

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**0200199Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

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## Clinical Pharmacology Review

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<b>NDA</b>	200-199/000
<b>Submission Date</b>	27 January 2010, 14 September 2010
<b>Brand Name</b>	Topotecan Hydrochloride Injection
<b>Generic Name</b>	Topotecan
<b>Indication</b>	In combination with cisplatin for the treatment of Stage IV-B, recurrent, or persistent carcinoma of the cervix
<b>Formulation</b>	A sterile solution at a concentration of 1 mg/mL in 1 mg/mL, 3 mg/mL and 4 mg/4 mL multi-dose vials
<b>Dosing Regimen</b>	0.75 mg/m <sup>2</sup> by intravenous infusion over 30 minutes on days 1, 2, and 3 followed by cisplatin 50mg/m <sup>2</sup> by intravenous infusion on day 1 repeated every 21 days
<b>Sponsor</b>	Sandoz, Inc.
<b>OCP Reviewer</b>	Hua Lillian Zhang, Ph.D.
<b>OCP Team Leader</b>	Qi Liu, Ph.D.
<b>OCPB Division</b>	Division of Clinical Pharmacology 5
<b>ORM Division</b>	Division of Drug Oncology Products

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## **1 EXECUTIVE SUMMARY**

This New Drug Application (NDA) is for Topotecan Hydrochloride Injection, 1 mg/mL in 1 mg/mL, 3 mg/mL and 4 mg/4 mL multi-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<sup>®</sup> for Injection (topotecan hydrochloride injection) that was previously approved by the FDA. The Applicant, Sandoz, Inc., has submitted this as a 505(b)(2) application and utilized the innovator's (GlaxoSmithKline's) HYCAMTIN<sup>®</sup> 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<sup>®</sup> 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 Section 3.

### **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<sup>®</sup> 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<sup>®</sup> for Injection (lyophilized RLD) is a lyophilized product containing the active substance in mannitol and tartaric acid and is available in single-dose vials at a strength of 4 mg topotecan as free base per vial (4 mg/4 mL upon reconstitution). Prior to use, the product will be diluted using Water for Injection and pH will be adjusted, if necessary, with hydrochloric acid and/or sodium hydroxide.

As an alternative to the RLD, the applicant submitted this application to market a new formulation. The applicant's proposed drug product is a ready-to-use aqueous solution presented as 1 mg/1 mL, 3 mg/3 mL, and 4 mg/mL of topotecan hydrochloride in multi-dose vials. All presentations contain the same concentration of topotecan hydrochloride (1 mg/mL as the free base) as the RLD. Water for Injection, tartaric acid, diluted hydrochloric acid, sodium hydroxide and nitrogen are the excipients. The excipients of the proposed product differ from the RLD (b) (4)

The applicant is seeking approval for the cervical cancer indication. The condition of use and route of administration for the proposed drug product are the same as prescribed and recommended for the use of the RLD. The approved dosage of RLD for cervical cancer is 0.75 mg/m<sup>2</sup> given as a 30 minute intravenous (i.v.) infusion on days 1, 2, and 3 followed by cisplatin 50 mg/m<sup>2</sup> by intravenous infusion on day 1 repeated every 21 days.

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<sup>®</sup> 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?**

Sandoz's Topotecan Injection is supplied as a ready to use solution available in 1mg/1ml, 3mg/3mL, and 4 mg/4mL multi-dose vials. Each 1mL contains topotecan hydrochloride equivalent to 1mg, 3mg and 4 mg of topotecan as free base. The 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 comparisons between the Sandoz'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 **Blue**.

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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HUA ZHANG  
10/04/2010

QI LIU  
10/04/2010