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APPLICATION NUMBER:

022453Orig1s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	22453
Supporting document/s:	13
Applicant's letter date:	June 22, 2012
CDER stamp date:	June 22, 2012
Product:	Topotecan hydrochloride, 1 mg base/mL
Indication:	(b) (4)
Applicant:	TEVA, US Generics; 1090 Horsham Road, North Wales, PA 19454
Review Division:	Division of Hematology Oncology Toxicology in support of Division of Oncology Products 2 (DOP2), Office of Hematology and Oncology Products (OHOP), CDER
Reviewer:	Dubravka Kufrin, PhD
Supervisor/Team Leader:	Whitney S. Helms, PhD
Division Director:	• John K. Leighton, PhD, DABT for DHOT, OHOP Patricia Keegan, MD for DOP2, OHOP
Project Manager:	Deanne Varney

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 22453 are owned by TEVA Inc. or are data for which TEVA Inc. has obtained a written right of reference.
Any information or data necessary for approval of NDA 22453 that TEVA Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a

listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that TEVA Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22453.

Memo to the file:

Submission 13 to NDA 22453 is a class 2 resubmission following a complete response issued to Teva Inc. due to a problem with a manufacturing facility inspection.

No new nonclinical pharmacology/toxicology studies have been included in the current submission. During the previous review cycle Drs. W. David McGuinn and S. Leigh Verbois determined that the combination of expert consultations and literature that Teva had submitted were sufficient to qualify both a novel impurity, (b) (4) (b) (4) present in this formulation of Topotecan Hydrochloride Injection.

No new issues requiring a pharmacology/toxicology assessment were identified in this complete response. There are, therefore, no outstanding issues that would prevent approval of this NDA from a pharmacology/toxicology perspective.

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/s/

DENALI D KUFRIN
10/16/2012

WHITNEY S HELMS
10/17/2012

I concur with Dr. Kufrin's determination that nonclinical issues associated with this application were addressed in a previous review cycle and that, as there were no new nonclinical issues raised during this cycle, that there are no pharmacology/toxicology issues that would inhibit approval of this application.

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PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA Number:	22-453
Serial Number:	000
Received by CDER:	December 17, 2008
Product:	Topotecan Hydrochloride Injection
Clinical Indication:	➢ (b) (4) carcinoma of small cell lung cancer ➢ in combination with cisplatin, for the treatment of stage IV-B, recurrent, or persistent carcinoma of the cervix
Sponsor:	Teva Parenteral Medicines, Inc.
Documents Reviewed:	N000, electronic submission \\Cdsesub1\evsprod\NDA022453\0000
Review Division:	Division of Drug Oncology Products
Reviewer:	W. David McGuinn, Jr., M.S., Ph. D., D.A.B.T.
Supervisor:	S. Leigh Verbois, Ph. D.
Division Director:	Robert Justice, M.D.
Project Manager:	Susan Jenney
Medical Officer:	Michael Brave, M.D.
Chemist:	Sue-Ching Lin, Ph. D.
Date of review submission to DFS:	September 16, 2009

EXECUTIVE SUMMARY

Recommendations

Recommendation on Approvability

Based on a prior FDA finding of safety and effectiveness as described in the topotecan approved labeling and information provided by the sponsor this application is approvable from the perspective of toxicology and pharmacology.

Recommendation for Non-clinical studies

None

Recommendations on Labeling

The label for this product will be reviewed separately.

Summary of Non-clinical findings

Overview of Non-clinical findings

The US Food and Drug Administration approved Topotecan IV for the treatment of ovarian cancer in May 1996 and for cervical cancer in June of 2006 under the trade name HYCAMPTIN (GlaxoSmithKline). In October 2007, the FDA approved HYCAMPTIN Oral for the treatment of small cell lung cancer. The sponsor of this NDA, Teva Parenteral Medicines, Inc. (b) (4) This is a 505(b)2 application based on the prior approval.

Topoisomerase I induces transient single strand breaks in the phosphodiesterase backbone of DNA to allow rotation that relieves torsional strain during replication or transcription. Topotecan binds reversibly with the DNA-topoisomerase assembly to form a tertiary complex that prevents the reformation of the phosphodiesterase bond. This inhibition eventually leads to catastrophic double strand breaks and cell death.

Topotecan is cytotoxic to dividing cells, thus its primary toxicity is myelosuppression manifested as dose limiting leukopenia and neutropenia. Anemia, nausea and vomiting occur frequently during treatment.

Topotecan is a potent mutagen and clastogen as its mechanism of action suggests. It is strongly positive in mammalian *in vitro* tests with and without metabolic activation and it is positive in the mouse micronucleus test.

Topotecan has a Pregnancy Category D. At doses approximately equal to the clinical dose on a mg/m^2 basis it causes embryo-lethality and reduced fetal weight in rabbits and rats. In rats, it diminishes fertility and causes fetal resorption, microphthalmia, pre-implant loss, with only mild maternal toxicity. In rats, it also causes numerous malformations in the developing fetus.

[1] Statements not specifically referenced to literature articles are excerpted directly from the product label for TOPOTECAN IV.

PHARMACOLOGY/TOXICOLOGY REVIEW

Introduction and Drug History

NDA number	22453
Review	number 1
Submission	000

Information location in EDR: \\Cdsesub1\evsprod\NDA022453\0000

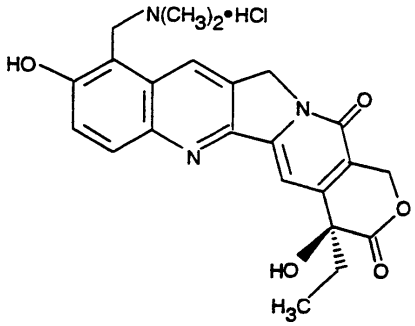
Information to sponsor	No
Sponsor	Teva Parenteral Medicines, Inc. (Teva)

Reviewer name	W. David McGuinn, Jr., M.S., Ph. D., D.A.B.T.
Division name	Division of Drug Oncology Products
Review completion date	September 16, 2009

Drug

Code Name:	SK&FS-104 864-A
Generic Name:	Topotecan
Trade Name:	(b) (4)
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 monohydrochloride
CAS Number:	123948-87-8

FW = 421.453 (free base) g/mole, FW = 457.91 (hydrochloride salt) $C_{23}H_{23}N_3O_5 \bullet HCl$



Structure:

Relevant INDs & NDAs	IND (b) (4)
	NDA 20-671

Drug class: Topoisomerase inhibitor

Intended clinical population:

- (b) (4) carcinoma of small cell lung cancer
- in combination with cisplatin, for the treatment of stage IV-B, recurrent, or persistent carcinoma of the cervix

Clinical formulation:

Table 2.3.P.1-1 Unit Composition for 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

Route of administration: IV

Dose and schedule:
- Small Cell Lung Cancer: the recommended dose is 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
- Cervical Cancer: the recommended dose of is 0.75 mg/m^2 by intravenous infusion over 30 minutes daily on days 1, 2, and 3; followed by cisplatin 50 mg/m^2 by intravenous infusion on day 1 repeated every 21 days.

Disclaimer: I have reconstructed all tabular and graphical information directly from the sponsor's electronic and paper submissions unless otherwise specified.

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22-453 are owned by Teva or are data for which Teva has obtained a written right of reference. Any information or data necessary for approval of NDA 22-453 that Teva does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Teva does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-453.

Toxicology

Toxicological Evaluation of Impurities in the Drug Product

1) Toxicological Evaluation of (b) (4)

Major finding

This report provides sufficient information to qualify the proposed specification limit of (b) (4) for the impurity (b) (4)

According to TEVA, the manufacturing process for their topotecan drug substance requires the solvent (b) (4). This compound remains present in the drug product at a maximum specification limit of no more than (b) (4). The maximum daily IV dose of topotecan is (b) (4)/day for five consecutive days every three weeks. Fifteen ppm within (b) (4)/day results in a daily exposure of (b) (4)/day.

(b) (4)

According to the MSDS, (b) (4) is a corrosive and a lachrymator. At toxic doses, chronic exposure causes renal and hepatic damage. The MSDS states that no information is available about carcinogenicity, mutagenicity, teratogenicity or developmental toxicity.

This memorandum cites two studies that evaluated the genotoxicity of (b) (4) and determined that the compound was negative in the Ames assay and did not cause sister chromatid exchange in Chinese hamster ovary cells (b) (4)

In order to justify the safety of an exposure of (b) (4) day, the memorandum uses the ICH Guidance Q3C to determine a permitted daily exposure (PDE). As a reference for (b) (4) toxicity, the memorandum cites a study by (b) (4) that determined an inhalational NOAEL of (b) (4) with a six hour exposure five days a week up to 28 weeks. This study is the one most frequently cited by the EPA in connection with (b) (4). At (b) (4) the density of air is (b) (4), so (b) (4) in air is (b) (4) The following formula converts an inhalational exposure to an Equivalent Dose (ED) in mg/kg:

(b) (4)

Where:

(b) (4)

Thus, the equivalent dose is (b) (4) /day.

The report then estimates a safe exposure by dividing this number by standard safety factors in the following formula (ICH Q3A).

$$\text{Predicted safe dose} = \frac{\text{NOAEL x Weight Adjustment}}{\text{F1 x F2 x F3 x F4 x F5}}$$

Where

F1 = 5 for extrapolation from rats to humans
F2 = 10 to account for variability between individuals
F3 = 2 for a study of at least 6-month duration
F4 = 1 for study with no severe toxicity
F5 = 1 if a no observable effect level was established

Using the estimated dose of (b) (4) day and a mean body weight of 75 kg this calculation results in an estimated safe dose of (b) (4) day. This predicted safe dose is over (b) (4) times greater than the proposed specification limit.

Additionally, the MSDS for (b) (4) provides single dose LD_{50} values:

Oral LD_{50} in the rat (b) (4)
Oral LD_{50} in the mouse
IP LD_{50} in the mouse

While the MSDS provides no information on the slope of the toxic dose response curves, all these are many times greater than the proposed specification limit.

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2) Toxicological Evaluation of (b) (4)

Major finding

This report is sufficient to qualify the proposed specification limit of no more than (b) (4) in the drug substance.

Teva's proposed specification limit for (b) (4) is no more than (b) (4) in the drug substance. With a dose of (b) (4) day this would result in an exposure to (b) (4) per day.

(b) (4)

(b) (4)

(b) (4) has an intraperitoneal LD_{50} of (b) (4) in the rat (compared to (b) (4) studied the non-clinical pharmacology of (b) (4) in rats with IV doses of (b) (4). They observed no toxicity after the low and mid dose but treatment with (b) (4) caused polyuria and hematuria. Elimination was slow and fit a three-compartment model with elimination half-lives of 140 and 429 minutes. Metabolism in the rat is similar to that of other camptothecins with glucoronidation of the (b) (4) group to form a glucuronide and hydrolysis of the lactone ring to form a carboxylate (b) (4) as shown in the following figure from the submission.

(b) (4)

The glucuronide and carboxylate metabolites are pharmacologically inactive.

(b) (4) treated 60 patients with various malignancies with 1 (b) (4). They gave doses of (b) (4) for five to 10 consecutive days. They observed a response rate of (b) (4). Dose-limiting toxicity and other adverse reactions included nausea, vomiting, diarrhea, and skin rash consistent with toxicities seen with other camptothecins. They observed no renal, pulmonary, or cardiac toxicity.

As would be expected for a topoisomerase I inhibitor, (b) (4) is genotoxic and mutagenic (b) (4)

A single dose of 3 mg/kg (18 mg/m or about 1 mg) caused no toxicity in rats (b) (4). The proposed specification limit is (b) (4) day or about (b) (4) day. This dose of (b) (4) is (b) (4) times less than the acute dose that caused no toxicity in rats. But (b) (4) is active so its presence is likely to contribute to any pharmacological effect of the drug substance.

Overall Summary and Evaluation:

Mechanism of Action

The enzyme, topoisomerase-I, induces transient breaks in the phosphordiester backbone of DNA. These breaks allow the DNA to rotate during the process of replication and transcription, thus relieving the torsional strain that would otherwise accumulate during these processes (M. Gupta *et al. Biochim Biophys Acta* 1995;**1262**(1):1-14, JT Stivers *et al. Bio Chem* 1997;**36**(17):5212-22). Topotecan is a derivative of the natural product, camptothecin, which is a pentacyclic alkaloid extracted from the Chinese tree *Camptotheca acuminate*. Camptothecin and its derivatives do not inhibit the initial strand breaking process of topoisomerase I but they then bind with topoisomerase-I and the adjacent DNA after the initiation of a break to form a ternary complex. The formation of this complex prevents the uncoupling of topoisomerase from the DNA and thus the reformation of the phosphodiester bond. This inhibition is not in itself toxic to

the cell, as the binding of the camptothecins is reversible, but a collision of the advancing replication fork of DNA with this ternary complex results in an irreparable double strand break that immediately causes cell death. See S Basili and S Moro (*Expert Opin. Ther. Patents*, 2009 19(5):555-574) for a thorough discussion of this process. This pharmacological mechanism is also the major mechanism of camptothecin toxicity.

(b) (4) is only poorly water-soluble and it has a low therapeutic index. In initial clinical trials, the drug caused life-threatening myelosuppression, diarrhea and hemorrhagic cystitis (FM Muggia, 1972, *Cancer Chemother Rep* 56:515). For these reasons development of this drug as a treatment for cancer was abandoned in the 1970s. Topotecan is more water-soluble than its parent camptothecin due to the substation of a dimethylaminomethyl group at the 10 carbon of the A ring. This substitution also increases the therapeutic index but does not alter the spectrum of toxicities.

Clinical Toxicity

In clinical studies, the dose-limiting toxicity of topotecan was leukopenia manifested as grade 4 in as many as 25% of patients. White blood cell count decreases with increasing topotecan dose or topotecan AUC. When topotecan is given 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. Other significant toxicities include anemia, neutropenia, thrombocytopenia, pain, infectious febrile neutropenia, cardiovascular changes and hepatic toxicity. All these toxicities relate to the drugs primary pharmacology, that is its interference will DNA synthesis, the resulting of DNA double strand breaks and cell death. The attendant nausea and vomiting are possibly neuropsychological toxicities.

Pharmacokinetics

The pharmacokinetics of topotecan has been evaluated in cancer patients following doses of 0.5 to 1.5 mg/m^2 given as a 30-minute infusion. Humans eliminate topotecan by multiexponential pharmacokinetics. The terminal elimination half-life is 2 to 3 hours. Total exposure is approximately dose-proportional. Binding of topotecan to plasma proteins is about 35%.

Topotecan undergoes a reversible pH dependent hydrolysis of its lactone ring. The compound can only form the inhibitory ternary complex with topoisomerase I and DNA if the lactone ring is intact. At pH less than or equal to 4, the lactone is exclusively present; the ring-opened hydroxy-acid form predominates at physiological pH. Human liver microsomes metabolize topotecan to an N-desmethyl metabolite.

In a mass balance excretion study in patients with solid tumors, the overall recovery of total topotecan and its N-desmethyl metabolite in urine and feces over 9 days averaged 73 ± 2% of the IV dose. Mean values of 51 ± 3% as total topotecan and 3 ± 1% as N-desmethyl topotecan were excreted in the urine. Fecal elimination of total topotecan was 18 ± 4% while fecal elimination of N-desmethyl topotecan was 1.7 ± 0.6%. An O-glucuronidation metabolite of topotecan and N-desmethyl topotecan was identified in the urine. These metabolites, topotecan-O-glucuronide and N-desmethyl topotecan-O-glucuronide, were less than 2% of the administered dose. Plasma clearance of topotecan decreases with increasing degree of renal impairment as plasma half-life increases. An increasing degree of hepatic impairment similarly caused a decrease in plasma clearance. *In vitro* inhibition studies using marker substrates, topotecan did not alter the activities of human cytochromes P450 1A2, 2A6, 2C8/9, 2C19, 2D6, 2E, 3A, or 4A or dihydropyrimidine dehydrogenase.

Carcinogenesis and Mutagenesis

No one has yet studied the carcinogenicity of topotecan. It is a potent mutagen and clastogen as its mechanism of action suggests. Topotecan was mutagenic to L5178Y mouse lymphoma cells and clastogenic to cultured human lymphocytes with and without metabolic activation. It caused a dependant increase in micronucleated bone marrow cells in mice (N Aydemir and R Bilaloglu, *Mutation Research*, 2003, 537;43–51. Topotecan did not cause mutations in bacterial cells.

Reproductive Toxicity

Topotecan has a Pregnancy Category D. Topotecan may cause fetal harm when administered to a pregnant woman. In rabbits, a dose of 0.10 mg/kg/day (about equal to the clinical dose on a mg/m^2 basis) given on days 6 through 20 of gestation caused maternal toxicity, embryolethality, and reduced fetal body weight. In the rat, a dose of 0.23 mg/kg/day (about equal to the clinical dose on a mg/m^2 basis) given for 14 days before mating through gestation day 6 caused fetal resorption, microphthalmia, pre-implant loss, and mild maternal toxicity. A dose of 0.10 mg/kg/day (about half the clinical dose on a mg/m^2 basis) given to rats on days 6 through 17 of gestation caused an increase in post-implantation mortality. This dose also caused an increase in total fetal malformations. The most frequent malformations were of the eye (microphthalmia, anophthalmia, rosette formation of the retina, coloboma of the retina, ectopic orbit), brain (dilated lateral and third ventricles), skull, and vertebrae.

Based on a prior FDA finding of safety and effectiveness as described in the topotecan approved labeling and information provided by the sponsor this application is approvable from the perspective of toxicology and pharmacology.

W. David McGuinn, Jr., M.S., Ph.D., D.A.B.T.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22453	ORIG-1	TEVA PARENTAL MEDICINE INC	TOPOTECAN HYDROCHLORIDE INJECTION

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/s/

WILLIAM D MCGUINN
09/16/2009

SANDI L VERBOIS
09/17/2009

MEMORANDUM

Date: September 16, 2009
From: S. Leigh Verbois, Ph.D.
Supervisory Pharmacologist
Division of Drug Oncology Products
To: File for NDA #22-453
Topotecan Hydrochloride
Re: Approvability of Pharmacology and Toxicology

Teva Parenteral Medicines, Inc submitted a 505(b)2 NDA application for the treatment of (b) (4) carcinoma of small cell lung cancer and for the treatment of stage IV-B, recurrent, or persistent carcinoma of the cervix in combination with cisplatin. The sponsor submitted data in the form of expert consultations and literature to qualify a novel impurity, (b) (4) Both (b) (4) have been adequately qualified by the sponsor. Based on this information, in combination with the Agency's previous finding of safety and efficacy, this application is approvable from a Pharmacology/Toxicology perspective.

Recommendations: I concur with Dr. William McGuinn's conclusion that pharmacology and toxicology data support the approval of NDA 22-453, topotecan hydrochloride. There are no outstanding nonclinical issues related to the approval of this NDA for the proposed indication.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22453	ORIG-1	TEVA PARENTAL MEDICINE INC	TOPOTECAN HYDROCHLORIDE INJECTION

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/s/

SANDI L VERBOIS
09/17/2009