on January 08, 2013.

- ONDQA Biopharm reviewer, Dr. Z. Dong has granted in-vivo bioequivalence (BE) request and recommended approval for this NDA from the Biopharmaceuticals 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.

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

4. **Nonclinical Pharmacology/Toxicology**

The Pharmacology/Toxicology reviewer, Dr. Ching-Jey Chang, concluded in his review 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.

5. **Clinical Pharmacology**

The reviewer of the clinical pharmacology section of the NDA, Dr. Qi Liu, reported that “a biowaiver was requested by the sponsor for Cyclophosphamide capsules under IND 112446 on 3/12/12 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.

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 330 Oak Street, Columbus, Ohio. The sponsor proposed to close this site and move to the new commercial facility located at 1809 Wilson Road, Columbus, Ohio. The Agency did not agree to have 1809 Wilson Road facility submitted in this current NDA submission, since the registration batches were manufactured at 330 Oak Street facility (communications dated November 08, 2012). However, the sponsor proposed to remove 1809 Wilson Road facility from the current NDA submission and proposed to submit a CBE-30 Supplemental NDA for the 1809 Wilson Road facility; however, the acceptability of the CBE-30 will be recommended by the Post-Marketing Branch.

- Exclusivity or patent issues of concern: No issues were noted for this NDA.

12. Labeling

General:
Planned labeling meetings for this NDA are scheduled for June 4, 10 and 26, 2013.

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

DMEPA comments to the applicant
DMEPA (Dr. Jibril Abdus-Samad) recommends the following comments be implemented by the applicant regarding the Container Labels, 25 mg and 50 mg:
1. Delete the following statement from the left side panel.

2. Revise the statement, Usual Dosage: See package insert for complete prescribing information, to read as follows:
Usual Dosage: See package insert.
This will create space for additional information to appear on the left side panel.

3. Relocate the statement, Each capsules contains xx mg cyclophosphamide Carton and immediate container labels:
DMEPA reported that the above proposed container closure revisions can improve the safe use of the drug product.

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

See above section titled “DMEPA” comments.
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 can not be approved from the CMC perspective, at this time, because of the outstanding CMC issues described in the CMC section above. Therefore, a Complete Response action is recommended.

Ali Al-Hakim, Ph.D.
Branch II Chief, Division I
Office of New Drug Quality Assessment
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/s/

ALI H AL HAKIM
04/30/2013