

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-277

SUMMARY REVIEW

Division Director Review of an NDA Complete Response

NDA 22-277

Drug: Temodar (temozolomide) for Injection, 100 mg/vial

Applicant: Schering Corporation

Date: February 27, 2009

This application for an intravenous formulation of temozolomide based on a study demonstrating bioequivalence to the approved oral formulation was originally submitted on January 24, 2008 (see the Division Director Summary Review of November 24, 2008). The complete response letter included the following deficiencies.

During a recent inspection of the Schering Plough (Brinny) Co. manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Additional information is needed to address several issues pertinent to clarifying the safety or efficacy of this product. We request that you propose studies and/or clinical trials, or include this information in your Complete Response, to address the following issues:

Perform a rodent bridging study comparing the toxicity of temozolomide alone with temozolomide spiked with (b) (4) [redacted]. 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) [redacted] which exceed (b) (4) [redacted] respectively, to adequately qualify these impurities at levels proposed in the current specifications for drug substance and drug product.

The applicant submitted a complete response to the action letter on December 23, 2008.

Chemistry Review

In a memorandum dated February 18, 2009, the CMC reviewers recommended approval, noted that the Office of Compliance issued an overall acceptable recommendation on January 8, 2009, and stated that there are currently no outstanding CMC deficiencies.

Pharmacology/Toxicology

The Pharmacology/Toxicology Review and Evaluation dated February 23, 2009 made the following recommendation on approvability.

The submitted nonclinical studies evaluated in the Pharmacology/Toxicology review of the original NDA submission adequately support the use of temozolomide (Temodar™) for the treatment of newly diagnosed glioblastoma multiforme (GBM) concomitantly with radiotherapy and as maintenance therapy and in the treatment of refractory anaplastic astrocytoma.

The review stated that “The current submission includes a draft protocol for a bridging study of temozolomide spiked with (b) (4) administered intravenously to rats. This protocol is reviewed herein and has been deemed acceptable.”

Conclusion

The applicant has adequately addressed the outstanding deficiencies in the complete response.

Regulatory Action

Approval

Recommendation for Postmarketing Studies

The rodent bridging study will be a postmarketing study requirement.

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

Robert Justice
2/27/2009 05:34:11 PM
MEDICAL OFFICER

Summary Review for Regulatory Action

Date	November 24, 2008
From	Robert L. Justice, M.D., M.S.
Subject	Division Director Summary Review
NDA/BLA # Supplement #	22-277
Applicant Name	Schering Corporation
Date of Submission	January 24, 2008
PDUFA Goal Date	November 24, 2008
Proprietary Name / Established (USAN) Name	Temodar for Injection/ temozolomide
Dosage Forms / Strength	Lyophilized powder/100 mg vial
Proposed Indication(s)	<ol style="list-style-type: none"> 1. TEMODAR® (temozolomide) is indicated for the treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment. 2. TEMODAR is indicated for the treatment of adult patients with refractory anaplastic astrocytoma, ie, patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine.
Action/Recommended Action for NME:	<i>Complete Response</i>

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	X
Statistical Review	N/A
Pharmacology Toxicology Review	X
CMC Review/OBP Review	X
Microbiology Review	X
Clinical Pharmacology Review	X
DDMAC	X
DSI	X
CDTL Review	X
OSE/DMEPA	X
OSE/DDRE	N/A
OSE/DRISK	X
Other: SEALD	X

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

DMETS=Division of Medication Errors and Technical Support

DSI=Division of Scientific Investigations

DDRE= Division of Drug Risk Evaluation

DSRCS=Division of Surveillance, Research, and Communication Support

CDTL=Cross-Discipline Team Leader

Signatory Authority Review

1. Introduction

This new drug application seeks approval of a new dosage form of Temodar. TEMODAR® (temozolomide) Capsules are indicated for the treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment and for the treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine. The new dosage form, Temodar (temozolomide) for Injection, is intended for patients who cannot take the capsules because of difficulty swallowing or because of nausea and vomiting. This review will summarize the recommendations of all disciplines involved in the review of the application.

2. Background

In previous meetings with the FDA it was agreed that in lieu of clinical studies, strict bioequivalence of the IV and oral formulations of temozolamide would need to be established for both maximum observed plasma drug concentration (C_{max}) and area under the plasma concentration-time curve (AUC) for both temolozamide and the active metabolite, MTIC. The applicant submitted reports on a pilot study used to determine the intravenous regimen and a bioequivalence study that demonstrated that Temodar for Injection administered intravenously over 90 minutes is bioequivalent to Temodar Capsules.

3. CMC/Device

The initial Chemistry Review made the following recommendation.

From the perspective of chemistry, manufacturing, and controls, this NDA is recommended for approval, pending an overall acceptable recommendation from the Office of Compliance.

The CMC reviewer's revisions of the package insert, patient information, and SPL Drug Listing Data Element, are included. These revisions were accepted by the applicant. Amendment 0007, October 17, 2008 contained the suggested corrections to the label. The corrections to the carton label and the vial label were conveyed to the applicant on October 30, 2008. The applicant's response to the CMC reviewer's and the DMEPA reviewer's final corrections is satisfactory. The responses were received as e-mail on November 12, 2008.

The CMC reviewer found that the acceptance criteria of NMT ^{(b) (4)} for ^{(b) (4)} impurity in the drug substance and ^{(b) (4)} of NMT ^{(b) (4)} in the drug product exceeds the

recommended ICH Q3A and ICH Q3B qualification thresholds. During the NDA review, it was determined by the Pharmacology-Toxicology reviewer (Dr. H. Rosenfeldt) that the (b) (4) impurities (b) (4) were not adequately qualified. The Pharmacology-Toxicology discipline did not find the submitted toxicity studies adequate to qualify these (b) (4) impurities. The (b) (4) impurities needed to be qualified, according to the toxicity studies recommended by the Division of Drug Oncology Pharmacology-Toxicology review team. The qualification of these (b) (4) impurities was deferred as a Pharmacology-Toxicology Phase IV commitment. Please refer to the Pharmacology-Toxicology review for further information.

The final CMC recommendation on 11/24/08 noted the following.

The Office of Compliance issued an overall withhold recommendation for this application on 20-NOV-2008. Accordingly, from a CMC perspective, approval of NDA 22-277 cannot be recommended until any related deficiencies are resolved.

The Microbiology Review recommended approval on the basis of product quality microbiology.

I concur with the final CMC recommendation that the application cannot be approved until the manufacturing site deficiencies identified by the Office of Compliance have been corrected.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Review and Evaluation provided the following recommendations.

A. Recommendation on approvability

The submitted nonclinical studies adequately support the use of temozolomide (Temodar™) for the treatment of newly diagnosed glioblastoma multiforme (GBM) concomitantly with radiotherapy and as maintenance therapy and in the treatment of refractory anaplastic astrocytoma.

B. Recommendation for nonclinical studies

Additional nonclinical studies are necessary given that clinical and nonclinical studies submitted with this NDA do not directly test intravenous exposures of impurities, (b) (4) at levels that are comparable to the proposed clinical formulation. The sponsor has submitted one oral toxicity study in rats of temozolomide spiked with enhanced levels of (b) (4), but this study relies on the unknown bioavailability of (b) (4) administered by this route.

The sponsor should directly test the toxicity profile of intravenous temozolomide spiked with (b) (4). The sponsor should conduct a rodent bridging study comparing the toxicity of temozolomide alone with temozolomide spiked with (b) (4).

This study should mimic a single cycle of the approved clinical schedule (daily x5 every 28 days) and utilize concentrations of (b) (4) which exceed (b) (4) respectively, to adequately qualify these impurities at levels proposed in the current specifications for drug substance and drug product, respectively.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that the applicant should conduct a rodent bridging study comparing the toxicity of temozolomide alone with temozolomide spiked with (b) (4). This should be a post-marketing study requirement if the study is not conducted prior to approval.

5. Clinical Pharmacology/Biopharmaceutics

The basis for this new drug application is provided in the Executive Summary of the Clinical Pharmacology Review.

The Applicant seeks approval of a New Drug Application (NDA 22-277/N-000) for TEMODAR (b) (4) for Injection under Section 505b(1) of the Food, Drug, and Cosmetic Act (21 CFR 314.50) for the same indications and at the same dosage and regimens as for the approved oral capsule drug product. TEMODAR (b) (4) for Injection is to be administered intravenously (IV) over a 1.5-hour infusion at the same dosage and regimen as for the oral capsule product.

The Applicant did not conduct any efficacy and/or safety clinical studies in support of TEMODAR (b) (4) for Injection. The decision for the approval of this NDA submission is solely based on the results obtained from the pivotal bioequivalence Study P02467.

The pivotal bioequivalence Study P02467 compared the exposure of the prodrug, temozolomide, and its cytotoxic alkylating active metabolite, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC) following a single dose of temozolomide (150 mg/m²/day) administered either as a 1.5- hour infusion of the new IV formulation (Test) or as the approved oral capsule formulation (Reference) in 22 subjects with primary CNS malignancies in a two-period, crossover design. According the FDA Guidance for Industry on the BA and BE Studies for Orally Administered Drug Products — General Considerations (<http://www.fda.gov/cder/guidance/5356fnl.pdf>), the new IV dosage form infused over 1.5 hours was found to be bioequivalent to the approved oral formulation (as capsules) at the same dosage and regimen (150 mg/m²/day) with respect to C_{max} and AUC_{inf} for both temozolomide and MTIC based on the data from 21 subjects (one subject was an outlier and was removed from the data analysis). The 90% CIs estimated for the geometric mean C_{max} and AUC_{inf} ratios (IV/PO) were within the bioequivalence range of 80- 125% for both temozolomide and MTIC.

In addition, the Applicant revised the current package insert for TEMODAR and submitted it in the PLR format (see Appendix 4.1).

The review made the following recommendation.

TEMODAR (b) (4) for Injection infused over 1.5 hours is bioequivalent to TEMODAR Oral Capsules at the same dosage and regimen (150 mg/m²/day). Thus, NDA 22-277/N-000 submitted for TEMODAR (b) (4) for Injection is acceptable from the clinical pharmacology perspective. Please forward the detailed OCP Labeling Recommendations as outlined under Section 3 of the review (pp. 20-22) to the Applicant.

The CDTL review was also provided by Clinical Pharmacology and recommended approval. However, at the time the review was completed the results of the manufacturing inspection were not available.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that TEMODAR for Injection infused over 1.5 hours is bioequivalent to TEMODAR Oral Capsules at the same dosage and regimen. However, the manufacturing site inspection deficiencies preclude approval at this time.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

See the Clinical Pharmacology/Biopharmaceutics Review for a detailed summary of the clinical program. The Clinical Review recommended approval and the Executive Summary provides the following summary.

An intravenous (IV) formulation of TMZ was developed as an alternative formulation to oral TMZ for patients who are unable to swallow TMZ, such as those with nausea and vomiting associated with increased intracranial pressure, or patients unable to swallow capsules.

In meetings with the FDA it was determined that strict bioequivalence (BE) of the IV and oral formulations of TMZ needed to be established for both maximum observed plasma drug concentration (C_{max}) and area under the plasma concentration-time curve (AUC) for both TMZ and the active metabolite, MTIC.

Two studies, a bioavailability (BA) study (P02466) in 13 subjects, and a BE study (P02467) in 22 subjects, were conducted in support of this application. Both studies were designed as open label, fixed-sequence/crossover studies with administration of TMZ for 5 consecutive days out of a 28-day cycle to subjects with primary central nervous system (CNS) malignancies (excluding primary CNS lymphoma). Patients either had or had not received prior chemotherapy.

Subjects were randomized to receive IV TMZ on Day 3 and oral on Day 4 or oral on Day 3 and IV on Day 4 of a 5 day TMZ treatment regimen according to a random code. Thus, TMZ was administered orally for 4 days with only one day administered by the IV route. Data from the pilot study P02466 was used to optimize the IV infusion duration and sample size for the pivotal BE trial. The two studies were conducted according to Good Clinical Practice.

In the pilot study, the IV formulation met the criteria for BE, as measured by AUC. In the pivotal study, the IV formulation met the criteria for BE, as compared to the oral formulation, with the 90% confidence intervals (CIs) of the treatment AUC and Cmax ratio estimates for both TMZ and MTIC within the bioequivalence range of 80% to 125%.

These two TMZ studies did not raise any new safety concerns and local tolerability was acceptable. Efficacy data for the IV TMZ formulation was not collected.

8. Safety

The Clinical Review provides the following conclusions regarding safety of TEMODAR for Injection.

The treatment-emergent adverse events (TEAEs) observed in the pilot (P02466) and the pivotal (P02467) studies were consistent with those reported previously with oral TMZ in brain tumor patients, with the exception of local reactions described above. No new toxicology concerns were raised by these studies, and the risk to benefit was considered favorable for the IV formulation...

Side effects known to be associated with temozolomide were common in this study: fatigue, nausea, vomiting, anorexia, headache, constipation, rash, convulsions, diarrhea, leucopenia and thrombocytopenia. Other side effects noted included alopecia, blurred vision, and stomatitis.

9. Advisory Committee Meeting

This application was not referred to review by ODAC because bioequivalence of two dosage forms was clearly demonstrated and there were no major new safety issues.

10. Pediatrics

Temodar has orphan drug exclusivity for the approved indications.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

Agreement has been reached with the applicant on the package insert, the pharmacist information sheet, the patient package insert, and carton and container labels.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: *Complete response based on the manufacturing site deficiencies identified by the Office of Compliance.*
- Risk Benefit Assessment: *Pending correction of the manufacturing site deficiencies, the risk:benefit assessment is acceptable. Except for reversible local toxicities associated with intravenous administration, the toxicity profile appears to be similar to that of Temodar Capsules.*
- Recommendation for Postmarketing Risk Management Activities: *Routine post-marketing surveillance.*
- Recommendation for other Postmarketing Studies: *The complete response letter requests that the applicant propose a rodent bridging study to qualify (b) (4) impurities. If the study results are not submitted with the complete response, the study should be a post-marketing requirement.*

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/s/

Robert Justice
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MEDICAL OFFICER