

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

***22-277***

**APPROVAL LETTER**



NDA 22-277

**NDA APPROVAL**

Schering Corporation  
Attention: Penelope Giles, Ph.D.  
Senior Director, Global Regulatory Affairs  
2000 Galloping Hill Road  
Kenilworth, NJ 07033

Dear Dr. Giles:

Please refer to your new drug application (NDA) dated January 23, 2008, received January 24, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Temodar (Temozolomide) for Injection 100 mg/vial.

We acknowledge receipt of your submissions dated May 16, 22, August 22, September 24, October 2, 16, 17, November 4, 14, December 4, 23, 2008, and February 24, 2009.

The December 23, 2008, submission constituted a complete response to our November 24, 2008, action letter.

This new drug application provides for the use of Temodar (Temozolomide) for Injection 100 mg/vial for the treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment and also for the treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

#### **REQUIRED PEDIATRIC ASSESSMENTS**

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

Because this drug product for these indications has an orphan drug designation, you are exempt from this requirement.

## POSTMARKETING REQUIREMENTS UNDER 505 (o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of intravenous exposure to (b) (4) impurities, (b) (4) at levels that exceed those present in previous clinical and non-clinical formulations. The submitted oral toxicity study in rats of temozolomide spiked with enhanced levels of (b) (4) (Study No. 03451), relies on the unknown bioavailability of (b) (4) administered by this route and therefore does not fully qualify the current specifications for (b) (4) proposed for drug substance and drug product, respectively. These impurities may be associated with clinically significant toxicities when administered intravenously.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct a study.

1. Perform a rodent bridging study comparing the toxicity of temozolomide alone with temozolomide spiked with (b) (4). The study should mimic a single cycle of the approved clinical schedule (intravenously daily x 5 every 28 days) and utilize concentrations of (b) (4) that are  $\geq$  (b) (4) to adequately qualify these impurities at levels proposed in the current specifications for drug substance and drug product.

The timetable you submitted on February 20, 2009, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	March 9, 2009
Study Start Date:	March 9, 2009
Final Report Submission:	December 31, 2009

We acknowledge that you submitted the draft protocol to the NDA 22-277 on December 23, 2008. The draft protocol is acceptable. Submit the final protocol to your IND 68,395, with a cross-reference letter to this NDA 22-277. Submit all final report(s) to your NDA. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing requirement as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

## **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling (text for the package insert, text for the pharmacist information sheet, text for the patient package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, “SPL for approved NDA 22-277.”

## **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 22-277.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

## PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling.

To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see [www.fda.gov/cder/ddmac](http://www.fda.gov/cder/ddmac)

## LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch  
Food and Drug Administration  
Suite 12B05  
5600 Fishers Lane  
Rockville, MD 20857

If you have any questions, call Paul Zimmerman, Regulatory Project Manager, at 301-796-1489.

Sincerely,

*{See appended electronic signature page}*

Robert Justice, MD  
Director  
Division of Drug Oncology Products  
Office of Oncology Drug Products  
Office of New Drugs  
Center for Drug Evaluation and Research

Enclosure

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Robert Justice  
2/27/2009 05:45:47 PM