CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-277

RISK ASSESSMENT and RISK MITIGATION 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 18, 2008
To:	Robert Justice, M.D., Director **Division of Drug Oncology Products**
Through:	Jodi Duckhorn, M.A., Team Leader **Patient Labeling and Education Team** **Division of Risk Management (DRISK)**
From:	Sharon R. Mills, BSN, RN, CCRP Patient Product Information Specialist **Patient Labeling and Education Team** **Division of Risk Management (DRISK)**
Subject:	Review of Patient Labeling (Patient Package Insert)
Drug Name(s):	Temodar (temozolomide) (b) (4) for Injection
Application Type/Number:	N22-277
Applicant/sponsor:	Schering Corporation
OSE RCM #:	2008-455

1 INTRODUCTION

Schering Corporation submitted an original New Drug Application, NDA 22-277 for Temodar (temozolomide)(b) (4) for Injection on January 23, 2008. Temodar is an alkylating agent indicated for the treatment of adult patients with:

- Newly diagnosed glioblastoma multiforme (GBM) concomitantly with radiotherapy and then as maintenance treatment
- Refractory anaplastic astrocytoma, i.e., patients who have experienced disease progression on a drug regimen containing nitrosurea and procarbazine.

The sponsor received approval for their New Drug Application, NDA 21-029, for Temodar (temozolomide) Capsules, a New Molecular entity, on August 11, 1999. The most recently approved labeling dated October 19, 2006 containspatient labeling (Patient Package Insert) and is posted on Drugs @ FDA.

The sponsor proposed a Patient Package Insert (PPI) for Temodar(b) (4) for Injection that is attached to a "Pharmacist Information Sheet." The Patient Labeling and Education Team provided preliminary review comments on the sponsor's proposed PPI for Temodar(b) (4) for Injection to DDOP on October 22, 2008 (RCM#2008-455). The preliminary comments recommended that the sponsor revise the PPI.

Schering Corporation responded to comments regarding the PPI and sent a revised the PPI to DDOP on October 27, 2008; however, the submitted proposed PPI was only for the new formulation and did not include the approved capsule formulation. On October 28, 2008 the review division agreed to convey to the sponsor that there should be one PPI for the Temodar product that should include both formulations. On October 30, 2008 the sponsor submitted a revised proposed PPI to DDOP via email, which includes both Temodar formulations.

2 MATERIAL REVIEWED

- DRAFT Professional Information for TEMODAR (temozolomide) for Injection and TEMODAR (temozolomide) Capsules revised throughout the review cycle and as agreed to by Schering Corporation and DDOP on November 13, 2008
- Revised DRAFT Patient Package Insert for TEMODAR(temozolomide) for Injection and TEMODAR (temozolomide) Capsules submitted by the sponsor October 30, 2008 and further revised and submitted to DDOP on November 12, 2008.

3 DISCUSSION

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft PPI submitted by the sponsor has a Flesch Kinkaid grade level of 8.4, and a Flesch Reading Ease score of 59.6%. To enhance patient comprehension, materials should be written at a 6^{th} to 8^{th} grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8^{th} grade reading level). The reading scores as submitted by the sponsor are acceptable. However, our changes to the PPI have improved the reading scores to a Flesch Kincaid grade level of 7.4 and a Flesch Reading Ease Score to 63.9%.

In our review of the PPI, we have:

- added important safety messages,
- simplified wording and clarified concepts where possible,
- ensured that the PPI is consistent with the PI,
- rearranged information due to conversion of the PI to PLR format,
- removed unnecessary or redundant information
- Although not required for Patient Information, we have put this PPI in the question–and-answer format specified in the Medication Guide Regulations (21 CFR 208.20) that we recommend for all FDA approved patient labeling.
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the PPI document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the PPI. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised PPI. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the PPI.

4 CONCLUSIONS AND RECOMMENDATIONS

1. We note that the sponsor has combined the proposed PPI for Temodar (temozolomide) for Injection with the existing PPI for Temodar (temozolomide) Capsules as requested. The sponsor has improved the readability of the document. See the Flesch Kincaid scores in the *Discussion* section above.
2. The sponsor added the section "What is the most important information I should know about Temodar?" at the beginning of the PPI as DRISK recommended; however, no content is included in the section. DRISK previously recommended that information about birth defects should be addressed at the top of the PPI in a section called "What is the most important information I should know about Temodar?" We referenced the November 2007 review of the PPI for Nexavar in which language about birth defects was handled in this way.

   Information about birth defects should be prominently placed as previously stated. The sponsor has added a section not generally used in patient labeling called **(b) (4)** As stated in the *Discussion* section above, although not required for Patient Information, we have put this PPI in the question–and-answer format

specified in the Medication Guide Regulations (21 CFR 208.20) that we recommend for all FDA approved patient labeling.

3. In the section "Who should not take TEMODAR?"

   - Language telling patients to tell your doctor if you have had an allergic reaction to DTIC, has been moved to "What should I tell my doctor before taking TEMODAR?"

   - We reiterate comments from the prior DRISK review that information on birth defects should be placed in the section "What is the most important information I should know about TEMODAR?" The sponsor included a section called **(b) (4)** This is not a standard section in patient labeling and there is no added value. We deleted this section. The bullet regarding breast-feeding has been moved to the section "What should I tell my doctor before taking TEMODAR?"

4. We moved the section "How should I take TEMODAR?" It now follows the section "What should I tell my doctor before taking TEMODAR?"

5. In the section "How should I take TEMODAR?" we have combined and simplified the instructions since the IV and oral regimens are the same. To avoid redundancy and excessive PPI length, we placed the information on dosing schedules at the beginning of the section, since the schedules are the same for IV and Capsule formulations. Too much information about the cycling of chemotherapy is confusing to patients. Patients should receive instructions from their doctor about their specific treatment regimen.

6. We moved the section "What should I avoid while taking TEMODAR?" It now follows the section "How should I take TEMODAR?"

7. In the section "What are the possible side effects of TEMODAR?"

   - We have placed serious side effects at the top of the section.

   - We refer patients back to the section "What is the most important information I should know about TEMODAR?" for information about pregnancy and birth defects.

   - We have made this section consistent with section 5 Warnings and Precautions by adding information about myelosuppression, Pneumocystis Carinii, secondary malignancies and secondary malignancies.

   - Headache and convulsions were moved up to the serious side effects based on PI language that both of these may be severe or life-threatening in newly diagnosed gliobalstoma multiforme patients being treated with TEMODAR.

   - Under common side effects, the sponsor should clarify whether hematomas and petechiae occur at the infusion site or this is a general statement in the PI, and add these to the PPI accordingly.

8. In the section "What are the ingredients in TEMODAR?" it is unnecessary to list the strengths (mgs.) of the active and inactive ingredients in the various capsule strengths. Since all of the capsules strengths contain the same inactive ingredients, we have eliminated redundancy and shortened the PPI by deleting multiple mentions of the inactive ingredients. We added information on the contents of the capsules.

Please let us know if you have any questions.

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/s/

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11/18/2008 10:21:45 AM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
11/18/2008 10:23:44 AM
DRUG SAFETY OFFICE REVIEWER

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:	October 22, 2008
To:	Robert Justice, M.D., Director **Division of Drug Oncology Products**
Through:	Jodi Duckhorn, M.A., Team Leader **Patient Labeling and Education Team** **Division of Risk Management (DRISK)**
From:	Sharon R. Mills, BSN, RN, CCRP Patient Product Information Specialist **Patient Labeling and Education Team** **Division of Risk Management (DRISK)**
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- Newly diagnosed glioblastoma multiforme (GBM) concomitantly with radiotherapy and then as maintenance treatment
- Refractory anaplastic astrocytoma, i.e., patients who have experienced disease progression on a drug regimen containing nitrosurea and procarbazine.

The sponsor received approval for their New Drug Application, NDA 21-029, for Temodar (temozolomide) Capsules, a New Molecular entity, on August 11, 1999. The most recently approved labeling dated October 19, 2006 contains a patient labeling (Patient Package Insert) and is posted on Drugs @ FDA.

The sponsor proposes a separate Patient Package Insert (PPI) for Temodar (b) (4) for Injection which is attached to a Pharmacist Information Sheet by perforation and is intended to be given to patients. DDOP has requested the Patient Labeling and Education Team review the proposed PPI.

2 MATERIAL REVIEWED

- DRAFT TEMODAR (temozolomide) for Injection Patient Package Insert (PPI) submitted by the sponsor on January 23, 2008.
- Currently approved TEMODAR (temozolomide) Capsules PPI, part of the Full Prescribing Information (FPI) approved on October 19, 2006.

3 DISCUSSION

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft PPI submitted by the sponsor has a Flesch Kinkaid grade level of 9.2, and a Flesch Reading Ease score of 53.8%. To enhance patient comprehension, materials should be written at a 6^{th} to 8^{th} grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8^{th} grade reading level). The draft PPI has an average of 13.9 words per sentence and 23.8% passive sentences.

4 CONCLUSIONS AND RECOMMENDATIONS

We are providing only preliminary comments about the PPI. We did not perform a line-by-line comparison of the PPI with the PI.

1. The sponsor should revise the proposed PPI. Although there are two different NDAs, one for the capsules and one for the powder for injection, both are included in the same PI. Just as there is one PI for the product, there should also be one PPI for all Temodar formulations.
2. The sponsor should state how they intend to distribute the PPI to patients. The proposed PPI for Temodar (b) (4) for Injection is attached to a Pharmacist Information Sheet by perforation and is intended to be given to patients. The approved PPI for Temodar

Capsules is also attached by perforation to a Pharmacist Information Sheet for the capsule formulation, and is intended to be given to patients. Ideally, all patients should receive the PPI to ensure that they have the important information to take Temodar safely. The sponsor should clarify whether the combined PPI will be attached to both Pharmacist Information Sheets by perforation and given to patients with either formulation.

3. The sponsor should improve the readability of the PPI document. To achieve improved readability, the sponsor should:

   - Use short, simple sentences. Avoid the use of technical terms or define them in patient friendly terms first, and include the technical term in parentheses.
   - Use active voice throughout.
   - Use cognitive accessibility principles such as "chunking" for comprehensibility. Chunking[1] allows people to access and retrieve information more readily. (The chunking principle involves classifying items into groups to avoid information overload.
   - Although not required for Patient Information, we recommend a question–and-answer format as specified in the Medication Guide Regulations (21 CFR 208.20) for all FDA approved patient labeling. This provides for consistency across patient labeling and ease of conversion to a Medication Guide if it becomes necessary.
   - Demonstrate good principles of type-size and design by using at least a 10-point font, and not using all upper case letters in the text. Use techniques such as bolded font, underlining, or placing text in boxes to call attention to important information.

     In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We recommend that the sponsor reformat the PPI document using on of the fonts listed above.
   - Demonstrate good principles of page layout and design by left justifying the margins and using ample white space throughout the document.

4. Information about birth defects should be addressed at the top of the PPI in a section called, "What is the most important information I should know about Temodar?" See the November 2007 OSE review of the PPI for Nexavar for an example of a PPI that is addressed in this way. You may reference this section in "What should I avoid while taking Temodar?"

5. Breast feeding language should be moved from the section "What should I avoid while taking Temodar?" to the section "What should I tell my doctor before taking Temodar?"

6. Serious side effects should be listed before common side effects in the section "What are the possible side effects of Temodar.

7. Add the following statement to the end of the section, "What are the possible side effects of TRADENAME?":

   > Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

   This verbatim statement is required for all Medication Guides effective January 2008 (see 21 CFR 208.20 (b)(7)(iii); also see Interim Final Rule, *Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products* in Federal Register Vol. 73, No.

2, p.402-404, 1/3/2008). Although not required for voluntary PPIs like Temodar, we recommend adding this language to all FDA-approved patient labeling for consistency.

8. Revise the section name "What are the possible or reasonably likely side effects of Temodar?" to "What are the possible side effects of Temodar?"
9. Add a section called "How should I store Temodar Capsules?" after the section "What are the possible side effects of Temodar?"
10. Revise the name of the section "General information about the use of prescription drug products" to say "General information about Temodar."
11. Add the section "What are the ingredients in Temodar?" after the section "General information about Temodar."

Please let us know if you have any questions. We will be happy to review a revised, patient-friendly PPI that includes information for both Temodar formulations.

[1] Gobet, F, Lane, PC, Croker, S, Cheng PC, Jones G, Oliver I, & Pine JM. Chunking mechanisms in human learning. *Trends in Cognitive Sciences 2001 5(6) 236-243*

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/s/

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10/22/2008 03:15:23 PM
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