CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022453Orig1s000

MEDICAL REVIEW(S)

Medical Officer's Memo (clinical)
NDA # 022453 / SEQUENCE # 0013
TOPOTECAN INJECTION, 1 MG BASE/ML
TEVA

Additional chemistry, manufacturing and controls (CMC) information to satisfactorily resolve cGMP-related issues within this pending New Drug Application.
No clinical information submitted to review.

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/s/

SHAKUNTALA M MALIK
09/27/2012

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Anthony J. Murgo, M.D., M.S.
Subject	Acting Deputy Division Director Summary Review 505(b)(2) application
NDA #	NDA 22-453
Applicant Name	Teva Parenteral Medicines, Inc.
Date of Submission	17-Dec-2008
PDUFA Goal Date	18-Oct-2009
Proprietary Name / Established (USAN) Name	Topotecan Injection (non-proprietary name)
Dosage Forms / Strength	Solution for intravenous injection /1 mg/mL
Proposed Indication(s)	1. (b) (4) small cell lung cancer, sensitive disease after failure of first-line chemotherapy 2. Stage IV-B, recurrent or persistent carcinoma of the cervix, not amenable to curative treatment with surgery and/or radiation therapy
Action/Recommended Action for 505(b)(2):	Complete Response

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	X
Statistical Review	N/A
Pharmacology Toxicology Review	X
CMC Review/OBP Review	X
Microbiology Review	X
Clinical Pharmacology Review	X
DDMAC	
DSI	N/A
CDTL Review	N/A
OSE/DMEPA	
OSE/DDRE	
OSE/DRISK	
Other	

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
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Introduction

Pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, Teva Parenteral Medicines submitted an original New Drug Application (NDA 22-453/S-000) for Topotecan Hydrochloride Injection on December 18, 2008. The reference listed drug (RLD) is Hycamtin® for Injection (topotecan hydrochloride; GlaxoSmithKline). The indications for Topotecan Hydrochloride Injection listed in the current application are for the treatment of small cell lung cancer sensitive disease after failure of first-line chemotherapy and for the treatment of stage 4-B recurrent or persistent carcinoma of the cervix (in combination with cisplatin) which is not amendable to curative treatment with surgery and/or radiation therapy. These two proposed indications have been approved for the RLD (NDA 20-671). (b) (4)

The RLD upon which the application is subject to a period of patent protection and therefore final approval of the application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be made effective until the period for Patent No. 5004758*PED has expired, i.e., November 28, 2010. Nevertheless, the application is not approvable because of unresolved deficiencies discovered during a recent manufacturing facility inspection. Satisfactory resolution of these deficiencies is required before this application is approvable.

1. Background

Topotecan's antineoplastic properties are related to the inhibition of topoisomerase I. There is considerable clinical efficacy and safety experience with the RLD (Hycamtin® for Injection) in cancer patients. The RLD is FDA approved for 3 indications: small cell lung cancer, cervical cancer (in combination with cisplatin) and ovarian cancer. The proposed 505(b)(2) formulation and the RLD have the same active moiety and both are intended for intravenous administration. The dosing regimens for this product for the treatment of small cell lung cancer and cervical cancer are the same as that for the RLD. Consequently, the current 505(b)2 application does not include new clinical studies data and relies on the publically available findings of safety and effectiveness for the RLD and on the published literature. As noted previously, the proposed indications are limited to treatment of small cell lung cancer and cervical cancer, (b) (4).

2. CMC/Device

The dosage form of the Teva Topotecan Hydrochloride Injection is different from the RLD Hycamptin® for Injection. Specifically, the Teva Topotecan Hydrochloride Injection is manufactured in a liquid dosage form (instead of the RLD lyophilized dosage form). The table below compares the qualitative and quantitative composition of Teva's Topotecan for Injection with the RLD. Teva's drug product has the same active and inactive ingredients, strength,

route of administration, and conditions of use as the RLD. In addition, the Teva injectable liquid formulation [redacted] (b) (4) to the reconstituted Hycamtin® for Injection lyophilized sterile injectable drug product.

Table 2 Qualitative and Quantitative composition (per vial and amount per unit) listed for Teva's Topotecan Hydrochloride Injection solution and the RLD Hycamtin®

Composition Raw Material	Toptotecan hydrochloride Injection (Teva) (buffered solution)	Toptotecan hydrochloride Injection (Teva) Concentration	RLD Hycamtin® (buffered lyophilized powder)	RLD Hycamtin® *Reconstituted Solution* Concentration
Topotecan free base	4 mg	1 mg/mL	4 mg	1 mg/mL
Mannitol, USP	48 mg	12 mg/mL	48 mg	12 mg/mL
Tartaric acid, NF grade	20 mg	5 mg/mL	20 mg	5 mg/mL
Sterile Water for Injection, USP	solvent	solvent	-	solvent
Sodium hydroxide, NF grade	pH adjuster	To adjust to a target pH		To adjust to a target pH
Hydrochloric acid, NF grade	pH adjuster	To adjust to a target pH		To adjust to a target pH

The sponsor submitted data in the form of expert consultations and literature to qualify a novel impurity, [redacted] (b) (4) The manufacturing process for the Teva topotecan drug substance requires [redacted] (b) (4) . These substances have been adequately qualified (See comments below concerning the Pharmacology/Toxicology findings).

I concur with the conclusions reached by the CMC review regarding the acceptability of the manufacturing of the drug product and drug substance. Based on the provided stability data, a 12-month expiration dating period is granted for the drug product when stored under the proposed refrigerated condition.

During a recent inspection of the Teva Parenterals, Inc. manufacturing facility for this application, an FDA field investigator conveyed deficiencies to the representative of the facility. Because these deficiencies remain unresolved, the application is not approvable.

3. Nonclinical Pharmacology/Toxicology

As noted above, the sponsor submitted data in the form of expert consultations and literature to qualify a novel impurity, [redacted] (b) (4) According to the Pharmacology/Toxicology review, both [redacted] (b) (4) have been adequately qualified by the sponsor. I concur with the conclusions reached by the

Pharmacology/Toxicology review that there are no outstanding toxicology and pharmacology issues that preclude approval.

4. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions of the Division of Clinical Pharmacology review that this application is approvable from a clinical pharmacology perspective.

5. Clinical Microbiology

I concur with the conclusions reached by the CMC product quality microbiology review that there are no outstanding clinical microbiology or sterility issues that preclude approval.

6. Clinical/Statistical-Efficacy

As noted previously, this 505(b)2 application does not include new clinical studies data and relies on the publically available findings of safety and effectiveness for the RLD and on the published literature. The proposed indications are limited to treatment of small cell lung cancer and cervical cancer, (b) (4) The dosing regimens for this product for the treatment of small cell lung cancer and cervical cancer are the same as that for the RLD. The recommended dosing for the treatment of small cell lung cancer is 1.5 mg/m^2 by intravenous infusion over 30 minutes daily for 5 consecutive days, starting on day 1 of a 21-day course. The recommended dosing for the treatment of cervical cancer 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 by intravenous infusion on day 1 repeated every 21 days (a 21-day course). I concur with the Clinical Reviewer that there are no clinical issues precluding approval.

7. Safety

As noted previously, there is considerable information on the clinical use of the RLD to support the safety of the Teva product. A REMS is not indicated.

8. Advisory Committee Meeting

An Advisory Committee meeting is not indicated.

9. Pediatrics

FDA is waiving the pediatric study requirement for this application. The necessary studies are impossible or highly impracticable to perform because there are too few children with these diseases to study.

10. Other Relevant Regulatory Issues

As noted in Section 2 (CMC) above, the application is not approvable because of unresolved deficiencies discovered during a recent manufacturing facility inspection. Satisfactory resolution of these deficiencies is required before this application is approvable.

Also of note, the RLD upon which the application is based (for the treatment of small cell carcinoma and treatment of cervical cancer indications) is subject to a period of patent protection and therefore final approval of the application under section 505(c)(3) of the Act (21 U.S.C. 355(c)(3)) may not be made effective until the period has expired, i.e., November 28, 2010.

11. Labeling

The proposed labeling of Teva's topotecan contains the same indications for carcinoma of the cervix and lung carcinoma (b) (4) . The package insert and the carton and immediate container labeling were reviewed by the various relevant FDA disciplines. Sponsor agreement on the final product labeling (FDA August 24, 2009 version) was given on August 27, 2009. There are no outstanding labeling issues.

12. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Complete Response because of unresolved manufacturing site deficiencies.

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/s/

JANET K JAMISON
10/16/2009

ANTHONY J MURGO
10/16/2009

MEMORANDUM

DATE August 28, 2009

TO NDA 22-453/SN-000

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

SUBJECT New Drug Application

1. Background

On December 17, 2009, Teva Pharmaceuticals submitted NDA 22-453 for Topotecan Hydrochloride Injection. In accordance with CFR 314.54(a)(1)(iii) and under Section 505(b)(2) of the Act, the Applicant identified GlaxoSmithKline's Hycamtin® as a previously approved drug under NDA 20-671 and relied on the Agency's prior findings of safety and efficacy for its proposed drug product.

Topotecan Hydrochloride Injection is pharmaceutically equivalent to Hycamtin®. The proposed drug product is a liquid formulation, 1 mg base/mL, and is identical to Hycamtin® upon reconstitution with the exception of the pH. For purposes of chemical stability, the pH of the proposed formulation is 2.2 as compared to 3.0 for reconstituted Hycamtin. The proposed product has the same route of administration (intravenous), has the same active and inactive ingredients, and is intended for the same indication as that of Hycamtin. Therefore, the Applicant did not conduct clinical studies and relied on the Agency's prior finding of efficacy for Hycamtin. In addition, the Agency waived bioequivalence studies, in accordance with 21 CFR 320.22(b)(1)(i) and (ii).

GlaxoSmithKline's product Hycamtin is approved for the following indications:

- metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy
- small cell lung cancer sensitive disease 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 (in the Phase 3 study) or at least 90 days (in the Phase 2 studies) after chemotherapy.
- stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amenable to curative treatment with surgery and/or radiation therapy.

The proposed labeling of Teva's Topotecan Hydrochloride Injection contains the same indications for carcinoma of the cervix and lung carcinoma [redacted] (b) (4)

On February 27, 2009, the Agency completed its filing review, and determined that the application was sufficiently complete to permit a substantive review. No potential clinical issues were identified at that time.

The incidences of (b) (4), cervical cancer and/or small cell lung cancer are extremely small in the pediatric population. On June 24, 2009, the Agency granted the Applicant a waiver for pediatric studies as required by the Pediatric Research Equity Act because of the necessary studies would be impossible or highly impracticable due to the small number of children with the diseases.

2. Recommendation

This reviewer recommends approval of Topotecan Hydrochloride Injection for the following indications:

- small cell lung cancer sensitive disease 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.
- stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amenable to curative treatment with surgery and/or radiation therapy.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22453	ORIG 1	TEVA PARENTAL MEDICINE INC	TOPOTECAN HYDROCHLORIDE INJECTION

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/s/

MICHAEL H BRAVE
08/26/2009

KE LIU
08/26/2009