

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
200582Orig1s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM

Date: November 8, 2010
From: S. Leigh Verbois, Ph.D.
Supervisory Pharmacologist
Division of Drug Oncology Products
To: File for NDA # 200582
Topotecan Injection
Re: Approvability of Pharmacology and Toxicology

Hospira, Inc submitted a 505(b)2 NDA application [REDACTED] (b) (4)

[REDACTED] All drug substance and drug product specifications have been set below ICH qualification thresholds, therefore no additional impurity qualification was required. Based on this information, in combination with the Agency's previous finding of safety and efficacy, this application is approvable from a Pharmacology and Toxicology perspective.

Recommendations: There are no outstanding nonclinical issues related to the approval of this NDA for the proposed indication.

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/s/

SANDI L VERBOIS
11/08/2010

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

PHARMACOLOGY and TOXICOLOGY REVIEW AND EVALUATION

NDA Application number: 200582
Supporting documents: 001
Sponsor's letter date: October 29, 2009
CDER stamp date: October 29, 2009
Product: Topotecan Injection
Indication: Topotecan Injection is a topoisomerase inhibitor indicated for the treatment of small cell lung cancer sensitive disease after failure of first-line chemotherapy.
Sponsor: Hospira Inc.
Review Division: Division of Drug Oncology Products
Reviewer: W. David McGuinn, Jr., M.S., Ph.D., D.A.B.T.
Supervisor/Team Leader: S. Leigh Verbois, Ph.D.
Division Director: Robert Justice, M.D.
Project Manager: Allison Adams-McLean

Recommendation

This NDA is approvable from a Pharmacology and Toxicology Perspective.

Labeling Review for Topotecan Injection

Given that the action on this NDA is a Complete Response, final recommendations will be made at the time of approval.

<u>Section:</u>	<u>Recommendation:</u>
HIGHLIGHTS OF PRESCRIBING INFORMATION	

INDICATIONS AND USAGE

Topotecan Injection is a topoisomerase inhibitor indicated for:

WARNINGS AND PRECAUTIONS

- **Pregnancy:** Can cause fetal harm. Advise women of potential risk to the fetus. (5.4, 8.1)

USE IN SPECIFIC POPULATIONS-

- **Nursing Mothers:** Discontinue nursing when receiving topotecan injection. (8.3)

FULL PRESCRIBING INFORMATION

2 DOSAGE AND ADMINISTRATION

Handling

Topotecan Injection is a cytotoxic anticancer drug. Prepare Topotecan Injection under a vertical laminar flow hood while wearing gloves and protective clothing. If Topotecan Injection solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If Topotecan Injection contacts mucous membranes, flush thoroughly with water.

2.3 Instructions for Handling, Preparation and Intravenous Administration

Use procedures for proper handling and disposal of anticancer drugs. Several guidelines on this subject have been published.¹⁻⁴

5 WARNINGS AND PRECAUTIONS

Pregnancy Category D.

Topotecan Injection can cause fetal harm when administered to a pregnant woman.

5.6 Pregnancy

Topotecan caused embryoletality, fetotoxicity, and teratogenicity in rats and rabbits when administered during organogenesis. There are no adequate and well controlled studies of Topotecan Injection in pregnant women. If this drug is used during pregnancy, or if a patient becomes pregnant while receiving Topotecan Injection, the patient should be apprised of the potential hazard to a fetus [*see Use in Specific Populations, Pregnancy (8.1)*].

Section:

Recommendation:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D. ‘See Warnings and Precautions’ section.

Topotecan Injection can 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/m² basis) given on days 6 through 20 of gestation caused maternal toxicity, embryoletality, 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/m² 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/m² 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.

There are no adequate and well controlled studies of Topotecan Injection in pregnant women. If this drug is used during pregnancy, or if a patient becomes pregnant while receiving Topotecan Injection, the patient should be apprised of the potential hazard to a fetus.

8.3 Nursing Mothers

Rats excrete high concentrations of topotecan into milk. Lactating female rats given 4.7 mg/m² IV (about twice the clinical dose on a mg/m² basis) excreted topotecan into milk at concentrations up to 48-fold higher than those in plasma. It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Topotecan Injection, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity testing of topotecan has not been performed. Topotecan is known to be genotoxic to mammalian cells and is a probable carcinogen. Topotecan was mutagenic to L5178Y mouse lymphoma cells and clastogenic to cultured human lymphocytes with and without metabolic activation. It was also clastogenic to mouse bone marrow. Topotecan did not cause mutations in bacterial cells.

15 REFERENCES

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.
2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999.

Section:

Recommendation:

http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html

3. American Society of Health-System Pharmacists. ASHP Guidelines on Handling Hazardous Drugs: Am J Health-Syst Pharm. 2006;63:1172-1193.
4. Polovich, M., White, J. M., & Kelleher, L. O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

**17 PATIENT
COUNSELING
INFORMATION**

**17.2 Pregnancy and
Breastfeeding**

Advise patients to use effective contraceptive measures to prevent pregnancy and to avoid breastfeeding during treatment with Topotecan Injection.

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

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/s/

WILLIAM D MCGUINN
08/06/2010

SANDI L VERBOIS
08/06/2010