

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
200582Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 200582 resubmission	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: Topotecan Dosage Form: Injection Strengths: 4 mg/4 mL (1 mg/mL)		
Applicant: Hospira, Inc.		
Date of Receipt: December 2, 2010		
PDUFA Goal Date: February 2, 2011		Action Goal Date (if different):
Proposed Indication(s): For the treatment of small cell lung cancer sensitive disease after the failure of first line chemotherapy.		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed 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)**

- 2) 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)
RLD = Hycamtin NDA 20671	Clinical

*each source of information should be listed on separate rows

- 3) 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)

The proposed product has the same route of administration (intravenous), has the same active ingredient, 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).

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary 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 #5.

- (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 #5.

If “YES,” list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

APPEARS THIS WAY ON ORIGINAL.

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 #5-9 accordingly.

- 5) 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 #10.

- 6) 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	20671	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.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

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

- 8) 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) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) 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.)

9) 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 a change in dosage form from freeze-dried solid (lyophilized) to solution.

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.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (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)? **No.**

*(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 #11.
If "YES" to (a), answer (b) and (c) then 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" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

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 below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (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 #12.

(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 #12.

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 below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired 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):

Patent No

50004758*PED

5674872* PED

Exp Date

Nov 28, 2010

Apr 7, 2015

No patents listed *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

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

Listed drug/Patent number(s):

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

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

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): 5,004,758

Expiry date(s): November 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). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the

NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 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): 5,674,872

Expires April, 7, 2015

Method(s) of Use/Code(s):U-910

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) 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

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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

/s/

ALLISON ADAMS-MCLEAN
01/25/2011

Internal Consult

Pre-decisional Agency Information

To: Allison Adams-Mclean, Project Manager, Division of Drug Oncology Products, (DDOP)

From: Adam George, Regulatory Reviewer Officer
Division of Drug Marketing, Advertising, and Communications,
(DDMAC)

CC: Karen Rulli, Professional Review Group II Leader, DDMAC
Michael Brave, Medical Officer, DDOP

Date: January 25, 2011

Re: Comments on draft labeling (Package Insert) for Topotecan for intravenous infusion

NDA 0200582

In response to your consult request via email on December 3, 2009, we have reviewed the draft Package Insert for Topotecan for intravenous infusion (Topotecan). We offer the following comments which pertain only to the draft version of the labeling which contains the indication for small cell lung cancer sensitive disease after failure of first-line chemotherapy.

Specific comments on the proposed labeling:

Section	Statement from draft	Comment
<ul style="list-style-type: none">5.1, Table 1 & 2 footnotes, 8.5	(b) (4)	<ul style="list-style-type: none">Throughout various sections of the PI the sponsor uses the phrase (b) (4) to categorize data that represent the clinical trial

Section	Statement from draft	Comment
		<p>experience of topotecan for the indication (b) (4) and for the indication of patients with small cell lung cancer. Use of this term misleadingly conveys the concept that these data are representative of a single clinical study in patients with (b) (4) small cell lung cancer. Please have the sponsor revise this statement in a manner that accurately conveys that these data come from separate studies that independently evaluated topotecan in (b) (4) small cell lung cancer.</p>

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/s/

ADAM GEORGE
01/25/2011

**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:	December 13, 2010
Application Type/Number:	NDA 200582
To:	Robert Justice, MD, Director Division of Drug Oncology Products
Through:	Denise Toyer, Pharm.D., Deputy Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Irene Z. Chan, PharmD, BCPS, Acting Team Leader Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name(s):	Topotecan Injection: 4 mg/4 mL
Applicant/sponsor:	Hospira Inc.
OSE RCM #:	2010-22-1

1 INTRODUCTION

Hospira submitted a Class 1 Resubmission to Complete Response on December 2, 2010, that included revised label and labeling in response to our recommendations in OSE RCM # 2010-22-1 dated November 5, 2010. There are currently three 505(b)(2) applications open for Topotecan Injection referencing the listed drug Hycamtin. In an effort to ensure consistency between the three applications, we are making an additional recommendation to the label and labeling for this product at this time.

2 CONCLUSIONS AND RECOMMENDATIONS

Review of the revised documents show that the Applicant implemented DMEPA's recommendations under OSE review #2010-22-1 dated November 5, 2010 (see Appendices A and B). We have identified an inconsistency between the label and labeling of this product and other 505(b)(2) Topotecan Injection applications currently under review within DMEPA. Thus, in order to reconcile this difference, we are providing a recommendation for the carton labeling and vial label in Section 2.1. to 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 the OSE Regulatory Project Manager, Sarah Simon, at 301-796-5205.

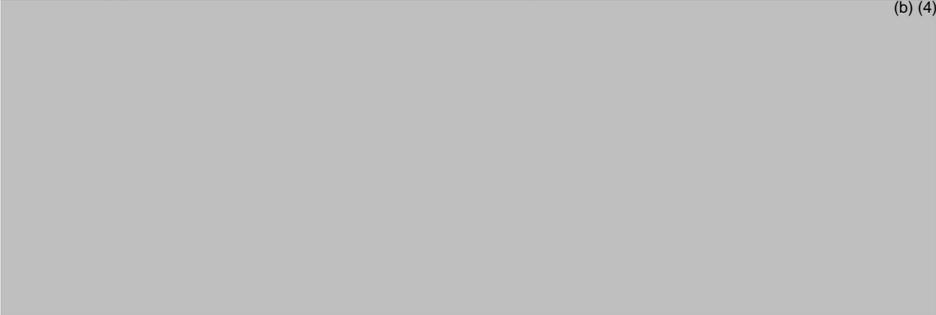
2.1 COMMENTS TO THE APPLICANT

A. GENERAL COMMENT

We previously recommended the following statement be added "For Intravenous Infusion after Dilution Only"; however, in an effort to maintain consistency with other products on the market, we ask that you revise this statement. Please replace with the following: "Must Dilute Before Intravenous Infusion" printed in bold font to avoid the risk of the medication being administered by intravenous push.

Appendix A: Container Label (4 mg/4 mL)

(b) (4)

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Appendix B: Carton Labeling (4 mg/4 mL)

(b) (4)

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

/s/

IRENE Z CHAN
12/13/2010

DENISE P TOYER
12/17/2010

RPM FILING REVIEW
(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 200582 BLA#	NDA Supplement #: BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Topotecan Established/Proper Name: topotecan Dosage Form: Injection Strengths: 4mg		
Applicant: Hospira Inc. Agent for Applicant (if applicable): N/A		
Date of Application: October 29, 2009 Date of Receipt: October 29, 2009 Date clock started after UN:		
PDUFA Goal Date: August 29, 2010	Action Goal Date (if different): Extended Goal Date November 29, 2010	
Filing Date: December 28, 2009	Date of Filing Meeting: December 9, 2009	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): the treatment of small cell lung cancer sensitive disease after failure of first-line chemotherapy.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical	

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): N/A				
List referenced IND Number(s): (b) (4)				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).				

505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).			X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>			X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm If yes, please list below:			X		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<p><i>If there is unexpired, 5 year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3 year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>					
Exclusivity		YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm			X		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>				X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>			X		

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance ¹ ? If not , explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	X			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? <i>If yes, date consult sent to the Controlled Substance Staff:</i>			X	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #				

Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?				
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?		X		
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?		X		
<i>Forms must be signed by the APPLICANT, not an Agent.</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>)	X			
<i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i>				
<i>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...”</i>				

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		X		
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>				
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>				
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>		X		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
REMS consulted to OSE/DRISK?			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	X			

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>			X	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>			X	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		X		

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>		X		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): April 3, 2008 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 9, 2009

BLA/NDA/Supp #: 200582

PROPRIETARY NAME: Topotecan

ESTABLISHED/PROPER NAME: topotecan

DOSAGE FORM/STRENGTH: 4 mg

APPLICANT: Hospira, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): for the treatment of small cell lung cancer sensitive disease after failure of first-line chemotherapy.

BACKGROUND: Topotecan hydrochloride is a semi-synthetic derivative of camptothecin with topoisomerase I inhibitory activity. It is marketed by GlaxoSmithKline (GSK) under the trade name Hycamtin®, with indications for 1) metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy, 2) small cell lung cancer (SCLC) sensitive disease after failure of first-line chemotherapy, and 3) in combination with cisplatin for 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 drug product, Topotecan Injection would be a ready-to-use aqueous solution containing total drug content of 4 mg supplied in sterile, single-use vials. The proposed product is formulated in Water for Injection, tartaric acid, and pH adjusted, if necessary, with hydrochloric acid and/or sodium hydroxide. Hospira's proposed product does not use the same inactive ingredients. The mannitol has been removed.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Adams-McLean	Y
	CPMS/TL:	Alice Kacuba	N
Cross-Discipline Team Leader (CDTL)	Sara Pope		Y
Clinical	Reviewer:	Michael Brave	Y

	TL:	Ke Liu	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Lillian Zhang	Y
	TL:	Qi Liu	Y
Biostatistics	Reviewer:	Chia-Wen, Ko	Y
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	William McGuinn	Y
	TL:	Leigh Verbois	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Debasis Ghosh	Y
	TL:	Sarah Pope	y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Bryan Riley	Y
	TL:		
CMC Labeling Review (<i>for BLAs/BLA supplements</i>)	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		

OSE/DMEPA (proprietary name)	Reviewer:	Walter Fava	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:	Latonia Ford	Y
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		

Other reviewers	Sarah Simon OSE	Y
Other attendees		

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> 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? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

Comments:	
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<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs/BLA supplements only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Amna Ibrahim, M.D.	
21st Century Review Milestones (see attached) (optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

ALLISON ADAMS-MCLEAN
11/15/2010

**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:	November 5, 2010
Application Type/Number:	NDA 200582
To:	Robert Justice, MD, Director Division of Drug Oncology Products
Through:	Carol A. Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Irene Z. Chan, PharmD, BCPS, Acting Team Leader Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name(s):	Topotecan Injection: 4 mg/4 mL
Applicant/sponsor:	Hospira Inc.
OSE RCM #:	2010-22-1

1 INTRODUCTION

(b) (4)
we are making additional recommendations to the label and labeling for this product at this time. This review serves as an addendum to OSE review 2010-22-1, dated August 16, 2010.

1.1 REGULATORY HISTORY

DMEPA reviewed the initial proposed label and labeling under OSE RCM #2010-22 dated May 27, 2010. In response to that review, the Applicant submitted a revised label and labeling on July 26, 2010. DMEPA had a teleconference with the Applicant on July 29, 2010 to request additional changes to the revised container label. The Applicant submitted a revised container label and carton labeling on August 10, 2010 as well as revised insert labeling on August 11, 2010 which DMEPA reviewed under OSE RCM #2010-22-1 dated August 16, 2010.

2 METHOD AND MATERIALS

DMEPA reviewed the revised label and labeling submitted on August 10, 2010 (see Appendices A and B) and August 11, 2010. We also compared the label and labeling against recommendations made for other 505(b)(2) Topotecan Injection applications currently under review within DMEPA.

3 CONCLUSIONS AND RECOMMENDATIONS

We have identified inconsistencies between the label and labeling of this product and other 505(b)(2) Topotecan Injection applications currently under review within DMEPA. Thus, in order to reconcile these differences, we provide recommendations on the insert labeling in Section 3.1 Comments to the Division. We request the recommendations for the carton labeling and vial label in Section 3.2 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 the OSE Regulatory Project Manager, Sarah Simon, at 301-796-5205.

3.1 COMMENTS TO THE DIVISION

A. GENERAL COMMENTS

1. (b) (4)
As part of a national campaign to decrease the use of dangerous abbreviations, FDA agreed to not use such abbreviations in the approved labeling of products. Therefore we recommend that (b) (4) be replaced with the text (b) (4)
2. The Applicant has utilized trailing zeros within the insert labeling. Trailing zeros can lead to 10-fold errors in dosing and as such are considered dangerous abbreviations. As stated above FDA agreed not to approve such abbreviations in the labeling of products. Therefore, DMEPA recommends removing all trailing zeros with the exception of when it is required to demonstrate the level of precision of the value being reported, such as for laboratory results, imaging studies that report size of lesions, or catheter/tube sizes.

B. HIGHLIGHTS OF PRESCRIBING INFORMATION

1. Warnings and Precautions

We have received reports of 10-fold overdoses of topotecan. Consider adding the following warning as a bullet under the Warnings and Precautions section: “10-fold overdoses of topotecan have occurred and resulted in serious adverse outcomes. Always check the dose prior to administration.”

C. FULL PRESCRIBING INFORMATION

1. Dosage and Administration Subsection

a As currently presented, the instructions for dose modifications and dosage adjustment in specific populations appear crowded and difficult to read. We recommend presenting the information in table format such as the following:

Table X: Dose Adjustments for Selected Hematologic Laboratory Abnormalities	
Monitoring Parameter	Action To Take
Severe neutropenia (defined as <500 cells/mm ³) during any course	Reduce the dose by 0.25 mg/m ² (to 1.25 mg/m ²) for subsequent courses OR Administer G-CSF (granulocyte-colony stimulating factor) following the subsequent course (before resorting to dose reduction) starting from day 6 of the course (24 hours after completion of topotecan administration)
Platelet count falls below 25,000 cells/mm ³	Reduce doses by 0.25 mg/m ² (to 1.25 mg/m ²) for subsequent courses

b Under preparation and administration in section 2.3, there are currently no instructions on proper dilution volume or rate of infusion. We recommend revising the first paragraph to read as follows: *The appropriate volume of Topotecan Injection is diluted in a minimum of 50 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP prior to administration. Infuse over 30 minutes.*

2. Warnings and Precautions

See comment B(1) above.

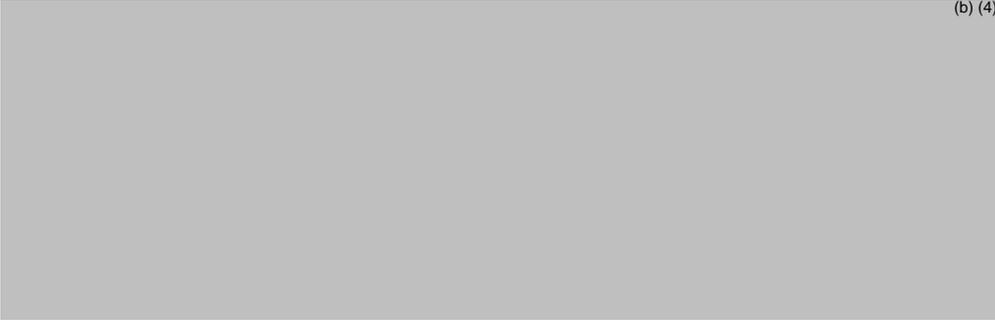
3.2 COMMENTS TO THE APPLICANT

A GENERAL COMMENTS FOR LABELS AND LABELING (b) (4)

1. We are concerned that the introduction of a solution dosage form may lead to the medication being administered by intravenous push instead of intravenous infusion. We recognize the statements (b) (4) and “Must be diluted before use” are present, however, we recommend combining these statements to read “For Intravenous Infusion after Dilution Only” printed in bold font.

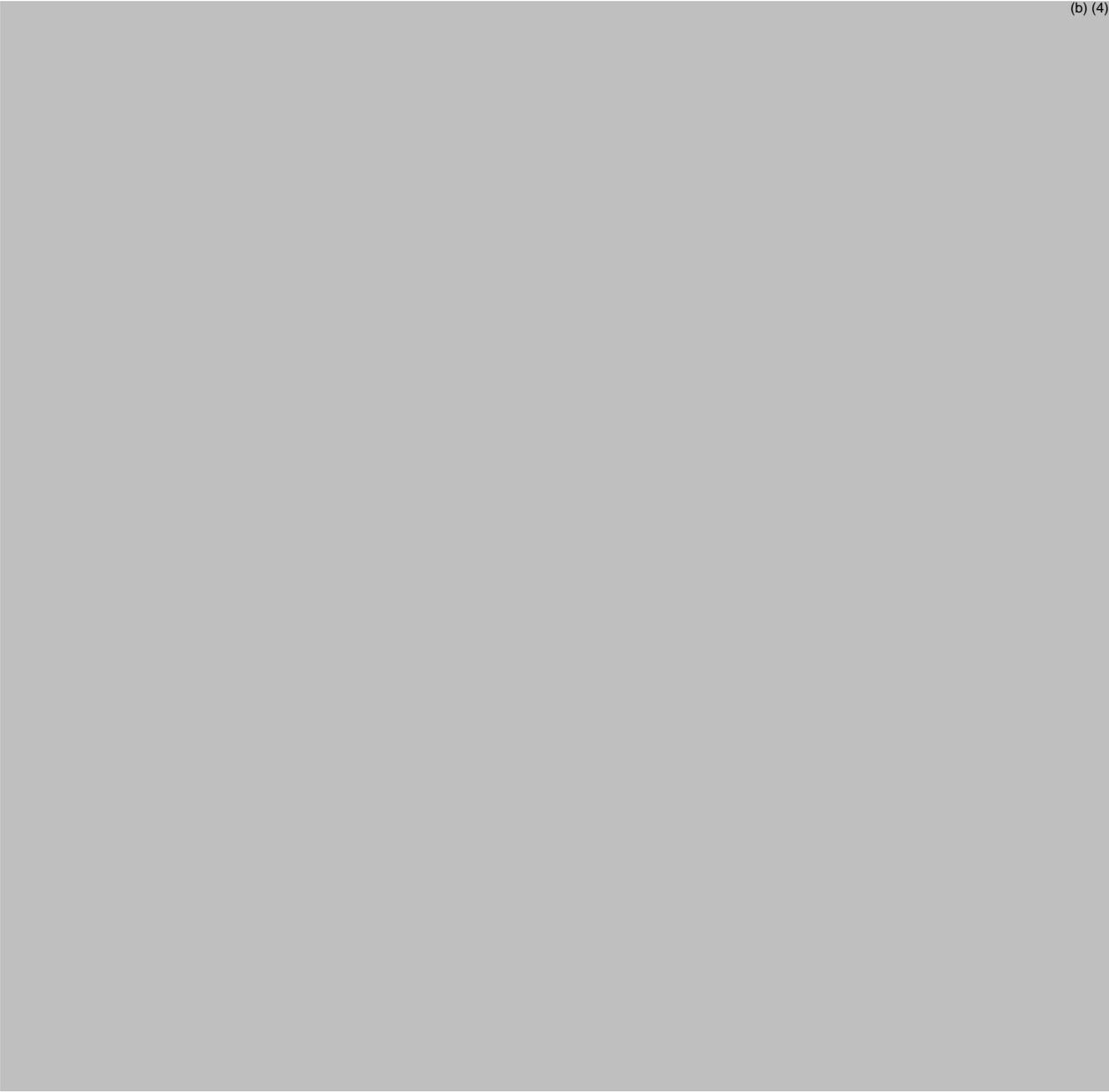
Appendix A: Container Label (4 mg/4 mL)

(b) (4)

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Appendix B: Carton Labeling (4 mg/4 mL)

(b) (4)

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/s/

IRENE Z CHAN
11/05/2010

CAROL A HOLQUIST
11/05/2010

**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:	August 16, 2010
Application Type/Number:	NDA 200582
To:	Robert Justice, MD, Director Division of Drug Oncology Products
Through:	Carlos Mena-Grillasca RPh, Team Leader Kellie Taylor, PharmD, MPH, Associate Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Walter Fava, RPh, MSED, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name(s):	Topotecan Injection 4 mg/4 mL
Applicant/sponsor:	Hospira Inc.
OSE RCM #:	RCM 2010-22-1

1 INTRODUCTION

This review responds to a request from the Division of Oncology Products for a review of the revised Topotecan labels and labeling submitted on July 27, 2010, in response to the Division of Medication Error Prevention and Analysis' previous comments to the Applicant. DMEPA reviewed the initial proposed label and labeling under OSE RCM #2010-22 dated May 27, 2010. In response to that review, the Applicant submitted revised labels and labeling on July 26, 2010. DMEPA had a teleconference with the Applicant on July 29, 2010 to request additional changes to the revised container label.

2 MATERIAL REVIEWED

The Applicant provided revised label and labeling on August 11, 2010. We also evaluated the recommendations pertaining to the previous revisions submitted in response to OSE review #2010-22.

3 DISCUSSION

Review of the revised documents show that the Applicant implemented DMEPA's recommendations under OSE review #2010-22 as well as recommendations provided in the teleconference on July 29, 2010. The Applicant's revisions did not introduce any additional areas of vulnerability that could lead to medication errors.

4 CONCLUSIONS AND RECOMMENDATIONS

The revised label and labeling submitted by the Applicant adequately addresses our concerns from a medication error perspective. We do not have any additional comments at this time.

If you have further questions or need clarifications, please contact Sarah Simon, OSE Project Manager, at 301-796-5205.

5 REFERENCES

OSE Review #2010-22, Label and Labeling Review for Topotecan Injection. Fava, W: May 27, 2010.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200582	ORIG-1	HOSPIRA INC	TOPOTECAN INJ

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

/s/

WALTER L FAVA
08/16/2010

CARLOS M MENA-GRILLASCA
08/16/2010

KELLIE A TAYLOR
08/16/2010



**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: June 25, 2010

To: Robert Justice, M.D., Division Director
Division of Drug Oncology Products (DDOP)

Through: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

From: Latonia M. Ford, RN, BSN, MBA
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Patient Package Insert)

Drug Name(s): Topotecan Injection

Application Type/Number: NDA 200-582

Applicant/sponsor: Hospira, Inc

OSE RCM #: 2009-2350

The Division of Drug Oncology Products (DDOP) requested that the Division of Risk Management (DRISK) review proposed patient labeling for a 505(b)(2) New Drug Application, NDA#200-582, submitted by Hospira Inc. on October 29, 2009 for Topotecan Injection.

DDOP informed DRISK that the Applicant has submitted updated labeling to reflect the Reference Listed Drug, NDA# 20-671, Hycamtin (topotecan hydrochloride) Injection, which does not have patient labeling. Since the Reference Listed Drug does not have patient labeling, DDOP has determined that this 505(b)(2) product will not have patient labeling. This memo serves to close-out this consult request for Topotecan Injection.

Please let us know if you have any questions.

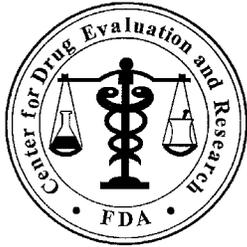
Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200582	ORIG-1	HOSPIRA INC	TOPOTECAN INJ

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/s/

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06/28/2010

SHARON R MILLS
06/28/2010



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: May 26, 2010

To: Robert Justice, MD, Director
Division of Drug Oncology Products

Through: Carlos Mena-Grillasca, RPh, Team Leader
Kellie Taylor, Pharm D., MPH, Associate Director
Carol A. Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Walter Fava, R.Ph., MSED., 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 200582

Applicant: Hospira

OSE RCM #: 2010-22

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1 INTRODUCTION

This review responds to a January 5, 2010 request from the Division of Drug Oncology Products for DMEPA evaluation of the labels and labeling for Topotecan. This review summarizes our evaluation of these labels and labeling.

2 METHODS AND MATERIALS

In order to assess issues with the proposed labels and labeling, we searched the Adverse Event Reporting System (AERS) database and employed proactive risk assessment of the labels and labeling.

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) SELECTION OF CASES

DMEPA conducted a previous AERS search for topotecan products during evaluation of the labels and labeling for another Topotecan Injection application (NDA (b)(4)) in OSE Review #2009-986 dated January 12, 2010. That application was a 505(b)(2) of the reference listed drug Hycamtin. In that review, an AERS search of Hycamtin was conducted on June 17, 2009. Twenty-two (n=22) cases of medication errors were identified from the search. However, none of the cases pertained to the labels and labeling.

Since this proposed product is also 505(b)(2) for the reference listed drug Hycamtin, we conducted an AERS search from the date of the aforementioned Topotecan review (June 18, 2009). 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%' (trade name), and verbatim terms of 'Hycamt%'.

2.2 LABELS AND LABELING

Using Failure Mode and Effects Analysis (FMEA) DMEPA evaluated the insert labeling submitted on October 29, 2009 and the container labels and carton labeling submitted on April 30, 2010 (see Appendices A and B).

3 RESULTS AND DISCUSSION

The following sections describe the results of our assessment and discussions of our findings.

3.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

Our search of AERS on April 2, 2010 retrieved three (n=3) cases including one case of an adverse event (n=1), one foreign case of wrong drug and inappropriate schedule of administration (n=1), and one accidental overdose of oral Topotecan (n=1). However, none of the cases pertained to the labels and labeling associated with this review and therefore are not relevant to this review (see Appendix C).

3.2 LABELS AND LABELING

Our evaluation noted areas where information on the container labels, carton and insert labeling can be improved to minimize the potential for medication errors. We provide recommendations in Section 4.1 *Comments to the Applicant*. We request the recommendations in Section 4.1 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 Sarah Simon, Project Manager, at 301-796-5205.

4 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation of the proposed container labels, carton and insert labeling submitted for Topotecan Injection, identified areas of needed improvement to minimize the potential for medication errors. Specifically, we note that the presentation of information such as the total drug content contains interfering graphics which make it difficult to understand. We provide recommendations to address our concerns in section 4.1 below, and request they be communicated to the Applicant prior to approval.

4.1 COMMENTS TO THE APPLICANT

A. Container Labels and Carton Labeling

1. Revise the concentration statement to appear in parentheses following the total drug content statement to be in accordance with USP General Chapters <1> requirements for injectable drug products. For example:

4 mg/4 mL
(1 mg/mL)

B. Container Label

1. Include the dilution statement (e.g. Must be diluted before use).
2. The two-toned background colors (green/black) used for presentation used to distinguish the strength of the total drug content statement is confusing. As currently presented, (b) (4) and minimizes the total amount of drug in the container. Revise the presentation so that the total drug content statement appears on a solid one color background which clearly displays '4 mg/4 mL' or states '4 mg per 4 mL'.
3. Revise the statement, (b) (4) to read, 'Single Use Vial: Discard Unused Portion'.
4. Include an expiration date and lot number.

C. Carton Labeling

See Comments B1 through B4 above and apply to carton labeling.

D. Insert Labeling

1. Highlights, Dosage Forms and Strengths section:
 - a. Present the total drug content followed by concentration and the dosage form (e.g. (b) (4)). As currently presented, no reference is made to the dosage form.

5 REFERENCES

5.1 REVIEWS

OSE Review #2009-986, Label and Labeling Review; Park, J. January 12, 2010.

5.2 DATABASES

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.

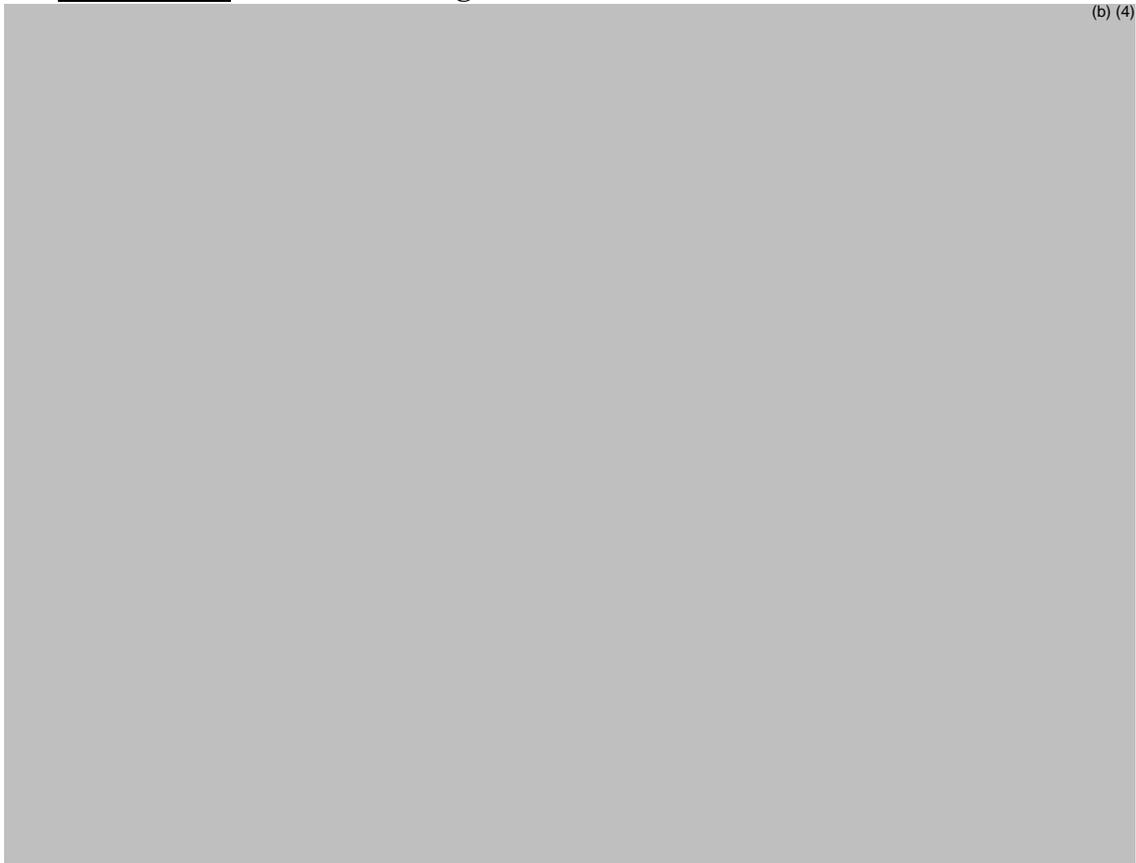
APPENDIX

Appendix A: Container Label



(b) (4)

Appendix B: Carton Labeling



(b) (4)

Appendix C: Topotecan medication error ISR numbers

ISR 6481247-X

ISR 6529905-2

ISR 6630207-4

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