

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
200582Orig1s000

MEDICAL REVIEW(S)

MEMORANDUM

DATE January 31, 2010

TO NDA 200582

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

SUBJECT Addendum to General Clinical Review dated January 25, 2011

Hospira submitted a New Drug Application on December 2, 2010 for Topotecan Injection under 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. This application contains no new clinical data and relies for approval on the FDA's findings of safety and effectiveness for Hycamtin[®].

On January 25, 2011, this reviewer filed a General Clinical Review concluding that this application was not approvable from a clinical standpoint because (b) (4)

[REDACTED]

This reviewer has reconsidered this question. References to (b) (4)

[REDACTED] This will provide clinicians with sufficient safety information and will maintain consistency between the labels of Hycamtin and Topotecan Injection.

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/s/

MICHAEL H BRAVE
02/01/2011

KE LIU
02/01/2011

MEMORANDUM

DATE January 25, 2011

TO NDA 200582

FROM Michael Brave, M.D.
Medical Officer, DDOP/ODE6/CDER

SUBJECT New Drug Application

1. Background

Topotecan hydrochloride is a semi-synthetic derivative of camptothecin with topoisomerase I-inhibitory activity. It is marketed under the trade name Hycamtin[®], with the following indications:

- as a single agent for the treatment of metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy (NDA 20-671; 28 May 1996);
- as a single agent for the treatment small cell lung cancer (SCLC) sensitive disease after failure of first-line chemotherapy (NDA 20-671/S-004; 30 Nov 1998);
- in combination with cisplatin for the treatment of Stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amenable to curative treatment with surgery and/or radiation therapy (NDA 20-671/S-014; 14 Jun 2006).

Hycamtin[®] is available in single-dose vials containing a sterile lyophilized buffered powder. The approved dose for ovarian cancer and SCLC is 1.5 mg/m² given as a 30 minute intravenous (IV) infusion once daily for 5 consecutive days, starting on Day 1 every 21 days. The approved dosage for cervical cancer is 0.75 mg/m² IV over 30 minute once daily on days 1, 2, and 3; followed by cisplatin 50 mg/m² IV on Day 1 every 21 days.

2. Submission

Hospira submitted the current application on December 2, 2010 for Topotecan Injection under 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. This application contains no new clinical data and relies for approval on the FDA's findings of safety and effectiveness for Hycamtin[®].

The proposed drug product is in the same dosage form (i.e. injectable solution) containing the same active ingredient at the same concentration after reconstitution as the RLD, and is intended for administration by intravenous infusion. The inactive ingredients in the proposed product are qualitatively and quantitatively the same as the inactive ingredients contained in the RLD, except that mannitol is removed. (b) (4)

The proposed drug product consists of the active ingredient, topotecan hydrochloride, in tartaric acid and water for injection, prepared with hydrochloric acid and/or sodium hydroxide for pH adjustment (range 2.6 to 3.2). Hospira states

that the proposed product offers convenience for practitioners by avoiding the reconstitution step when preparing the drug for administration. The proposed product will be packaged in (b) (4) 4mg/4 mL (1mg/mL) multi-dose vials.

The Applicant seeks approval for the same (b) (4) SCLC indications which Hycamtin currently has. (b) (4)

Reviewer's comment: (b) (4)

(b) (4). *Adverse events must be interpreted keeping the patient population in mind. The toxicity profile of topotecan in (b) (4) SCLC cancer may be significantly different (b) (4) more pulmonary events in lung cancer). Removing one disease but not the other from the title of the table without adjusting the results could make that table misleading.*

3. Pre-submission regulatory activity

- 3 Feb 2009 The Applicant initially submitted NDA (b) (4) for Topotecan injection. This NDA received a RTF letter due to lack of stability data.
- 29 Oct 2009 Applicant first re-submitted the NDA (now 200582).
- 12 Jan 2010 DODP issued a 74-day filing letter which identified no potential review issues and classified the review as Standard, with a user fee goal date of August 29, 2010.
- 18 Jun 2010 OPS/IO concluded that the application was expected to have no significant adverse environmental impact. No environmental impact statement was required.
- 22 Jul 2010 ONDQA granted the Applicant's request for a waiver for *in vivo* BA/BE data. Based on 21 CFR 320.22(b)(1) regulations and the information showing that 1) the product contains the same active ingredient and inactive ingredients with the exception of (b) (4) mannitol, and 2) the route of administration, dosage form and indications of the product are the same as the RLD product, the *in vivo* BA/BE of Hospira's Topotecan Injection is self-evident.
- 19 Jul 2010 OCP/DCP5 completed its review and found this NDA acceptable from a clinical pharmacology perspective.
- 26 Jul 2010 DDOP in collaboration with DRM concluded that the proposed product label was acceptable.
- 27 Jul 2010 OSE found six postmarketing reports suggestive of topotecan-induced injection site reactions. Two of these occurred on single agent topotecan, including one

with a serious outcome requiring a phlebectomy. It could not be determined if these cases of phlebitis were related to variability in admixture preparation and administration. OSE recommended adding "local infusion/injection site reactions, including phlebitis" to the postmarketing experience section of the package insert.

- 20 Jul 2010 ONDQA concluded that from a CMC perspective, the NDA was Not Approvable due to lack of response to a deficiency letter to the DMF holder.
- 8 Aug 2010 DDOP determined that this NDA was approvable from a Pharmacology and Toxicology perspective.
- 18 Aug 2010 The Applicant submitted an amendment to provide a status update for DMF (b) (4) (SN-009).
- 24 Aug 2010 DDOP determined that SN-009 constituted a major amendment. This extended the user fee goal-date to November 29, 2010.
- 11 Nov 2010 This reviewer determined that the NDA was approvable from a clinical standpoint.
- 26 Nov 2010 DDOP issued a Complete Response to the because of deficiencies identified during a field inspection of the Hospira worldwide, Inc. (Rocky Mount, NC).
- 2 Dec 2010 The Applicant re-submitted NDA 200582. DDOP considered this to be a Class 1 response to the November 26, 2010, action letter. The user fee goal date is therefore February 2, 2011.

4. Conclusion

This 505(b)(2) application is not approvable from a clinical standpoint because (b) (4) SCLC indications can not be separated in the product label. Tables 1 and 2 in the proposed package insert (and in the Hycamtin package insert) combine adverse events from both populations. Adverse events must be interpreted keeping the patient population in mind. The toxicity profile of topotecan in (b) (4) SCLC cancer may be significantly different (b) (4) more pulmonary events in lung cancer). Removing one disease but not the other from the title of the table without adjusting the results could make that table misleading.

The ultimate recommended action will also depend upon resolution of the deficiencies in manufacturing which required the Division to issue a Complete Response on November 26, 2010.

5. Recommendations

This reviewer recommends communicating the following to the Applicant:

Tables 1 and 2 in your proposed package insert contain information regarding (b) (4) small cell lung cancer. Adverse events must be interpreted keeping the patient population in mind. The toxicity profile of topotecan in (b) (4) SCLC cancer may be significantly different ((b) (4) more pulmonary events in lung cancer). Removing one disease but not the other from the title of the table without adjusting the results could make that table misleading. (b) (4)

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/s/

MICHAEL H BRAVE
01/25/2011

KE LIU
01/25/2011

Summary Review for Regulatory Action

Date	November 26, 2010
From	Amna Ibrahim MD
Subject	Deputy Division Director Summary Review
NDA/BLA #	200582
Supplement #	0
Applicant Name	Hospira, Inc.
Date of Submission	October 29, 2009 Major amendment: August 18, 2010
PDUFA Goal Date	November 29, 2010
Proprietary Name / Established (USAN) Name	Topotecan Injection
Dosage Forms / Strength	4 mg/ml
Proposed Indication(s)	small cell lung cancer sensitive disease after failure of first-line chemotherapy
Action/Recommended Action for NME:	Complete Response

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Michael Brave MD/Ke Liu MD
Statistical Review	Chia-Wen Ko, Ph.D/ Shenghui Tang, Ph.D
Pharmacology Toxicology Review	S. Leigh Verbois, Ph.D.
CMC Review/OBP Review	Debasis Ghosh PhD/ Sarah Pope Miksinski, Ph.D
Clinical Pharmacology Review	Hua Lillian Zhang, Ph.D.
DSI	Not applicable
CDTL Review	Sarah Pope Miksinski, Ph.D.
OSE/DMEPA	Irene Z. Chan, PharmD, BCPS/Carol A. Holquist, RPh
OSE/DRISK	Latonia M. Ford, RN, BSN, MBA/Sharon R. Mills, BSN, RN, CCRP
Other	

OND Office of New Drugs
DDMAC Division of Drug Marketing, Advertising and Communication
OSE Office of Surveillance and Epidemiology
DMEPA Division of Medication Error Prevention and Analysis
DSI Division of Scientific Investigations
DDRE Division of Drug Risk Evaluation
DRISK Division of Risk Management
CDTL Cross Discipline Team Leader

1. Introduction

Hospira Inc., has submitted NDA 200582 for Topotecan Injection as a 505b(2) submission. HYCAMTIN is the reference listed drug supplied by GlaxoSmithKline. It is supplied for intravenous use and is indicated for

- metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy,
- small cell lung cancer sensitive disease after failure of first-line chemotherapy and
- combination therapy 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.

Due to existing patents, Hospira Inc is requesting approval only for the indication of small cell lung cancer sensitive disease after failure of first line chemotherapy.

2. Background

Hospira, Inc. initially submitted NDA (b) (4) for Topotecan Injection on 3/2/2009. This NDA received an RTF letter due to the lack of stability data. It was resubmitted on October 29, 2009. Per applicant, “(t)he proposed drug product Topotecan Injection is an aqueous injectable dosage form, at a concentration of 1 mg/mL topotecan, containing a total of drug content of 4 mg in a 5 mL sterile, single-use glass vial. The proposed drug product is in the same dosage form containing the same active ingredient at the same concentration as the RLD, Hycamtin[®], after reconstitution, and is intended for administration by intravenous infusion. The inactive ingredients in the proposed product are qualitatively and quantitatively the same as the inactive ingredients contained in the RLD, except that mannitol is removed.” They also state that “(t)he conditions of use (indication) and route of administration for the subject drug, Topotecan Injection, are the same as prescribed and recommended for the use of the Reference Listed Drug, except for ovarian cancer indication covered under the method of use patent certification provided in Section 1.3.5 and the advance staged cervical cancer indication covered under a patent not listed in the Orange Book. The proposed drug offers convenience for practitioners by avoiding the reconstitution step when preparing the drug for administration.”

According to the CDTL review by Sarah Pope Miksinski, PhD, the Agency granted a standard review with an initial PDUFA goal date of 29-AUG-2010. Based on a major Chemistry, Manufacturing and Controls (CMC) amendment received on 18-AUG- 2010, the review clock was extended three months to 29-NOV-2010.

3. CMC/Device

Per the review of Debasis Ghosh, M. Pharm., Ph.D. signed on 11/19/2010, cosigned by Sarah Pope Miksinski PhD, on 11/19, 2010, “The CMC information of the drug substance is provided in DMF (b) (4). At the time of the completion of Review # 2 on 27-Jul-2010, the status of DMF (b) (4) was inadequate. Since drug substance, drug product, and labeling issues are all related to the information contained in the DMF (b) (4), the satisfactory resolution of DMF issues was necessary to address outstanding CMC deficiencies in the NDA.” Per Dr Miksinski, a subsequent review of DMF (b) (4) determined that the DMF is now adequate to support this NDA.

Per Dr Pope Miksinski’s CDTL review, “Topotecan Injection is an aseptically-filled, non-preserved product. The microbiology reviewer (Dr. B. Riley) recommended approval of this NDA in his review dated 29- APR-2010. Of particular note is the reviewer’s confirmation that

the drug product acidity (pH < 4) makes it unlikely that microorganisms would proliferate in the solution, despite the lack of preservatives in the formulation.”

According to Dr Pope Miksinski’s review, “An Establishment Evaluation Request (EER) was submitted to the Office of Compliance on 09-DEC-2009. An overall acceptable recommendation was issued for the application on 18-DEC-2009. This recommendation was subsequently changed to an overall “withhold” recommendation on 11-AUG-2010.”

4. Nonclinical Pharmacology/Toxicology

Leigh Verbois PhD, in her review states that all drug substance and drug product specifications have been set below ICH qualification thresholds, therefore no additional impurity qualification was required. Based on this information, in combination with the Agency’s previous finding of safety and efficacy, this application is approvable from a Pharmacology and Toxicology perspective. There are no outstanding nonclinical issues related to the approval of this NDA for the proposed indication.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Per review Hua Lillian Zhang, Ph.D. by dated 6/22/2010, cosigned on 7/19/2010 by Qi Liu PhD, “there is no bioequivalent study nor any other clinical studies submitted in this application. The Applicant is relying on the findings of safety and effectiveness for HYCAMTIN® to support the approval of their product. The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 considers this NDA acceptable from a clinical pharmacology perspective.’

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Clinical reviewer Michael Brave MD and clinical team leader Ke Liu MD (review signed on 11/12/2010) conclude that this application is acceptable from a clinical standpoint.

According to the statistical review by Chia-Wen Ko, Ph.D (dated 7/14/2010), cosigned by Shenghui Tang, Ph.D., Team Leader and Rajeshwari Sridhara, Ph.D., Division Director, “There are no clinical data submitted in this 505 (b)(2) application. Referenced clinical studies for this application include 1 randomized comparative study and 3 single-arm studies in recurrent or progressive small cell lung cancer patients used in the NDA 20-671 application.”

“The proposed label section 14 on clinical studies is compared to Hycamtin® product label for discrepancies. One discrepancy is found (please see the primary findings section below). The sponsor will be asked to correct the discrepancy.” According to the review, “The numbers 26 and 19 in proposed label Table 4 are referring to number of patients evaluable for response duration. This should be clarified, as in Hycamtin® product label Table 8.”

8. Safety

Not applicable

9. Advisory Committee Meeting

Not applicable

10. Pediatrics

A pediatric waiver is not required because this is a 505b(2) application and there is no new indication.

11. Other Relevant Regulatory Issues

- DSI Audits: not done
- Financial Disclosure: not applicable
- Other consults- DDMAC: not done

12. Labeling

- Proprietary name: none proposed.
- Physician labeling: labeling will not be included in the action letter
- Carton and immediate container labels: labeling will not be included in the action letter
- Patient labeling/Medication guide: no patient labeling accompanies the PI for the RLD. There was no patient’s labeling or medication guide in this NDA.

Per CDTL review “Of particular note are two pending labeling (PI) recommendations stated in the final CMC memo (18-NOV-2010), one of which relates to an (b) (4)

statement in the Highlights section and one of which relates to [REDACTED] (b) (4)
[REDACTED] Due to timing along with the intended “CR” action, these two recommendations were not incorporated into the PI prior to inclusion in the action letter. Therefore, both of these recommendations should be revisited during any subsequent review cycles.”

13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action:**

Per CDTL review by Dr Sarah Miksinski, an overall acceptable recommendation must be received from the Office of Compliance before this product can be recommended for approval from a CMC perspective.

I agree with the “Complete Response” recommendation.

- **Risk Benefit Assessment**

I agree with the CDTL assessment. Dr Miksinski states that the review of this NDA is based primarily on chemistry, manufacturing and controls data. While the NDA is recommended for approval from all remaining disciplines, the application has received an overall withhold recommendation from the Office of Compliance. Therefore, the cGMP status for all manufacturing sites is unacceptable, and the proposed manufacturing sites are not confirmed as suitable for producing drug product for the commercial market.

- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies**
Not applicable

- **Recommendation for other Postmarketing Requirements and Commitments**
Not applicable

Amna Ibrahim MD
Deputy Division Director
DDOP, OODP

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/s/

AMNA IBRAHIM
11/26/2010

Cross-Discipline Team Leader Review

Date	22-NOV-2010
From	Sarah Pope Miksinski, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	200582
Applicant	Hospira, Inc.
Date of Submission	29-OCT-2010 18-AUG-2010 (major amendment clock extended)
PDUFA Goal Date	29-NOV-2010 (based on extension)
Proprietary Name / Established (USAN) names	Topotecan Injection
Dosage forms / Strength	4 mg/mL
Proposed Indication(s)	Indicated for the treatment of small cell lung cancer sensitive disease after failure of first line chemotherapy
Recommended:	Complete Response

1. Introduction

Hospira, Inc. initially submitted NDA (b) (4) for Topotecan Injection on 02-MAR-2009. NDA (b) (4) was deemed unfileable due to the lack of stability data, and the Agency issued a “Refuse to File” letter to Hospira on 01-MAY-2009. NDA (b) (4) was subsequently withdrawn by Hospira on 21-MAY-2009.

The current NDA 200582 includes information previously submitted in NDA (b) (4) along with the requested additional stability data. NDA 200582 was filed by the Agency on 12-JAN-2010. The Agency granted a standard review with an initial PDUFA goal date of 29-AUG-2010. There were no comments conveyed in the 74-day letter. Based on a major Chemistry, Manufacturing and Controls (CMC) amendment received on 18-AUG-2010, the review clock was extended three months to 29-NOV-2010.

This CDTL memo serves to highlight the critical approvability issues discussed in all review disciplines and recommends a “Complete Response” action for this application. All individual discipline reviews may be found in DARRTS. Final container labels were provided on 19-JUL-2010. However, final PI labeling is still pending due to the recommended “Complete Response” action. Any updated container/carton and/or PI labeling will need to be reviewed by all disciplines during subsequent review cycles.

2. Background

The Reference Listed Drug for this submission is Hycamtin® (topotecan hydrochloride) for Injection (NDA 20-671), which is currently marketed by GlaxoSmithKline. The proposed drug product is an aqueous injectable dosage form intended for dilution and intravenous injection. It is supplied at a concentration of 1 mg/mL topotecan (free base), and each dosage unit contains a total drug content of 4 mg in a 5 mL sterile, single-use glass vial. The proposed drug product contains the same active ingredient as the RLD, and the prepared/post-reconstitution drug product solution is the same concentration as the RLD.

The inactive ingredients in the proposed product are qualitatively and quantitatively the same as the inactive ingredients contained in the RLD, with the exception of the removal of mannitol relative to the RLD. (b) (4)

No Pre-NDA meeting was conducted for NDA 200582. However, a preNDA meeting was held on 14-NOV-2008 for NDA (b) (4). Hospira indicates that NDA 200582 addresses the issues related to the Agency's 21-MAY-2009 Refuse to File letter issued for NDA (b) (4)

Dosing Regimen and Administration

The recommended dose of Topotecan Injection is 1.5 mg/m² by intravenous infusion over 30 minutes daily for five consecutive days, starting on day 1 of a 21-day course.

3. CMC

NDA 200582 was initially submitted on 29-OCT-2010 as a 505(b)(2) application. The NDA included a full dossier of CMC information, along with proposed container/carton and PI labeling. Chemistry Review #1 (09-JUL-2010) identifies three unresolved CMC deficiencies, two of which are related to the inadequacy of DMF (b) (4). The remaining deficiency was related to the proposed container/carton labels. As of late July/2010, a response to the inadequate DMF had not been received, and the CMC reviewer (Dr. D. Ghosh) subsequently recommended a CR action for this NDA due to the inadequacy of the cross-referenced, Type II DMF (b) (4) (see Chemistry Review #2 dated 27-JUL-2010).

The DMF deficiencies cannot be stated in the current memo. However, the specific content of the DMF deficiencies is located in the 15-JUN-2010 review for DMF (b) (4). In a 18-AUG-2010 submission to NDA 200582, the Applicant confirmed that the DMF holder submitted a response to the DMF deficiencies, and the review clock for NDA 200582 was subsequently extended based on this confirmation and DMF amendment. A subsequent review of DMF (b) (4) determined that the DMF is now adequate to support this NDA.

- General product quality considerations

The major product quality issue related to the inadequacy of DMF (b) (4) to support this NDA. DMF (b) (4) was deemed inadequate (see review by Dr. A. Russell) on 15-JUN-2010, and following the DMF holder's response to the deficiencies, the DMF was determined to be adequate on 09-NOV-2010.

The inadequacy of DMF (b) (4) rendered it impossible to confirm the exact salt composition of the drug substance in both DMF (b) (4) and NDA 200582. (b) (4)

This discrepancy impacted several quality areas of the NDA and rendered the NDA not approvable without resolution of the DMF deficiencies.

Once the DMF deficiencies related to the salt content (b) (4) had been resolved, review of NDA 200582 continued under a clock extension, and the appropriate CMC subsections were re-reviewed and updated as needed (see the final CMC memo dated 18-NOV-2010). The resolution of the DMF deficiencies effectively also resolved the pending NDA deficiencies, with the exception of the overall withhold recommendation from the Office of Compliance (see below bullet).

NDA 200582 included a request for a biowaiver. This request was evaluated in a 22-JUL-2010 review (Dr. A. Dorantes) which granted the Applicant's request.

The Applicant's original submission included 18 months of real time (2-8°C) stability data for three registration batches of the drug product. The submission also includes 12 months of intermediate data (15°C), and six months accelerated (25°C) stability data for the drug product. All studies were conducted on both upright and inverted configurations. Forced degradation studies indicated that topotecan is not susceptible to light-induced instability, so further photostability studies were not conducted. Based on the stability data provided, an 18-month expiration dating period can be granted for room temperature storage conditions. However, due to the intended "CR" action, an expiration dating period will not be specified in the action letter, and updated stability data should be reassessed for adequacy, as needed, in future review cycles.

- Facilities review/inspection
An Establishment Evaluation Request (EER) was submitted to the Office of Compliance on 09-DEC-2009. An overall acceptable recommendation was issued for the application on 18-DEC-2009. This recommendation was subsequently changed to an overall "withhold" recommendation on 11-AUG-2010.
- Microbiology
Topotecan Injection is an aseptically-filled, non-preserved product. The microbiology reviewer (Dr. B. Riley) recommended approval of this NDA in his review dated 29-APR-2010. Of particular note is the reviewer's confirmation that the drug product acidity (pH < 4) makes it unlikely that microorganisms would proliferate in the

solution, despite the lack of preservatives in the formulation. The review also captures the reviewer's concurrence with microbiological aspects of the proposed primary stability protocol, as well as the acceptability of the proposed specifications for endotoxins and sterility in the drug product.

- Other notable issues (resolved or outstanding)
None

4. Nonclinical Pharmacology/Toxicology

There were no new nonclinical pharmacology/toxicology studies provided in this submission. The final Pharmacology/Toxicology memo was finalized in DFS on 08-NOV-2010 and captures a recommendation of approval for the NDA. The finalized memo also references the CMC review, which confirms that acceptance criteria for all impurities in the drug substance and drug product are proposed at levels at or below the ICH qualification threshold (ICH Q3A and B). Therefore, an official Pharmacology/Toxicology consult was not initiated for the drug substance or drug product impurity profile.

5. Clinical Pharmacology

There was no clinical pharmacology data submitted to this NDA. The clinical pharmacology reviewer recommended approval of this NDA in her review dated 19-JUL-2010. This review also captures related revisions to the PI.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

There are no new clinical data provided in the current submission. The clinical reviewer (Dr. M. Brave) recommends approval of this NDA in his 12-NOV-2010 memo.

8. Safety

No new clinical data were provided for this submission.

9. Advisory Committee Meeting

Not applicable

10. Pediatrics, Geriatrics, and Special Populations

Not applicable

11. Other Relevant Regulatory Issues

- Application Integrity Policy (AIP): This was not raised during the pre-approval inspections for this NDA.
- Exclusivity or patent issues of concern: No issues were noted for this NDA.
- Financial disclosures: Not applicable
- Other GCP issues: None
- DSI audits: Not applicable
- Other discipline consults: None
- Any other outstanding regulatory issues: None

12. Labeling

General:

All disciplines participated in internal labeling meetings held throughout the review clock. Specific labeling recommendations are captured in each discipline-specific review.

Proprietary name:

There was no proprietary name proposed for this product.

DMEPA comments:

In an initial review dated 26-MAY-2010, DMEPA identified several specific deficiencies in the proposed container/carton labeling. These deficiencies were subsequently conveyed to the firm. In an updated review dated 16-AUG-2010, the DMEPA reviewer evaluated updated labels submitted on 11-AUG-2010. As stated in the 16-AUG-2010 review, all previously-recommended revisions were effectively implemented, and “the Applicant’s revisions did not introduce any additional areas of vulnerability that could lead to medication errors.”

Overlapping container/carton labeling comments are covered in the 30-JUL-2010 CMC review. The CMC reviewer confirmed that the updated container/carton labels reflected the recommended changes and were acceptable from a CMC standpoint.

Issues not resolved at the time of CDTL memo completion:

Of particular note are two pending labeling (PI) recommendations stated in the final CMC memo (18-NOV-2010), one of which relates to an (b) (4) statement in the Highlights section and one of which relates to (b) (4)

Due to timing along with the intended “CR” action, these two recommendations were not incorporated into the PI prior to inclusion in the action letter. Therefore, both of these recommendations should be revisited during any subsequent review cycles.

Carton and immediate container labels:

See above section titled “DMEPA comments.” Overlapping container/carton labeling comments are also covered in the 30-JUL-2010 CMC review. The CMC reviewer confirmed that the updated (19-JUL-2010) container/carton labels reflected the recommended changes and were acceptable from a CMC standpoint.

Patient labeling/Medication guide:

This is not required for this product.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**
This reviewer does not recommend approval of this NDA. As per the chemistry reviews and final CMC memo dated 18-NOV-2010, an overall acceptable recommendation must be received from the Office of Compliance before this product can be recommended for approval from a CMC perspective.
- **Risk Benefit Assessment**
The review of this NDA is based primarily on chemistry, manufacturing and controls data. While the NDA is recommended for approval from all remaining disciplines, the application has received an overall withhold recommendation from the Office of Compliance. Therefore, the cGMP status for all manufacturing sites is unacceptable, and the proposed manufacturing sites are not confirmed as suitable for producing drug product for the commercial market.
- **Recommendation for Postmarketing Risk Management Activities**
This does not apply to this NDA.
- **Recommendation for other Postmarketing Study Commitments**
None
- **Recommended Comments to Applicant**
The standard language for conveying an unacceptable Compliance recommendation should be inserted into the action letter.

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/s/

SARAH P MIKSINSKI
11/22/2010

MEMORANDUM

DATE November 12, 2010

TO NDA 200-582

FROM Michael Brave, M.D.
Medical Officer, DDOP/ODE6/CDER

SUBJECT New Drug Application

1. 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 reference listed drug (RLD) Hycamtin is a lyophilized powder. It is a single use vial which is to be reconstituted with 4 mL of water for injection. The reconstituted solution is then diluted with an appropriate volume of either 0.9% Sodium Chloride Injection or 5% Dextrose Injection prior to intravenous infusion. Since the lyophilized dosage form contains no antibacterial preservative, the reconstituted product should be used immediately.

2. Submission

Reference is made to the Refuse-to-File letter issued on 8/21/09 to the previously submitted application for Topotecan Injection (NDA (b) (4)). This new application NDA 200-582 was re-filed following the withdrawal of NDA (b) (4) and provides additional stability data and justification to address the concerns in the Refuse-to-File letter.

Hospira submitted the current application on October 29, 2009 for Topotecan Injection 4 mg/4 ml under 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. This application relies for approval on the FDA's findings of safety and effectiveness for Hycamtin[®].

The proposed drug product is in the same dosage form (i.e. injectable solution) containing the same active ingredient at the same concentration after reconstitution as the RLD, and is intended for administration by intravenous infusion. The inactive ingredients in the proposed product are qualitatively and quantitatively the same as the inactive ingredients contained in the RLD, except that mannitol is removed. (b) (4)

The proposed drug

product consists of the active ingredient, topotecan hydrochloride, in tartaric acid and water for injection, prepared with hydrochloric acid and/or sodium hydroxide for pH adjustment (range 2.6 to 3.2). Hospira states that the proposed product offers convenience for practitioners by avoiding the reconstitution step when preparing the drug for administration.

(b) (4)

The application contains no new clinical data. Referenced clinical studies for this application include 1 randomized comparative study and 3 single-arm studies in patients with recurrent SCLC used in the NDA 20-671 application.

3. Post-submission regulatory activity

On January 12, 2010, DODP issued a 74-day filing letter which identified no potential review issues. The review classification for this application is Standard. Therefore, the user fee goal date is August 29, 2010.

On June 18, 2010, the Office of Pharmaceutical Science concluded that this application is not expected to have significant effect on the human environment. Therefore, an environmental impact statement will not be prepared.

On July 22, 2010, ONDQA completed its review of the Applicant's request for a waiver for *in vivo* BA/BE data to support the approval of Topotecan Injection 4 mg/4ml. ONDQA concluded that, based on 21 CFR 320.22(b)(1) regulations and the information showing that 1) the product contains the same active ingredient and inactive ingredients with the exception of (b) (4) mannitol, and 2) the route of administration, dosage form and indications of the product are the same as the RLD product, the *in vivo* BA/BE of Hospira's Topotecan Injection is self-evident. The biowaiver was therefore granted.

On July 19, 2010, The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 completed its review and found this NDA acceptable from a clinical pharmacology perspective.

On July 26, 2010, the DODP review team in collaboration with the Division of Risk Management completed its review of the most recent proposed product label, submitted July 19, 2010, and found the proposed product label acceptable.

On July 27, 2010, the Office of Surveillance and Epidemiology (OSE) found six postmarketing reports suggestive of drug-induced injection site reactions with topotecan. Two of these occurred on single agent topotecan, including one with a serious outcome requiring a phlebectomy to correct possible drug-induced phlebitis. However, due to lack of information in the reports, there was no way to determine if these cases of phlebitis were related to variability in admixture preparation and administration. Nevertheless, given the AERS data, OSE recommended adding local infusion/injection site reactions, including phlebitis, to the postmarketing experience section of topotecan product labeling.

On July 30, 2010, ONDQA concluded that from the perspective of Chemistry, Manufacturing and Controls (CMC), this NDA is Not Approvable due to lack of response to a deficiency letter to the DMF holder. Therefore, CMC recommended that a Complete Response (CR) letter be issued indicating this unresolved issue.

On August 8, 2010 DDOP determined that this application was approvable from a Pharmacology and Toxicology perspective.

On August 18, 2010, the Applicant submitted an amendment to provide a status update for the relevant DMF (b) (4) for the API material (SN-009).

On August 24, 2010, DDOP determined that SN-009 constituted a major amendment and therefore extended the user fee goal date by three months to November 29, 2010.

4. Conclusion

This application is acceptable from a clinical standpoint.

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/s/

MICHAEL H BRAVE
11/12/2010

KE LIU
11/12/2010