CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-160

OTHER REVIEW(S)

Cycle 1

MEMORANDUM

To: **Dorothy Pease**
Division of Drug Oncology Products

From: **Iris Masucci, PharmD, BCPS**
Division of Drug Marketing, Advertising, and Communications
for the Study Endpoints and Label Development (SEALD) Team, OND

Date: **November 16, 2007**

Re: **Comments on draft labeling for oxaliplatin**
NDA 22-160

We have reviewed the proposed label for oxaliplatin (FDA version received 11/14/07) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the review division after a full review of the submitted data.

GENERAL COMMENTS

- In general, generic names of drugs are not capitalized. Please change all instances of "Oxaliplatin" to "oxaliplatin" in the labeling text (except, of course, when the word begins a line or sentence).

HIGHLIGHTS

- (b) (4)

  The product title line is currently incorrect. It must contain the drug name ("Oxaliplatin"), dosage form (for chemists to determine), and route of administration (presumably "for intravenous use").

  The line with the initial U.S. approval date should appear directly under the product title line, with an extra hard return added between it and the boxed warning. The approval date should be the year that any oxaliplatin formulation was first approved for marketing in the U.S., not the initial approval date of this particular formulation.

Boxed Warning

- The first two lines in the boxed warning should be centered within the box. Then, the actual warning text should remain left-justified.

Dosage Forms and Strengths

- This section must be revised to represent the formulation for this particular product. We suggest:

(b) (4)

Please note that we have emphasized (b) (4) here.

Adverse Reactions

- The email address that currently appears in the adverse reaction reporting statement should be deleted. Websites that are dedicated to adverse reaction reporting can be included here (if they exist), but email addresses should not be.

Revision Date

- Please ensure that the proper month/year of approval for this NDA is filled in, replacing the current "February 2007."

FULL PRESCRIBING INFORMATION

2.3 Preparation of Infusion Solution

- (b) (4) ***dilution must never be performed with a sodium chloride solution or other chloride containing solutions.***

(b) (4) *. The solution must be* (b) (4) *diluted in an infusion solution of 250-500 mL of 5% Dextrose Injection, USP."*

These two paragraphs need to be revised to reflect that this formulation is already a solution and does not need reconstitution. We recommend:

(b) (4)

3 Dosage Forms and Strengths

- This section must be revised to again reflect that this product comes as a solution. We suggest language similar to what was recommended for "Dosage Forms and Strengths" in Highlights.

17.2 FDA-approved Patient Labeling

- Please correct the product title lines at the beginning of the patient labeling. The current version implies that there are two available dosage forms. The product title should be consistent with the title that appears at the beginning of Highlights.

- The date "Issued: February 2007" should be deleted. Any date appearing at the end of a PPI should reflect the approval date for the document.

Company Information

- Please see 21 CFR 201.1 for the requirements for manufacturer/distributor/etc. information at the end of the label. As currently written, the only mention of Teva USA is under the Adverse Reaction reporting section of Highlights.

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/s/

Iris Masucci
11/20/2007 01:16:40 PM
DDMAC REVIEWER

Laurie Burke
11/28/2007 02:06:56 PM
INTERDISCIPLINARY

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

Date:	December 6, 2007
To:	Robert Justice, MD, Director Division of Drug Oncology Products
Thru:	Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Errors and Technical Support
From:	Linda Y. Kim-Jung, Pharm.D., Team Leader Division of Medication Errors and Technical Support
Subject:	DMETS Label and Labeling Review
Drug Name(s):	Oxaliplatin Injection
Application Type/Number:	NDA#: 22-160
Submission Number:	N/A
Applicant/sponsor:	Teva USA
OSE RCM #:	2007-2353

1 BACKGROUND

1.1 INTRODUCTION

This memorandum is in response to a November 14, 2007 request from the Division of Drug Oncology Products for a review of the container labels and carton labeling for Oxaliplatin. There is no proposed tradename for this product at this time.

1.2 REGULATORY HISTORY

Oxaliplatin is the subject of a 505(b)(2) application, which references the drug Eloxatin. Eloxatin for injection (a powder for injection) was approved on August 9, 2002, but was discontinued subsequent to the approval of Eloxatin Injection on January 31, 2005..

1.3 PRODUCT LABELING

Oxaliplatin is an antineoplastic agent indicated for use in combination with infusional 5-fluorouracil/leucovorin for adjuvant treatment of stage III colon cancer and advanced carcinoma of the colon or rectum. The usual dose is 65 mg/m^2 to 85 mg/m^2 intravenous (IV) infusion in 5% dextrose in water (D5W) 250 to 500 mL over 120 minutes. Oxaliplatin will be supplied in 50mg/10 mL and 100mg/20 mL vials.

2 METHODS AND MATERIALS

2.1 PROPOSED LABELING

DMETS reviewed the container labels and carton labeling submitted on February 9, 2007 and package insert labeling submitted on November 27, 2007.

2.2 AERS SELECTION OF MEDICATION ERROR CASES

Since Eloxatin was previously approved, DMETS conducted a search of the Agency's Adverse Event Reporting System (AERS) for medication errors associated with the use of Eloxatin. Errors associated with the use of Eloxatin should be taken into consideration when reviewing the labels and labeling for Oxaliplatin in order to prevent such errors from occurring with Oxaliplatin after it is introduced into the marketplace. DMETS searched (AERS) using the trade name "Eloxatin," the established name "Oxaliplatin", and the verbatim terms "Eloxa%" and "Oxalipla"% as well as the MedDRA high level terms "maladministrations", "medication monitoring errors", "medication errors due to accidental exposure", and "medication errors NEC" and the preferred terms "overdose", "accidental overdose", "multiple drug overdose", and "multiple drug overdose accidental".

3 RESULTS

3.1 PROPOSED LABELING

3.1.1 Container Label and Carton Labeling

3.1.1.1 The proposed carton labeling does not include the mg/mL concentration following the total drug content.

3.1.1.2 There is a very prominent warning statement: (b) (4) on the principal display of the carton labeling.

3.1.1.3 This product is a single use vial. However, the statement "Discard Unused Portion" is not readily visible on the carton labeling because it is on the side panel. In contrast, the container label does not include the statement "Discard Unused Portion".

3.1.2 Package Insert Labeling

3.1.2.1. The drug name is incorrectly stated as "Oxaliplatin for Injection".

3.1.2.2 The proposed insert labeling includes error prone abbreviations (e.g., 5-FU, LV, D5W, IV, Q2W etc) throughout the entire labeling.

3.2 MEDICATION ERROR CASES

The AERS search identified 16 medication errors associated with the use of Eloxatin. These cases can be categorized into the following error type: wrong admixture, improper dose, wrong rate, wrong drug and labeling confusion.

3.2.1. Wrong Infusion Solution

Six cases (n=6) were associated with the use of normal saline rather than dextrose in the administration of Eloxatin. One of those cases resulted in bronchospasm, hypotension, and fainting. No causalities were reported in these cases and the remaining five cases did not result in any adverse effects.

3.2.2 Improper Dose

Four cases (n=4) were associated with inappropriate doses of Eloxatin. Two cases stated that patients were administered overdoses of Eloxatin, one of which resulted in facial spasms and neurological symptoms. One case involved a patient receiving an incorrect dose of Eloxatin because the patient's body surface area was calculated incorrectly at 2.14 m^2 instead of 1.93m^2. The patient experienced nausea, vomiting, and dehydration.

In the fourth case, a patient with decreased creatinine clearance received an incorrect dose of Eloxatin due to the fact that the patient's dose was not appropriately decreased. The patient's general condition deteriorated. Causality was not included in any of the four aforementioned cases.

3.2.3 Wrong Rate

One case (n=1) reported a patient being administered Eloxatin too quickly. Eloxatin was administered over one hour rather than recommended two hours. The patient experienced rigors, fever, and dark urine. No causality was included in the report.

3.2.4 Wrong Drug

One of the sixteen cases (n=1) involved Eloxatin being administered instead of Camptosar (Irinotecan). The patient became diaphoretic and dizzy, complaining of tingling of hands and tingling around the lips. No causality was included in the report.

3.2.5 Labeling Confusion

Four cases (n=4) were associated with the labels and labeling of Eloxatin. All four cases cited concerns about the lack of a stated concentration on the principal display panel of the container labels and carton labeling. None of these cases resulted in a medication error.

4 DISCUSSION

Copies of the labels and labeling for the proposed product were provided in black and white, and may not represent the true color to be marketed or contain a scale for size. Therefore, DMETS cannot fully assess if there are any safety concerns with respect to the layout, font, color contrast, prominence, etc utilized on the labels and labeling. However, in our review of the draft container labels, carton and insert labeling, we have identified design issues that will result in failures in the dispensing (including preparation) and administration phase of the medication use process. The failures identified are already confirmed in review of the postmarketing reports with Eloxatin. Since this product is labeled in the same manner as Eloxatin, we anticipate the same type of errors seen with Oxaliplatin.

Specifically, there is no expression of the concentration (mg/mL) on the labels/labeling. Without the stated mg/mL concentration, it will be difficult for practitioners to calculate how many milliliters to add to the infusion bag (5% Dextrose). Although, DMETS previously recommended including this information on the Eloxatin labels and labeling it is not currently present on the label (please refer to OSE review #2006-881 dated January 4, 2007 and #05-881 dated September 30, 2005). As a result, practitioners have expressed concern with the lack of a concentration on the Eloxatin labels and labeling. If this information is not included on the Oxaliplatin label, the same errors are likely to occur. This lack of information coupled with the fact that this product is individually dosed on the patient's body surface area compounds the potential for confusion and dose calculation errors. Thus, it would be conducive to have "mg/mL" information readily available on the label/labeling of the product.

Our analyses also noted that despite the current warnings on the labels and labeling against the use of non-dextrose infusion solutions, there are errors in which the drug was added to sodium chloride containing solutions. The current warning on the principal display panel of the Eloxatin carton labeling is very prominent and it says in capital and bolded letters, "See package insert for further required dilution. DO NOT MIX OR ADD TO SODIUM CHLORIDE/CHLORIDE-CONTAINING SOLUTIONS." The wording and presentation of this statement is error-prone because the words 'mix or add to sodium

chloride' are so prominent and it may reinforce a confirmation bias by leading the reader to add this product to a sodium containing solution, such as normal saline. Rather than saying "what not to do", a direct instruction on "what to do" would be less confusing. Since the product should only be mixed with 5% Dextrose Injection, this information should be communicated to the reader and it may be easier to comprehend at the time of preparation.

In addition, this product is preservative free and it will be marketed in a single use vial. Thus, the unused portion of the solution remaining in the vial should be discarded, as it may become contaminated if stored and used for another dose. However, the information to discard the unused portion is not included on the container label. Although the carton labeling does have the statement "discard unused portion", it is presented on the side panel where it can be easily overlooked. Additionally, cartons are also discarded once the vial is removed and the only labeling in the sterile environment for preparation would be the label on the vial. Thus, it would be beneficial to include this information on the container label.

When evaluating the package insert labeling, we noted the use of error-prone abbreviations and acronyms (e.g., 5 FU, LV, D5W, IV, Q2W etc). On June 14, 2006, FDA launched a national campaign warning health care providers and consumers not to use error-prone abbreviations, acronyms, or symbols. As part of this campaign, FDA agreed to not include such abbreviations in our approved labeling because these abbreviations and acronyms are carried over to prescribing practices. Thus, we request that the Divisions not approve or use such symbols in their labels and labeling. We also note this product is referred as "Oxaliplatin for Injection" throughout the labeling. Since this product is a solution, the current dosage form is inaccurate and may lead practitioners to think they have to reconstitute Oxaliplatin.

5 CONCLUSIONS AND RECOMMENDATIONS

As proposed, the container label, carton and insert labeling are designed in such a manner that contributes to error. DMETS has conducted a failure modes and effects analysis (FMEA) and applied principals of human factors in addition to considering postmarketing error cases in order to identify areas of needed improvement to ensure the safe use of the product.

Collectively, the areas identified as problematic represent areas that can be easily remedied prior to approval of this product. Although they may appear minor and editorial in nature, if not revised before approval it could have a significant impact on the safe use of the product. We recommend implementation of the following recommendations prior to approval.

5.1 CONTAINER LABEL AND CARTON LABELING

5.1.1 Revise the warning statement: [redacted] (b) (4) on the principal display of the container label and carton labeling to say "what to do" instead of "what not to do".

For example, "Only Mix or Add to 5% Dextrose Solution" which may be easier to comprehend for the readers who are preparing this product. Also, avoid using all capital letters as it detracts from the readability of this important warning statement.

5.1.2 Include the mg/mL concentration immediately below the total drug content. For example:

100 mg/20 mL
(5 mg/mL)

5.1.3 For the carton labeling, relocate the statement "Discard Unused Portion" from the side panel to immediately follow the statement "Single Use Vial" on the principal display panel. For the container label, add the statement "Discard Unused Portion" so that it immediately follows the statement "Single Use Vial" on the principal display panel. For example: "Single Use Vial – Discard Unused Portion".

5.2 PACKAGE INSERT LABELING

5.2.1 Do not use abbreviations and acronyms (e.g., 5-FU, LV, IV, D5W, Q2W etc) throughout the labels and labeling. Write out these words.

5.2.2 Revise the statement "Oxaliplatin for Injection" to read "Oxaliplatin Injection", throughout the entire insert labeling.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy DMETS on any communication to the sponsor with regard to this review. If you have further questions or need clarifications, please contact Samuel Chan, project manager, at 301-796-2283.

6.4 REFERENCES

6.4.1 Adverse Event Reporting System (AERS)

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

6.4.2 OSE Review #2006-881, DMETS Medication Error Post-marketing Safety Review on Eloxatin, dated January 4, 2007.

6.4.3 OSE Review #05-881, DMETS Medication Error Post-marketing Safety Review on Eloxatin, dated September 30, 2005.

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/s/

Linda Kim-Jung
12/6/2007 01:24:26 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
12/6/2007 01:30:39 PM
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Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	February 25, 2009
To:	Rik Lostritto, Director Division of Pre-marketing Assessment III and Manufacturing Science
Through:	Todd Bridges, RPh, Team Leader Denise Toyer, Pharm.D., Deputy Director Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Raichell S. Brown, Pharm.D., J.D., Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name(s):	Oxaliplatin Injection 50 mg/10 mL and 100 mg/20 mL
Application Type/Number:	NDA #: 22-160
Applicant:	Teva Parenteral Medicines, Inc.
OSE RCM #:	2009-129

CONTENTS

EXECUTIVE SUMMARY

The results of the Label and Labeling Risk Assessment found that the presentation of information on the proposed container label and carton labeling vulnerable to confusion that could lead to medication errors. Specifically, the total drug contents are not sufficiently differentiated, the drug concentration is improperly presented, the dosage form lacks prominence, and presentation of other information on the principle display panel is ambiguous. The Division of Medication Error Prevention and Analysis believes the risks identified can be addressed and mitigated prior to drug approval. Accordingly, recommendations provided in Section 6 aim at reducing the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Pre-marketing Assessment III and Manufacturing Science on January 21, 2009 to evaluate the labels and labeling of Oxaliplatin Injection for the potential to contribute to medication errors. The Applicant submitted revised container labels and carton labeling. However, the insert labeling is in the preliminary stages of drafting and, therefore, will be reviewed by the Division of Medication Error Prevention and Analysis at a later date. There is no proposed trade name for this product at this time.

1.2 REGULATORY HISTORY

The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed the labels and labeling, and insert labeling for Oxaliplatin and provided recommendations for improvement in OSE Review # 2007-2353, dated December 6, 2007. The Division forwarded our comments from that review to the Applicant via e-mail dated December 13, 2007. In response, the applicant submitted revised labels and labeling on August 29, 2008.

Oxaliplatin is the subject of a 505(b)(2) application submitted on February 9, 2007 that references Eloxatin. The applicant based the filing of a 505(b)(2) application on prior NDAs for Eloxatin submitted by Sanofi-Aventis. Eloxatin for Injection, a lyophilized powder for injection, was approved on August 9, 2002; however, it was discontinued subsequent to the approval of Eloxatin Injection, an aqueous solution, on January 31, 2005.

On September 17, 2007, the Applicant notified the Agency that Sanofi-Aventis filed suit against the Applicant under 21 CFR 314.107(f)(2). The Applicant received Notice of Certification on May 7, 2007. Consequently, no approval of this application may be effective until November 7, 2009 unless the court extends or reduces the 30 month stay of approval.

1.3 PRODUCT INFORMATION

Oxaliplatin is an antineoplastic agent indicated for use in combination with infusional 5-fluorouracil and leucovorin for:

- Adjuvant treatment of stage III colon cancer in patients who have undergone complete resection of the primary tumor and
- Treatment of advanced colorectal cancer.

The usual dose is 65 mg/m^2 to 85 mg/m^2 intravenous infusion in 250 mL to 500 mL of 5% dextrose injection. It is administered over 120 minutes simultaneously with 5-fluorouracil, but in separate intravenous bags using a Y line, on the first day of a two day regimen. The two-day regimen is repeated every two weeks.

Oxaliplatin Injection will be supplied in vials of 50 mg/10 mL and 100 mg/20 mL.

2 METHODS AND MATERIALS

This section describes the methods and materials used by medication error prevention staff to conduct a label, labeling, and/or packaging risk assessment. The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SEARCH

DMEPA previously reviewed labels and labeling for this NDA. (See OSE Review # 2007-2353). During the previous OSE Review, DMEPA conducted an AERS search of the proprietary name Eloxatin because Oxaliplatin Injection is currently approved and marketed under the proprietary name Eloxatin. Errors associated with the use of Eloxatin are taken into consideration when reviewing the labels and labeling for Oxaliplatin Injection in order to prevent the same errors from occurring with Oxaliplatin Injection after it is introduced into the marketplace.

For the current label and labeling review of Oxaliplatin Injection, DMEPA conducted another AERS search limiting the time frame from June 1, 2007 to the present (February 2, 2009) in order to capture cases reported since the last DMEPA labeling review of this NDA (#22-160). DMEPA searched AERS using the: MedDRA High Level Group Term (HLGT) "Medication Errors" and Preferred Term (PT) "Pharmaceutical Product Complaint"; active ingredient term "Oxaliplatin"; trade name "Eloxatin"; and verbatim terms "Eloxa%" and "Oxalipla%".

2.2 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, dosage form, container quantity, expiration. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug such as the correct dosing and administration.

Given the critical role the label and labeling have in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

Because DMEPA staff analyzes reported misuse of drugs, we are able to use this experience to identify potential errors with all medication similarly packaged, labeled, or prescribed. We use Failure Mode and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling; thereafter, we provide recommendations that aim at reducing the risk of medication errors.

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[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

For this product, the applicant submitted the following revised labels and labeling for our review on August 29, 2008 (see Appendices A through D for images):

- Container Label: 50 mg/10 mL Single Vial
- Container Label: 100 mg/20 mL Single Vial
- Carton Labeling: 50 mg/10 mL
- Carton Labeling: 100 mg/20 mL

Additionally, we reviewed the comments provided in the previous label and labeling review for this NDA, OSE review # 2007 -2353, to identify outstanding areas of concern.

3 RESULTS

3.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SEARCH

No additional cases, to those identified in the previous DMEPA Review of Oxaliplatin Injection (NDA #22-160), were found when DMEPA conducted an AERS search of the proprietary name Eloxatin on February 2, 2009.

DMEPA notes that some of the label and labeling recommendations, designed to minimize the medication errors identified in the AERS search conducted for the prior label and labeling review of this NDA, have been incorporated into the revised labels and labeling submitted for this current review.

3.2 LABEL AND LABELING RISK ASSESSMENT

Review of the container labels and carton labeling identified areas of vulnerability that could lead to medication error.

3.2.1 All Labels and Labeling

Lack of Differentiation of the Total Drug Contents. The colors blue and green are used for the trade dress for both 50 mg/10 mL and 100 mg/20 mL, of Oxaliplatin Injections. Additionally, the numerical strengths of both the 50 mg/10 mL and 100 mg/20 mL products are expressed in the same black font color.

Lack of Prominence of the Dosage Form. Expression of the dosage form, Injection, is less prominent that other important information such as the product name, total drug content, and concentration.

Ambiguous Presentation of Information on Principle Display Panel. The statement "Discard Unused Portion" is immediately followed by, and on same line with, the statement (b) (4). " Also, the words (b) (4) in the statement (b) (4) are used to define the appropriate dilution solution for preparation of the infusion solution.

3.2.2 Container Labels

Improper Placement of the Statement of Drug Concentration. The statement of drug concentration (5 mg/mL) appears directly adjacent to the statement of total drug content (50 mg/10 mL or 100 mg/20 mL).

Improper Use of Red Ink for Both Critical and Non-critical Information. Red Ink is properly used on the principle display panel to cause the critical statements (b) (4) and "Caution: Contains Cytotoxic Agent" to stand out. However, red ink is also used for the non-critical information "Made in The Netherlands" and "Irvine, CA 92618."

4 DISCUSSION

Our Label and Labeling Risk Assessment found the dosage form lacks appropriate prominence and the similarity of the container labels for both strengths introduces vulnerability that could lead to medication errors involving selection of the wrong product. We also identified the improper placement of the product concentration on the container labels. Additionally, other information presented on the principle display panel lacks clarity.

4.1 INSUFFICIENT DIFFERENTIATION OF THE TOTAL DRUG CONTENTS

Oxaliplatin Injection will be available in two vials containing different total drug content. As a result, differentiation from one another through labels and labeling is necessary. The trade dress on both the 50 mg/10 mL and the 100 mg/20 mL uses the colors blue and green. However, the difference in the shades of the blue and green colors is inadequate to achieve the goal of differentiation of the two different total drug contents. Using the same colors causes all labels and labeling to look too similar. Further, both strength statements, 50 mg/10 mL and 100 mg/20 mL, are presented in the same black font color which also contributes to the similar appearance of the labels and labeling.

Based on post-marketing experience, labels and labeling that are not adequately differentiated increase the risk of confusion and contribute to product selection errors. This is particularly true when the similarly labeled products are likely to be placed side-by-side on the pharmacy shelf/storage area, the concentrations overlap, and, in this case, the total drug content does not stand out.

4.2 IMPROPER PRESENTATION OF PRODUCT CONCENTRATION

The statement of drug concentration appears adjacent to the statement of total drug content on the container label. However, the preferred position for expression of drug concentration is directly below the statement of total drug content. The proper placement is noted on the carton labeling.

When labels and labeling vary from the preferred format, it is more difficult and/or time-consuming for practitioners to locate and identify important information. Additionally, placing the total drug content and concentration side-by-side diminishes the prominence of the total drug content.

4.3 LACK OF PROMINENCE OF THE DOSAGE FORM

The word "Injection" is in a font that is smaller and less bold than the word "Oxaliplatin." Expression of the dosage form should have prominence commensurate to that of the product name.

4.4 AMBIGUOUS PRESENTATION OF INFORMATION ON PRINCIPLE DISPLAY PANEL

The statements "Discard Unused Portion" immediately followed by, and on same line with, (b) (4) are illogically paired. In addition, use of the words (b) (4) in the statement (b) (4)" may infer that a step, in addition to the process of dilution, is required for preparation of the infusion solution. Revising these statements into formats that health care practitioners are accustomed to seeing fosters greater clarity and comprehension of the information.

4.5 IMPROPER USE OF RED INK FOR BOTH CRITICAL AND NON-CRITICAL INFORMATION

The statements (b) (4) and "Caution: Contains Cytotoxic Agent" are presented in red ink on the principle display panel. Use of red ink, in the context of the other colors used on the label, immediately draws readers' eyes to these critical statements. However, the use of red ink for the non-critical statements, "Made in The Netherlands" and "Irvine, CA 92618" may undermine the utility of the red ink for the critical statements. If readers' eyes are drawn to the statements in red ink that read "Made in The Netherlands" or "Irvine, CA 92618" when first looking at the container label, they

will realize that it is not critical information and, as a result, may fail to give any other red ink special attention.

5 CONCLUSIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information on the proposed container labels and carton labeling introduces vulnerability to confusion that could lead to medication errors. Specifically, the concerns involve the lack of prominence of the word "Injection"; lack of differentiation between the two strengths; improper placement of the statement of drug concentration; ambiguous placement of information on the principle display panel; and improper use of red ink for both critical and non-critical information. The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and mitigated prior to drug approval. Recommendations provided in Section 6 aim at reducing the risk of medication errors.

6 RECOMMENDATIONS

6.1 COMMENTS TO THE DIVISION

Based on our assessment of Oxaliplatin Injection container label and carton labeling, we have identified areas of needed improvement. We recommend implementation of the label and labeling revisions outlined in Section 6.2 below.

We would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy us on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Sandra Griffith, Project Manager, at 301-796-2445.

6.2 COMMENTS TO THE APPLICANT

We have evaluated your container labels and carton labeling. This evaluation of this container labels and carton labeling resulted in identification of several areas of needed improvement. Please revise your labels and labeling as follows:

A. All Labels and Labeling

1. Revise the expression of the dosage form in a prominence that is commensurate to that of the established name.

2. When comparing the 50 mg/10 mL and 100 mg/20 mL labels and labeling side-by-side, they appears similar. This similarity stems from the similar colors utilized in the trade dress. In addition, the numerical strengths on both the 50 mg/10 mL and the 100 mg/20 mL are expressed in the same black font color. Colors utilized in the trade dress serve, in part, to differentiate strengths of the same product.

   For that reason, please revise the labels and labeling to differentiate the two different total drug contents of Oxaliplatin Injection. Using different colors, blocking the statement of total drug content (along with the statement of concentration) with different contrasting colors, or other means to minimize the potential for selection errors between the two different total drug contents. Ensure that the colors used within the trade dress of each vial provide sufficient contrast for easy readability.

3. Presentation of information on labels and labeling in a manner that is customary fosters clarity and greater comprehension of the information. Furthermore, linking

relevant phrases to one another helps to ensure that important steps conveyed on the labels and labeling are not omitted due to fragmentation of those steps. Accordingly, please revise the information on the labels and labeling as follows:

- Place the statement "Discard Unused Portion" immediately after, and on the same line as, the statement "Single Use Vial."

- Revise the statement [redacted] (b) (4) ' to read "Must Be Diluted Prior To Use With 5% Dextrose Injection."

- Delete the statement [redacted] (b) (4) " because it duplicative and crowds the principle display panel; the side panel has a reference to [redacted] (b) (4)

B. Container Label

1. The statement of drug concentration appears adjacent to the statement of total drug content. However, the preferred position for expression of drug concentration is directly below the statement of total drug content. If space allows, revise the container labels by positioning the drug concentration directly below the statement of total drug content (as it appears on the carton labeling).

2. Red ink is used for both critical and non-critical information. Use of red ink for the non-critical statements, "Made in The Netherlands" and "Irvine, CA 92618" undermines the utility of the red ink used to emphasize the critical statements, "Only [redacted] (b) (4) and "Caution: Contains Cytotoxic Agent." If a reader's eyes are drawn to the statements in red ink that read "Made in The Netherlands" or "Irvine, CA 92618" when he first looks at the container label, he will realize that it is not critical information and, as a result, may fail to give any other red ink special attention. Therefore, revise the container labels so that "Made in The Netherlands" and "Irvine, CA 92618" are in black ink (as appears on the carton labeling).

7. REFERENCES

7.1 PRIOR OSE REVIEWS

1. *OSE Review #2007-2353 DMETS Label and Labeling Review for Oxaliplatin Injection, Kim-Jung, L; December 6, 2007.*
2. *OSE Review #2006-881 DMETS Medication Error Post-Marketing Safety Review of Eloxatin (Oxaliplatin) Injection, Abate, R.; January 4, 2007.*
3. *OSE Review #2005-0223 DMETS Medication Error Post-Marketing Safety Review of Eloxatin (Oxaliplatin) Injection. Arnwine, K; September 30, 2005.*

7.2 ADVERSE EVENTS REPORTING SYSTEM (AERS)

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

APPENDICES

Appendix A: Container Label 50 mg/10 mL Single Vial

Appendix B: Container Label 100 mg/20 mL Single Vial

Appendix C: Carton Labeling for 50 mg/10 mL

Appendix D: **Carton Labeling for 100 mg/20 mL**

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/s/

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