

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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OTHER REVIEW(S)

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

Through: Melina Griffis, RPh, Team Leader
Carlos M Mena-Grillasca, RPh, Team Leader
Carol A. Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Irene Z. Chan, PharmD, BCPS, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Topotecan Injection: 1 mg/mL, 3 mg/3 mL, and 4 mg/4 mL

Applicant: Sandoz

OSE RCM #: 2010-604

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1 INTRODUCTION

This review evaluates the labels and labeling contained in the Applicant's original NDA submission, dated January 27, 2010, and labeling amendment dated April 16, 2010. The Division of Medication Error Prevention and Analysis (DMEPA) identified areas of vulnerability that can lead to medication errors, and we provide recommendations in Section 5 that aim at reducing the risk of medication errors with regard to the proposed product labels and labeling.

1.1 REGULATORY HISTORY

On January 27, 2010, Sandoz Inc. submitted a 505(b)(2) New Drug Application for Topotecan Injection. The reference listed drug that is the basis for this 505(b)(2) submission is Hycamtin (Topotecan Hydrochloride) for Injection, marketed by GlaxoSmithKline (NDA 020671). Sandoz is seeking approval for only the indication of small cell lung cancer sensitive disease after failure of first-line chemotherapy (b)(4). In addition, Sandoz is proposing two manufacturing sites for the production of this product, Ebewe Pharma (b)(4), and they have submitted labels and labeling for both manufacturers.

2 METHODS AND MATERIALS

2.1 FDA ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

Topotecan Hydrochloride for Injection is currently marketed under the proprietary name Hycamtin; therefore, DMEPA conducted a search of the FDA Adverse Event Reporting System (AERS) database on April 22, 2010, to identify medication errors involving Hycamtin.

The MedDRA High Level Group Terms (HLGT) “Medication Errors” and “Product Quality Issues” were used as search criteria. The search criteria used for Products were active ingredient “Topotecan” and “Topotecan Hydrochloride”, trade name “Hycamtin”, and verbatim substance search “Hycam%” and “Topotec%”. No date limitations were set.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the labels or labeling of the product, the case was considered pertinent to this review. Those reports that did not describe a medication error or did not describe an error applicable to this review (e.g. errors related to accidental exposure) were excluded from further analysis.

2.2 LABEL AND LABELING

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis (FMEA) in our evaluation of the labels and labeling submitted (see Appendices A and B). DMEPA also reviewed the vial label and carton labeling currently approved for Hycamtin (see Appendices C and D). These were reviewed so that comparisons could be made between the two product lines. Additionally, we reviewed the most recently approved insert labeling for Hycamtin.

3 RESULTS

3.1 FDA ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

The AERS search conducted on March 30, 2010, yielded 25 cases (see Appendix E). Of these cases, 8 were deemed irrelevant to our review. The irrelevant cases pertained to the following:

- Report of adverse drug reactions unrelated to a medication error (n=2).
- Accidental exposure of a pharmacist to topotecan in the workplace (n=1)

- Product quality complaint unrelated to medication error (n=2)
- Case where topotecan was listed as a concomitant medication only (n=1)
- Literature report of a possible drug interaction not previously identified (n=1)
- Report of potential medication error for topotecan capsules that does not affect the labeling of topotecan injection (n=1). In this case, the reporter noted that dispensing topotecan capsules in increments of 10 leads to a potential for error and confusion.

The remaining 17 cases are summarized as follows:

- Improper Dose - Overdose (n=13)

In 11 of the 13 cases, the cause of error was not reported. In the remaining 2 of 13 cases, the cause of error was identified as a lack of dose adjustment for renal function. One of the two patients had renal insufficiency and the other patient had renal failure prior to receiving Hycamtin.

Two cases, where the cause was not reported, reported a 10-fold overdose. In one of the cases, a patient received 40 mg/m² instead of the prescribed dose of 4 mg/m². Four days later, this patient was admitted to the hospital with a three to four day history of nausea, vomiting, abdominal pain, and weakness. This patient had positive blood cultures and developed pancytopenia and electrolyte imbalance, including hyponatremia. In the second case, a patient was administered 25 mg instead of 2.5 mg of Hycamtin. There were no outcomes reported in this case.

Hematologic outcomes occurred in 10 cases and included thrombocytopenia, leucopenia, anemia, and neutropenia. In several cases, pancytopenia was observed.

Non-hematologic outcomes of these medication errors included reduced creatinine clearance, fever, worsening renal failure, septicemia, bloody urine, nausea, vomiting, shortness of breath, weakness, sore gums, blood in sputum, abdominal pain, hypotension, tachycardia, mucositis, diffuse skin rash, electrolyte imbalances, oral candidiasis, suspected pneumonia, and severe dehydration.

- Improper Dose – Underdose (n=1)

A patient took oral Topotecan 2 mg twice daily instead of his prescribed dose of medication. The prescribed dose was not reported. No cause or outcomes were reported in this case.

- Wrong Route of Administration (n=1)

In this case, a physician ordered Topotecan to be administered subcutaneously. The physician had copied orders from an oncologist who had written “Topotecan 0.75 mg/sq m”, using the “sq m” abbreviation to mean square meter. The “sq” was misinterpreted by the physician to mean subcutaneous. This error did not reach the patient.

- Improper Technique (n=1)

In this case, a nurse administered 3 mg of Hycamtin undiluted by intravenous push over less than one minute via porta-cath. The patient reported increased nausea lasting two days. The cause of error was not reported.

- Wrong Drug (n=1)

In this case, a patient was administered Hycamtin instead of the intended drug, Avastin (bevacizumab). The cause of error was not reported. The reporter described the occurrence of mild thrombocytopenia that occurred seven days after receiving the Hycamtin in error.

3.2 LABEL AND LABELING

Sandoz is proposing two manufacturing sites for the production of this product, Ebewe Pharma and (b) (4) they have submitted labels and labeling for both manufacturers. Sandoz is only proposing the (b) (4) at the Ebewe Pharma site. The only difference between the packaging configurations for the two sites is the “manufactured by” statement. Otherwise, the labels and labeling are identical.

Hycamtin is available as a 4 mg single-use vial (see Appendix C). Comparison of the proposed labels and labeling of the 4 mg/4 mL strength of Topotecan Injection against the currently approved Hycamtin labels and labeling did not identify any vulnerability that may lead to medication errors.

Our review of the labels and labeling find the presentation of information on the proposed labels and labeling introduces vulnerability to confusion that can lead to medication errors. Vulnerabilities that were identified include the following:

- Inadequate strength differentiation within the product line
- Font not prominent enough for route of administration presentation
- Oversized distributor logo that distracts from the name and strength presentation

4 DISCUSSION

DMEPA has determined that improved presentation of dose modification guidelines and dosage adjustment within the insert labeling is needed. Two postmarketing medication error cases, in which both patients received an improper dose (overdose) because their doses were not properly adjusted for their renal function, prompted our review of the most recently approved insert labeling. We determined the dosage adjustment instructions are confusing. We make recommendations to decrease the risk of improper dose medication errors in section 5 below. Additionally, we identified two AERS cases where a 10-fold overdose occurred. We recommend adding a warning to the insert labeling alerting healthcare professionals that 10-fold overdoses of topotecan have occurred and resulted in serious adverse outcomes.

Another concern surrounds the introduction of an injection solution dosage form that may lead to improper technique errors (e.g. intravenous push instead of infusion). The product currently under review is an injection solution that requires further dilution. This differs from the reference listed product, Hycamtin, which is a powder that needs reconstitution prior to further dilution. Since we have a case where topotecan injection was administered undiluted as an intravenous push, we recommend modifying the route of administration presentation on the vial labels and carton labeling to read “For Intravenous Infusion after Dilution Only”.

DMEPA also finds the presentation of information on the proposed labels and labeling introduces vulnerability to confusion that can lead to medication errors. It was determined that the labels and labeling need improvement in the following areas: increased strength differentiation within the product line, increased prominence of route of administration presentation, and a less distracting distributor logo that does not detract from the name and strength presentation of the product. We provide recommendations in Section 5 below.

DMEPA also compared the proposed labels and labeling of the 4 mg/4 mL strength of Topotecan Injection against the currently approved Hycamtin labels and labeling. Because color may be utilized as a tool by healthcare professionals for drug selection or strength identification, the fact that the 4 mg strengths of each product use the same color scheme may decrease the risk of therapeutic duplication and/or improper dose errors since seeing two vials with the same color scheme may cause a practitioner to pause and reinspect the vials. DMEPA does not feel strongly for or against the use of the same color scheme for the 4 mg/4 mL strength between the two product lines. However, in order to increase the strength differentiation within the product line for Topotecan Injection, different colors for the 1 mg/mL

and 3 mg/3 mL strengths should be utilized.

5 RECOMMENDATIONS AND CONCLUSIONS

Our evaluation of the proposed labels and labeling noted areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 5.1 Comments to the Division. We request the recommendations for the carton labeling and vial labels in Section 5.2 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.

5.1 COMMENTS TO THE DIVISION

A. GENERAL COMMENTS

1. The name is currently presented as Topotecan Hydrochloride Injection. We defer to CMC for the proper designation of the product name.
2. We recommend revising the strength “1 mg/1 mL” to read *1 mg/mL*.
3.  (b) (4)
4. The Applicant has utilized the abbreviation “IV” within the insert labeling to represent intravenous. The abbreviation, I.V can be misinterpreted to mean I.U or I.N. 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 IV be replaced with the text “intravenous”.
5. The Applicant has utilized trailing zeros within the insert labeling. Trailing zeros can lead to 10-fold errors in dosing. 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. Dosage Forms and Strengths
 - a As currently presented, the dosage form is not present. Include the statement *Topotecan Injection is available in the following strengths:* under the section heading.
 - b Add the strength per mL enclosed by parenthesis following the strength per total volume expression (e.g. 3 mg/3 mL (1 mg/mL)).
2. Warnings and Precautions

We have received reports of 10-fold overdoses of topotecan. Consider adding the following warning as the first 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:

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.*
- c Under preparation and administration in section 2.3, stability information is currently presented. We recommend moving the stability information to Section 16 How Supplied/Storage and Handling, which is customarily where this information is located.

2. Dosage Forms and Strengths

See comment B(1) above.

3. Warnings and Precautions

See comment B(2) above.

4. Adverse Reactions

As currently presented, the adverse reaction tables in this section do not have columns or rows that are clearly delineated. We recommend inserting column borders within the tables to clearly separate the different columns of information. We also recommend incorporating row borders or some other means to distinguish one row from the next.

5. Description

As currently presented, the statement (b) (4). We recommend the statement be revised to read *Each mL contains topotecan hydrochloride equivalent to 1 mg of topotecan as free base*, but we defer to the CMC reviewer for final determination.

6. How Supplied/Storage and Handling

- a Because this product has data to demonstrate the stability of the product only during 28 days after first opening, we recommend adding the following statement: *Opened*

vials must be used within 28 days after the first use. They must be discarded if not used within 28 days.

- b See comment B(1)(b) above.

5.2 COMMENTS TO THE APPLICANT

A. VIAL LABELS (1 mg/mL, 3 mg/mL, 4 mg/mL)

Ensure the container is labeled so that a sufficient area of the container remains uncovered for its full length or circumference to permit visual inspection of the contents.

B. VIALS LABELS (1 mg/mL, 3 mg/mL, 4 mg/mL) AND CARTON LABELING (1 mg/ml)

The statement “1 mg/1 mL” should be revised to read *1 mg/mL*.

C. VIAL LABELS AND CARTON LABELING (1 mg/mL, 3 mg/mL, 4 mg/mL)

1. Per CMC recommendations, revise the name on the labels and labeling to read Topotecan Injection. It is currently presented as Topotecan Hydrochloride Injection.
2. Our review of the labels and labeling identified the need for more adequate visual differentiation within the product line in order to avoid selection errors between strengths. (b) (4).
Change the colors utilized to differentiate the 1 mg/mL and 3 mg/3 mL strengths. Use a unique color for each strength. The color currently utilized for the 4 mg/4 mL strength may be left as is.
3. As currently presented, we are concerned the introduction of a solution dosage form may lead to the medication being administered by intravenous push instead of intravenous infusion. Since this product requires dilution prior to administration, we recommend printing the statement in bold font and modifying the route of administration presentation on the vial labels and carton labeling to read ***For Intravenous Infusion after Dilution Only***.
4. This product has data to demonstrate the stability of the product only during 28 days after first opening. Add the following statement to the side panel: *Use within 28 days after first use.*
5. The logo containing the triangle graphic and “SANDOZ” is distracting and overly prominent. Remove or minimize this logo since it is larger than the name and strength presentation.

D. CARTON LABELING (1 mg/mL, 3 mg/mL, 4 mg/mL)

1. Include the statement, *Each mL contains topotecan hydrochloride equivalent to 1 mg of topotecan as free base* to the side panel.
2. See comment B(2) above. To ensure there is adequate room without crowding the principle display panel, consider moving the “Rx only” statement to the side panel.

Appendix A: Retail Vial Labels (1 mg/mL, 3 mg/3 mL, and 4 mg/4 mL)

(b) (4)

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(b) (4)

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(b) (4)

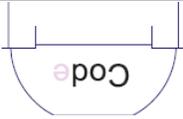
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(b) (4)

(b) (4)

Appendix B: Carton Labeling (1 mg/mL, 3 mg/3 mL, 4 mg/4 mL)

(b) (4)



(b) (4)





(b) (4)



(b) (4)



[REDACTED]

(b) (4)

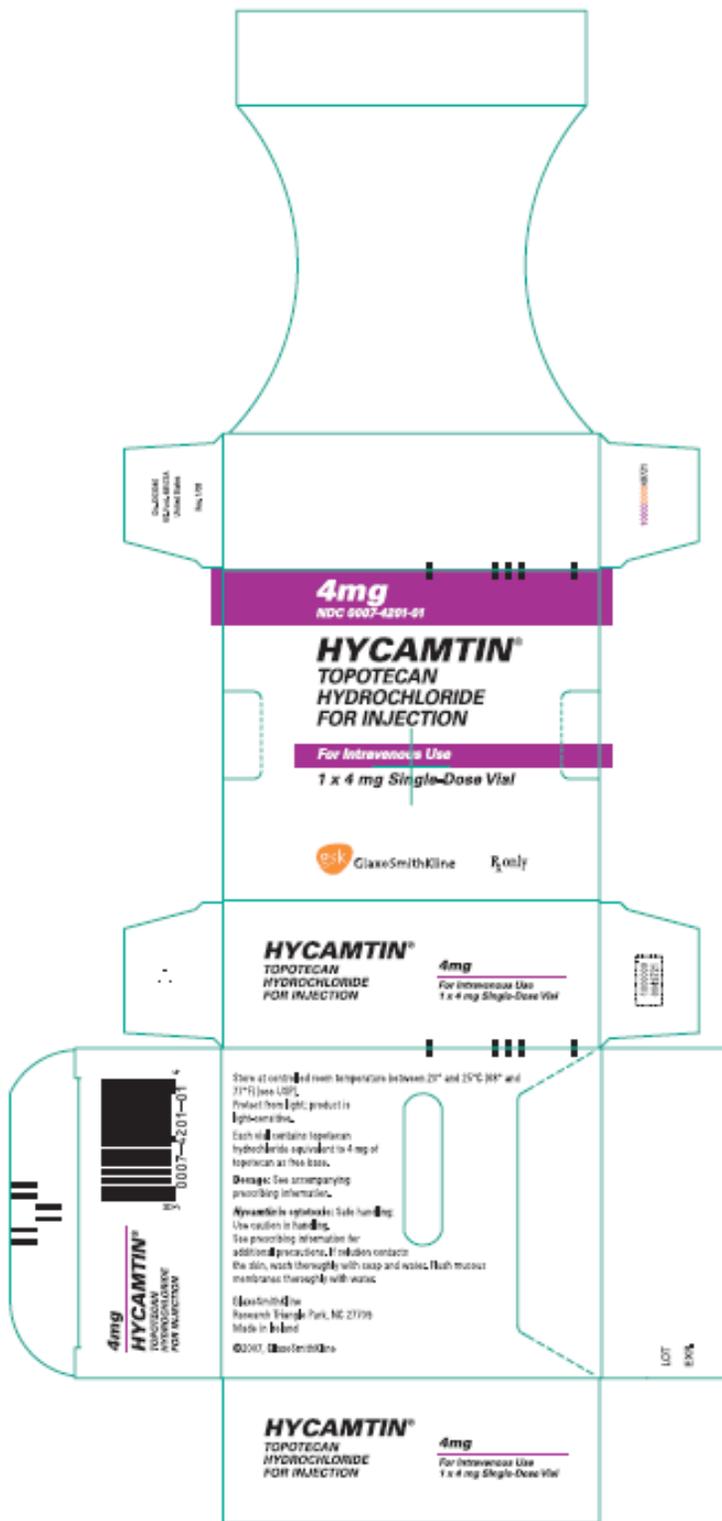
[REDACTED]

(b) (4)

Appendix C: Approved Hycamtin Vial Label (4 mg)

4mg NDC 0007-4201-01 HYCAMTIN® TOPOTECAN HYDROCHLORIDE FOR INJECTION For Intravenous Use GlaxoSmithKline <i>Rx only</i>	Store at controlled room temperature between 20° and 25°C (68° and 77°F) [see USP]. Protect from light; product is light-sensitive. Dosage: See accompanying prescribing information. Hycamtin is cytotoxic, Safe handling: Use caution in handling. See prescribing information for additional precautions. If solution contacts the skin, wash thoroughly with soap and water. Flush mucous membranes thoroughly with water.		LOT	EXP.

Appendix D: Approved Hycamtin Carton Labeling (4 mg)



Appendix E: Hycamtin AERS Cases

ISR Number	Comment
1000002195-X	Improper Dose - overdose
3016609-6	Improper Dose - overdose
3134325-7	Improper Dose - overdose
3130916-8	Improper Dose - overdose
3198896-7	Improper Dose - overdose
3600319-8	Improper Dose - overdose
3816408-9	Improper Dose - overdose
4322729-6	Improper Dose – overdose (10 fold)
4391475-5	Improper Dose - overdose
1842542-9	Improper Dose - overdose
6047644-1	Improper Dose – overdose (10 fold)
6128309-4	Improper Dose - overdose
6630207-4	Improper Dose - overdose
3845999-7	Improper Dose - underdose
6529905-2	Wrong Drug
4412757-4	Wrong Route of Administration
4724352-8	Improper Technique – undiluted IV push
3163794-1	Drug Interaction
3241090-1	Accidental Exposure
3977059-9	Concomitant Medication Only
5088916-7	Product Quality Complaint
6139803-4	Product Quality Complaint
5551123-5	Adverse Drug Reaction
6481247-X	Adverse Drug Reaction
5927383-5	Category A related to Hycamptin Capsules

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/s/

IRENE Z CHAN
09/24/2010

MELINA N GRIFFIS
09/24/2010

CAROL A HOLQUIST
09/24/2010