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*APPLICATION NUMBER:*  
**0200199Orig1s000**

**MEDICAL REVIEW(S)**

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*MEMORANDUM*

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**DATE** February 6, 2011

**TO** NDA 200-199

**FROM** Michael Brave, M.D.  
Medical Officer, DDOP/OODP/CDER

**SUBJECT** New Drug Application

1. Background

Topotecan hydrochloride is a semi-synthetic derivative of camptothecin with topoisomerase I-inhibitory activity. It is marketed by GlaxoSmithKline (GSK) under the trade name Hycamtin<sup>®</sup>, with indications for 1) metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy, 2) small cell lung cancer (SCLC) sensitive disease after failure of first-line chemotherapy, and 3) in combination 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.

The currently marketed Hycamtin product is a lyophilized powder. It is supplied as 1 mg/mL, 3 mg/3mL (1 mg/mL), and 4 mg/4mL (1 mg/mL) multi-dose vials which should be diluted in a minimum of 50 mL of 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection USP prior to intravenous infusion over 30 minutes. Topotecan Injection diluted for infusion is stable for 4 hours at room temperature or 24 hours at refrigerated temperature in ambient lighting conditions.

2. Submission

The Applicant submitted the current application on January 27, 2010 for Topotecan Hydrochloride Injection 1 mg/mL under 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The proposed drug product is in the same dosage form (i.e. injectable solution) containing the same active ingredient at the same concentration after reconstitution as the RLD, and is intended for administration by intravenous infusion. The proposed formulation differs from the reference listed drug (RLD) in excipients only. The RLD is a lyophilized product and contains the excipients mannitol and tartaric acid; hydrochloric acid and sodium hydroxide are used in the RLD to adjust pH. The proposed formulation differs from the RLD in (b) (4). In addition, (b) (4)

The Applicant conducted no clinical studies. This application relies for approval on the FDA's findings of safety and effectiveness for GSK's Reference Listed Drug (RLD) Hycamtin<sup>®</sup>.

The proposed clinical indications for cervical cancer and SCLC are the same as those of the RLD. (b) (4)

The application contains no new clinical data.

### 3. Post-submission regulatory activity

- 30 Mar 2010 DODP issued a 74-day filing letter which identified no potential review issues. The review classification for this application is Standard. Therefore, the user fee goal date was to be November 27, 2010.
- 1 Jun 2010 ONDQA recommended that the Applicant's request for a biowaver be granted.
- 22 Sept 2010 OPS completed its environmental assessment and issued a finding of no significant impact (FONSI).
- 22 Sept 2010 DMEPA completed its labeling review and recommended improved presentation of dose modification guidelines and dosage adjustment within the inert. Additionally, they identified two AERS cases where a 10-fold overdose occurred and recommend adding a warning to the insert labeling alerting healthcare professionals that 10-fold overdoses of topotecan have occurred and resulted in serious adverse outcomes.
- 24 Sept 2010 FDA informed the Applicant that the application was not approval because (b) (4) DMF (b) (4) was inadequate.
- 30 Sept 2010 DDOP received an unsolicited major amendment to this application. The receipt date was within three months of the user fee goal date. Therefore DDOP extended the user fee goal date to February 27, 2011.
- 4 Oct 2010 OCP recommended approval from a clinical pharmacology standpoint.
- 28 Oct 2010 OPS/NMDS recommended for approval from a microbiology quality standpoint.

### 4. Conclusion

This application is acceptable from a clinical standpoint.

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/s/  
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02/07/2011

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