CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022453Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Memo	
NDA/SDN	22453/14
Receipt Date	June 25, 2012
Goal Date	December 14, 2012
Submission Type	Resubmission/Class 2, 505(b)(2)
Brand Name	Topotecan Injection
Generic Name	Topotecan hydrochloride
Reference Listed Drug	Hycamtin®, NDA 20671
Proposed Indication	Small cell lung cancer and cervical cancer
Dosing Regimen	Small cell lung cancer: 1.5 mg/m^2 by IV infusion over 30 minutes for 5 consecutive days, starting on Day 1 of a 21-day cycle Cervical cancer: 0.75 mg/m^2 by IV infusion over 30 minutes on Days 1, 2, and 3, repeated every 21 days
Formulation	Solution containing 4 mL of 1 mg base/mL in single-dose vials
Applicant	Teva Pharmaceuticals
Clinical Pharmacology Reviewer	Ruby Leong, Pharm.D.
Clinical Pharmacology Team Leader	Hong Zhao, Ph.D.
OCP Division	Division of Clinical Pharmacology 5
OND Division	Division of Oncology Products 2

The original NDA submitted as a 505(b)(2) application on December 17, 2008 was reviewed by the Office of Clinical Pharmacology and found to be acceptable (refer to clinical pharmacology review dated 08/28/2009).

Given that a biowaiver was granted (refer to Biopharmaceutics review dated 08/31/2012) and that the current 505(b)(2) NDA resubmission does not contain new clinical study information, a clinical pharmacology review is not necessary for this resubmission.

Signatures:

Ruby Leong, Pharm.D.
Reviewer
Division of Clinical Pharmacology 5

Hong Zhao, Ph.D.
Team Leader
Division of Clinical Pharmacology 5

Cc: DOP2: RPM – **D Varney**; MTL – **J Johnson**; MO – **S Malik**
DCP5: DDD – **B Booth;** DD – **A Rahman**

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/s/

RUBY LEONG
10/03/2012

HONG ZHAO
10/03/2012
I concur.

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 22-453 Resubmission/Class 2	**Reviewer:** Elsbeth Chikhale, PhD	
Submission Date:	June 12, 2012		
Division:	Division of Oncology Products	**Team Leader:** Angelica Dorantes, PhD	
Applicant:	Teva Pharmaceuticals, USA	**Acting Supervisor:** Rik Lostritto, PhD	
Trade Name:	TBD	**Date Assigned:**	August 10, 2012
Established Name:	Topotecan HCl Injection	**Date of Review:**	August 31, 2012
Indication:	Small Cell Lung Cancer and Cervical Cancer	**Type of Submission:** Resubmission of New Drug Application – 505(b)(2)	
Dosage form/ strengths	Solution for Injection/ 1 mg/mL		
Route of Administration	IV infusion		
Type of Review:	Biowaiver Request		

SUBMISSION:

The proposed drug product is a sterile solution for IV infusion containing topotecan as the active ingredient. This application is an electronic NDA resubmission, filed as a 505(b)(2) application, with Hycamtin® (NDA 20-671) as the reference listed drug (RLD). The original NDA (submitted 12/18/2008) was not approved (CR letter dated 10/16/2009) due to deficiencies found during the inspection of the drug product manufacturer (Teva Parenterals, Inc.). This was the only deficiency noted in the CR letter.

The original NDA included a bioequivalence (BE) waiver request; however, the evaluation of this request was not documented. The Clinical Pharmacology review for the original NDA mentions that ONDQA granted the biowaiver, but the CMC review does not include this information. Therefore, the BE waiver request for Topotecan HCl Injection is being evaluated in this Biopharmaceutics review.

BIOPHARMACEUTIC INFORMATION:

The proposed Topotecan HCl Injection (containing 1 mg topotecan free base/mL) is a single dose formulation (4 mL/vial) that is ready for immediate dilution and administration (unlike the RLD that is supplied as a sterile lyophilized powder). Once reconstituted, the only difference between the proposed product and the RLD is in the pH: the pH of Teva's formulation was developed to be 2.2 (2.0-2.5) for finished drug product to ensure physical and chemical stability of the liquid

formulation, whereas Hycamtin® has a pH of 3.0 (2.5-3.0) upon reconstitution. In the original NDA, the applicant requests a waiver of the *in vivo* bioequivalence study requirement as allowed under 21 CFR 320.22(b)(1), because:

- Topotecan HCl Injection is a parental drug product intended for administration by injection
- The proposed drug product contains the same active and inactive ingredients in the same concentration as the RLD

ASSESSMENT OF THE BIOWAIVER REQUEST

The compositions for the formulations of the proposed Teva drug product and the RLD product (Glaxo SmithKline) are as follows:

Ingredients	**Teva's Formulation (4 mL fill per vial)**	**GlaxoSmithKline's Formulation (upon reconstitution with 4 mL WFI)**
Each mL contains:		
Topotecan Hydrochloride[1]	1 mg	1 mg
Mannitol, USP	12 mg	12 mg
Tartaric Acid	5 mg	5 mg
Sodium Hydroxide, NF	To adjust pH	To adjust pH
Hydrochloric Acid, NF	To adjust pH	To adjust pH
Water for Injection, USP	q.s.	q.s.

[1]Topotecan hydrochloride used is equivalent to 1 mg/mL topotecan free base

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 meets the following:

- 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 difference in pH (2.2 versus 3.0) will not affect the bioavailability of this drug product. Therefore, we consider that the in vivo BA/BE of the proposed Topotecan HCl Injection is self-evident, and the Applicant's request for a biowaiver for their proposed Topotecan HCl Injection product is acceptable and the biowaiver is granted.

RECOMMENDATION:

A waiver from the CFR's requirement to provide data from an *in vivo* bioequivalence study is granted. From the Biopharmaceutics perspective, NDA 22-453 for Topotecan HCl Solution for Injection (1 mg/mL) is recommended for APPROVAL.

Signature
Elsbeth Chikhale, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

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

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/s/

ELSBETH G CHIKHALE
08/31/2012

ANGELICA DORANTES
08/31/2012

Clinical Pharmacology Review

NDA	22-453/000
Submission Date:	17 December 2008
Brand Name:	Topotecan Hydrochloride Injection®
Generic Name:	Topotecan Hydrochloride
Formulation:	(b) (4) concentrate for injection with accompanying diluent
OCP Reviewer:	Jeanne Fourie, PhD
OCP Team Leader:	Julie Bullock, PharmD
OCP Division:	Division of Clinical Pharmacology V
ORM Division:	Division of Drug Oncology Products
Sponsor:	Teva Parenteral Medicines Inc.
Submission Type; Code:	Original NDA; S-000
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.
Indication:	Treatment of Small Cell Lung Cancer after failure of first-line chemotherapy. Treatment of Stage IV-B recurrent or persistent carcinoma of the cervix in combination with cisplatin.

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1 EXECUTIVE SUMMARY

Pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, Teva Parenteral Medicines submitted an original New Drug Application (NDA 22-453/S-000) for Topotecan Hydrochloride Injection® with the reference listed drug as Hycamtin® for Injection (topotecan hydrochloride; GlaxoSmithKline). These two proposed indications have been approved for the reference listed drug (NDA 20-671). The indications for Topotecan Hydrochloride Injection® listed in the current application are for the treatment of small cell lung cancer sensitive disease after failure of first-line chemotherapy and for the treatment of stage 4-B recurrent or persistent carcinoma of the cervix (in combination with cisplatin) which is not amendable to curative treatment with surgery and/or radiation therapy.

The qualitative and quantitative compositional comparison to the reference listed drug (Hycamtin®; GlaxoSmithKline), indicated that the *in vivo* bioequivalence of the Teva drug product was self-evident. Therefore, a waiver of the bioequivalence requirements for Topotecan Hydrochloride Injection® was granted. The current 505(b)2 application thus does not include clinical studies and relies on the FDA's findings of safety and effectiveness for Hycamtin® (NDA 20-671).

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in NDA 22-453. This application is acceptable from a clinical pharmacology perspective.

Phase IV commitments

None.

Labeling Recommendations

The Clinical Pharmacology sections of the labeling for Topotecan Hydrochloride Injection® (Teva Parenteral Medicines Inc.) have been reproduced within the Detailed Labeling Recommendations Section below.

Signatures:

Reviewer: Jeanne Fourie, Ph.D. Division of Clinical Pharmacology 5	Team Leader: Julie M Bullock, Pharm.D. Division of Clinical Pharmacology 5

Cc: DDOP: CSO - J Jamison; MTL - K Liu; MO - M Brave,
DCP-5: Reviewers - J Fourie,
DDD - B Booth
DD - A Rahman

1.2 CLINICAL PHARMACOLOGY SUMMARY

Hycamtin® for Injection (topotecan hydrochloride) is a product of GlaxoSmithKline and was approved for use by the FDA on May 28, 1996 (NDA 20-671). Hycamtin® for Injection is indicated for the treatment of metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy, small cell lung cancer sensitive disease after failure of first-line chemotherapy, and in combination with cisplatin in the treatment of stage 4-B, recurrent, or persistent carcinoma of the cervix which is not amendable to curative treatment with surgery and/or radiation therapy.

Hycamptin® for Injection is available in single-dose vials containing a sterile lyophilized buffered powder at a strength of 4 mg topotecan as free base per vial. The reconstituted solution is intended for administration by intravenous infusion. The approved dosage for small cell lung cancer is 1.5 mg/m^2 administered intravenously as a 30 minute daily infusion for 5 consecutive days, starting on day 1 of a 21-day cycle. The approved dosage for cervical cancer is 0.75 mg/m^2, administered intravenously as a 30 minute daily infusion on days 1, 2, and 3; followed by cisplatin 50 mg/m^2 by intravenous infusion on day 1 repeated every 21 days. In the current application, Hycamtin® for Injection is designated as the reference listed drug (RLD) by the applicant.

Teva Parenteral Medicines submitted the current application to market a new drug product, Topotecan Hydrochloride for Injection®, [redacted]$^{(b)(4)}$ concentrate for injection with accompanying diluent) as an alternative to the RLD. The indications for which the applicant is seeking approval are:

- The treatment of small cell lung cancer sensitive disease after failure of first-line chemotherapy and;
- The treatment (in combination with cisplatin) of stage 4-B, recurrent, or persistent carcinoma of the cervix which is not amenable to curative treatment with surgery and/or radiation therapy.

These two indications are identical to the approved indications for the RLD. The applicant is not seeking approval for the ovarian cancer indication of the RLD.

The Teva drug product consists of a sterile, buffered, clear light yellow to greenish solution. It is available in one 4 mL fill single-dose glass vial. Each mL of the product solution contains topotecan hydrochloride (equivalent to 1 mg topotecan free base), 12 mg of mannitol, USP, and 5 mg of tartaric acid, NF. The drug product should be stored at 2 - 8°C. The pH of the drug product is adjusted to pH 2.2 (range 2.0 to 2.5) with sodium hydroxide or hydrochloric acid. Topotecan Hydrochloride Injection® is intended for dilution with 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP prior to intravenous infusion. The list of ingredients, their pharmaceutical functions and amount per unit basis are presented in the table below.

Table 1 Unit Composition for Teva's Topotecan Hydrochloride Injection®

Ingredients	Function of Components	Concentration (mg/mL)	Content per Vial (mg/Vial)
Topotecan Hydrochloride[1]	Active pharmaceutical ingredient	1 mg base/mL	4 mg base
Mannitol, USP	Tonicity adjuster	12 mg/mL	48 mg
Tartaric acid, NF	Buffer	5 mg/mL	20 mg
Sodium Hydroxide, NF	pH adjuster	To adjust to a target pH of 2.2	To adjust to a target pH of 2.2
Hydrochloric Acid, NF	pH adjuster	To adjust to a target pH of 2.2	To adjust to a target pH of 2.2
Water for Injection, USP	Solvent	q.s.	q.s.

[1]Topotecan hydrochloride used is equivalent to 1 mg/mL Topotecan free base

The table below compares the qualitative and quantitiative composition of Topotecan for Injection® with Hycamptin® for Injection. Teva's drug product has the same active and inactive ingredients, strength, route of administration, and conditions of use as the innovator drug product. In addition, the Teva injectable liquid formulation has an identical composition to the GlaxoSmithKline reconstituted Hycamtin® for Injection lyophilized sterile injectable drug product. The dosage form of Topotecan Hydrochloride Injection is different from the RLD. Specifically, Topotecan Hydrochloride Injection® is manufactured in a liquid dosage form (instead of the RLD lyophilized dosage form). The pH of Teva's formulation was developed to be 2.2 (2.0-2.5) for finished drug product, which ensures physical and chemical stability of the liquid formulation. In contrast, Hycamtin® for Injection, has a pH of 3.0 (2.5-3.0) upon reconstitution.

Table 2 Qualitative and Quantitative composition (per vial and amount per unit) listed for Teva's Topotecan Hydrochloride Injection solution and the RLD Hycamtin®

Composition Raw Material	Toptotecan hydrochloride Injection (Teva) (buffered solution)	Toptotecan hydrochloride Injection (Teva) Concentration	RLD Hycamtin® (buffered lyophilized powder)	RLD Hycamtin® *Reconstituted Solution* Concentration
Topotecan free base	4 mg	1 mg/mL	4 mg	1 mg/mL
Mannitol, USP	48 mg	12 mg/mL	48 mg	12 mg/mL
Tartaric acid, NF grade	20 mg	5 mg/mL	20 mg	5 mg/mL
Sterile Water for Injection, USP	solvent	solvent	-	solvent
Sodium hydroxide, NF grade	pH adjuster	To adjust to a target pH		To adjust to a target pH
Hydrochloric acid, NF grade	pH adjuster	To adjust to a target pH		To adjust to a target pH

Recommendation:
Based on the qualitative and quantitative composition of the Topotecan Hydrochloride Injection® and the RLD formulations, the Office of New Drug Quality Assessment (ONDQA) granted Teva a waiver of the bioequivalence requirements for Topotecan Hydrochloride for Injection® in accordance with 21 CFR 320.22 (b)1. The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in NDA 22-453. This application is acceptable from a clinical pharmacology perspective.

2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

Refer to the RLD original NDA 20-671 (Approval Date: 5/28/96) for the issues listed in Section 2.1.2 to Section 2.4.

Section 2.6 and Section 4 are not applicable to this application.

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

2.1.3 What are the proposed dosage and route of administration?

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

2.2.4.3 Does this drug prolong the QT or QTc interval?

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

2.2.5.1 What are the single dose and multiple dose PK parameters?

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

2.2.5.3 What are the characteristics of drug absorption?

2.2.5.4 What are the characteristics of drug distribution?

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

2.2.5.6 What are the characteristics of drug metabolism?

2.2.5.7 What are the characteristics of drug excretion?

2.2.5.8 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

2.2.5.9 How do the PK parameters change with time following chronic dosing?

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Pediatric patients

2.3.2.2 Renal impairment

2.3.2.3 Hepatic impairment

2.3.2.4 What pregnancy and lactation use information is there in the application?

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

2.4.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

2.4.2.7 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

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

See General Clinical Pharmacology Section 1.2, for the quantitative and qualitative comparisons between the Teva to-be-marketed formulation and the RLD.

2.5.3 What moieties should be assessed in bioequivalence studies?

Based on the qualitative and quantitative compositional comparison to the RLD, ONDQA granted Teva a waiver of the bioequivalence requirements for Topotecan Hydrochloride Injection® in accordance with 21 CFR 320.22 (b)1. The applicant's 505(b)2 application for Topotecan Hydrochloride Injection® did not include clinical studies and relies on the FDA's findings of safety and effectiveness for Hycamtin® for Injection (NDA 20-671).

2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?

2.6 ANALYTICAL SECTION

2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

2.6.2 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

3 DETAILED LABELING RECOMMENDATIONS

Only relevant Clinical Pharmacology sections of Teva's Topotecan Hydrochloride Injection® label are included below.

2.3 Adjustment of Dose in Special Populations

Dosing in Renal Impairment

No dosage adjustment of Topotecan Injection appears to be required for treating patients with mild renal impairment (Cl_{cr} 40 to 60 mL/min.). It is recommended to adjust the dosage of Topotecan Injection to 0.75 mg/m^2 for patients with moderate renal impairment (20 to 39 mL/min.). Insufficient

data are available in patients with severe renal impairment to provide a dosage recommendation for Topotecan Injection. *[See Clinical Pharmacology (12.3)]*

Initiate treatment of cervical cancer with Topotecan Injection in combination with cisplatin only if patient serum creatinine is ≤1.5 mg/dL. In the clinical trial, cisplatin was discontinued for a serum creatinine >1.5 mg/dL. Insufficient data are available regarding continuing monotherapy with Topotecan Injection after cisplatin discontinuation in patients with cervical cancer.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Topoisomerase I relieves torsional strain in DNA by inducing reversible single strand breaks. Topotecan binds to the topoisomerase I-DNA complex and prevents religation of these single strand breaks. The cytotoxicity of topotecan is thought to be due to double strand DNA damage produced during DNA synthesis, when replication enzymes interact with the ternary complex formed by topotecan, topoisomerase I, and DNA. Mammalian cells cannot efficiently repair these double strand breaks.

12.2 Pharmacodynamics

The dose-limiting toxicity of topotecan is leukopenia. White blood cell count decreases with increasing topotecan dose or topotecan AUC. When topotecan is administered at a dose of 1.5 mg/m^2/day for 5 days, an 80% to 90% decrease in white blood cell count at nadir is typically observed after the first cycle of therapy.

12.3 Pharmacokinetics

The pharmacokinetics of topotecan have been evaluated in cancer patients following doses of 0.5 to 1.5 mg/m^2 administered as a 30-minute infusion. Topotecan exhibits multiexponential pharmacokinetics with a terminal half-life of 2 to 3 hours. Total exposure (AUC) is approximately dose-proportional. Binding of topotecan to plasma proteins is about 35%.

(b) (4)

Metabolism

Topotecan undergoes a reversible pH dependent hydrolysis of its lactone moiety; it is the lactone form that is pharmacologically active. At pH ≤4, the lactone is exclusively present, whereas the ring-opened hydroxy-acid form predominates at physiologic pH. In vitro studies in human liver microsomes indicate topotecan is metabolized to an N-demethylated metabolite. The mean metabolite:parent AUC ratio was about 3% for total topotecan and topotecan lactone following IV administration.

(b) (4)

In vitro inhibition studies using marker substrates known to be metabolized by human P450 CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E, CYP3A, or CYP4A or dihydropyrimidine dehydrogenase indicate that the activities of these enzymes were not altered by topotecan. Enzyme inhibition by topotecan has not been evaluated *in vivo*.

Elimination

Renal clearance is an important determinant of topotecan elimination. In a mass balance/excretion study in 4 patients with solid tumors, the overall recovery of total topotecan and its N-desmethyl metabolite in urine and feces over 9 days averaged 73.4 ± 2.3% of the administered IV dose. Mean values of 50.8 ± 2.9% as total topotecan and 3.1 ± 1.0% as N-desmethyl topotecan were excreted in the urine following IV administration. Fecal elimination of total topotecan accounted for 17.9 ± 3.6% while fecal elimination of N-desmethyl topotecan was 1.7 ± 0.6%. An O-glucuronidation metabolite of topotecan and N-desmethyl topotecan has been identified in the urine. These metabolites, topotecan-O-glucuronide and N-desmethyl topotecan-O-glucuronide, were less than 2% of the administered dose.

Gender

The overall mean topotecan plasma clearance in male patients was approximately 24% higher than that in female patients, largely reflecting difference in body size.

Age

Topotecan pharmacokinetics have not been specifically studied in an elderly population, but population pharmacokinetic analysis in female patients did not identify age as a significant factor. There were no apparent differences in the pharmacokinetics of topotecan in elderly patients, once the age-related decrease in renal function was considered. Decreased renal clearance, which is common in the elderly, is a more important determinant of topotecan clearance *[see Warnings and Precautions (5) and Dosage and Administration (2)]*. This drug is substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function *[see Dosage and Administration (2)]*.

Race

The effect of race on topotecan pharmacokinetics has not been studied.

Renal Impairment

In patients with mild renal impairment (creatinine clearance of 40 to 60 mL/min.), topotecan plasma clearance was decreased to about 67% of the value in patients with normal renal function. In patients with moderate renal impairment (Cl_{cr} of 20 to 39 mL/min.), topotecan plasma clearance was reduced to about 34% of the value in control patients, with an increase in half-life. Mean half-life, estimated in 3 renally impaired patients, was about 5.0 hours. Dosage adjustment is recommended for these patients *[see Dosage and Administration (2)]*.

Hepatic Impairment

No dosage adjustment appears to be required for treating patients with impaired hepatic function (plasma bilirubin >1.5 to <10 mg/dL). Plasma clearance in patients with hepatic impairment (serum bilirubin levels between 1.7 and 15.0 mg/dL) was decreased to about 67% of the value in patients without hepatic impairment. Topotecan half-life increased slightly, from 2.0 hours to 2.5 hours, but these hepatically impaired patients tolerated the usual recommended topotecan dosage regimen.

4 APPENDICES

None.

4.1 INDIVIDUAL STUDY REVIEWS

Not applicable.

4.2 QT REVIEW

Not applicable.

4.3 ANALYTICAL

Not applicable.

4.3.1 Office of Clinical Pharmacology

5 *NEW DRUG APPLICATION FILING AND REVIEW FORM*

5.1.1.1.1 General Information About the Submission

NDA Number	22-453/000	**Brand Name**	Topotecan Hydrochloride Injection®
DCP Division (I, II, III, IV, V)	V	**Generic Name**	Topotecan Hydrochloride
Medical Division	Oncology	**Drug Class**	
OCP Reviewer	Jeanne Fourie, Ph.D.	**Indication(s)**	-Small Cell Lung Cancer after failure of first-line chemotherapy. -Stage IV-B recurrent or persistent carcinoma of the cervix in combination with cisplatin.
OCP Team Leader	Julie M Bullock, Pharm.D.	**Dosage Form**	(b) (4) Injection Concentrate with an accompanying diluent
Date of Submission	December 17, 2008	**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.
Due Date of OCP Review	June 18, 2009	**Route of Administration**	Intravenous Infusion
5.1.1.2 Standard PDUFA Due Date	October 18, 2009	**Sponsor**	Teva Parenteral Medicines, Inc.

5.1.1.2.1.1.1.1 Clinical Pharmacology Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies				
HPK Summary				
Labeling	**X**			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
5.2 HEALTHY VOLUNTEERS-				
single dose:				
multiple dose:				
5.2.1 Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				

gender:				
geriatrics:				
renal impairment:				
hepatic impairment:				
pediatrics:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
QTC studies:				
In-Vitro Release BE				
(IVIVC):				
Bio-wavier request based on BCS	**X**			
BCS class				
III. Other CPB Studies				
Biliary Elimination				
Pediatric development plan				
Literature References				
Total Number of Studies				

5.2.1.1.1.1 Filability and QBR comments

5.2.1.2	**"X" if yes**	**5.2.1.2.1.1.1.1.1 Comments**
5.2.1.3 Application filable?	**X**	
5.2.1.4 Comments sent to firm?		
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date	**Jeanne Fourie, Ph.D.**	
Secondary reviewer Signature and Date	**Julie M Bullock, Pharm.D**	

CC: HFD-150 (CSO – J Jamison**;** MTL –K Liu**;** MO –M Brave) HFD-860 (Reviewer - **J Fourie;**

TL- J Bullck; DDD - **B Booth;** DD - **A Rahman**)

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22453	ORIG 1	TEVA PARENTAL MEDICINE INC	TOPOTECAN HYDROCHLORIDE INJECTION

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/s/

JEANNE FOURIE
08/27/2009

JULIE M BULLOCK
08/28/2009