CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200582Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW

Office of New Drugs Quality Assessment

Application No.:	NDA 200-582	**Reviewer:** Angelica Dorantes, Ph.D	
Submission Date:	December 2, 2010	**Supervisor:** Patrick J. Marroum, Ph.D	
Division:	Division of Oncology Drug Products	**Date Assigned:**	December 13, 2010
Sponsor:	Hospira, Inc.	**Date of Review:**	January 26, 2010
Trade Name:	Topotecan Injection 4 mg/4 ml	**Type of Submission:** Class 1 Resubmission to Complete Response Letter dated November 26, 2010	
Generic Name:	Topotecan Injection		
Indication:	Topotecan injection is a topoisomerase I inhibitor indicated for the treatment of small cell lung cancer sensitive disease after failure of first line chemotherapy.		
Formulation/strengths	4 mg/4 mL (1 mg/mL) single-dose vial		
Route of Administration	Intravenous		

SUBMISSION:

The Class 1 Resubmission for NDA 200-582 for Topotecan Injection 4 mg/4 ml dated December 2, 2010, is addressing the deficiencies included in the FDA's Complete Response Letter dated November 26, 2010.

The Resubmission does not include any Biopharmaceutics information.

RECOMMENDATION:

In the Original submission (*NDA 200-582 for Topotecan Injection submitted on October 29, 2009*), Hospira requested a waiver for the CFR's requirement to provide in-vivo BA/BE data to support the approval of their product. On July 14, 2010, ONDQA-Biopharmaceutics granted a BA/BE waiver for the Topotecan Injection 4mg/4ml product.

With respect to the current Class 1 Resubmission for NDA 200-582 for Topotecan Injection 4mg/4ml dated December 3, 2010, ONDQA-Biopharmaceutics does not have any comments.

Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: Class 1 Re-submission for NDA 200-582, Debbie Mesmer

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/s/

ANGELICA DORANTES
01/29/2011

PATRICK J MARROUM
01/31/2011

BIOPHARMACEUTICS REVIEW

Office of New Drugs Quality Assessment

Application No.:	NDA 200-582	**Reviewer:** Angelica Dorantes, Ph.D	
Submission Date:	October 29, 2009	**Supervisor:** Patrick J. Marroum, Ph.D	
Division:	DDOP	**Date Assigned:**	April 4, 2010
Sponsor:	Hospira, Inc.	**Date of Review:**	July 15, 2010
Trade Name:	Topotecan Injection 4 mg/4 ml	**Type of Submission:** 505 (b)(2) NDA	
Generic Name:	Topotecan Injection		
Indication:	Topotecan injection is a topoisomerase I inhibitor indicated for the treatment of small cell lung cancer sensitive disease after failure of first-line chemotherapy.		
Formulation/strengths	4 mg/4 mL (1 mg/mL) single-dose vial		
Route of Administration	Intravenous		
Type of Review:	**BIOWAIVER REQUEST**		

BACKGROUND:

Topotecan hydrochloride is a semi-synthetic derivative of camptothecin and is an anti-tumor drug with topoisomerase I-inhibitory activity. It is marketed by GSK under the trade name Hycamtin®. The currently marketed topotecan product for injection is a lyophilized powder. It is a single use vial which should be reconstituted with 4 mL of water for injection. The reconstituted solution is then diluted with an appropriate volume of either 0.9% Sodium Chloride Injection or 5% Dextrose Injection prior to intravenous infusion. Since the lyophilized dosage form contains no antibacterial preservative, the reconstituted product should be used immediately.

SUBMISSION:

Reference is made to the Refuse To File letter issued on 8/21/09 to the previously submitted application for Topotecan Injection (b) (4). This new application NDA 200-582 is herein re-filed following the withdrawal of (b) (4) and provides additional stability data and justification to address the concerns in the refuse to file letter.

In this application dated October 29, 2009, Hospira submitted NDA 200-582 for Topotecan Injection 4 mg/4 ml under 505 (b)(2) of the Federal Food, Drug, and Cosmetic Act. This 505 (b)(2) application relies for approval on the FDA's findings of safety and effectiveness for the Reference Listed Drug. This product has the same dosage form (i.e., injectable solution) as the Reference Listed Drug Hycamtin® held by GlaxoSmithKline. The proposed drug product is in the same dosage form containing the same active ingredient at the same concentration after reconstitution as the Reference Listed Drug (RLD) Hycamtin® held by GlaxoSmithKline RLD, and is intended for administration by intravenous infusion. The inactive ingredients in the proposed product are qualitatively and quantitatively the same as the inactive ingredients contained in the RLD, except that mannitol is removed. (b) (4)

(b) (4)

Hospira states that the proposed product offers convenience for practitioners by avoiding the reconstitution step when preparing the drug for administration. Hospira, Inc. requests (b) (4) month expiration dating for Topotecan Injection based on the enclosed 6 months accelerated and 12 months long term storage condition data. Hospira commits that the first three (3) commercial batches of Topotecan Injection will be placed into the stability program and evaluated at regular intervals to support the proposed expiration date. Yearly, thereafter, at least one (1) commercial batch will be placed in our stability program and the test results reported to the Agency in the annual reports. Hospira, Inc. requests a therapeutic equivalence designation of "AP" (as defined in the FDA Orange Book) for their Topotecan Injection product upon approval of the NDA. The proposed drug is of the same pharmacological and therapeutic class as that of the RLD, and can be expected to have the same therapeutic effect as the RLD when administered to patients per the label claimed conditions.

BIOPHARMACEUTICS:

Formulation: The formulation consists of one vial. The proposed drug product is in the same dosage form containing the same active ingredient at the same concentration as the RLD, Hycamtin®, after reconstitution. Excipients are the same as those used in the RLD except for mannitol. (b) (4) The quantitative composition and function of each component in the Drug product vial and Diluent vial is listed in the following tables.

Comparison Between Generic Drug and Reference Listed Drug

	Reference Listed Drug	Generic Equivalent
	GlaxoSmithKline **Hycamtin®**	**Hospira, Inc.** **Topotecan Injection**
Conditions of Use	*Ovarian Cancer*: Is indicated for the treatment of metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy.[1] *Small Lung Cancer*: Is indicated for the treatment of small cell lung cancer sensitive disease after failure of first line chemotherapy. *In combination with cisplatin*: Is indicated for the treatment of stage IV B, recurrent, or persistent carcinoma of the cervix which is not amenable to curative treatment with surgery and/or radiation therapy.	*Small Lung Cancer*: Is indicated for the treatment of small cell lung cancer sensitive disease after failure of first line chemotherapy.
Active Ingredient(s)	Topotecan Hydrochloride	Topotecan Hydrochloride
Inactive Ingredient(s)	Mannitol Tartaric Acid Hydrochloric Acid Sodium Hydroxide	Water for Injection Tartaric Acid Hydrochloric Acid Sodium Hydroxide
Route of Administration	Injection (Intravenous)	Injection (Intravenous)
Dosage Form	Injectable	Injectable
Strength	Hycamtin® Freeze Dried product: EQ 4 mg/vial (free base) Concentration after reconstitution: 4 mg/4 mL	Topotecan Injection solution: 4 mg/ 4 mL Concentration: 4 mg/4 mL (1 mg/ mL) ***NO RECONSTITUTION REQUIRED***

[1]Per 21 CFR 314.50(i)(1)(iii)(A), Hospira Inc., is **not** seeking approval for and will **not** make reference to these labeled indications for which patent 5674872 and 5674872*PED method of use U 910 is applicable.

BIOWAIVER REQUEST:

In this submission, Hospira Inc. is requesting that the Agency's requirement for the submission of in vivo BA/BE data to support the approval of Topotecan Injection 4 mg/4ml be waived.

According to CFR 320.22(b), for certain drug products the in vivo bioavailability (BA) or bioequivalence (BE) of the drug product may be self-evident and the Agency can waive the requirement for the submission of in vivo BA/BE data of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident if the drug product:

- Is a parenteral solution intended solely for administration by injection, and
- Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

The Reference Listed Drug (RLD), Hycamtin® (topotecan hydrochloride) for Injection, is a sterile lyophilized powder available in sterile, single-dose vials. Each vial contains topotecan hydrochloride equivalent to 4 mg of topotecan as free base. The proposed drug product, Topotecan Injection would be a ready-to-use aqueous solution containing total drug content of 4 mg supplied in sterile, single-use vials. The proposed product is formulated in Water for Injection, tartaric acid, and pH adjusted, if necessary, with hydrochloric acid and/or sodium hydroxide. The solution pH ranges from 2.6 to 3.2. Hospira's proposed product does not use the same inactive ingredients. The mannitol has been removed. (b) (4)

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Reviewer Comment:

In this submission, Hospira Inc. provided information showing that their proposed formulation, route of administration, dosage form and indications of their product, Topotecan Injection 4 mg/4 ml are similar to those of the Referenced Listed Drug (RLD) product, Hycamtin® (topotecan HCl) Injection of GlaxoSmithKline. Topotecan HCl Injection is a dosage form intended solely for IV administration and is a true solution.

RECOMMENDATION:

The ONDQA-Biopharmaceutics has reviewed the information included in NDA 20-195 for Docetaxel Injection 20 mg and 80 mg. Based on the Agency's CFR 320.22(b)(1) regulations and the information showing that **1)** their product contains the same active ingredient and inactive ingredients with the exception of (b) (4) mannitol, **2)** the route of administration, dosage form and indications of their product are the same as the RLD product, ONDQA-Biophamaceutics considers that the in vivo BA/BE of Hospira's Topotecan Injection is self-evident. Therefore, the sponsor's request for a biowaiver for Topotecan Injection 4 mg/4 ml is acceptable and the biowaiver is granted.

Please convey the Recommendation as appropriate to the sponsor.

Angelica Dorantes, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: NDA 200-582, Debbie Mesmer

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200582	ORIG-1	HOSPIRA INC	TOPOTECAN INJ

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/s/

ANGELICA DORANTES
07/21/2010

PATRICK J MARROUM
07/22/2010

Clinical Pharmacology Review

NDA	200-582/000
Submission Date	29 October 2009
Brand Name	Topotecan Injection®
Generic Name	Topotecan
Indication	For the treatment of Small cell lung cancer after failure of first-line chemotherapy
Formulation	A sterile solution at a concentration of 4 mg/4 mL in single-dose vials
Dosing Regimen	1.5 mg/m^2 by intravenous infusion over 30 minutes daily for 5 consecutive days (starting on day 1 of a 21-day course)
Sponsor	Hospira, Inc.
OCP Reviewer	Hua Lillian Zhang, Ph.D.
OCP Team Leader	Qi Liu, Ph.D.
OCPB Division	Division of Clinical Pharmacology 5
ORM Division	Division of Drug Oncology Products

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1 EXECUTIVE SUMMARY

This New Drug Application is for Topotecan Injection, 4 mg/4 mL in single-dose vials. The proposed drug product has the same active ingredient, final dosage form prior to use, and route of administration as the innovator drug HYCAMTIN® for Injection (topotecan hydrochloride injection) that was previously approved by the FDA. The Applicant, Hospira, Inc., has submitted this as a 505(b)(2) application and utilized the innovator's (GlaxoSmithKline's) HYCAMTIN® as the reference listed drug (RLD).

There is no bioequivalent study nor any other clinical studies submitted in this application. The Applicant is relying on the findings of safety and effectiveness for HYCAMTIN® to support the approval of their product.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 considers this NDA acceptable from a clinical pharmacology perspective.

For labeling recommendations, please refer to

1.2 PHASE 4 REQUIREMENT

None.

1.3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Topotecan hydrochloride is an anti-tumor drug with topoisomerase I-inhibitory activity. HYCAMTIN® for Injection (topotecan hydrochloride injection) was approved by the FDA for the following indications:

- as a single agent for the treatment of metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy on 28-May-1996 (NDA 20-671);
- as a single agent for the treatment small cell lung cancer sensitive disease after failure of first-line chemotherapy on 30-Nov-1998 (NDA 20-671/S-004)
- in combination with cisplatin for the treatment of Stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amenable to curative treatment with surgery and/or radiation therapy on 14-June-2006 (NDA 20-671/S-014).

HYCAMTIN® for Injection (lyophilized RLD) is available in single-dose vials containing a sterile lyophilized buffered powder at a strength of 4 mg topotecan as free base per vial (4 mg/4 mL upon reconstitution).

As an alternative to the RLD, the Applicant submitted this application to market a new formulation, an aqueous solution formulation of topotecan hydrochloride injection, and is seeking approval for the small cell lung caner indication. The condition of use and route of administration for the subject drug, Topotecan Injection, are the same as prescribed and recommended for the use of the RLD. The approved dosage of RLD for small cell lung cancer is 1.5 mg/m^2 given as a 30 minute intravenous (i.v.) infusion once daily for 5 consecutive days, starting on day 1 of a 21-day cycle.

The proposed drug product, Topotecan Injection, is a ready-to-use aqueous solution at a concentration of 1 mg/mL topotecan as free base per vial, containing total drug content of 4 mg supplied in sterile, single-use vials. It is formulated in Water for Injection, tartaric acid, and pH adjusted, if necessary, with hydrochloric acid and/or sodium hydroxide. Hospira's proposed product does not use the same inactive ingredients. The mannitol has been removed. (b) (4) See for the formulation comparison between the Applicant proposed product and the RLD.

Table 1 Formulation Comparison Between Topotecan Injection and HYCAMTIN®

Specification	Hospira's Proposed Formulation	Hycamtin® (Theoretical Amount after Reconstitution)
Topotecan	1.0 mg/mL	1.0 mg/mL
Tartaric Acid	5.0 mg/mL	(b) (4)
(b) (4)	(b) (4)	
Water for Injection		
(b) (4)		
Sodium Hydroxide	q.s. pH 2.6-3.2	
Hydrochloric Acid	q.s. pH 2.6-3.2	

The inactive ingredients in the proposed product are qualitatively and quantitatively the same as the inactive ingredients contained in the RLD, except that mannitol is removed.

As both formulations are intended solely for i.v. administration and are true solutions when they are administered to patients so that the *in vivo* bioequivalence of Topotecan Injection is considered self-evident, a waiver of the bioequivalence requirements for Topotecan Injection is granted by the Office of New Drug Quality Assessment (ONDQA) in accordance with 21 CFR 320.22 (b)1. The current 505(b)2 application thus does not include any clinical studies and relies on the FDA's findings of safety and effectiveness for RLD.

2 QUESTION BASED REVIEW

Refer to HYCAMTIN® original NDA 20-671 (Approval Date: 28-May-1996) and its supplements S-004 (Approval Date: 30-November-1998) and S-014 (Approval Date: 14-June-2006) for the Clinical Pharmacology related issues.

2.1 GENERAL ATTRIBUTITES

2.1.3 What are the proposed dosage and route of administration?

Topotecan Injection is provided as a sterile solution containing 4 mg/4mL (1mg/mL) of topotecan as free base for i.v. infusion over 30 minutes daily. Its final dosage form prior to use and route of administration are the same as that of RLD

2.2 GENERAL CLINICAL PHARMACOLOGY

2.3 INTRINSIC FACTORS

2.4 EXTRINSIC FACTORS

2.5 GENEARL BIOPHARMACEUTICS

2.5.2 What is the composition of the to-be-marketed formulation?

2.5.3 What moieties should be assessed in bioequivalence studies?

Refer to Section 1.3 for the quantitative and qualitative comparisons between the Hospira's to-be-marketed formulation and the RLD. The application dose not include bioequivalence study

nor any other clinical studies and relies on the findings of safety and effectiveness for the RLD.

2.6 ANALYTICAL SECTION

Not applicable.

3 DETAILED LABELING RECOMMENDATIONS

Only relevant Clinical Pharmacology sections of the Applicant's Topotecan Injection label are included below. The changes proposed by the Applicant are in Red. The reviewer's comments are in Pink and Blue.

6 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200582	ORIG-1	HOSPIRA INC	TOPOTECAN INJ

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/s/

HUA ZHANG
06/22/2010

QI LIU
07/19/2010