CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
0200199Orig1s000

CHEMISTRY REVIEW(S)
NDA 200-199

Topotecan Injection

Sandoz, Inc.

Debasis Ghosh, M. Pharm., Ph.D.

Review Chemist

Office of New Drug Quality Assessment
Division I Branch II

CMC REVIEW OF NDA 200199
For the Division of Drug Oncology Products (HFD-150)
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CMC Review Data Sheet

1. NDA  200199

2. REVIEW #: 1

3. REVIEW COMPLETION DATE:  10-Feb-2011

4. REVIEWER: Debasis Ghosh, M. Pharm., Ph.D.

5. PREVIOUS DOCUMENTS:

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6. SUBMISSION(S) BEING REVIEWED:

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<td>Amendment 0001 (labeling)</td>
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<td>Amendment 0002 (CMC)</td>
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<td>Amendment 0003 (labeling)</td>
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<td>Amendment 0004 (labeling)</td>
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<td>Amendment 0005 (EA)</td>
<td>20-May-2010</td>
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<td>Amendment 0006 (CMC)</td>
<td>29-Jul-2010</td>
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<td>Amendment 0008 (CMC, labeling)</td>
<td>20-Sep-2010</td>
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<td>Amendment 0011 (CMC)</td>
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<tr>
<td>Amendment 0012 (labeling)</td>
<td>01-Oct-2010</td>
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<td>Amendment 0018 (CMC)</td>
<td>10-Feb-2011</td>
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7. NAME & ADDRESS OF APPLICANT:

Name: Sandoz, Inc
Address: 506 Carnegie Center
        Suite 400
        Princeton, NJ 08540
        USA
Representative: Bernadette Attinger, Director, Regulatory Affairs
        777 Township Line Road
        Suite 180
        Yardley, PA 19067
Telephone: 267-291-1225

8. DRUG PRODUCT NAME/CODE/TYPE:

   a) Proprietary Name: N/A
   b) Non-Proprietary Name: Topotecan Injection
   c) Code Name/# (ONDQA only): N/A
   d) Chem. Type/Submission Priority (ONDQA only):
      - Chem. Type: 5 (new formulation)
      - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2);
   - The Reference Listed Drug (RLD) is Hycamtin (topotecan hydrochloride)
     for Injection - NDA 20671 was approved on 28-May-2006.
   - GlaxoSmithKline’s Hycamtin is supplied as a sterile lyophilized powder.
     Each vial contains topotecan hydrochloride equivalent to 4 mg of topotecan
     base. Upon reconstitution with 4 mL of diluent, the concentration of
     reconstituted solution is 1 mg/mL.
   - Each vial of the proposed Topotecan Injection contains topotecan
     hydrochloride equivalent to 1 mg, 3 mg, and 4 mg of topotecan base in
     1 mL, 3 mL, and 4 mL of solution, respectively. The concentration of each of
     the reconstituted solution is 1 mg/mL.

10. PHARMACOL. CATEGORY: Anticancer

11. DOSAGE FORM: Injectable solution

12. STRENGTH/POTENCY: 1 mg/mL (1 mg/1 mL, 3 mg/3 mL, 4 mg/4 mL)
    [The product strength is based on the equivalent amount of topotecan free
     base]
13. ROUTE OF ADMINISTRATION: Intravenous Injection

14. Rx/OTC DISPENSED: √Rx       ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

     ______SPOTS product – Form Completed

     √Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

   Chemical Name:
   (S)-10-[(Dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3’,4’:6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione hydrochloride

   Structure:
   Chemical Structure for topotecan hydrochloride is reproduced from the submission (Original Submission and Amendment 006, 29-Jul-2010)

   ![Chemical Structure](image)

   Drug Substance obtained from
   Where x =

   Molecular Formula (monohydrochloride salt): C_{23}H_{23}N_{3}O_{5}.HCl
   Molecular Weight (monohydrochloride salt):
   Molecular Weight (free base): 421.45
   CAS Number: 119413-54-6

   Drug Substance obtained from
   Where x =

   Molecular Formula: C_{23}H_{23}N_{3}O_{5}
Molecular Weight
Molecular Weight (free base): 421.45
CAS Number: 1228035-86-6
17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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<th>CODE</th>
<th>STATUS</th>
<th>DATE REVIEW COMPLETED/POSTED IN DARRTS</th>
<th>COMMENTS</th>
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<td>Item 1</td>
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<td>Item 2</td>
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Note: Due to the

1 Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

2 Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

<table>
<thead>
<tr>
<th>DOCUMENT</th>
<th>APPLICATION NUMBER</th>
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<tr>
<td>NDA</td>
<td>20671</td>
<td>Hycam tin for Injection (RLD)</td>
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<tr>
<td>NDA</td>
<td>20981</td>
<td>Hycam tin Capsules</td>
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18. STATUS:

ONDQA:

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<th>REVIEWER</th>
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<td>Biometrics</td>
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<td>EES</td>
<td>“Overall Acceptable”</td>
<td>18-Jun-2010</td>
<td>Office of Compliance</td>
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<td>Pharm/Tox</td>
<td>N/A</td>
<td>N/A</td>
<td>Dave McGuinn</td>
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<td>Biopharm</td>
<td>“The Biowaiver request can be granted.”</td>
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<td>John Z Duan</td>
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<td>LNC</td>
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<td>Methods Validation</td>
<td>N/A, according to the current ONDQA policy</td>
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<td>DMEPA*</td>
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<td>09-Dec-2010</td>
<td>Irene Z Chan</td>
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<td>“No Significant Impact (FONSI) is recommended.”</td>
<td>20-Sep-2010</td>
<td>Emily A. McVey</td>
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<td>Microbiology</td>
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<td>Steven Fong</td>
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*DMEPA: Division of Medication Error Prevention and Analysis
The CMC Review for NDA 200199

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the perspective of Chemistry, Manufacturing and Controls (CMC), this NDA is recommended for approval.

Based on drug product stability data, 18 months expiration dating period is granted for drug product when stored at 2°C to 8°C (36°F to 46°F) protected from light.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

Drug substance, topotecan hydrochloride, is a . The proposed drug substance (topotecan hydrochloride) is received from . It should be noted that the reference listed drug (RLD), .

The applicant referenced drug substance information in DMF and DMF Letters of Authorization to review the information contained in the DMF and DMF were provided.

The physical description, melting range, pKa, and solubility of drug substances obtained from and are comparable. Topotecan has one chiral center and it originates from the starting material, . The manufacturing process of drug substance does not alter the chirality of the molecule.

of topotecan hydrochloride exhibits at least 11 polymorphs and produced polymorph only with per molecule. Lab consistently produced one polymorphic form which is a .
the proposed drug product, a sterile solution, has no effect on the ratio of hydrochloride, particle size or hygroscopicity of drug substance. It should be noted that all polymorphic forms are soluble in water and the drug substance solution is stable at refrigeration temperature. The reconstituted RLD formulation and the proposed drug product solution formulation are similar or equivalent.

DMF and DMF are adequate to support NDA 200199. All three strengths (1mg/1 mL, 3 mg/3 mL, 4mg/4 mL) of drug products were prepared from bulk solution of drug substance obtained from each vendor.

(2) Drug Product

Drug product, Topotecan Injection, is a clear yellow to yellow-green sterile aqueous solution. It is supplied as a solution in a clear Type I glass vial with grey rubber closure and aluminum seal with plastic flip-off top. Each mL contains topotecan hydrochloride equivalent to 1.0 mg topotecan base, 5 mg tartaric acid NF, sodium hydroxide and hydrochloric acid for pH adjustment, and water for injection, USP. It has a pH of 2.0-2.5 and Drug product is intended to be diluted with appropriate volume of a suitable intravenous solution prior to the administration.

Topotecan Injection is a solution but Hycamtin (RLD) is a lyophilized powder. Each vial of Hycamtin contains topotecan hydrochloride equivalent to 4 mg of topotecan free base, mannitol, and tartaric acid. Each mL of Topotecan injection (4 mg/4 mL, 3mg/3 mL, 1 mg/1 mL) contains 1 mg of topotecan free base which is exactly the same as the reconstituted solution of Hycamtin.

The proposed drug product is manufactured using the following steps:

Since the drug substance is photosensitive, hygroscopic and cytotoxic, special handling measures are in place to address the degradation due to light, moisture, and oxygen and to reduce the exposure to manufacturing personnel during the preparation of drug product.

Based on the stability data provided, 18 months expiration dating period is granted for drug product when stored at 2°C-8°C (36°F-46°F) protected from light.
Executive Summary Section

B. Description of How the Drug Product is Intended to be Used
Drug product, Topotecan Injection, is proposed for the treatment of Small cell lung cancer and Cervical Cancer. The drug product is intended for dilution with 0.9% sodium chloride injection, USP, or 5% dextrose injection, USP prior to intravenous infusion. The recommended dose for Small cell lung cancer is 1.5 mg/m² by intravenous infusion over 30 minutes daily for 5 consecutive days, starting on day one of 21-day course. The recommended dose for Cervical cancer is 0.75 mg/m² by intravenous infusion over 30 minutes on days, 1,2, and 3 followed by cisplastin 50 mg/m² by intravenous infusion on day 1 repeated every 21 days.

C. Basis for Approvability or Not-Approval Recommendation

• The CMC information of the drug substance is provided in DMF and DMF. Based on a review by Anne Marie Russell of ONDQA on 05-Nov-2010 in support of a similar product (NDA), DMF was found to be adequate. Resolved

• The NDA received an overall ‘acceptable’ recommendation from the Office of Compliance (see EES Report Summary in Sec IIC). Resolved

• Environmental Assessment recommendation is FONSI (no significant impact). Resolved

• Labeling issues are pending. Resolved

III. Administrative
A. Reviewer’s Signature:
(See appended electronic signature page)
Debasis Ghosh, M. Pharm., Ph.D., Reviewer, ONDQA

B. Endorsement Block:
(See appended electronic signature page)
Sarah Pope Miksinski, Ph.D., Branch Chief, Div 1, Branch II, ONDQA

C. CC Block: entered electronically in DARRTS

92 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DEBASIS GHOSH
02/14/2011

SARAH P MIKSINSKI
02/14/2011
## ONDQA BIOPHARMACEUTICS REVIEW

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<td>1/27/10</td>
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<tr>
<td>Drug Name:</td>
<td>Topotecan HCl Injection</td>
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<td>Formulation:</td>
<td>Injection</td>
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<td>Strength:</td>
<td>1 mg/1mL, 3 mg/3mL and 4 mg/4mL</td>
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<td>Sponsor:</td>
<td>Sandoz</td>
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<td>Reviewer:</td>
<td>John Duan, Ph.D.</td>
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<tr>
<td>Submission Type:</td>
<td>Biowaiver Request</td>
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The current submission is a 505(b)(2) application for topotecan injection. The proposed drug product contains the same active ingredient as the reference listed drug (RLD) HYCAMTIN (topotecan hydrochloride for injection) but differs in excipients.

## COMMENTS

(b)(4)

## RECOMMENDATION

The biowaiver request can be granted.

---

John Duan, Ph.D.  
Reviewer  
ONDQA Biopharmaceutics  

---

Patrick Marroum, Ph.D.  
ONDQA Biopharmaceutics  

---

cc: NDA 200-199  
Patrick Marroum, Angelica Dorantes, John Duan
APPENDIX.

Comparison of the Proposed Drug and Reference Listed Drug

The conditions of use prescribed, recommended, or suggested in the labeling proposed for the drug product have been previously approved for the reference listed drug. The proposed drug product contains the same active ingredient as the reference listed drug (RLD) HYCAMTIN (topotecan hydrochloride for injection) but differs in excipients.

The proposed Sandoz product is a ready to use product whereas the RLD is a lyophilized product. The addition of water for injection, USP as a solvent is necessary in a ready to use product.

The reference listed drug and Sandoz’s proposed drug product are both formulated to 1 mg/mL of topotecan. The RLD is provided as a 4 mg/4mL product after reconstitution. The proposed Sandoz product is supplied as a 1 mg/mL ready to use product in 1 mg/1mL, 3 mg/3mL and 4 mg/4mL presentations.

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<td>Water for Injection</td>
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<td>Tartaric Acid</td>
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The biowaver request

The applicant requested a biowaver. The biowaver is recommended to be granted based on the following considerations.

1. (b) (4) which may not affect the bioavailability.

2. The proposed product is a parenteral solution intended solely for administration by injection and therefore its in vivo bioavailability can be considered self-evident.
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<td>ORIG-1</td>
<td>SANDOZ INC</td>
<td>TOPOTECAN HYDROCHLORIDE INJECTION</td>
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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.

/s/

JOHN Z DUAN
06/01/2010

PATRICK J MARROUM
06/01/2010