

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**0200199Orig1s000**

**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: 200199  
Supporting document/s: 000  
Applicant's letter date: January 27, 2010  
CDER stamp date: January 27, 2010  
Product: Topotecan Hydrochloride Injection  
Indication: 

- Small cell lung cancer sensitive disease after failure of first-line chemotherapy
- Combination therapy with cisplatin for stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amenable to curative treatment with surgery and/or radiation therapy

  
Applicant: Sandoz Inc.  
Review Division: DDOP  
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# 1 Executive Summary

## 1.1 Introduction

The US Food and Drug Administration approved the Reference Listed Drug (RLD) for the treatment of ovarian cancer in May 1996 and for cervical cancer in June of 2006. The sponsor of this NDA, Sandoz, Inc. intends to market a new formulation of topotecan for intravenous administration. This is a 505(b)2 application based on the prior approval. The submission included no new nonclinical data as none was required for approval of this application. There were no novel excipients or impurities caused by the change in formulation that required qualification in nonclinical studies

## 1.2 Brief Discussion of Nonclinical Findings

Topoisomerase I relieves torsional strain in DNA by inducing reversible single strand breaks. Topotecan binds to the topoisomerase I-DNA complex and prevents re-ligation 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.

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 designation. At doses approximately equal to the clinical dose on a mg/m<sup>2</sup> 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.

## 1.3 Recommendations

### 1.3.1 Approvability

Based on a prior FDA finding of safety and effectiveness as described in the reference-listed drug (RLD) approved labeling and information provided by the sponsor, this application is approvable from the perspective of toxicology and pharmacology.

### 1.3.2 Additional Non Clinical Recommendations

None

### 1.3.3 Labeling

1) The label should include the following in the Highlights section under Warnings and Precautions

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

2) The label should include the following in the Highlights section under Use in Specific Populations

- Nursing Mothers: Discontinue nursing when receiving Topotecan Injection. (8.3)

3) Section 5.4, Warnings and Precautions section, should read as follows:

#### **5.4 Pregnancy**

##### **Pregnancy Category D**

Topotecan Injection can cause fetal harm when administered to a pregnant woman. 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 taking Topotecan Injection, the patient should be apprised of the potential hazard to the fetus. [see *Use in Specific Populations, Pregnancy (8.1)*].

4) Section 8.1, Specific Populations, Pregnancy, should read as follows:

#### **8.1 Pregnancy**

Pregnancy Category D [see **Warnings and Precautions (5.4)**].

Topotecan Injection can cause fetal harm when administered to a pregnant woman. In rabbits, a dose of 0.1 mg/kg/day (about equal to the clinical dose of 1.5 mg/m<sup>2</sup> on a mg/m<sup>2</sup> 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 of 1.5 mg/m<sup>2</sup> on a mg/m<sup>2</sup> 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 0.1 mg/kg/day (about half the clinical dose of 1.5 mg/m<sup>2</sup> on a mg/m<sup>2</sup> 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 the fetus. [see **Warnings and Precautions (5.4)**]

5) Section 8.3, Use in Specific Populations, Nursing Mothers should read as follows:

Rats excrete high concentrations of topotecan into milk. Lactating female rats given 4.72 mg/m<sup>2</sup> IV (about thrice the clinical dose of 1.5 mg/m<sup>2</sup> on a mg/m<sup>2</sup> 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, discontinue breastfeeding when women are receiving Topotecan Injection.

6) Section 13.1 should read as follows:

### 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.

Topotecan given to female rats prior to mating at a dose of 1.4 mg/m<sup>2</sup> IV (about equal to the clinical dose of 1.5 mg/m<sup>2</sup> on a mg/m<sup>2</sup> basis) caused superovulation possibly related to inhibition of follicular atresia. This dose given to pregnant female rats also caused increased pre-implantation loss. Studies in dogs given 0.4 mg/m<sup>2</sup> IV (about 1/4th the clinical dose of 1.5 mg/m<sup>2</sup> on a mg/m<sup>2</sup> basis) of topotecan daily for a month suggest that treatment may cause an increase in the incidence of multinucleated spermatogonial giant cells in the testes. Topotecan may impair fertility in women and men.

## 2 Drug Information

### 2.1 Drug

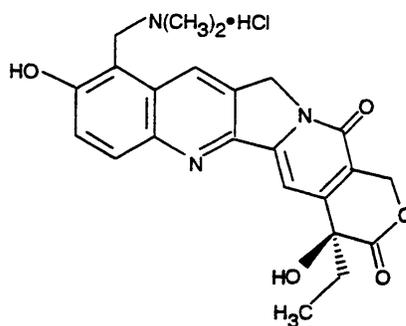
CAS Registry Number:	123948-87-8
Trade Name:	Topotecan injection
Generic Name:	Topotecan
Code Name:	None
Chemical Name	(S)-10-[(dimethylamino)methyl]-4-ethyl-

4,9-dihydroxy-1H-  
pyrano[3',4':6,7]indolizino[1,2-b]-quinoline-  
3,14-(4H,12H)-dione monohydrochloride

Molecular Formula  
Molecular Weight

$C_{23}H_{23}N_3O_5 \cdot HCl$   
421.453 g/mol (free base) (b) (4)

Structure:



Pharmacologic class:  
Relevant INDs and NDA

Topoisomerase inhibitor  
IND (b) (4) IND (b) (4), NDA 20-671

## 2.3 Drug Formulation

Dissolved in water for injection titrated with HCl

## 2.4 Comments on Novel Excipients

None

## 2.5 Comments on Impurities/Degradants of Concern

None

## 2.6 Proposed Clinical Population and Dosing Regimen

1.5 daily for five days starting on Day 1 of a 21-day course; IV, 30 minute infusion in patients with:

- Small cell lung cancer sensitive disease after failure of first-line chemotherapy
- Combination therapy with cisplatin for stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amenable to curative treatment with surgery and/or radiation therapy

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/s/  
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02/09/2011

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02/10/2011