

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
0200199Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 200199

SUPPL #

HFD # 150

Trade Name Topotecan

Generic Name Topotecan Hydrochloride

Applicant Name Sandoz, Inc.

Approval Date, If Known 2-26-2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505b2

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 020671

Hycamtin

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

Investigation #2

!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====

Name of person completing form: Alice Kacuba

Title: CPMS

Date: March 4, 2011

Name of Office/Division Director signing form: Amna Ibrahim, M.D.

Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

ALICE KACUBA
03/04/2011

AMNA IBRAHIM
03/07/2011



DEBARMENT CERTIFICATION

Sandoz Inc., hereby certifies that it has not and will not use, in any capacity, the services of any person debarred under Section 306(a) or (b) of the Federal Food, Drug and Cosmetic Act, in connection with this application.

We hereby certify that neither Sandoz Inc., nor any affiliated persons responsible for the development or submission of the application have been convicted as described in Section 306(a) and (b) within five years before the date of this application.

Benaditt
Name

12/9/09
Date

Kacuba, Alice

From: Kacuba, Alice
Date: Wednesday, February 16, 2011 3:55 PM
To: 'bernadette.attinger@parentarx.com'
Subject: NDA 200199 FDA revised labeling.
Importance: High
Follow Up Flag: Follow up
Due By: Thursday, February 17, 2011 3:00 PM
Flag Status: Flagged
Attachments: 2-15-11 FDA-revised-pi-with-track-changes.doc

Hi,

Allison does not work here any longer so I will finish this NDA action.

Attached is our latest FDA revised labeling. Please review and return concurrence by Thursday at 3 PM.

Please (hopefully) return a clean copy. We have address your comments and accepted some changes but I think there are a few FDA revisions.

And, please look at all tables and make them look like RLD. Several reviews say the tables are not same in format. So review the format and what needs to be shaded, etc.

Call me if questions. You will most likely get VM but I will return your call.

I understand that we have agreed upon carton and container lables. Is that your undertsanding as well?

Thank you.

Alice
Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
OND/CDER/FDA
301-796-1381
(f)301-796-9845
alice.kacuba@fda.hhs.gov



2-15-11
sed-pi-witf

22 Pages Have Been Withheld In Full As b(4) (CCI/TS)
Immediately Following This Page

Adams-McLean, Allison

To: Attinger, Bernadette
Cc: Kacuba, Alice
Subject: NDA 200199 Topotecan Request for Information

Dear Ms. Attinger, during review of your submission the DMEPA reviewer has the following request:

1. 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.

2. Change the term [REDACTED] ^{(b) (4)}” in order to comply with USP standards. This should be reflected in all labels and labeling including the insert labeling.

Please respond by no later than February 8, 2011, @ 10:30 AM and feel free to contact me if you have any questions. Thanks in advance.

Allison Adams-McLean, RN, BSN, MHA
LCDR, USPHS
Senior Regulatory Project Manager
FDA, CDER, OODP, DDOP, Bldg. 22 Rm 5235
0903 New Hampshire Avenue
Silver Spring MD, 20993-0002
301-796-3996
Allison.Adams-McLean@fda.hhs.gov

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/s/

ALLISON ADAMS-MCLEAN
02/04/2011

Adams-McLean, Allison

To: Attinger, Bernadette
Subject: NDA 200199 Topotecan

Dear Ms. Attinger, the last submitted labeling update was October 1, 2010, the review team for NDA 200199, request you submit amended labeling to be in accordance with the RLD, no later than January 19, 2011 @ 4:30 PM. Please update the entire labeling as appropriate and included track changes. Please contact me if you have any questions. Thank you.

Allison Adams-McLean, RN, BSN, MHA
LCDR, USPHS
Senior Regulatory Project Manager
FDA, CDER, OODP, DDOP, Bldg. 22 Rm 5235
10903 New Hampshire Avenue
Silver Spring MD, 20993-0002
301-796-3996
Allison.Adams-McLean@fda.hhs.gov

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/s/

ALLISON ADAMS-MCLEAN
01/13/2011

Dear Ms. Attinger, we acknowledge receipt of your October 1, 2010 submission however, the DMEPA reviewer requests the following information;

- Please submit the revise carton labeling for the [REDACTED] ^{(b) (4)} vials carton labeling

Please respond by Friday December 3, 2010 @ 10:30 a.m.

Allison Adams-McLean, RN, BSN, MHA
LCDR, USPHS
Senior Regulatory Project Manager
FDA,CDER,OODP,DDOP, Bldg.22 Rm 5235
10903 New Hampshire Avenue
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Allison.Adams-McLean@fda.hhs.gov

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/s/

ALLISON ADAMS-MCLEAN
11/29/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200199

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Sandoz, Inc.
Attention: Bernadette Attinger
Director, Regulatory Affairs
777 Township Line Road, Suite 180
Yardley, PA 19067

Dear Ms. Attinger:

Please refer to your January 27, 2010, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Topotecan Injection 1mg/ mL, 3mg/ 3mL, 4mg/ 4mL.

On September 30, 2010, we received your September 24, 2010, unsolicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is February 27, 2011.

In addition, in accordance with the “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012,” the timeline for communicating labeling changes and/or postmarketing requirements/commitments, provided in our April 16, 2010, filing communication letter, no longer applies and no new timeline will be provided.

If you have any questions, call Allison Adams-McLean, Regulatory Project Manager, at (301) 796-3996.

Sincerely,

{See appended electronic signature page}

Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
Center of Drug Evaluation and Research

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/s/

ALICE KACUBA
11/09/2010

Adams-McLean, Allison

To: Attinger, Bernadette
Subject: NDA 200199/Topotecan Request for Inforamiton

Dear Ms. Attinger, The CMC reviewer has the following Request for Information:

1. DRUG SUBSTANCE:

1. **Revise/Update the drug substance information (e.g the specification for the [REDACTED] (b) (4) for drug substance) based on updated information from the drug substance supplier, [REDACTED] (b) (4); [REDACTED]**

2. DRUG PRODUCT

2. **Confirm the use and availability of an internal quality control mechanism at the proposed drug product manufacturing site (Ebewe) that addresses the issue of batch-to-batch variation of [REDACTED] (b) (4) in the drug substance.**
3. **Harmonize the proposed acceptance criteria for release and stability attributes (e.g. [REDACTED] (b) (4) for drug product.**

Please respond by Wednesday September 22, 2010 @ 10:30 AM.

Allison Adams-McLean, RN, BSN, MHA
LCDR, USPHS
Senior Regulatory Project Manager
FDA, CDER, OODP, DDOP, Bldg. 22 Rm 5235
10903 New Hampshire Avenue
Silver Spring MD, 20993-0002
301-796-3996
Allison.Adams-McLean@fda.hhs.gov

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/s/

ALLISON ADAMS-MCLEAN
09/17/2010

Adams-Mclean, Allison

To: Attinger, Bernadette
Subject: Request for Information

Dear Ms. Attinger:

Please refer to your New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Topotecan Hydrochloride Injection.

We have the following requests for additional information:

(1) The *Preparation for Intravenous Administration* section of the proposed label states that the (b) (4)

[Redacted]

Reference is made to *Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7.* (b) (4)

[Redacted]

Generally, "no growth" is interpreted as not more than a 0.5 log₁₀ increase from the initial count; however other evidence of growth may be significant. The test should be run at the label's recommended storage conditions, be conducted for 2 to 3-times the label's recommended storage period, and use the label-recommended fluids inoculated with low numbers (≤ 100 CFU/mL) of challenge microbes. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of these data, the product labeling should recommend that the post-constitution storage period is not more than 4 hours at room temperature or 24 hours at refrigerated temperature.

(2) *Label Section 3.0, Dosage Forms and Strengths*, describes the 1 mg/mL, 3 mg/3 mL, and 4 mg/4 mL product vials as (b) (4)

[Redacted]

(3) Tables 1 and 2 in your proposed package insert contain information regarding both (b) (4) and (b) (4)

[Redacted]

(4) Please reformat tables to show rows and columns for clarity.

In order for us to complete our review, please respond to the information requested by no later than September 20, 2010, at 10:30 AM. Please submit an amendment to your application with your response to the information request using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Allison.Adams-McLean@fda.hhs.gov) or FAX (301-796-9845).

Sincerely,

{See appended electronic signature page}

Allison Adams-McLean, RN, BSN, MHA
LCDR, USPHS
Senior Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200199	ORIG-1	SANDOZ INC	TOPOTECAN HYDROCHLORIDE INJECTION

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/s/

ALLISON ADAMS-MCLEAN
09/14/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200199

ADVICE/INFORMATION REQUEST

Sandoz, Inc.
Attention: Bernadette Attinger
Director of Regulatory Affairs
506 Carnegie Center, Suite 400
Princeton, NJ 08540

Dear Ms. Attinger:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Topotecan Injection, 1mg/1mL, 3mg/3mL, 4mg/4mL.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and found the Drug Master File ^{(b) (4)} for Topotecan Hydrochloride to be inadequate to support the NDA. A letter dated June 9, 2010, detailing the deficiencies has been sent to the designated agent.

If you have any questions, call Deborah Mesmer, Regulatory Health Project Manager, at 301-796-4023.

Sincerely,

{See appended electronic signature page}

Sarah Pope Miksinski, Ph.D.
Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200199	ORIG-1	SANDOZ INC	TOPOTECAN HYDROCHLORIDE INJECTION

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/s/

WILLIAM M ADAMS
06/24/2010
William Adams, acting for Sarah Pope Miksinski

{See appended electronic signature page}	
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200199	ORIG-1	SANDOZ INC	TOPOTECAN HYDROCHLORIDE INJECTION

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/s/

DEBORAH M MESMER
06/22/2010

DEBASIS GHOSH
06/22/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200199

INFORMATION REQUEST

Sandoz, Inc.
Attention: Bernadette Attinger
Director of Regulatory Affairs
506 Carnegie Center, Suite 400
Princeton, NJ 08540

Dear Ms. Attinger:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Topotecan hydrochloride injection, 1mg/1mL, 3mg/3mL, 4mg/4mL.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information request. We request a written response by June 10, 2010, to continue our evaluation of your NDA.

- Provide an Environmental Assessment (EA) of the naturally occurring source material for the drug substance.
- The drug substance topotecan hydrochloride is a semi-synthetic compound. In accordance with 21CFR 25.21(b), an Environmental Assessment related to the naturally occurring source material is required to be submitted to the NDA. Refer to "Guidance for Industry, Environmental Assessment of Human Drug and Biologic Applications," which can be obtained from the FDA website: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070561.pdf>.
- The EA should include the non-confidential information rather than provide reference to the drug substance master file. A master file reference may be provided for the confidential information, although this information must be summarized to the extent possible and included in the EA for public release.

If you have any questions, call Deborah Mesmer, Regulatory Health Project Manager, at 301-796-4023.

Sincerely,

{See appended electronic signature page}

Sarah Pope Miksinski, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200199	ORIG-1	SANDOZ INC	TOPOTECAN HYDROCHLORIDE INJECTION

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/s/

WILLIAM M ADAMS
05/18/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200199

FILING COMMUNICATION

Sandoz Inc.
Attention: Bernadette Attinger
Director, Regulatory Affairs
777 Township Line Road Suite 180
Yardley, PA 19067

Dear Ms. Attinger:

Please refer to your new drug application (NDA) dated January 27, 2009, received January 27, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Topotecan Hydrochloride Injection 1mg/ml.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is November 27, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by November 8, 2010.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Allison. Adams-McLean, Regulatory Project Manager, at (301) 796-3996.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center of Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200199

ORIG-1

SANDOZ INC

TOPOTECAN
HYDROCHLORIDE INJECTION

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/s/

ALICE KACUBA

04/16/2010

Signed for Dr. Robert Justice.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200199

ADVICE/INFORMATION REQUEST

Sandoz,
Attention: Bernadette Attinger
Director, Regulatory Affairs
777 Township Line Road
Suite 180
Yardley, PA 19067

Dear Ms. Attinger:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Topotecan Hydrochloride Injection.

We have the following requests for additional information:

Please submit a revised labeling that has a side by side comparison between GlaxoSmithKline's most recent approved labeling for Hycamtin and Topotecan Hydrochloride.

In order for us to complete our review, please respond to the information requested by no later than April 19, 2010, at 10:30 AM. Please submit an amendment to your application with your response to the information request using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Allison.Adams-McLean@fda.hhs.gov) or FAX (301-796-9845).

Sincerely,

{See appended electronic signature page}

Allison Adams-McLean, RN, BSN, MHA
LCDR, USPHS
Senior Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200199	ORIG-1	SANDOZ INC	TOPOTECAN HYDROCHLORIDE INJECTION

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/s/

ALLISON ADAMS-MCLEAN
04/05/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO: CDER-DDMAC-RPM	FROM: (Name/Title, Office/Division/Phone number of requestor) Allison Adams-McLean DDOP-RPM 301-796-3996
------------------------------	--

REQUEST DATE March 31, 2010	IND NO.	NDA/BLA NO. 200199	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
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NAME OF DRUG Topotecan Hydrochloride Injection	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Anti-tumor drug	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) October 23, 2010
--	------------------------------------	---	--

NAME OF FIRM: Sandoz, Inc.	PDUFA Date: November 27, 2010
-------------------------------	-------------------------------

TYPE OF LABEL TO REVIEW

TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	TYPE OF APPLICATION/SUBMISSION <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION
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EDR Location: \\CDSESUB1\EVSPROD\NDA200199\200199.enx

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: June 21, 2010	2:00 – 3:00 PM	WO 22 Rm 2201
Labeling Meetings: 1. September 8, 2010	11-12:00 PM	WO 22 Rm 2376
2. September 13, 2010	2:00 – 3:00 PM	WO 22 Rm 2376
3. September 20, 2010	2:00- 3:00 PM	WO 22 Rm 2376
4. September 28, 2010	2:00 -3:00 PM	WO 22 Rm 2376

Wrap-Up Meeting: TBA

SIGNATURE OF REQUESTER
Allison Adams-McLean

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)
 eMAIL

HAND

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200199	ORIG-1	SANDOZ INC	TOPOTECAN HYDROCHLORIDE INJECTION

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/s/

ALLISON ADAMS-MCLEAN
03/31/2010



APPEARS THIS WAY ON ORIGINAL

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200199	ORIG-1	SANDOZ INC	TOPOTECAN HYDROCHLORIDE INJECTION

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/s/

DEBORAH M MESMER
03/03/2010

TERRANCE W OCHELTREE
03/03/2010

REQUEST FOR CONSULTATION

TO (Office/Division): Patrick Marroum CDER/OPS/ONDQA,
Angelica Dorantes CDER/OPS/ONDQA

FROM (Name, Office/Division, and Phone Number of Requestor): Debbie
Mesmer ONDQA, 301-796-4023 on behalf of Terrance
Ocheltree

DATE March 3, 2010	IND NO.	NDA NO. 200199	TYPE OF DOCUMENT NDA submission	DATE OF DOCUMENT January 27, 2010
NAME OF DRUG Topotecan Hydrochloride Injection		PRIORITY CONSIDERATION to be determined	CLASSIFICATION OF DRUG Oncology	DESIRED COMPLETION DATE April 5, 2010 for priority May 28, 2010 for standard review

NAME OF FIRM: Sandoz Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input checked="" type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: A biopharmaceutics review is requested. The applicant has requested a bio-waiver. \\CDSESUB1\EVSPROD\NDA200199\200199.enx. Please inform Debbie Mesmer of the assigned reviewer.

Chemistry reviewer: Debasis Ghosh
ONDQA PAL: Terry Ocheltree
OND RPM: Not yet assigned.
ONDQA RPM: Debbie Mesmer

SIGNATURE OF REQUESTOR
{See appended electronic signature page}

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

Reference ID: 2917704
PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER



APPEARS THIS WAY ON ORIGINAL

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200199	ORIG-1	SANDOZ INC	TOPOTECAN HYDROCHLORIDE INJECTION

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/s/

DEBORAH M MESMER
03/03/2010

TERRANCE W OCHELTREE
03/03/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200199

NDA ACKNOWLEDGMENT

Sandoz Inc.
Attention: Bernadette Attinger
Director, Regulatory Affairs
777 Township Line Road
Suite 180
Yardley, PA 19067

Dear Ms. Attinger:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Topotecan Hydrochloride Injection 1 mg/ ml

Date of Application: January 27, 2010

Date of Receipt: January 27, 2010

Our Reference Number: NDA 200199

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 28, 2010, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Product
5901-B Ammendale Road

Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>

If you have any questions, call Allison Adams-McLean, Regulatory Project Manager, at (301) 796-3996.

Sincerely,

{See appended electronic signature page}

Alice Kacuba, R.N., M.S.N., RAC
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
Center of Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200199	ORIG-1	SANDOZ INC	TOPOTECAN HYDROCHLORIDE INJECTION

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/s/

ALLISON ADAMS-MCLEAN
03/23/2010

*My canceled so
preliminary comments
Bernadette
my mins.*

From: Woody, Dillard
Sent: Friday, June 13, 2008 3:32 PM
To: 'Bernadette.Attinger@parentarx.com'
Cc: Kacuba, Alice; Woody, Dillard
Subject: FDA response to Topotecan Hydrochloride Injection questions

Hello Bernadette,

Below are the responses to your questions.

1. We have decided to propose only one API manufacturer at the additional manufacturing site. Please confirm that if we produce 3 batches of finished product of each presentation for stability at the alternate site and the alternate site receives an acceptable GMP evaluation that this is acceptable to show equivalence of the two manufacturing sites. Please note that the product and all components of the process will be held to the same acceptance criteria at both facilities.
FDA Response: Yes. If you produce three batches of the finished product of each presentation for stability at the alternate site using the API from the chosen API manufacturer, and if similar manufacturing process and controls are followed and if the product characterization/batch analysis data and stability data are comparable, and if the alternate site receives an acceptable cGMP evaluation, then your proposed approach to qualify the new site with one API source is acceptable.

2. Please clarify the meaning of a lab scale batch with regards to size and GMP requirements.
FDA Response: A pilot scale batch is typically expected to be one-tenth to one-fifth the proposed commercial scale depending on the complexity of the manufacturing process. In this case, considering the nature of the process, a one-tenth scale would be considered a pilot scale. Any scale less than this scale would be considered a lab scale. If you choose to make a lab scale batch to meet the three-batch criteria, then this process and controls, and the equipment used, etc. should be shown to adequately represent the proposed commercial scale.

If you need further information please email me. In addition, please inform me of your decision whether or not you need a telecon.

Thank you,
Woody

Linked Applications

Sponsor Name

Drug Name

IND (b) (4)

EBEWE PARENTA
PHARMACEUTICALS
INC

TOPOTECAN HCL INJECTION

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/s/

DILLARD H WOODY
06/30/2008