CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-277

OTHER REVIEW(S)

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

Date:	November 6, 2008
To:	Robert Justice, M.D., Director Division of Drug Oncology Products, HFD-150
Through:	Kellie Taylor, Pharm.D., MPH, Team Leader Denise Toyer, Pharm.D., Deputy Director Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis, HFD-420
From:	Tara Turner, Pharm.D., Safety Evaluator Division of Medication Error Prevention and Analysis, HFD-420
Subject:	Labeling Review
Drug Name(s):	Temodar (Temozolomide) for Injection 100 mg/vial
Application Type/Number:	NDA #: 22-277
Applicant:	Schering Corporation
OSE RCM #:	2008-348

CONTENTS

EXECUTIVE SUMMARY

The results of the Label and Labeling Risk Assessment found that the presentation of information on the proposed container label, carton and insert labeling appears to be vulnerable to confusion that could lead to medication errors. Specifically, the concerns surround the presentation of the product strength and route of administration as well as the instructions for proper dosage, administration and storage of the drug product. The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 6 that 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 Drug Oncology Products (DDOP) to evaluate the labeling of Temodar for injection for the potential to contribute to medication errors. The labeling includes container label, carton and insert labeling, including a pharmacist information sheet and a patient package insert.

On January 23, 2008, the applicant submitted the subject NDA, which provides for an injectable formulation of Temodar for the same indications and dosing regimens already approved for the oral capsules. In the cover letter, the applicant states that "Temodar for intravenous administration was developed because some patients such as those with brain stem involvement may have difficulty swallowing capsules".

1.2 REGULATORY HISTORY

Temodar (temozolomide) Oral Capsules was first approved on August 11, 1999 under NDA 21-029 for the treatment of adult patients with newly diagnosed glioblastoma multiforme or refractory anaplastic astrocytoma.

The Division of Medication Error Prevention and Analysis has completed three post-marketing reviews for the oral capsule product (see RCM# 02-0116 dated November 25, 2002; 02-0116-1 dated October 24, 2003; 02-0116-2 dated June 29, 2004). These reviews address medication errors resulting from confusion between the net quantity statement and product strength, overdoses resulting from usage exceeding the labeled dosing interval of 5 days, and proprietary name confusion.

1.3 PRODUCT INFORMATION

Temodar (temozolomide) is an alkylating agent indicated for the treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment, or refractory anaplastic astrocytoma, ie, patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine. The product is currently available as an oral capsule in the following strengths: 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg. The initial dosage for patients with newly diagnosed glioblastoma multiforme is 75 mg/m^2 orally once daily for 42 days concomitant with focal radiotherapy followed by maintenance treatment for 6 cycles. Dosage in cycle 1 (maintenance) is 150 mg/m^2 once daily for 5 days followed by 23 days without treatment. At the start of cycle 2, the dose can be escalated to 200 mg/m^2. The initial dose for patients with refractory anaplastic astrocytoma is 150 mg/m^2 once daily for 5 consecutive days per 28-day treatment cycle. Starting with cycle 2, the dose may be increased to 200 mg/m^2 for 5 consecutive days per 28-day treatment cycle. Treatment can be continued until disease progression. Dosage should be adjusted according to nadir neutrophil and platelet counts in the previous cycle and the neutrophil and platelet counts at the time of initiating the next cycle. The subject NDA provides for an injectable formulation for the same indications

and dosing regimens already approved for the oral capsules. The product is formulated as a lyophilized powder which is supplied in single-use glass vials containing 100 mg Temozolomide per vial. When reconstituted with 41 mL Sterile Water for Injection, the resulting solution will contain 2.5 mg/mL Temozolomide. Up to 40 mL may be withdrawn from each vial to make up the total dose which is transferred into an empty 250 mL PVC infusion bag. The dose should be infused intravenously using a pump over a period of 90 minutes, which is bioequivalent to the oral capsule formulation. The lyophilized powder should be refrigerated. Reconstituted product may be stored at room temperature and must be used within 14 hours, including infusion time.

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)

On September 9, 2008, the Division of Medication Error Prevention and Analysis conducted a search of the FDA Adverse Event Reporting System (AERS) database to determine if any additional medication errors involving Temodar oral capsules have been reported since the date of our last AERS search, the results of which were incorporated into the post-marketing review dated October 24, 2003. The following criteria were used: MedDRA High Level Group Term (HLGT) 'Medication Errors' and the Preferred term (PT) 'Pharmaceutical Product Complaint' with the active ingredient (temozolomide), trade name (Temodar and temozolomide), and verbatim terms 'Temod%' and 'Temoz%'.

The cases were manually reviewed to exclude duplicate cases. Additionally, cases that did not describe a medication error were excluded from further analysis. The cases that did describe a medication error were categorized by type of error. We excluded the types of errors associated with risks that would not translate to the new injectable formulation. We reviewed the cases within each category to identify contributing factors.

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, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has 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]

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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.

Because medication error prevention staff analyze reported misuse of drugs, we staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. We use FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted on January 23, 2008 the following labels and insert labeling for our review (see Appendices A and B for images):

- Container Label: 100 mg vial
- Carton Labeling: 100 mg vial
- Insert Labeling, including Pharmacist Information Sheet and Patient Package Insert (no images)

Additionally, on April 29, 2008, we met with the medical officer, Dr. Martin Cohen, to discuss concerns with the packaging and administration of the product.

3 RESULTS

3.1 AERS SELECTION OF CASES

The AERS search retrieved a total of 26 medication error cases involving Temodar oral capsules that were thought to also be relevant to the new injectable formulation. The breakdown of cases is as follows:

- 9 cases of wrong duration involving administration of Temodar beyond the recommended 5 days per treatment cycle. 4 of these cases are foreign reports. For those cases where causality was cited, 2 cases were due to communication errors in the hospital or clinic, 1 case occurred when the patient mistakenly refilled his prescription, and 2 cases occurred because the patients misunderstood written and verbal dosing instructions, despite correct prescribing.
- 17 cases of wrong dose involving patients who took the 5 day supply in one dose, physicians who prescribed the wrong dose, patients who took the wrong dose, patients who took an extra dose after a treatment cycle had ended, and patients who felt they received the wrong dose because of side effects they experienced. 9 of these cases are foreign reports. Possible causes cited were intentional misuse and patient's lack of understanding of written instructions.

3.2 LABEL AND LABELING RISK ASSESSMENT

Review of the container label and carton labeling identified several areas of vulnerability that could lead to medication error, specifically with respect to clear communication of the product strength and route of administration, as well as the instructions for proper dosage, administration, and storage.

During our April 29, 2008 meeting with the medical officer, we discussed issues of concern regarding the preparation and administration of Temodar for injection. As part of the discussion we learned that this product will most likely be administered in a clinic or other outpatient setting. We were unable to resolve our other questions but they are described in detail in Section 4.

3.2.1 All Labels and Labeling

The dosage form is presented as (b) (4) This dosage form is not defined in the CDER Data Standards Manual.

3.2.2 Container Label

The product strength is located at the top of the label, above the proprietary and established names.

The established name is presented in a thin green font against a shaded peach background, which provides poor color contrast and decreases its prominence relative to the proprietary name and dosage form.

There is no statement indicating that the vial is for single use only.

There is no statement instructing healthcare practitioners to discard the unused portion of medication after single use.

3.2.3 Carton Labeling

There is a picture outline of a vial which takes up greater than 1/3 of the principal display panel.

The established name is presented in a thin green font against a shaded peach background, which decreases its prominence relative to the proprietary name and dosage form.

There is no statement indicating that the vial is for single use only.

There is no statement instructing healthcare practitioners to discard the unused portion of medication after single use.

3.2.4 Insert Labeling

In the Highlights of Prescribing Information and in the Dosage and Administration section (2.1) of the Full Prescribing Information, there is a confusing statement that (b) (4)

In the Warnings and Precautions (Section 5) of the Full Prescribing Information, there is no information cautioning against the administration of the medication at a rate faster or slower than recommended.

In the Preparation and Administration (Section 2.2) of the Full Prescribing Information, there are no storage recommendations for the reconstituted product. There is no statement indicating that the pharmacist should not further dilute the reconstituted product. There is no statement indicating that the lines should be flushed to ensure that the patient receives the full dose.

Additionally, we identified areas of vulnerability in the Pharmacist Information Sheet. In the section "What is Temodar?", there is no statement that the product is indicated only for adult patients. In the section "How is Temodar dosed?", there are instructions for rounding off the calculated dose based on the patient's BSA. These instructions are not found in the insert labeling. The dosing information is presented in two sections as follows: "How might the dose of Temodar be modified for Refractory Anaplastic Astrocytoma?" and "What is the Temodar treatment regimen?". This manner of presentation is confusing because it lacks organization.

4 DISCUSSION

The results of the Label and Labeling Risk Assessment found that the presentation of information on the container labels, carton, and insert labeling appears to be vulnerable to confusion that could lead to medication errors. Specifically, the concerns surround the presentation of information on the principal display panel of the carton and container, as well as the instructions for proper dosage, administration, and storage of the drug product throughout the professional labeling.

Additionally, we evaluated the post-marketing cases of wrong duration and wrong dose for their applicability to the proposed injectable formulation. (b) (4) We note that the Dosage and Administration (Section 2) of the insert labeling has been revised to recommend initial treatment daily for 42 days followed by a maintenance dose daily for 5 days per 28 day cycle. We believe the recommended dosing regimens are clearly outlined in the proposed insert labeling and note that many of the medication errors were foreign reports and/or involved patient misunderstanding of the dosing regimen.

4.1 ESTABLISHED NAME

The dosage form is presented as (b) (4) in the established name. We are concerned that the inclusion of the word (b) (4) may inadvertently be a source of administration errors because it does not accurately describe the final product that will be administered to the patient. We note that this dosage form does not appear to be consistent with those presented in the CDER Data Standards Manual.

4.2 PRESENTATION AND PROMINENCE OF PRODUCT STRENGTH

On the container label, the product strength appears near the top of the principal display panel, above the proprietary and established names. In its current location, the strength is difficult to find and has less prominence than the centrally located drug information. A more prominent location would be immediately beneath the dosage form where healthcare practitioners would typically expect to find this information.

4.3 INADEQUATE PROMINENCE OF ESTABLISHED NAME

On the container label and carton labeling, the established name is presented in thin green font against a shaded peach background. This decreases the prominence of the established name. The use of a heavier font in a more strongly contrasting color consistent with the font use to display the proprietary name and dosage form will improve the readability and prominence.

4.4 INAPPROPRIATE SIZE OF GRAPHIC

The carton labeling displays a picture outline of a vial. This graphic extends over 1/3 of the principal display panel and is distracting.

4.5 LACK OF SINGLE USE/DISCARD AFTER USE STATEMENT

The insert labeling describes the product packaging as single-use glass vials. However, this information is not found on the container label or carton labeling. Further, the label and labeling fails to communicate to healthcare practitioners that this vial should be discarded after a single use. Since some patients may require a portion of a vial for a complete dose, practitioners may believe that they can save the remaining drug for another patient or for later administration. Thus, a "Discard after use" statement would warn healthcare practitioners against using a single vial for multiple doses. It would also help to reinforce the product's usage within 14 hours.

4.6 PACKAGE INSERT LABELING

We identified several issues regarding the preparation and administration of Temodar for injection, which we discussed with the medical officer. In the Dosage and Administration (Section 2.1) there is a statement that (b) (4) This information would be more clearly communicated with a statement that the oral and intravenous dosing is the same.

Furthermore, the preparation instructions indicate that the pharmacist should transfer the calculated dose into an empty 250 mL PVC infusion bag. This type of product preparation is not standard and therefore introduces the risk of administration errors (i.e. reconstituted solution may be given via a syringe or placed in a bag with diluent). To decrease the risk of confusion, there should be a specific statement, in the labeling and on the carton and container, to not further dilute the dose. The extra statement will help to highlight this unusual procedure for the pharmacist.

Similarly, we note that the Warnings and Precautions (Section 5) does not contain any information warning against the administration of the product at rates faster or slower than recommended in the labeling. Due to the unusual preparation instructions cited above, we are concerned that the product may be drawn into a syringe and administered via intravenous push or further diluted with another intravenous fluid for infusion. Additionally, it may be helpful to list the consequences of these potential administration errors, if known.

We note that the insert labeling states that no data are available on the compatibility of Temodar with other intravenous substances or additives. If that is the case, the intravenous lines should be flushed before and after each dose is administered. However, the insert labeling provides no recommendations for line flushing. Similarly, intravenous lines should be flushed to ensure that the patient receives the full prescribed dose of Temodar. This could be especially problematic in the case of a smaller patient (i.e. 1 m^2) who receives the lower recommended dose (i.e. 75 mg/m^2) whose calculated dose would be 75 mg. This is equivalent to 30 mL of the 2.5 mg/mL solution. When infusing such a small volume over 90 minutes it is possible that some of the drug solution, possibly representing a significant portion of the dose, may be left over in the tubing.

Additionally, the Preparation and Administration (Section 2.2) and the Pharmacist Information Sheet, do not provide information on storage recommendations for the reconstituted product. Healthcare practitioners need this information in order to schedule preparation of the product to meet the physician's ordered administration time and to ensure that the patient receives effective treatment.

The Pharmacist Information Sheet contains information that is inconsistent with the insert labeling. In the "What is Temodar" section, there is no statement that Temodar is indicated for adult patients. This information is stated in the insert labeling and should be consistent across product labeling to decrease the risk of confusion. In the "How is Temodar dosed" section there is a description of how a dose is calculated based on the patient's body surface area and then rounded off to the nearest 5 mg. This information is not included in the insert labeling. Finally, the dosage information is located in two different sections ("How might the dose of Temodar be modified for Refractory Anaplastic Astrocytoma?", and "What is the Temodar treatment regimen?"). The information would be easier to comprehend if the dosing recommendations were grouped and titled according to the approved indications, as presented in the insert labeling. Additionally, since this information is an abbreviated summary of the full package insert, the Pharmacist Information Sheet should cross reference the pertinent sections in the full insert labeling so that practitioners can readily refer to the full product information.

5 CONCLUSIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information on the proposed container label, carton and insert labeling introduces vulnerability to confusion that could lead to medication errors. Specifically, the concerns surround the presentation of the product strength and route of administration as well as the instructions for proper dosage, administration and storage of the drug product. The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

6 RECOMMENDATIONS

6.1 COMMENTS TO THE DIVISION

Based upon our assessment of the labels and labeling, and the review of post-marketing medication error reports, the Division of Medication Error Prevention and Analysis has identified areas of needed improvement. We have provided recommendations in Section 6.2 and request this information be forwarded to the Applicant.

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.

6.1.1 All Labels and Labeling

Delete the word (b) (4) from the dosage form statement so that it reads "(Temozolomide) for Injection".

6.1.2 Insert Labeling

1. The statement (b) (4) We request that the applicant clarify the wording of the statement. Wording such as "The recommended dosing for TEMODAR as an intravenous infusion over 90 minutes is the same as the dosing for the oral capsule formulation. Bioequivalence has been established only when TEMODAR for Injection was given over 90 minutes (See Section 12.3)" may provide greater clarity.
2. Add storage requirements for the reconstituted product in Section 2.2.
3. Add a statement "Do not further dilute the reconstituted solution" to Section 2.2.
4. Add instructions to flush lines before and after each Temodar infusion to Section 2.2.
5. Add information to Section 5 regarding adverse events that may occur if the product is infused at a rate faster or slower than recommended or if the product is further diluted in an intravenous solution (i.e. sodium chloride 0.9%, dextrose 5%).

6.1.3 Pharmacist Information Sheet

1. See Insert Labeling comments 1 to 4.
2. In the "What is Temodar?" section, add a statement that the product is for use only in adult patients.
3. In the "How is Temodar dosed?" section, modify the information to make it consistent with the insert labeling. Specifically, the proposed language advises pharmacists to (b) (4) advice which is not presented in the insert labeling.
4. Modify the presentation of dosage information by grouping and titling the information according to indication.
5. Modify the language in "How is TEMODAR for Injection prepared?" and "How is TEMODAR for Injection administered?" according to the recommendations provided above for the Insert Labeling.
6. Add storage requirements for the reconstituted product in the section "How is TEMODAR for Injection prepared?".
7. Cross reference all information presented in the Pharmacist Information Sheet to the full prescribing information. The information presented in the Pharmacist Information Sheet is an abbreviated summary of the full prescribing information, and pharmacists may not realize this reading only the proposed sheet. Additionally, the cross-referencing of the information would aid practitioners in locating any further information they may require when preparing and administering the product.

6.2 COMMENTS TO THE APPLICANT

6.2.1 All Labels and Labeling

Delete the word (b) (4) from the dosage form statement so that it reads "(temozolomide) for injection".

6.2.2 Container Label

1. Relocate the product strength so that it appears directly beneath the established name and dosage form "(temozolomide) for injection".
2. Increase the prominence of the established name. The established name should have prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors including typography, layout, contrast, and other printing features. Please also ensure that it is ½ the size of the proprietary name. Additionally, use a heavier, darker font for the established name that provides better contrast against the shaded background.
3. Add a "Single use; discard after use" statement to the label.
4. To avoid administration errors, please consider adding the following language to the Usual Dosage statement following the directions for reconstitution:

   > "This product does not require additional dilution after reconstitution. Administer the solution via intravenous infusion over 90 minutes."

   Present this information in **bold** font.

6.2.3 Carton Labeling

1. Delete the vial outline graphic on the principal display panel. It distracts from other important drug information.
2. Increase the prominence of the established name. The established name should have prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors including typography, layout, contrast, and other printing features. Please also ensure that it is ½ the size of the proprietary name. Additionally, use a heavier, darker font for the established name that provides better contrast against the shaded background.
3. Add a "Single use; discard after use" statement.
4. To avoid administration errors, please consider adding the following language to the Usual Dosage statement following the directions for reconstitution:

   > "This product does not require additional dilution after reconstitution. Administer the solution via intravenous infusion over 90 minutes."

   Present this information in **bold** font.

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/s/

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11/6/2008 03:37:49 PM
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