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APPLICATION NUMBER:

022453Orig1s000

SUMMARY REVIEW

Division Director Summary Review

Date	January 4, 2013
From	Patricia Keegan
Subject	Division Director Summary Review
NDA #	NDA 22453
Applicant Name	Teva Pharmaceuticals USA
Date of Submission	December 17, 2008
Complete Response Letter	October 16, 2009
Date of Re-submission	June 25, 2012
PDUFA Goal Date	December 25, 2012
Proprietary Name / Established (USAN) Name	none/ Topotecan Injection
Dosage Forms / Strength	Injection/ 1 mg (base) per mL
Proposed Indication(s)	▪ for the treatment of (b) (4) small cell lung cancer (b) (4) after failure of first-line chemotherapy. In clinical studies submitted to support approval, sensitive disease was defined as disease responding to chemotherapy but subsequently progressing at least 60 days (b) (4) after chemotherapy ▪ in combination with cisplatin is indicated 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.
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager Reviews	Deanne Varney
Medical Officer Review	Shakun Malik
Pharmacology Toxicology Review	Dubravka Kufrin
CMC Review	Debasis Ghosh
ONDQA Biopharmaceutics Review	Elsbeth Chikhale
Microbiology Review	Denise Miller
Clinical Pharmacology Review	Ruby Leong
DMEPA Review	James Schlick
OPDP/DPDP Review	Carole Broadnax

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
DPDP= Division of Professional Drug Promotion
DMEPA=Division of Medication Error Prevention and Analysis

Reference ID: 3245734

Division Director Summary Review

1. Introduction

On December 17, 2009, Teva Pharmaceuticals submitted NDA 22-453 for Topotecan Hydrochloride Injection, seeking approval under the provisions of 21 CFR 314.54(a)(1)(iii) and Section 505(b)(2) of the Food, Drug, and Cosmetic Act. In support of this NDA, Teva stated their intent to rely on the Agency's prior findings of safety and efficacy for GlaxoSmithKline's Hycamtin® (topotecan hydrochloride) for Injection approved under NDA 020671. In addition, Teva relied on published literature to support the qualification (safety data supporting release specifications) of certain impurities not present in the listed drug product.

As compared to the listed drug, Hycamtin, which is supplied as a is lyophilized powder in a 4 mg single dose vial, Teva's product is supplied as an injectable solution containing 1 mg topotecan (freebase) in 1 mL. Teva requested approval for (b) (4) indications for Hycamptin, for treatment of non-small cell lung cancer and for treatment, in combination with cisplatin, of (b) (4) cancer. (b) (4) The application contained CMC information, a request for waiver from the requirements from PREA, a request for a waiver from the requirement to conduct bioequivalence studies, and literature supporting the qualification of impurity levels. No new toxicology or human clinical study data were provided.

The major issues considered in the application were the acceptability of the manufacturing facilities, adequacy of CMC characterization, and compliance of physician labeling and carton/container labeling with applicable regulations and FDA Guidance to Industry.

2. Background

The listed drug referenced by Teva for this 505(b)(2) application is Hycamtin, which was approved under NDA 020671 [Hycamtin (topotecan hydrochloride) for Injection; GlaxoSmithKline] on May 28, 1996. The active moiety, topotecan, is also approved under the following applications.

Reference ID: 3245734

NDA	Name	Applicant	Date of approval
NDA 020981	Hycamtin (topotecan) Capsules	GlaxoSmithKline	October 12, 2007
NDA 200582	Topotecan Injection	Hospira	February 2, 2011
NDA 200199	Topotecan Injection	Sandoz	February 25, 2011

Regulatory History of NDA 22453

November 14, 2008: pre-NDA meeting scheduled under IND 103440. Preliminary responses to Teva's questions were provided by facsimile transmission on November 13, 2008. In their responses, FDA provided the following advice

- Provide non-clinical studies in rodent and clinical studies of (b) (4) at a dose of (b) (4) for 5 days, to support the proposed upper limit for the (b) (4) specification of (b) (4)%.
- Clinical studies would not be required to support the NDA
- The requirement to conduct a bioequivalence study would be waived in accordance with 21 CFR §320.33(b)(i) and (ii).

NDA regulatory history

- December 17, 2008: NDA submitted
- February 27, 2009: NDA filed
- June 24, 2009: PeRC meeting: The Committee recommended that waiver from the requirement to conduct pediatric studies under PREA should be granted.
- October 16, 2009: Complete Response letter issued, citing the following deficiency:
  - "During a recent inspection of the Teva Parenterals, Inc. manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved."
  - Draft physician labeling and carton/container labeling were attached to the complete response letter.
- June 25, 2012: Resubmission containing a Complete Response to the October 16, 2009 letter

3. CMC

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing sites were determined to be acceptable as stated in the EES Summary appended to Dr. Ghosh's review dated 12/4/2012. The environmental assessment was completed during the first review cycle with a finding of no significant impact. Stability testing supports an expiry of 24 months when stored at 5° C, protected from light. There are no outstanding CMC issues that preclude approval.

Reference ID: 3245734

The drug product under this NDA is supplied as a solution for further dilution for intravenous infusion. The Teva product differs from the listed drug, Hycamtin, in that the former is a solution and the listed drug is a lyophilized powder, and that prior to reconstitution, the products differ in the concentration of inactive ingredients. In addition, The pH of the Teva topotecan product is 2.2 whereas the reconstituted Hycamtin has a pH of 3.0.

A waiver from the requirement to conduct an *in vivo* bioequivalence study was granted, as stated in the Biopharmaceutics review dated 08/31/2012.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology or toxicology issues that preclude approval. Dr. Kufrin noted that no nonclinical pharmacology or toxicology data had been provided in the resubmission. Drs. W. David McGuinn and S. Leigh Verbois provided reviews of information in the original NDA submission. These reviewers concluded that the combination of expert consultations and literature publications provided in the NDA were sufficient to qualify both a novel impurity, (b) (4), and a (b) (4), present in this formulation of Topotecan Injection.

5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology reviewers, as stated in their reviews data August 28, 2009 and October 3, 2012, that there are no outstanding clinical pharmacology issues that preclude approval. The resubmission contained no new clinical study or pharmacokinetic data, therefore a clinical pharmacology review was not required for the resubmission.

6. Clinical Microbiology

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

I concur with the conclusions reached by the clinical reviewer that there are no outstanding issues that preclude approval. Neither the original submission nor the resubmission contained clinical study information. The approval of this application is based on FDA's prior findings of safety and effectiveness for the listed drug, Hycamtin (NDA 020671; GlaxoSmithKline).

8. Safety

I concur with the conclusions reached by the clinical reviewer that there are no outstanding issues that preclude approval. Neither the original submission nor the resubmission contained clinical study information or post-marketing safety information. The approval of this application is based on FDA's prior findings of safety and effectiveness for the listed drug, Hycamtin (NDA 020671; GlaxoSmithKline).

9. Advisory Committee Meeting

The Division did not refer this application to an Advisory Committee because the drug is not a new molecular entity and the application relied on the prior findings of safety and effectiveness for the FDA-approved, listed drug, Hycamtin (NDA 020671; GlaxoSmithKline).

10. Pediatrics

Teva submitted a request for waiver for the requirement to conduct studies under the Pediatric Research Equity Act (PREA). The request was reviewed by the clinical review team and reviewed by the PeRC on June 24, 2009, both of which agreed that the pediatric study requirement for this application should be waived because necessary studies are impossible or highly impracticable because there are too few children with small cell lung cancer or carcinoma of the cervix to study.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues

12. Labeling

- Proprietary name – A proprietary name was not proposed or requested.
- Physician labeling
  - Indications and Usage; (b) (4)
  - Other sections of product labeling revised for brevity, use of "command language,". and consistency with FDA Guidance on Product Labeling (various sections) and with Physician Labeling Review format.
  - Removal of statements not supported by substantial evidence of effectiveness (statistical comparison of response duration between treatment arms in section 14)
  - Removal of Contraindications based on theoretical risks, i.e., hypersensitivity to ingredients (b) (4)

Reference ID: 3245734

- [redacted] (b) (4)
- Renaming of subsections (e.g., 5.4) for clarity in describing the risk
- Removal of non-serious adverse reactions reported at very low rates which cannot be attributed to topotecan based on lack of comparative data in control group. Removal of adverse reactions based on leukopenia, which provides little information over incidence of neutropenia, and removal of adverse reactions reported as post-marketing events that are also described under Clinical Trial experience.

- Carton and immediate container labels DMEPA previously reviewed the labels and labeling for Topotecan Injection contained in the original NDA during the first review cycle. DMEPA's recommendations for modification to carton/container and physician labeling were conveyed to Teva and all recommendations were implemented. During the current review cycle, based on medication error reports of inappropriate storage and differences in storage conditions for the Teva product as compared to the listed drug, Hycamptin, DMEPA requested that Teva display the storage parameters more prominently; this change was also conveyed to Teva. There are no outstanding issues regarding carton/container labeling.

- Patient labeling/Medication guide: Teva did not submit proposed patient labeling or a Medication Guide and the listed drug does not have patient labeling or a Medication Guide. There was no new information identified during the review of this application which would have required patient labeling or a Medication Guide to ensure safe use of the parenterally administered, prescription drug product.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval

- Risk Benefit Assessment: This NDA relies on FDA's prior findings of safety and effectiveness for the listed drug, Hycamptin (NDA 030671). The application contains adequate information on chemistry, manufacturing, controls to support approval and final product labeling. No new safety risks are predicted based on the differences in the formulation between this product and the approved drug, Hycamptin, thus I have concluded that the favorable risk:benefit assessment identified for Hycamptin also applies to Teva's product for the two indications that are not subject to marketing exclusivity.

  Rationale and justification that supports regulatory action, including noting whether this is consistent or differs with recommendations from other disciplines (including outstanding unresolved issues)

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies: I concur with the review team's assessment that a REMS with elements to assure safe use were not required to ensure safe use of this product.

Reference ID: 3245734

- Recommendation for other Postmarketing Requirements and Commitments: I concur with the review team's assessment that post-marketing requirements were not needed to ensure safe use of this product. No post-marketing commitments were requested.

Reference ID: 3245734

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/s/

PATRICIA KEEGAN
01/15/2013