CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022453Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review #2

DATE	20-DEC-2012
From	Nallaperumal Chidambaram, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA #	22453
Applicant	Teva Parenteral Medicines, Inc.
Date of Submission	25-JUN-2012
PDUFA Goal Date	25-DEC-2012
Proprietary Name/ Established (USAN) names	Topotecan Hydrochloride Injection
Dosage forms / Strength	4 mg/4 mL
Proposed Indication(s)	• Small cell lung cancer • Cervical Cancer
Recommendation:	**Approval**

1. Introduction

NDA 22453 was initially submitted to the Agency on 17-DEC-2008. The Agency subsequently undertook a "Complete Response" action on 16-OCT-2009 due to deficiencies noted during inspection of the drug product manufacturing facility and that satisfactory resolution of those deficiencies is required before this application can be approved. The Applicant resubmitted the NDA on 25-JUN-2012, and the Agency conveyed the fileability determination in a 5-JUL-2012 letter.

The two pending issues that were noted in the CR letter are related to (1) Facility inspection, and (2) labeling issues.

This CDTL memo serves to summarize the critical issues noted in all review disciplines and recommends an "**approval**" action for this application. All individual discipline reviews may be found in DARRTS.

2. Background

The Reference Listed Drug for this submission is Hycamtin (topotecan hydrochloride) for Injection (NDA 20-671), is a sterile lyophilized powder. Hycamtin is a single dose vial and is currently marketed by GSK. The proposed drug product topotecan hydrochloride is a sterile, single-use vial (4

mg/4 mL) in a 4 mL vial. Each mL contains topotecan hydrochloride equivalent to 1 mg of topotecan free base, 12 mg of mannitol, USP, 5 mg of tartaric acid, NF. Sodium hydroxide and hydrochloric acid may be used to adjust the pH.

Dosing Regimen and Administration

The recommended dose of Topotecan Hydrochloride Injection is as follows:

Small Cell Lung Cancer

- The recommended dose of Topotecan Injection is 1.5 mg/m^2 by intravenous infusion over 30 minutes daily on days 1 to 5 of each 21-day cycle until disease progression.

Cervical Cancer

- The recommended dose of Topotecan Injection is 0.75 mg/m2 by intravenous infusion over 30 minutes daily on days 1, 2, and 3 of each 21-day cycle. Administer cisplatin 50 mg/m2 by intravenous infusion on day 1 of each 21-day cycles.

3. CMC

NDA 22453 was submitted on 17-DEC-2008 as a 505(b)(2) application. The Agency subsequently undertook a "Complete Response" action on 16-OCT-2009 due to a "withhold" recommendation from the Office of Compliance. The Applicant resubmitted the NDA on 25-JUN-2012.

General product quality considerations

The CMC reviewer (Dr. Debasis Ghosh) recommended approval pending resolution of labeling issues in his review #2 dated 04-DEC-2012, and full approval of this NDA dated 19-DEC-2012. Details regarding resolution of labeling issues are noted at the end of this memo.

The drug substance is a (b) (4) The manufacturing and controls information is cross-referenced to a DMF. This DMF was found to be adequate (Refer to Dr. D. Ghosh's review dated 02-OCT-2012).

The inactive ingredients in the proposed product and the RLD product are qualitatively similar but quantitatively different (RLD is a lyophilized powder for Injection, and the proposed product is an Injection). It should be noted that the proposed drug product and the RLD are identical after reconstitution. The inactive ingredients in the RLD are: mannitol, 48 mg, and tartaric acid, 20 mg. Hydrochloric acid and sodium hydroxide may be used to adjust the pH. The solution pH ranges from 2.5 to 3.5, whereas, the inactive ingredients in the proposed drug product are: 12 mg of mannitol, USP, 5 mg of tartaric acid, NF. Sodium hydroxide and hydrochloric acid

may be used to adjust the pH. The proposed product has a pH range of 2.0 to 2.5.

Based on provided stability data, and statistical regression analysis, a (b) (4) shelf-life was found to be acceptable when stored at (b) (4) under ambient humidity conditions and protected from light.

ONDQA Biopharm review

The Biopharm reviewer (Dr. E. Chikhale) noted in her review dated 31-AUG-2012 that the original NDA included a bioequivalence (BE) waiver request; however, the evaluation of this request was not documented. The clinical pharmacology review dated 28-AUG-2009 refers to ONDQA as having granted a biowaiver, but the original CMC review does not include this information. Owing to this, the BE waiver request was evaluated in the resubmission.

The proposed Topotecan Hydrochloride Injection (contains topotecan hydrochloride equivalent to 1 mg topotecan free base/mL) is a single-use vial (4 mg/4 mL) that is readily diluted and administered. However, the RLD is a sterile lyophilized powder. The only difference after reconstitution is the difference in pH as noted above (see General Product Considerations). The applicant has requested a waiver of the *in vivo* bioequivalence study requirement as allowed under 21 CFR 320.22(b)(1), because:

• Topotecan HCl Injection is a parental drug product intended for administration by injection, and
• The proposed drug product contains the same active and inactive ingredients in the same concentration (after dilution) as the RLD (after reconstitution).

According to 21 CFR 320.22(b) indicates that for certain drug products the in vivo bioavailability (BA) or bioequivalence (BE) of the drug product may be self-evident and the Agency can waive the requirement from the submission of *in vivo* BA/BE data for these drug products. In addition, a drug product's *in vivo* bioavailability or bioequivalence may be considered self-evident if the drug product meets the following:

• Is a parenteral solution intended solely for administration by injection, and
• Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

The Biopharm reviewer noted that the small difference in pH (2.2 *vs*. 3.0) noted between the proposed drug product and the RLD will not affect the bioavailability of the proposed drug product. Based on the above, the reviewer found the applicant's request for a biowaiver for their proposed product Topotecan Hydrochloride Injection acceptable and a biowaiver was therefore granted.

Facilities review/inspection
The Office of Compliance issued an overall acceptable recommendation for this application on 31-AUG-2012.

Microbiology
The microbiology reviewer (Dr. D. Miller) noted that her original Microbiology review dated 13-JUL-2009 recommended approval from a quality Microbiology perspective. In the current review cycle, the reviewer sent in a information request on 01-OCT-2012 and evaluated the response dated 12-OCT-2012 and determined that the information is acceptable and has recommended approval from a quality Microbiology perspective dated 24-OCT-2012.

Other notable issues (resolved or outstanding): None

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology reviewer (Dr. D. Kufrin) in her review dated 16-OCT-2012 had noted that no nonclinical studies were submitted and none were identified in the complete response letter sent on 16-OCT-2009. The original reviewers (Drs. D. McGuinn and L. verbois) based on expert consultations and literature references, had noted that the applicant had submitted sufficient information to qualify the novel impurity (b) (4) . In the current review cycle, owing to the above, the reviewer has noted that there are no outstanding issues and that this application is recommended for approval from her perspective.

5. Clinical Pharmacology

The Clinical Pharmacology reviewer (Dr. Ruby Leong) in her review dated 03-OCT-2012 indicated that a Biowaiver was granted by ONDQA Biopharm (refer to 31-AUG-2012) and that the resubmission does not contain new clinical study information, therefore, a clinical pharmacology review is not necessary for this resubmission.

The original review was performed by Dr. Jeanne Fourie Zirkelback (refer to her review dated 28-AUG-2009).

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The clinical reviewer (Dr. Shakuntala M. Malik) in her review dated 27-SEP-2012 indicated that no new clinical information was submitted to review.

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 application is not in the AIP list.
Exclusivity or patent issues of concern: None.
Financial disclosures: No issues
Other GCP issues: None
DSI audits: None
Other discipline consults: DMEPA/Micro/Biopharm

The DMEPA reviewer (Dr. J. Schlik) in his review dated 16-NOV-2012 recommended changes to container, carton and tray liner labeling.

Any other outstanding regulatory issues: None

12. Labeling

The CMC reviewer noted that the NDC numbers for vial and the packaging were found to be different from the normal practice of specifying same NDC number for both the vial and the carton. The applicant proposed to have different NDC numbers for vial and carton. Following a teleconference with the applicant and after consultation with the SPL team, and on the conclusion of DMEPA review dated 19-DEC-2012, the review team agreed to accept the proposed changes as noted below:

Package Insert:

How Supplied Section:

Topotecan Injection is supplied as a single-use vial. Each vial contains 4 mL of sterile solution of topotecan hydrochloride. Each mL contains topotecan hydrochloride equivalent to 1 mg of topotecan free base.

NDC 0703-4714-01 (Package of 1 Single-Use Vial NDC 0703-4714-71)
NDC 0703-4714-02 (Package of 5 Single-Use Vials NDC 0703-4714-71)

All issues were resolved satisfactorily. Please refer to DMEPA review dated 16-NOV-2012 and 19-DEC-2012 respectively.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
This reviewer recommends approval of this NDA

Risk Benefit Assessment
The review of this NDA is based primarily on chemistry, manufacturing and controls data. All Chemistry, manufacturing and controls deficiencies are resolved and the application has received an overall acceptable recommendation from the Office of Compliance. Therefore, the Applicant has adequately supported the commercialization of the proposed drug product.

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

Recommendation for other Postmarketing Study Commitments
None

Recommended Comments to Applicant
Based on provided stability data and also on statistical regression analysis, the proposed shelf-life of (b) (4) is granted when stored at (b) (4) at ambient humidity conditions and protected from light.

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

/s/

NALLAPERUM CHIDAMBARAM
12/20/2012