CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022453Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 22-453	NDA Supplement #:S-	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: Topotecan Dosage Form: Injection Strengths: 1 mg base / mL		
Applicant: Teva Pharmaceuticals, USA		
Date of Receipt: December 18, 2008 Date of Resubmission: June 25, 2012		
PDUFA Goal Date: October 18, 2009 Resubmission PDUFA Date: December 25, 2012	Action Goal Date (if different): October 9, 2009 Resubmission Action Goal Date: December 14, 2012	
Proposed Indications: 1 - Small cell lung cancer sensitive disease after failure of first-line chemotherapy. 2 - Stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amendable to curative treatment with surgery and/or radiation therapy.		

GENERAL INFORMATION

1. Is this application for a drug that is an "old" antibiotic as described in the Guidance to Industry, Repeal of Section 507 of the Federal Food, Drug and Cosmetic Act? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES ☐ NO ☒

*If "**YES**," proceed to question #3.*

2. Is this application for a recombinant or biologically-derived product and/or protein or peptide product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

3. List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 20-671	Clinical
NDA 20-671	Nonclinical

4. Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Within the current NDA application, Teva Parenteral Medicines, Inc. relies on the clinical efficacy and safety data established for GlaxoSmithKline's listed drug product, Hycamtin. The applicant was granted a waiver for evidence of bioavailability in accordance with 21 CFR Section 320.22(b)(1) since the drug product meets the required criteria as follows:

- **Topotecan Hydrochloride Injection, 1 mg Base/mL, is a parenteral drug product intended for administration by injection.**
- **The proposed drug product, Topotecan Hydrochloride Injection, 1 mg Base/mL contains the same active and inactive ingredients in the same concentration as GlaxoSmithKline's listed drug product, Hycamtin®, that is the subject of an approved full new drug application, NDA 20-671.**

RELIANCE ON PUBLISHED LITERATURE

5. (a) Does the application rely on published literature to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #6.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #6*
*If "**YES**", list the listed drug(s) identified by name and answer question #5(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?
YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #6-10 accordingly.

6. Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #11.*

7. Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Hycamtin® (topotecan hydrochloride)	NDA 20-671	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

8. If this is a supplement, does the supplement rely upon the same listed drug(s) as the original (b)(2) application? N/A

YES ☐ NO ☐

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

9. Were any of the listed drug(s) relied upon for this application:
   a. Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

   b. Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c. Described in a monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d. Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d.1.*
*If "**NO**", proceed to question #10.*

Name of drug(s) discontinued from marketing:

1. Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

10. Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for an injectable solution containing 1 mg base/mL whereas the RLD is lyophilized powder in a 4 mg single dose vial.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

11. (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES ☐ NO ☒

*If "**NO**," to (a) proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" and there are no additional pharmaceutical equivalents listed, proceed to question #13.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

12. (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES ☒ NO ☐

*If "**NO**", proceed to question #13.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☒ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #13.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all*

of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

13. List the patent numbers of all patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

    Listed drug/Patent number(s): 5004758, 5674872 (Ovarian indication, Hycamtin. Applicant is not seeking approval for this indication)

14. Did the applicant address (with an appropriate certification or statement) all of the patents listed in the Orange Book for the listed drug(s)?

    YES ☒ NO ☐

    *If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

    Listed drug/Patent number(s):

15. Which of the following patent certifications does the application contain? *(Check all that apply <u>and</u> identify the patents to which each type of certification was made, as appropriate.)*

    ☐ No patent certifications are required (e.g., because application solely based on published literature that does not cite a specific innovator product or for an "old antibiotic" (see question 1.))

    ☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

    ☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

    Patent number(s):

    ☒ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

    Patent number(s): 5004758, Exp. 5/28/2010

    ☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

Patent number(s):

If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

Date Received:

Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.

YES ☐ NO ☐

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):
If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

Date Received:

Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.

YES ☐ NO ☐

☐ Written statement from patent owner that it consents to an immediate effective date of approval (applicant must also submit paragraph IV certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☒ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s): 5674872

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/s/

DEANNE R VARNEY
12/20/2012

MEMORANDUM #1-DG

To: NDA 22453
From: Debasis Ghosh, M. Pharm., Ph.D.
Through: Nallaperumal Chidambaram, Ph.D.

Date: Dec 19, 2012

Sub: Resolution of Labeling Issues

Sponsor: TEVA Pharmaceuticals USA
Product: Topotecan Injection
Document Reviewed: Labeling Response SD 020 [12/12/2012]
Labeling Response SD 021 [12/14/2012]

Summary:
On 17-Dec-2008 (received 18-Dec-2008), the applicant (TEVA USA) originally filed an application to commercialize Topotecan Injection 4 mg/4 mL (1 mg/mL) under 505(b)(2) of the Federal, Food Drug, and Cosmetic Act as a treatment for small cell lung cancer and cervical cancer. The Agency provided a CR (Complete Response) to the application on 16-Oct-2009. The applicant resubmitted the application as a response to CR and updated CMC and other information on 22-Jun-2012 (received 25-Jun-2012).

CMC Review #1 and Review#2 were completed on 28-Aug-2009 and 04-Dec-2012, respectively.

The applicant satisfactorily addressed outstanding labeling issues as noted in Review #2. In addition, the Division of Medication Error and Prevention and Analysis (DMEPA) confirmed the satisfactory resolution of labeling issues (See DARRTS James Schlick 16-Nov-2012 and 19-Dec-2012).

Recommendations:

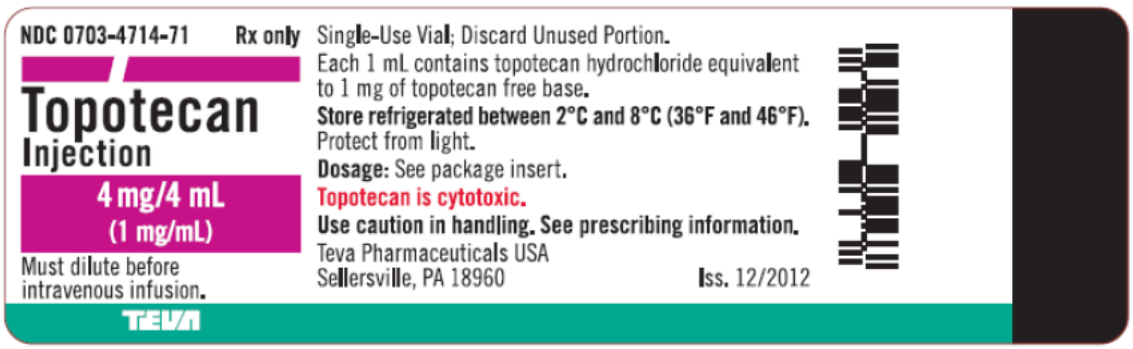
From a CMC standpoint, this NDA is recommended for approval.*

*it has been assumed that the applicant agrees with FDA's recommendation for making changes to the How Supplied Section in Package Insert.

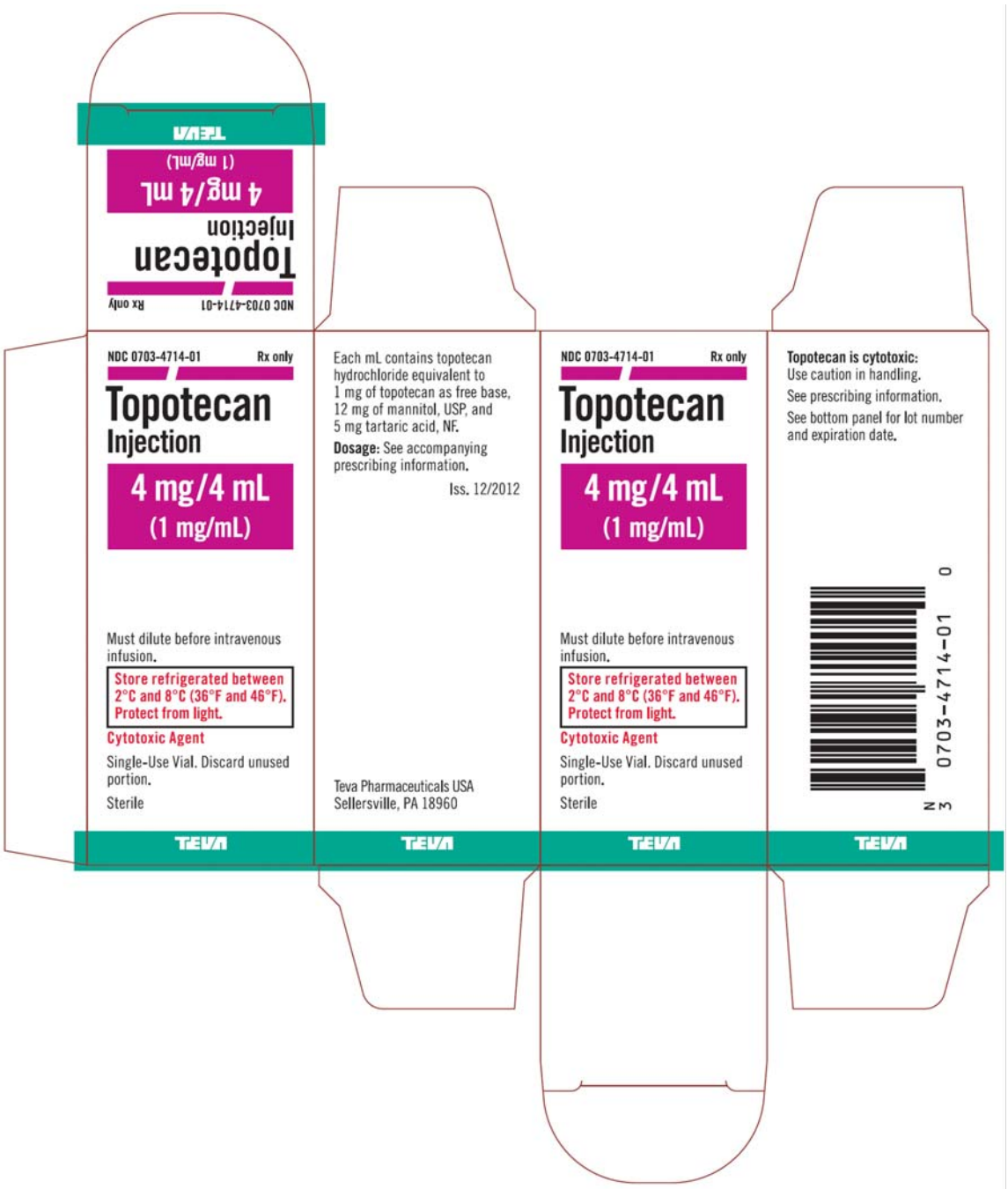
Review Notes:

The applicant provided final **Tray** label on 07-Dec-2012:

The applicant provided final **Vial** label on 12/7/12:



The applicant provided final **Carton** label on 13-Dec-2012:



Evaluation: Adequate
It has been noted that the applicant addressed all the outstanding issues mentioned in the Review #2. However, the NDC numbers for vial and the packaging are found to be different. It has been noted that this assignment of different NDC numbers for vial and packaging are not used traditionally. After a teleconference with the company, consultation with (1) SPL team and (2) DMEPA team, and (3) Dr. Keegan, we have agreed to accept the changes. Different NDC numbers for vial and packaging are now acceptable.

Package Insert:

The applicant provided PI (Final Draft) on 13-Dec-2012. The applicant accepted all CMC recommendations.

Since the applicant proposed a new NDC number for vial, the Agency recommended the following changes (in blue) in How Supplied Section of PI and communicated it to the applicant on 19-Dec-2012.

Topotecan Injection is supplied as single-use vials. Each vial contains 4 mL of the sterile solution. 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)

Evaluation: Adequate
It has been assumed that the applicant agrees with FDA's recommendation for making changes to the How Supplied Section in Package Insert.

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/s/

DEBASIS GHOSH
12/19/2012

NALLAPERUM CHIDAMBARAM
12/20/2012
I concur.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	December 19, 2012
Reviewer:	James Schlick, RPh, MBA Division of Medication Error Prevention and Analysis
Team Leader:	Todd Bridges, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Topotecan Injection 4 mg/4 mL (1 mg/mL)
Application Type/Number:	NDA 022453
Applicant/sponsor:	Teva Pharmaceuticals
OSE RCM #:	2012-2218-1

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Contents

1 INTRODUCTION

This review evaluates the revised container label and carton labeling for Topotecan Injection (NDA 022453) submitted in response to the Division of Medication Error Prevention and Analysis' comments in the November 16, 2012 OSE Review 2012-2218.

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Label submitted December 6, 2012 (Appendix A)
- Carton Labeling submitted December 6, 2012 (Appendix B)
- Tray Labeling for 5 Count Pack submitted December 6, 2012 (Appendix C).

2.2 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed Topotecan Injection in OSE Review 2012-2218, and we looked at the review to ensure all our recommendations were implemented.

3 DISCUSSION

During review of the revised labels and labeling, the ONDQA reviewer for this application noted that the NDC number on the vial label differs from the NDC number on the one vial carton labeling (see NDC numbers listed below). This method of assigning NDC numbers is different than the traditional method where a single NDC is typically used to identify both a single vial and the carton for that single vial.

- NDC 0703-4714-71 for Single-Use Vial (container label)
- NDC 0703-4714-01 for Single-Use Vial (carton labeling)
- NDC 0703-4714-02 for Tray Labeling for 5 count pack

There was a teleconference on December 17, 2012 with the Applicant, Teva to discuss their method of assigning NDC numbers for this product. Teva indicated during the teleconference that the NDC assignments were based on current guidance from the FDA's Structured Product Labeling (SPL) team. Subsequent to the teleconference, the Office of Regulatory Science and Innovation, Division of Scientific Computing and Medical Information, confirmed that Teva's method of assigning NDC numbers to this product is the preferred method.

Although the traditional method of allowing a single NDC identify both a single vial and the carton for that single vial has not been problematic from a safety perspective, DMEPA's preliminary assessment did not identify a safety issue if each layer of packaging contains a

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

different NDC number. Therefore, DMEPA does not object to the Applicant's proposal to have different NDC numbers for the vial label and the single vial carton labeling.

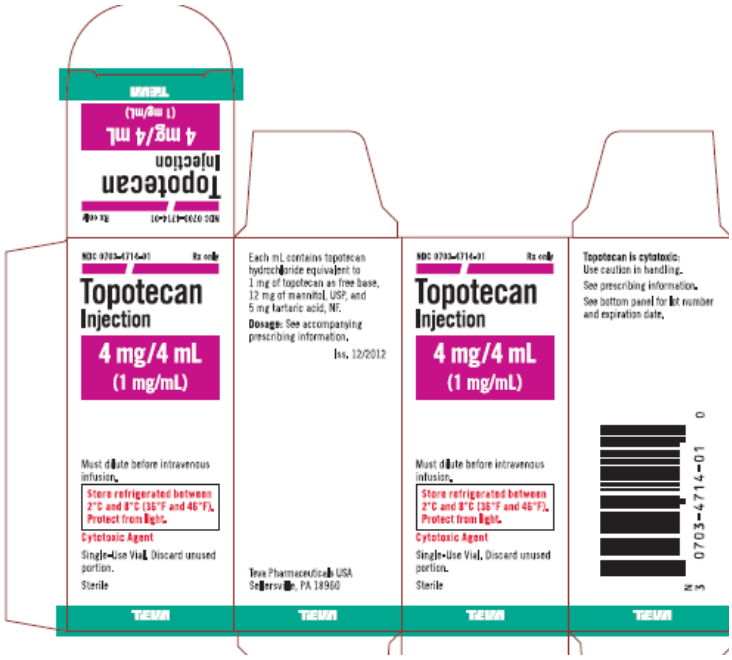
4 CONCLUSION

DMEPA finds the Applicant's revisions to the label and labeling acceptable.
If you have questions or need clarifications, please contact France Fahnbulleh, OSE project manager, at 301-796-0942.

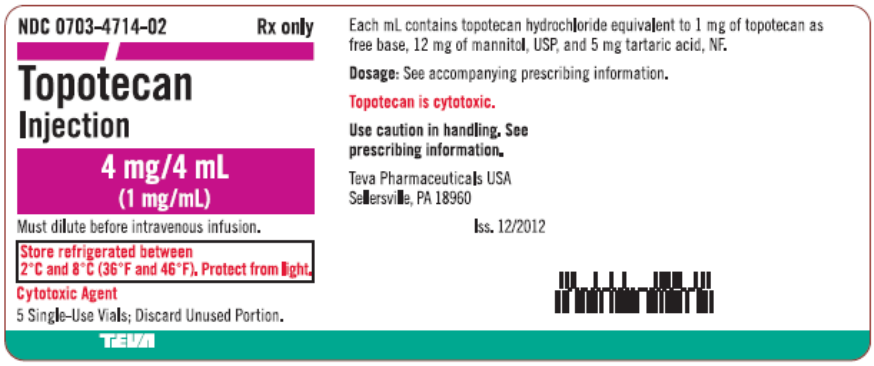
APPENDICES

Appendix A: Container Label

Appendix B: Carton Labeling



Appendix C: Tray Labeling for 5 Count Pack



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/s/

JAMES H SCHLICK
12/19/2012

TODD D BRIDGES
12/19/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 29, 2012

To: Deanne Varney, Regulatory Project Manager
Division of Oncology Products 2 (DOP-2)
Office of Hematology Oncology Drug Products

From: Carole Broadnax, PharmD, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 022453
Topotecan HCL Injection
OPDP Labeling Comments

OPDP/DPDP has reviewed the proposed labeling (Package Insert (PI) and carton/container) as requested in your consult dated September 20, 2012.

DPDP's comments are based on the substantially complete version of the proposed PI titled, "20121126 – PI Track Changes_FDA edits.doc" and carton/container labeling sent via electronic mail to OPDP (Carole Broadnax) from DOP 2 (Deanne Varney) on November 27, 2012. OPDP's comments for the PI are provided directly in the attached document. Please note that OPDP hid DOP 2's comments, deletions, and formatting changes so that OPDP's comments are easier to read.

OPDP does not have comments for the carton and container labeling at this time.

Thank you for your consult. If you have any questions, please contact Carole Broadnax at (301) 796-0575 or Carole.Broadnax@fda.hhs.gov.

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CAROLE C BROADNAX
11/29/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	November 16, 2012
Reviewer(s):	James Schlick, RPh, MBA Division of Medication Error Prevention and Analysis
Team Leader	Todd Bridges, RPh Division of Medication Error Prevention and Analysis
Associate Director	Scott Dallas, RPh Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Topotecan Injection 4 mg/4 mL (1 mg/mL)
Application Type/Number:	NDA 022453
Applicant:	Teva Pharmaceuticals
OSE RCM #:	2012-2218

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Contents

1 INTRODUCTION

This review evaluates the proposed label and labeling for Topotecan Injection, NDA 022453, for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

The Applicant for Topotecan Injection, Teva, received a Complete Response letter dated October 6, 2009 outlining deficiencies with the manufacturing facility for their submitted 505(b)(2) New Drug Application. The Applicant has submitted a Class II resubmission dated June 22, 2012, and the resubmission is the subject of this review.

1.2 PRODUCT INFORMATION

The following product information is provided in the June 22, 2012 Class II resubmission.

- Active Ingredient: Topotecan
- Indication of Use:
    - Small cell lung cancer after failure of first-line chemotherapy.
    - Stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amenable to curative treatment with surgery and/or radiation therapy.
- Route of Administration: Intravenous Infusion
- Dosage Form: Solution for intravenous infusion
- Strength: 1 mg/mL
- Dose and Frequency:
    - Small cell lung cancer: 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.
    - 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).
- How Supplied: Single vial containing 4 mg/4 mL and a carton containing 5 vials with 4 mg/4 mL in each vial.
- Storage: Store refrigerated between 2ºC and 8 ºC.
- Container and Closure System: Glass vial with gray stopper.

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) for Topotecan medication error reports. We also reviewed the Topotecan labels and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FAERS database using the strategy listed in Table 1.

Table 1: FAERS Search Strategy	
Date	April 22, 2010 to August 27, 2012
Drug Names	Active ingredient: Topotecan Trade name: Hycamtin Verbatim term: Topotec* and Hycamt*
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The last post marketing search completed for Topotecan was conducted in OSE Review # 2010-604 on April 22, 2010. Therefore, the time frame for this search begins with this date. The FAERS database search identified 15 reports. Each report was reviewed for relevancy and duplication. Duplicates were merged into a single case. After individual review, 12 reports were not included in the final analysis for the following reasons:

- Adverse event reported in a clinical trial not related to a medication error
- Medication error related to a concomitant medication and not Topotecan.
- Medication errors related to the oral dosage form of Topotecan, not considered pertinent to this review.

2.2 LITERATURE SEARCH

We searched PubMed and the ISMP publications on October 22, 2012 for additional cases and actions concerning Topotecan. The PubMed search consisted of the search terms "topotecan" and "medication error". The following ISMP newsletters were searched:

- ISMP Acute Care Newsletter
- ISMP Community Edition
- ISMP Nursing Edition
- ISMP Canada Safety Bulletin

The PubMed and ISMP publication searches did not reveal additional cases.

2.3 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Label submitted June 22, 2012 (Appendix B)
- Carton Labeling submitted June 22, 2012 (Appendix C)
- Tray Liner for Package Containing 5 Single Use Vials submitted June 22, 2012 (Appendix D)
- Insert Labeling submitted June 22, 2012

2.4 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed the labels and labeling for Topotecan Injection in OSE Review # 2009-986. The recommendations outlined in this previous review were conveyed to the Applicant and implemented.

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FAERS search and the risk assessment of the Topotecan Injection product design as well as the associated label and labeling.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, three Topotecan medication error cases (n=3) remained for our detailed analysis. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter[2]. All three cases for additional analysis involved an incorrect dose given to the patient.

Incorrect Dose

The first case (8049224 v1) occurred in July 2011 and involved a patient who received a 10 fold overdose. The patient received 29 mg of Topotecan rather than the intended 2.9 mg. The patient was given Neulasta after the error was noted. The outcome of the case was unknown as well as the cause of the 10 fold dosing error. The second case (8520362 v1) involved a foreign case where the patient received a 4 fold overdose. The patient received 16 mg rather than 4 mg intravenously. The patient was hospitalized due to anemia and neutropenia. The third case (8236929 v1) involved a patient who received

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

[2] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf. Accessed June 1, 2011.

an overdose of Topotecan. No additional information was provided and the outcome is unknown.

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

Based on the assessment of the product, there are two issues that require additional discussion, ten-fold overdoses and concerns with the product storage. Three cases reporting the administration of 10 times the intended dose were evaluated for contributing factors and potential root cause of the errors. The case narratives did not provide much detail on how the errors occurred. However, based on the doses prescribed vs. doses delivered we suspect prescribers wrote the prescribed dose with a trailing zero or the decimal point was overlooked when the order was transcribed. For example, "a patient was administered 25 mg instead of 2.5 mg of Hycamtin (Topotecan HCl)" and "a patient received 40 mg/m^2 instead of the prescribed dose of 4 mg/m^2". Therefore, DMEPA evaluated the package inserts of each marketed Topotecan product to determine if any trailing zeroes related to dose, administration, strength, or how supplied were present that could contribute to a ten fold overdose. There were no trailing zeroes found in the package insert. Thus, DMEPA plans to request medication error data from some external databases in an attempt to identify additional errors and further causality of these errors to determine if any label or labeling revisions are required to mitigate this risk.

With respect to the second issue involving the prominence of the storage statement on the container label and carton labeling of the proposed product we noted the referenced listed drug, Hycamtin lyophilized powder, requires unopened vials be stored at room temperature. The proposed Teva product, an injection, requires that unopened vials be stored at refrigerated temperatures. Additionally, there are eight approved generic lyophilized powder products stored at room temperature and two approved 505 (b) (2) injection solution products stored under refrigeration. Because the proposed Teva product is stored differently than the approved generic products, the storage parameters should be more prominently displayed on the product to mitigate the risk of incorrect storage of unopened vials.

4 CONCLUSIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information to promote the safe use of the product. In addition, DMEPA will request medication error data from external sources to further clarify the root cause(s) of the ten-fold dosing errors involving topotecan to determine if additional label revisions or regulatory action is warranted.

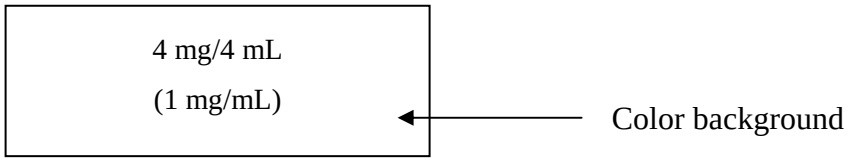
5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Comments to the Applicant

1. Carton and Tray Liner Labeling and Container Label

a. Ensure the color background includes the strength statement “1 mg/mL” located directly below the statement “4 mg/4 mL” each place it is presented. For example:



b. Ensure an area for expiration date and lot number is provided on the label.

c. The NDC numbers need to be different for each packaging configuration to distinguish each product configuration and comply with the bar code rule 21 CFR 201.25. Ensure that each packaging configuration has a different NDC number and include the number on the revised label and labeling.

d. On the carton labeling, incorporate the statement “Discard Unused Portion” to appear immediately after or under the statement “Single-Dose Vial”. Additionally, revise the statement [redacted] (b) (4) to read “Single Use Vial”.

e. Add the statement “Single Use Vial; Discard Unused Portion” to the top of the side panel on the container label. Consider deleting the statement “Each mL contains…” if additional space is needed.

f. On the tray liner, revise the statement [redacted] (b) (4) ” to read “5 Single Use Vials; Discard Unused Portion”

2. Carton and Tray Liner Labeling

a. To increase the prominence of the storage statement, “Add a box with a black line around the storage statement and use bold red font for the letters in the statement. Additionally, revise the storage statement to read “Store refrigerated between 2ºC and 8ºC (36ºF and 46 ºF). Protect from light.

For example:

Store refrigerated between 2ºC and 8ºC (36ºF and 46 ºF). Protect from light.

b. To increase the prominence of the storage statement, move the statement from the side panel to the principal display panel. The storage statement should appear below the statements “For Intravenous Use” and “Must be diluted before use.” In order to make room for the storage statement on

the principal display panel, consider deleting the statement "Each mL contains topotecan hydrochloride…" This statement is redundant as it is also conveyed on the side panel.

B. Comments to the Division

1. Full Prescribing Information

a. Instructions for Handling, Preparation and Intravenous Administration, Section 2.4

1. The package insert does not state how much diluent the product needs to be diluted in before administration. Consider revising the package insert to include an appropriate diluent volume or appropriate volume range required prior to administration.

2. Remove the unopened vial stability statement. This statement is redundant since it is included in Section 16.

If you have questions or need clarifications, please contact Frances Fahnbulleh, OSE project manager, at 301-796-0942.

APPENDICES

APPENDIX A. DATABASE DESCRIPTION

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JAMES H SCHLICK
11/16/2012

SCOTT M DALLAS on behalf of TODD D BRIDGES
11/16/2012

SCOTT M DALLAS
11/16/2012

CAROL A HOLQUIST
11/16/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	July 9, 2009
To:	Robert Justice, MD, Director Division of Drug Oncology Products
Through:	Carlos Mena-Grillasca, RPh, Acting Team Leader Carol A. Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Judy Park, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name:	Topotecan Injection 1 mg/mL
Application Type/Number:	NDA 22-453
Applicant:	Teva Parenteral Medicines, Inc.
OSE RCM #:	2009-986

CONTENTS

1 EXECUTIVE SUMMARY

This review is in response to a May 19, 2009 request from the Division of Drug Oncology Products for an evaluation of the labels and labeling for Topotecan Hydrochloride to identify areas that could lead to medication errors. The Applicant submitted container label, carton and insert labeling for review and comment. Using Failure Mode and Effects Analysis,[1] the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the label and labeling to identify vulnerabilities that could lead to medication errors. Our evaluation noted areas of needed improvement and we have provided recommendations in Section 3.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis (FMEA) in our evaluation of the container labels, carton and insert labeling submitted on June 15, 2009 (see Appendices A and B).

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) SELECTION OF CASES

The proposed product is a 505(b)(2) of Hycamtin. Therefore, our analysis included evaluating 22 medication error cases related to Hycamtin which were identified from a search of the AERS database. The search was conducted using the High Level Group Terms (HGLT) 'Medication Errors', and 'Product Quality Issues', with the search criteria of 'topotecan%' (active ingredient), 'Hycamtin%' (tradename), and verbatim terms of 'Hycamt%'.

This search on June 17, 2009 identified 22 cases of medication errors. These cases pertains to wrong dose (n = 13), dose not adjusted for renal impairment (n=2), wrong route of administration (n=2), accidental exposure (n=1), drug interaction (n=1), and product complaint issues (n=3). However, upon review, none of the cases pertained to this review.

3 RECOMMENDATIONS

Our evaluation noted areas where information on the container labels and insert labeling can be improved to minimize the potential for medication errors. We provide recommendations in Section 3.1 *Comments to the Applicant.* We request the recommendations in Section 3.1 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Sandra Griffith, Project Manager, at 301-796-2445.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3.1 COMMENTS TO THE APPLICANT

A. General Comment for All Labels and Labeling

1. Remove the (b) (4) from the established name and the word (b) (4) from the strength so that the established name correctly reflects the strengths (1 mg/mL). The established name should read: Topotecan Injection
2. Include the total drug content followed by the concentration [i.e. 4 mg/4 mL (1 mg/mL)].

B. Container Label

1. If space permits, include the statement, "Each mL contains topotecan hydrochloride equivalent to 1 mg of topotecan free base."
2. Include a dilution statement (e.g. Must be diluted before use).

C. Carton Labeling

1. Include the statement, "Each mL contains topotecan hydrochloride equivalent to 1 mg of topotecan as free base."
2. Include a dilution statement (e.g. Must be diluted before use).

D. Insert Labeling

1. Highlights, Dosage Forms and Strengths section:
   a. Present the total drug content followed by concentration (e.g. Single-dose vial containing 4 mg/4 mL of a 1 mg/mL solution).
   b. Remove the (b) (4) as it causes confusion with the fill volume (4 mL).

4 REFERENCES

1. Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufacturers that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

APPENDIX

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/s/

Carlos M Mena-Grillasca
7/9/2009 03:31:57 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
7/9/2009 03:56:22 PM
DRUG SAFETY OFFICE REVIEWER

REGULATORY PROJECT MANAGER LABELING REVIEW
Division of Drug Oncology Products

Application Number: NDA 22-453

Name of Drug: Topotecan Hydrochloride Injection

Applicant: Teva Parenteral Medicines, Inc.

Material Reviewed:

Submission Date: December 17, 2008

Receipt Date: December 18, 2008

Background and Summary

NDA 22-453 is a 505(b)(2) application submitted for 2 indications (1 - Small cell lung cancer sensitive disease after failure of first-line chemotherapy. 2 - Stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amendable to curative treatment with surgery and/or radiation therapy). The submitted package insert was reviewed for PLR format requirements. The review was performed and checked by the CPMS prior to issuing the filing letter.

Review

The following were identified and communicated in the filing letter sent to the sponsor:

HIGHLIGHTS OF PERSCRIBING INFORMATION:

1. The summarized statements need to refer to a section in the full prescribing information in the format (X.X).
2. White space is needed between each major section.
3. Add the BOXED WARNING and summarize the warnings.
4. "**See full prescribing information for complete boxed warning**" must be placed immediately following the heading of the BOXED WARNING.
5. "Pregnancy: Can cause fetal harm. Advise women of potential risk to the fetus." is not included under WARNINGS AND PRECAUTIONS and should reference (5.X) and (8.1).
6. Add a major section for PATIENT COUNSELING INFROMATION and add the statement "**See 17 for PATIENT COUNSELING INFORMATION.**"

PERSCRIBING INFORMATION: CONTENTS:

7. Add the BOXED WARNING title to the beginning of the table of contents in upper case, bolded letters.

8. Line up 1.1 to line up with the rest of the subheadings.
9. Change 1.3 to 1.2. Subsection 1.3 does not exist in the full prescribing information.
10. Change the title "General" for subsection 5.1 to identify the content of the subsection.
11. Change the subheading numbers for the CLINICAL PHARMACOLOGY to match the sections in the Full Prescribing Information.
12. Add a horizontal line between the Table of Contents and the Full Prescribing Information.

FULL PRESCRIBING INFORMATION:

13. Change the references throughout the Full Prescribing information in the format: *[see Section Title (X.X)]*. For example *[see Indications and Usage (1.1)]*. Note the formatting used in the reference.
14. Add the subject of the warning in your BOXED WARNING. This will also be the title for the HIGHLIGHTS and TABLE OF CONTENTS. For example: WARNING: SUBJECT OF WARNING.
15. Bold all the words contained in your BOXED WARNING and include a cross reference to more detailed discussion in other sections.
16. Add an "S" after the word "FORM" in the title of section 3.
17. Add the statement under DOSAGE AND ADMINISTRATION: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"
18. Change the title for section 5.1 to reflect the true contents of the subsection.
19. Change the title for subsection 5.2 to match the title in the Table of Contents.
20. Add a subsection under WARNINGS AND PRECAUTIONS for Pregnancy and add the statement "(*Name of drug*) can cause fetal harm when administered to a pregnant woman. (*Briefly describe the human data and any pertinent animal data.*) If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus." Cross reference to subsection (8.1).
21. Change the nonspecific terms from the ADVERSE REACTIONS section according to Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format (http://www.fda.gov/cder/guidance/5537fnl.htm).
22. Reword the title to Table 7 to not use promotional words such as [redacted] (b) (4) ".
23. For Table 7, center the column for CAV (%) to be consistent with the rest of the table.
24. Add the manufacturer information at the end of the label.

{See appended electronic signature page}

Susan Jenney, M.S.
Regulatory Health Project Manager

Supervisory Comment/Concurrence:
{See appended electronic signature page}

Alice Kacuba, R.N., M.S.N., RAC
Chief, Project Management Staff

Filename: NDA 22453 PLR PM labeling review 150.doc
PM LABELING REVIEW

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/s/

Susan Jenney
3/11/2009 03:08:01 PM
CSO

Alice Kacuba
3/11/2009 03:15:04 PM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-453 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Not Applicable
Established Name: Topotecan Hydrochloride Injection
Strengths: 1 mg Base/mL

Applicant: Teva Parenteral Medicines, Inc.
Agent for Applicant (if applicable): Not Applicable

Date of Application: December 17, 2008
Date of Receipt: December 18, 2008
Date clock started after UN: Not Applicable
Date of Filing Meeting: February 11, 2009
Filing Date: February 16, 2009
Day 74: March 2, 2009
Action Goal Date (optional): To be determined User Fee Goal Date: October 18, 2009

Indication(s) requested:
1. Small cell lung cancer sensitive disease after failure of first-line chemotherapy.
2. Stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amendable to curative treatment with surgery and/or readiation therapy.

Type of Original NDA: (b)(1) ☐ (b)(2) ☒
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application.*

Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☒ NO ☐
  If yes, explain: NDA 20-981 has exclusivity until October 10, 2010 (capsule formulation).

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? N/A
  YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? N/A YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☒
   This application is: All electronic ☒ Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☐
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☒ NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   Additional comments:

3. This application is an eCTD NDA. YES ☒

If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, _____ Years NO ☒
NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
YES ☒ NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☐ NO ☒
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☐ NO ☒

- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: None

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) November 14, 2008 NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO ☒
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☒ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☐ NO ☒
  No trade name submitted. All others sent to DMETS.

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☒ YES ☐ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application: N/A

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☐ NO ☒
  If no, did applicant submit a complete environmental assessment? YES ☒ NO ☐

If EA submitted, consulted to EA officer, OPS? YES ☒ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐
- If a parenteral product, consulted to Microbiology Team? YES ☒ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 11, 2009

NDA #: 22-453

DRUG NAMES: Topotecan Hydrochloride Injection

APPLICANT: Teva Parenteral Medicines, Inc.

BACKGROUND:
Teva Parenteral Medicines, Inc. submitted NDA 22-453 on December 17, 2008, (received on December 18, 2008) for small cell lung cancer sensitive disease after failure of first-line chemotherapy and stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amendable to curative treatment with surgery and/or radiation therapy.

ATTENDEES:

Julie Bullock, Pharm.D., Clinical Pharmacology Reviewer
Jeanne Fourie, Ph.D., Clinical Pharmacology Reviewer
Debasis Ghosh, Ph.D., Chemistry Reviewer
Amna Ibrahim M.D., Clinical Team Leader, DDOP, OODP
Janet Jamison, R.N., Safety Project Manager
Susan Jenney, M.S., Regulatory Health Project Manager
Robert Justice, M.D., Director, DDOP
Sue Ching Lin, Ph.D., Chemistry Reviewer
Ke Liu, M.D., Clinical Team Leader, DDOP
Amy McKee, M.D., Clinical Reviewer, DDOP
Denise Miller, Microbiology Reviewer, OPS
Anthony Murgo, M.D., Associate Director, OODP
Edgardo R. Parrilla Castellar, M.D., Ph.D., Visiting Clinical Fellow, NIH
Haripada Sarker, Ph.D., Pharmaceutical Assessment Lead, ONDQA
Shenghui Tang, Ph.D., Biostatistics Teamleader
S. Leigh Verbois, Ph.D., Supervisory Pharmacologist

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	**Reviewer**
Medical:	M. Brave
Secondary Medical:	K. Liu
Statistical:	N/A
Pharmacology:	D. McGuinn
Statistical Pharmacology:	N/A
Chemistry:	D. Ghosh and S. Lin
Environmental Assessment (if needed):	To be determined
Biopharmaceutical:	J. Fourie
Microbiology, sterility:	D. Miller
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	N/A
Regulatory Project Management:	S. Jenney
Other Consults:	N/A

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☐ NO ☒
  If no, explain: No clinical studies.
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☒ FILE ☐ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? YES ☐ NO ☒

PHARMACOLOGY/TOX N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☒

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Sterile product? YES ☒ NO ☐
  If yes, was microbiology consulted for validation of sterilization?
  YES ☒ NO ☐

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing review issues have been identified.
- ☒ Filing review issues to be communicated by Day 74. List (optional): CMC and CMC micro

ACTION ITEMS:

1. ☒ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
Scheduled meeting with the PeRC committee.

5. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

{See appended electronic signature page}

Susan Jenney
Regulatory Project Manager

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

/s/

Susan Jenney
2/25/2009 01:45:57 PM
CSO