CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

0200199Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	2/25/2011
From	Amna Ibrahim MD
Subject	Deputy Division Director Summary Review
NDA/BLA # **Supplement #**	200199
Applicant Name	Sandoz Inc
Date of Submission	1/27/2010 9/30/2010 (major amendment)
PDUFA Goal Date	2/27/2011
Proprietary Name / **Established (USAN) Name**	Topotecan Injection
Dosage Forms / Strength	Intravenous/1 mg/mL, 3 mg/3 mL, 4 mg/4 mL
Proposed Indication(s)	1. Small cell lung cancer sensitive disease after failure of first-line chemotherapy 2. 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.
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Brave, Michael/Liu, Ke
Statistical Review	NA
Pharmacology Toxicology Review	McGuinn, William D
CMC Review/OBP Review	Ghosh, Debasis
Product Microbiology Review	Fong, Steven E
Clinical Pharmacology Review	Zhang, Hua
DDMAC	Adam, George
DSI	NA
CDTL Review	Pope, Sarah
OSE/DMEPA	Chan, Irene Z

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader

1. Introduction

Sandoz Inc submitted a New Drug Application (NDA) for Topotecan Hydrochloride Injection on 1/27/2010. Because of a major Chemistry, Manufacturing and Controls (CMC) amendment, the review clock was extended three months to 2/27/2011.The reference listed drug (RLD) for this 505(b)(2) submission is Hycamtin (topotecan hydrochloride for injection), marketed by GlaxoSmithKline (NDA 20-671; approved May 28, 1996).

2. Background

The proposed indications are small cell lung cancer and cervical cancer. (b) (4) (b) (4) As noted by Sarah Pope Miksinski PhD (CDTL), the proposed drug product contains the same active ingredient as the RLD, and the prepared/post-reconstitution drug product solution is the same concentration as the RLD.

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. As noted by Dr Miksinski, the major product quality issue related to the inadequacy of DMF (b) (4) to support this NDA. DMF (b) (4) was deemed inadequate (see review by Dr. A. Russell) on 15- JUN-2010, and following the DMF holder's response to the deficiencies, the DMF was determined to be adequate on 09-NOV-2010. A biowaiver was requested and granted by John Duan PhD. Manufacturing site inspections were acceptable. Steven Fong PhD, product quality microbiology reviewer recommended approval in his review. Stability testing supports an 18-month expiration dating period can granted for real time (2-8^{o}C) storage conditions when protected from light. There are no outstanding issues.

As recommended by the CDTL, Dr Miksinski, the following language confirming the granted expiration dating period should be placed in the action letter: "Based on the stability data provided, an 18-month expiration dating period is granted for the drug product, when stored at 2^{o}C -8^{o}C (36^{o}F -46^{o}F) and protected from light."

4. Nonclinical Pharmacology/Toxicology

According to William McGuinn, PhD, 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. Dr McGuinn also stated that 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.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Per Hua Zhang PhD, there is no bioequivalent study nor any other clinical studies submitted in this application.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

According to Michael Brave MD, the applicant did not conduct clinical studies. This application relies for approval on the FDA's findings of safety and effectiveness for GSK's Reference Listed Drug (RLD) Hycamtin®. He stated that this application is acceptable from a clinical standpoint.

8. Safety

Not applicable.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

Not applicable.

11. Other Relevant Regulatory Issues

- DSI Audits: None
- Financial Disclosure: None
- Other consults: None

There are no other unresolved relevant regulatory issues

12. Labeling

- Proprietary name: Not applicable
- Physician labeling: Issues were discussed and resolved
- Carton and immediate container labels: There are no remaining issues
- Patient labeling/Medication guide: There is no medication guide or patient labeling
- DMEPA comments: Deficiencies identified by the DMEPA reviewer Iren Chan were addressed by the applicant. As stated by Dr Pope that in the final review, the CMC reviewer confirms that the updated container/carton labels reflected the recommended changes and were acceptable from a CMC standpoint. The DMEPA reviewer confirmed the same via an 08-FEB-2011 email. In a 22-FEB-2011 email, the DMEPA reviewer also confirmed that the Applicant's proposed PI (received 17- FEB-2011) was acceptable.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action
  This NDA should be approved. There are no remaining deficiencies for this submission.

- Risk Benefit Assessment
  The proposed drug product contains the same active ingredient as the RLD, and the prepared/post-reconstitution drug product solution is the same concentration as the RLD. As stated by the CDTL, the review of this NDA is based primarily on chemistry, manufacturing and controls data. The risk benefit profile should be the same as the RLD. There are no outstanding deficiencies for this NDA

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  None.

- Recommendation for other Postmarketing Requirements and Commitments
  None.

Amna Ibrahim MD
Deputy Division Director
Division of Drug Oncology Products

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/s/

AMNA IBRAHIM
02/25/2011