

**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

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1. NDA 200199
2. REVIEW #: 1
3. REVIEW COMPLETION DATE: 10-Feb-2011
4. REVIEWER: Debasis Ghosh, M. Pharm., Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Original IND (b) (4)

Document Date

06-Mar-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original NDA Submission
Amendment 0001 (labeling)
Amendment 0002 (CMC)
Amendment 0003 (labeling)
Amendment 0004 (labeling)
Amendment 0005 (EA)
Amendment 0006 (CMC)
Amendment 0008 (CMC, labeling)
Amendment 0010 (CMC)
Amendment 0011 (CMC)
Amendment 0012 (labeling)
Amendment 0013 (CMC)
Amendment 0014 (labeling)
Amendment 0015 (labeling)
Amendment 0016 (labeling)
Amendment 0017 (labeling)
Amendment 0018 (CMC)

Document Date

27-Jan-2010
12-Mar-2010
25-Mar-2010
26-Mar-2010
16-Apr-2010
20-May-2010
29-Jul-2010
20-Sep-2010
22-Sep-2010
30-Sep-2010
01-Oct-2010
05-Oct-2010
30-Nov-2010
19-Jan-2011
07-Feb-2011
08-Feb-2011
10-Feb-2011

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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]

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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

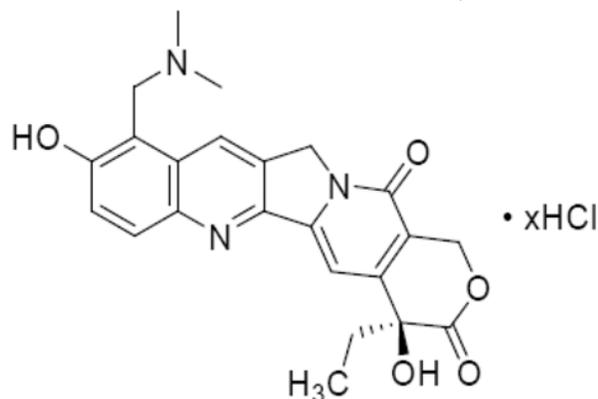
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name:

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

Structure:

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



Drug Substance obtained from (b) (4)

Where x = (b) (4)

Molecular Formula (monohydrochloride salt): C₂₃H₂₃N₃O₅.HCl

Molecular Weight (monohydrochloride salt): (b) (4)

Molecular Weight (free base): 421.45

CAS Number: 119413-54-6

Drug Substance obtained from (b) (4)

Where x = (b) (4)

Molecular Formula (b) (4)

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Molecular Weight [REDACTED] (b) (4)

Molecular Weight (free base): 421.45

CAS Number: 1228035-86-6

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17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER & Date of LOA	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED/ POSTED IN DARRTS	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	05-Nov-2010	Reviewer: Ann Marie Russell
	II			1	Adequate	07-Oct-2010	Reviewer: Debasis Ghosh
	III			1,4	Adequate	09-Apr-2009	Reviewer: Stevens Donald Reviewed: (b) (4)
	III			4	Adequate	NA	See review P.7
	III			4	Adequate	NA	See review Sec P.7

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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20671	Hycamtin for Injection (RLD)
NDA	20981	Hycamtin Capsules

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	“Overall Acceptable”	18-Jun-2010	Office of Compliance
Pharm/Tox	N/A	N/A	Dave McGuinn
Biopharm	“The Biowaiver request can be granted.”	01-Jun-2010	John Z Duan
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA*	Pending	09-Dec-2010	Irene Z Chan
EA	“No Significant Impact (FONSI) is recommended.”	20-Sep-2010	Emily A. McVey
Microbiology	‘Approve’	18-Oct-2010	Steven Fong

*DMEPA: Division of Medication Error Prevention and Analysis

Executive Summary Section

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 (b) (4)

The proposed drug substance (topotecan hydrochloride) is received from (b) (4)

It should be noted that the reference listed drug (RLD), (b) (4)

The applicant referenced drug substance information in DMF (b) (4) and DMF (b) (4) Letters of Authorization to review the information contained in the DMF (b) (4) and DMF (b) (4) were provided.

The physical description, melting range, pKa, and solubility of drug substances obtained from (b) (4) and (b) (4) are comparable. Topotecan has one chiral center and it originates from the starting material, (b) (4). The manufacturing process of drug substance does not alter the chirality of the molecule.

(b) (4) of topotecan hydrochloride exhibits at least 11 polymorphs (b) (4) and (b) (4) produced polymorph (b) (4) only with (b) (4) per molecule. (b) (4) lab consistently produced one polymorphic form which is a (b) (4)

Executive Summary Section

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

(b) (4) 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 (b) (4) is stable at refrigeration temperature. The reconstituted RLD formulation and the proposed drug product solution formulation are similar or equivalent.

DMF (b) (4) and DMF (b) (4) 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 (b) (4) 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 (b) (4). 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 (b) (4)

The proposed drug product is manufactured using the following steps: (b) (4)

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 cisplatin 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 (b) (4) and DMF (b) (4). Based on a review by Anne Marie Russell of ONDQA on 05-Nov-2010 in support of a similar product (NDA (b) (4)), DMF (b) (4) 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

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/s/

DEBASIS GHOSH
02/14/2011

SARAH P MIKSINSKI
02/14/2011

ONDQA BIOPHARMACEUTICS REVIEW

IND#: 200-199
Submission Date: 1/27/10
Drug Name: Topotecan HCl Injection
Formulation: Injection
Strength: 1 mg/1mL, 3 mg/3mL and 4 mg/4mL
Sponsor: Sandoz
Reviewer: John Duan, Ph.D.
Submission Type: Biowaiver Request

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

Date

Patrick Marroum, Ph.D.
ONDQA Biopharmaceutics

Date

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. (b) (4)

[Redacted]

The proposed Sandoz product is a ready to use product whereas the RLD is a lyophilized product. (b) (4)

[Redacted] 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.

Active Ingredient	Topotecan Hydrochloride	Topotecan Hydrochloride
Inactive Ingredients	Mannitol	Water for Injection
	Tartaric Acid	Tartaric Acid
	Hydrochloric acid	Hydrochloric acid
	Sodium Hydroxide	Sodium Hydroxide
Route of Administration	Intravenous	Intravenous
Dosage Form	Injectable	Injectable
Strengths	4mg Base/Vial (reconstituted 4mg/4mL)	1mg/mL (1mg/1mL, 3mg/3mL and 4mg/4mL)

The biowaiver request

The applicant requested a biowaiver. The biowaiver 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.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200199	ORIG-1	SANDOZ INC	TOPOTECAN HYDROCHLORIDE INJECTION

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/s/

JOHN Z DUAN
06/01/2010

PATRICK J MARROUM
06/01/2010