CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

0200199Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	22-FEB-2011
From	Sarah Pope Miksinski, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	200199
Applicant	Sandoz, Inc.
Date of Submission	27-JAN-2010 30-SEP-2010 (major amendment – clock extended)
PDUFA Goal Date	27-FEB-2011 (based on extension)
Proprietary Name / Established (USAN) names	Topotecan Injection
Dosage forms / Strength	1 mg/mL, 3 mg/3 mL, 4 mg/4 mL
Proposed Indication(s)	Indicated for the treatment of cervical cancer and small cell lung cancer
Recommended:	**Approval**

1. Introduction

Sandoz, Inc. submitted NDA 200199 for Topotecan Injection on 27-JAN-2010. The NDA was filed by the Agency on 16-APR-2010. The Agency granted a standard review with an initial PDUFA goal date of 27-NOV-2010. There were no comments conveyed in the 74-day letter. Based on a major Chemistry, Manufacturing and Controls (CMC) amendment received on 30-SEP-2010, the review clock was extended three months to 27-FEB-2011.

This CDTL memo serves to highlight the critical approvability issues discussed in all review disciplines and recommends an "Approval" action for this application. All individual discipline reviews may be found in DARRTS. Final container labels were provided on 07-FEB-2011. The most recent PI labeling was received on 17-FEB-2011. This labeling was confirmed as acceptable for all disciplines.

2. Background

The Reference Listed Drug for this submission is Hycamtin® (topotecan hydrochloride) for Injection (NDA 20-671), which is currently marketed by GlaxoSmithKline. The proposed drug product is an aqueous injectable dosage form intended for dilution and intravenous injection. It is supplied at a concentration of 1 mg/mL topotecan (free base) in three dosing volumes (1 mL, 3 mL, and 4 mL). 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.

The inactive ingredients in the proposed product are qualitatively and quantitatively the same as the inactive ingredients contained in the RLD, (b) (4)

Dosing Regimen and Administration
For small cell lung cancer, the recommended dose of Topotecan Injection is 1.5 mg/m^2 by intravenous infusion over 30 minutes daily for five consecutive days, starting on day 1 of a 21-day course. For cervical cancer, the recommended dose is 0.75 mg/m^2 by intravenous infusion over 30 minutes daily on days 1, 2, and 3 followed by cisplatin 50 mg/m^2 on day 1 repeated every 21 days.

3. CMC

NDA 200199 was initially submitted on 27-JAN-2010 as a 505(b)(2) application. The NDA included a full dossier of CMC information, along with proposed container/carton and PI labeling. During the review, the CMC reviewer noted outstanding deficiencies with one of the cross-referenced Type 2 Drug Master Files (DMF (b) (4)). The DMF deficiencies cannot be stated in the current memo. However, the specific content of the DMF deficiencies is located in the 15-JUN-2010 review for DMF (b) (4). In an 30-SEP-2010 submission to NDA 200199, the Applicant confirmed that the DMF holder submitted a response to the DMF deficiencies, and the review clock for NDA 200199 was subsequently extended based on this confirmation and DMF amendment. A subsequent review of DMF (b) (4) determined that the DMF is now adequate to support this NDA.

- General product quality considerations
  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.

  The inadequacy of DMF (b) (4) rendered it impossible to (b) (4) of the drug substance in both DMF (b) (4) and NDA 200199. Most notably, the drug substance, as supplied by one of the proposed suppliers (b) (4), is not supplied as a (b) (4), as originally stated in the NDA. Instead, (b) (4) process resulted in a (b) (4) This discrepancy impacted several quality areas of the NDA.

  Once the DMF deficiencies related to the (b) (4) had been resolved, review of NDA 200199 continued under a clock extension, and the appropriate CMC subsections were reviewed and updated as needed (see the final CMC review dated 14-FEB-2011). The resolution of the DMF deficiencies effectively also resolved the pending NDA deficiencies.

NDA 200199 included a request for a biowaiver. This request was evaluated in a 27-JAN-2010 review (Dr. J. Duan) which granted the Applicant's request.

The Applicant's original submission included 18 months of real time (2-8^{o}C) and accelerated (25^{o}C) stability data for nine batches of the drug product, as derived from (b) (4), and 12 months of real time and accelerated stability data for an additional nine batches derived from (b) (4). All studies were conducted on (b) (4) configurations. Based on the stability data provided, an 18-month expiration dating period can granted for real time (2-8^{o}C) storage conditions when protected from light. The granted expiration dating period should be captured in the action letter.

- Facilities review/inspection
  An Establishment Evaluation Request (EER) was submitted to the Office of Compliance on 26-MAR-2010. An overall acceptable recommendation was issued for the application on 18-JUN-2010.

- Microbiology
  Topotecan Injection is an (b) (4) product. The microbiology reviewer (Dr. S. Fong) recommended approval of this NDA in his review dated 18-OCT-2010. Of particular note is the reviewer's confirmation that the drug product is supported as a "multi-dose" product. The review captures the reviewer's concurrence with microbiological aspects of the proposed primary stability protocol, as well as the acceptability of the proposed specifications for endotoxins and sterility in the drug product. The review also captures the assessment of the proposed Comparability Protocol detailing the Applicant's proposed move from the current (b) (4) manufacturing site to the proposed (b) (4) manufacturing site (b) (4)

- Other notable issues (resolved or outstanding)
  During the review cycle, the Applicant's proposed Comparability Protocol was discussed internally between the Microbiology and CMC reviewers. As stated previously, both reviewers determined that the proposed Comparability Protocol was acceptable. Both reviewers also agreed with the Applicant's proposed (b) (4) (b) (4)

  In order to ensure consistency, this secondary reviewer also confirmed that the proposed Comparability Protocol could be considered and approved as recommended by the primary reviewers (CMC, Microbiology). Reference is made to an internal discussion with Dr. R. Lostritto and Mr. M. Folkendt on 02-FEB-2011, in which this confirmation was obtained. Reference is also made to a 09-FEB-2011 internal discussion between the CMC review team, the Microbiology reviewer, and representatives from the Office of Compliance. During this internal discussion, all parties were aligned in the recommendation of approval for the proposed Comparability Protocol, as well as its proposed (b) (4). In a

subsequent teleconference with the Applicant (also held on 09-FEB-2011), the Agency requested the addition of language into the Comparability Protocol that outlines the Applicant's understanding and commitment that the proposed site will be ready for inspection at the time of the [redacted] (b) (4). In the teleconference, the Agency also conveyed that the Office of Compliance would confirm the proposed acceptability of the new site when the supplement was received, and the Applicant acknowledged this understanding.

[redacted] (b) (4)

4. Nonclinical Pharmacology/Toxicology

There were no new nonclinical pharmacology/toxicology studies provided in this submission. The final Pharmacology/Toxicology memo was finalized (Dr. W. McGuinn) in DARRTS on 10-FEB-2011 and captures a recommendation of approval for the NDA. Labeling recommendations for the proposed PI are also captured in the review.

5. Clinical Pharmacology

There was no clinical pharmacology data submitted to this NDA. The clinical pharmacology reviewer (Dr. H. Zhang) recommended approval of this NDA in her review dated 04-OCT-2010. This review also captures related revisions to the PI.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

There are no new clinical data provided in the current submission. The clinical reviewer (Dr. M. Brave) recommends approval of this NDA in his 07-FEB-2011 memo.

8. Safety

No new clinical data were provided for this submission.

9. Advisory Committee Meeting

Not applicable

10. Pediatrics, Geriatrics, and Special Populations

Not applicable

11. Other Relevant Regulatory Issues

- Application Integrity Policy (AIP): This was not raised during the pre-approval inspections for this NDA.
- Exclusivity or patent issues of concern: No issues were noted for this NDA.
- Financial disclosures: Not applicable
- Other GCP issues: None
- DSI audits: Not applicable
- Other discipline consults: None
- Any other outstanding regulatory issues: None

12. Labeling

General:
All disciplines participated in internal labeling meetings held throughout the review clock. Specific labeling recommendations are captured in each discipline-specific review.

Proprietary name:
There was no proprietary name proposed for this product.

DMEPA comments:
In an initial review dated 23-SEP-2010, DMEPA (Dr. I. Chan) identified several specific deficiencies in the proposed container/carton labeling. These deficiencies were subsequently conveyed to the Applicant. In an updated review dated 09-DEC-2010, the DMEPA reviewer evaluated updated labels submitted on 01-OCT-2010. Additional revisions were recommended, and following internal team discussion, these comments were issued to the Applicant.

Overlapping container/carton labeling comments are covered in the 14-FEB-2011 CMC review. 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.

Carton and immediate container labels:
See above section titled "DMEPA comments." Overlapping container/carton labeling comments are also covered in the 14-FEB-2011 CMC review. The CMC reviewer confirmed that the updated (08-FEB-2011) container/carton labels reflect the recommended changes and are acceptable from a CMC standpoint.

Patient labeling/Medication guide:
This is not required for this product.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action
  This reviewer recommends approval of this NDA. There are no outstanding deficiencies for any disciplines involved in the review of this submission. All disciplines were involved in labeling discussions. The final proposed labeling reflects the recommended revisions from all disciplines and is acceptable.

- Risk Benefit Assessment
  The review of this NDA is based primarily on chemistry, manufacturing and controls data. However, the NDA is recommended for approval from all disciplines.

- Recommendation for Postmarketing Risk Management Activities
  This does not apply to this NDA.

- Recommendation for other Postmarketing Study Commitments
  None

- Recommended Comments to Applicant
  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."

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/s/

SARAH P MIKSINSKI
02/22/2011