CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-277

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review
Amendment

Date	11/10/2008.
From	Brian Booth, Deputy Director DCP 5
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	22-277 000
Applicant	Schering Plough
Date of Submission	1/23/2008
PDUFA Goal Date	
Proprietary Name / Established (USAN) names	TEMODAR for injection/temozolomide
Dosage forms / Strength	One hundred mg of lyophilized powder for intravenous infusion
Proposed Indication(s)	1. indicated for the treatment in adult patients of newly diagnosed gliobastoma multiforme in combination with radiotherapy and then as maintenance treatment. 2. indicated for the treatment of adult patients with refractory anaplastic astrocytoma i.e. patients who have experienced disease progression on a drug regimen containing nitrosurea and procarbazine.
Recommended:	*Approval*

1. Purpose of this amendment

The purpose of this amendment is to correct a couple of typos, and to move the summary of microbiological review to the CMC section. It was errantly place in a section reserved for antibiotics.

2. Introduction

Temodar capsules for the treatment of glioblastoma multiforme and anaplastic astrocytoma were approved for the US market in 1999. The applicant submitted TEMODAR for injection to IND 68395 in order to develop this new formulation for patients who are unable to take capsules. During the course of development, the Agency agreed with the applicant that if bioequivalence of the parent and metabolite MTIC was established between the capsule and intravenous formulations, no study of the safety and effectiveness would be needed. The applicant submitted an NDA (N22-277) based on a pivotal bioequivalence study, as well as studies on nonclinical pharmacology toxicology, chemistry manufacturing and controls, and microbiology for the intravenous product.

3. Background

Temodar capsules were approved for the treatment of glioblastome multiforme and anaplastic astrocytoma in 1999. The applicant submitted an IND for an intravenous formulation in 2003. The Agency agreed with the applicant, that bioequivalence of the two products would be sufficient to demonstrate acceptability of the intravenous product for the same indications. Both the oral and intravenous products contain the same active moiety, temozolomide, which rapidly undergoes non-enzymatic conversion to yield the active metabolite MTIC. The same effectiveness and safety profiles would be expected for the intravenous formulation as the capsule formulation, if the Cmax and AUC of the parent and the active metabolite meet the bioequivalence criteria compared to the oral formulation. Other issues of importance would be any novel impurities in the powder formulation, which might raise toxicological issues, as well as the typical CMC and microbiology issues associated with an intravenous product. Each of the clinical pharmacology, nonclinical pharmacology and toxicology, and the chemistry and microbiological issues are addressed below.

4. CMC

The pro-drug temozolomide is a cytotoxic alkylation agent related to a series of I midazotetrazinones. At neutral and alkaline pH, temozolomide is rapidly hydrolyzed to the active 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide (MTIC). There have not been any major changes in the temozolomide manufacturing process, and since the approval of the NDA 21-029, the drug substance manufacturing site has remained the same.

The levels of drug related impurities and degradation products, except for the process impurity (b) (4) in the drug substance are based on the ICH Q3A recommendations. The (b) (4) impurity exceeded the qualification threshold and was consulted to the Pharmacology-Toxicology reviewer for assessment of qualification. There is no structural alert genotoxic impurity in the drug substance, nor was any genotoxicity observed.

The drug substance specifications are the same as in the approved NDA 21-029 with additional tests for sterility and bacterial endotoxins.

The drug product is formulated as a lyophilized powder and contains temozolomide (100 mg), Mannitol, USP (600 mg), L-threonine, USP (160 mg), Polysorbate 80, NF (120mg), Sodium Citrate Dihydrate, USP (235.2 mg) and Hydrochloric acid, NF (160.0 mg). Prior to administration, the lyophilized powder is to be reconstituted with (b) (4) of Sterile Water for Injection, USP to achieve a label strength of 2.5 mg/mL. Stability studies on the reconstituted product showed that it should be used within 14 hours, including the infusion time, with the provision that the increase of up to (b) (4) for the level of the degradation product (b) (4) be qualified. The reconstituted solution should be clear and essentially free of visible particles.

This formulation contains conventional excipients that have already been used in approved drug products for injection. The specifications for the excipients of the formulation included tests for Bacterial Endotoxins and Microbial Limits.

Temozolomide is susceptible to hydrolysis at alkaline pH. Therefore, the lyophilized formulation needs to be protected from moisture and contained at a stable pH.

The lyophilized drug product is for intravenous administration, consequently (b) (4) are required to be qualified for the intravenous route. The Pharmacology-Toxicology review team was alerted to the proposed specifications for both (b) (4) and the applicant made a Phase IV (Pharmcology-Toxicology) commitment to perform additional qualification studies on these (b) (4) impurities.

Temozolomide for Injection is not sensitive to light as demonstrated by the photostability studies. Therefore, protection from light is not necessary and a clear vial is appropriate.

Therefore, the requested 36 months shelf life at refrigerated conditions of 2°C-8°C (36°F-46°F) is acceptable.

Temodar was also assessed for microbiological product quality. The product is a sterile, lyophilized powder for injection. The product was assessed for container closure/package integrity, (b) (4) process, (b) (4) manufacturing process, control of drug product specifications and stability. Each of these parameters was deemed adequate. The stability data supported a shelf life of 36 months for a refrigerated product. The first (b) (4) production batches of the drug product will be placed on stability. Thereafter, (b) (4) will be placed on stability annually.

Container Closure integrity – Sterility testing will be performed at 0, 24 and 36 months. Endotoxin testing will be performed at 0, 24 and 36 months. The low pH of the reconstituted solution makes microbial proliferation extremely unlikely even at room temperature. Therefore, the post-reconstitution holding time is acceptable. There are no outstanding deficiencies and no postmarketing commitments are recommended.

The CMC and microbiology review teams recommend approval and no postmarketing commitments are recommended.

5. Nonclinical Pharmacology/Toxicology

Temozolomide toxicity in mice, rats, and dogs occurred in hematopoietic organs, male reproductive organs, and the retina at doses less than or equal to 125 mg/m^2, 0.63 times the maximum recommended clinical dose.. Temozolomide hematopoietic toxicity was manifested as white and red blood cell decreases in both rats and dogs, although this toxicity improved after the first cycle of treatment. At doses greater than 125 mg/m^2 temozolomide toxicity also occurred in the gastrointestinal tract, liver, kidney, brain and lung.

Primary clinical signs in rats and dogs were similar and indicated gastrointestinal toxicity and carcinogenesis. Primary clinical signs in rats also indicated neurological, kidney, and eye toxicities. These clinical signs included cold to touch, hunched posture, limited use of swollen limbs, swollen thoracic/cervical/abdominal/inguinal regions, thin appearance, convulsion, red urine, mucoid feces, corneal abrasions, exopthalmus, eye ulceration and hair loss. Tissue

masses in cervical and abdominal regions were observed at doses ≥ 50 mg/m^2. Primary clinical signs in dogs indicated anemia in addition to gastrointestinal toxicity and carcinogenesis. These clinical signs included vomiting, fecal changes, pale gums, diminished appetite, and hypoactivity. Higher doses of temozolomide caused dehydration, anorexia, and prostration. One male dosed with 125 mg/m^2 temozolomide had a tissue mass in the scrotum.

Histopathological changes in rats and dogs treated with temozolomide included signs of necrosis, hemorrhage and atrophy in the gastrointestinal tract, liver and kidney necrosis, and bone marrow depletion. Pathology studies in rats and dogs also noted a low incidence of hemorrhage and degeneration of the retina at doses of 125 mg/m^2 or greater when administered on a daily x5 schedule.

Intravenous administration of temozolomide does not significantly change the range of end-organ temozolomide toxicities when compared to oral administration. However, the intravenous formulation of temozolomide did produce mild to moderate venous irritation in rats and rabbits. Much of this local irritation correlated with the intravenous formulation as opposed to temozolomide itself when compared to saline control.

Temozolimide is a mutagen and a clastogen. Temozolomide mutagenicity was demonstrated with *in vitro* reverse mutation (Ames) assays in bacteria and temozolomide clastogenicity in mammalian cells was demonstrated with assays using human peripheral blood lymphocytes.

Temozolomide is carcinogenic in rats at doses greater than 25 mg/m^2. Tumor masses developed in rats treated with greater than 50 mg/m^2 temozolomide after three months of treatment. Tumor masses developed in rats treated with greater than 25 mg/m^2 temozolomide after six months of treatment. At 25 – 50 mg/m^2 rats developed mammary carcinomas in both sexes, while rats treated with temozolomide doses greater than 125 mg/m^2 developed a wide spectrum of neoplasms, including mammary carcinomas, fibrosarcomas of the heart, eye, seminal vesicles, salivary glands, abdominal cavity, uterus, and prostate, carcinomas of the seminal vesicles, schwannomas of the heart, optic nerve, and harderian gland, and adenomas of the skin, lung, pituitary, and thyroid gland.

Temozolomide impairs male fertility in rats and dogs via increases in syncytial cells/immature sperm, and testicular atrophy. Testicular atrophy occurred at doses equal to or greater than 50 mg/m^2 in rats and 125 mg/m^2 in dogs.

Temozolomide is teratogenic and embryotoxic. Five consecutive days of oral temozolomide administration of 75 and 150 mg/m^2 (0.38 and 0.75 times the highest recommended human dose) in rats and rabbits, respectively during the period of organogenesis caused numerous malformations of the external and internal soft tissues and skeleton in both species. A dose of 150 mg/m^2 caused embryolethality in rats and rabbits as indicated by increased resorptions.

Specifications for an impurity, (b) (4) and a degradant, (b) (4) have been set outside the threshold for qualification. The drug substance specification for (b) (4) has been set at (b) (4) However, this process impurity has only been qualified to (b) (4) (Batch #7812-090) for intravenous administration. The drug product specification for (b) (4) has been set at (b) (4) with

additional degradant increases of up to (b) (4) following reconstitution; this degradant has only been qualified to (b) (4) when administered intravenously.

The nonclinical pharmacology and toxicology review team recommend approval of TEMODAR for injection. One postmarketing requirement to address potential toxicity associated with (b) (4) is proposed.

6. Clinical Pharmacology/Biopharmaceutics

Temozolomide is an imidazole tetrazine derivative of the alkylating agent dacarbazine. Temozolomide is not directly active but undergoes rapid, spontaneous, non-enzymatic conversion at physiologic pH to the cytotoxic compound, monomethyl triazeno imidazole carboxamide (MTIC). Both temozolomide and dacarbazine are prodrugs of MTIC. Unlike dacarbazine, temozolomide does not require metabolic activation by the cytochrome P450. The cytotoxicity of MTIC is primarily due to the alkylation (methylation) of DNA, mainly at the O_6 position of guanine. The O_6-methylguanine formation inhibits DNA replication through errant repair of the methyl adduct which eventually causes cell death via stimulation of p53 and apoptosis.

The approved dosage for refractory anaplastic astrocytoma is 150 mg/m^2/day orally once daily for 5 consecutive days, repeated every 28 days. Patients with newly diagnosed glioblastoma multiforme are to be administered temozolomide orally at 75 mg/m^2 once daily for 42 days concomitantly with focal radiotherapy, followed by maintenance doses of 150 mg/m^2/day for 5 days of a 28-day cycle for 6 cycles. The overall clinical pharmacology information on TEMODAR Oral Capsules was addressed in the original NDA 21-029 submission dated 12-Aug-1998. The most common non-hematological adverse events associated with TEMODAR were nausea and vomiting. These effects were usually mild to moderate (grade 1 to 2). The incidence of severe nausea and vomiting is around 4% each.

In this application, the applicant has developed a new intravenous (IV) formulation of temozolomide (Viz., "**TEMODAR for Injection**") to be used in patients who cannot swallow the oral capsules (e.g., patients with dysphagia) and in patients who cannot tolerate the oral capsules for other reasons that may occur in association with glioma (e.g., nausea and vomiting). TEMODAR for Injection contains 100 mg/vial of lyophilized powder which is to be reconstituted with Sterile Water for Injection before use. The reconstituted product contains 2.5 mg/mL of temozolomide. TEMODAR for Injection is to be used for the same indications at the same dosage and regimen as for the oral capsules.

In support of the current NDA 22-277, for TEMODAR for Injection, the applicant conducted two studies: a pilot study (Study PO2466) to determine an adequate dosing regimen, and a pivotal bioequivalence study (Study P02467) to compare the exposure of temozolomide and its active metabolite, MTIC after a 1.5-hour IV infusion of temozolomide to that after the oral capsules.

The pilot study (Study P02466) was conducted in 13 patients with primary CNS malignancies. On Days 1, 2, and 5, patients received 200 mg/m2/day of temozolomide orally once daily for 5 days of a 28-day treatment cycle. On Days 3 and 4, patients were randomized to receive a single 150 mg/m2/day dose of temozolomide either orally on one day or as a 1-hour IV infusion on the other day. The results of this study showed that the 90% CI estimates for the geometric mean AUC_{inf} ratio (IV/PO) for temozolomide fell within of the acceptable bioequivalence range of 80-125%. However, the corresponding 90% CI estimates for the geometric mean C_{max} ratio (IV/PO) fall outside bioequivalence range (90% CI=100-131%). Based on a population PK analysis of this study and the subsequent trial simulations of the data obtained in this study, it was demonstrated that a 1.5-hour IV infusion of temozolomide would have a comparable C_{max} value to the oral formulation (see Pharmacometric Review, pp. 35). Therefore, the 1.5-hour IV infusion was used in the pivotal bioequivalence Study P02467.

Study P02467 was a Phase 1, randomized, multi-center, open-label, two-period, crossover study in 22 patients with primary CNS malignancies. On Days 1, 2, and 5, patients received 200 mg/m2/day of temozolomide once daily for 5 days of each 28-day treatment cycle. On Days 3 and 4, patients were randomized to receive a single 150 mg/m2/day dose of temozolomide either as a 1.5-hour intravenous infusion (Test) on one day, or as the approved oral capsule formulation (Reference) on the other day. Based on the data from 21 subjects, the results of this study demonstrated that TEMODAR for Injection infused over 1.5 hours met the bioequivalence criteria when compared to the approved oral capsule formulation at the same dosage and regimen (150 mg/m2/day) with respect to C_{max} and AUC_{inf} for both temozolomide and MTIC. 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. An inspection of the study site by the Division of Scientific Investigations revealed some minor violations, but no 483s were issued and study was deemed adequate (vida infra).

The application is acceptable from the clinical pharmacology perspective, and no postmarketing commitments recommended.

7. Clinical Microbiology

NA

8. Clinical/Statistical- Efficacy

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 (Cmax) 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. The reviewer recommends approval, and no postmarketing commitments are proposed.

9. Safety

No trial to assess the safety profile of TEMODAR for injection was conducted. The toxicity profile of the bioequivalence study is discussed briefly discussed in the Clinical Pharmacology section.

10. Advisory Committee Meeting

NA

11. Pediatrics

NA

12. Other Relevant Regulatory Issues

DSI Review

The Division of Scientific Investigations conducted an audit of records of clinical conduct for two clinical investigator sites and the analytical portion of the following multi-center bioequivalence study:

Protocol P02467: SCH 52365: A Bioequivalence Trial of Oral and Intravenously Administered Temozolomide in Patients with Primary CNS Malignancies. The review division requested that DSI audit clinical study records for two of the clinical sites that participated in this multi-center study. The following clinical sites were inspected:

- Max Schwarz, M.D. Centre for Clinical Studies, Melbourne, Australia
- Maria G. Pallota, M.D. Hospital Italiano-Sociedad Italiana De Beneficencia en Buenos Aires, Buenos Aires, Argentina

The analytical portion of Study P02467 was conducted at (b) (4) (now known as (b) (4) . Following the inspections at the clinical sites (Dr. Schwarz, 6/16-20/08 and Dr. Pallota, 6/23-27/08), no significant deficiencies were found. Form 483 was not issued at either site. Following the inspection of (b) (4) (b) (4) , Form 483 was issued. Our review of the objectionable findings follows.

Analytical Site: (b) (4)

1. The incurred sample reproducibility (ISR) criterion supplied by the sponsor for Study P02467 does not reflect the performance of the analytical method.

As required by the sponsor, (b) (4) reassayed 10% of the study samples to evaluate ISR. Schering's criteria stated that incurred sample repeats are considered acceptable if the original and reassay values from (b) (4) of the repeated samples have a relative percent difference (RPD) (b) (4) However, an ISR criterion of RPD (b) (4) is liberal considering that the assay performance during method validation and study conduct was tight (≤10% CV for temozolomide). Although the sponsor needs to have an ISR criterion that is reflective of assay performance, a majority of the samples reanalyzed in the study were reproducible in that only 19% of the incurred sample repeats for temozolomide, and 25% for the MTIC metabolite, had an RPD that exceeded 20%.

2. An investigation of the high failure rate of analytical runs in Study P02467T (temozolomide) was not conducted although 33% (5 of 15) of the runs failed to meet the acceptance criteria for standards or QCs.

Although there was no documentation to indicate that the high failure rate was evaluated, the firm claimed that they monitored the study conduct closely. The firm's current procedures require an investigation if more than (b) (4) of the total anticipated runs are rejected for a given study.

3. Failure to document all aspects of study conduct. For example: a. The lot of matrix used for the calibration standards in Studies P02467T (temozolomide) and P02467M (MTIC) was not documented at the time the calibration standards were prepared for each analytical run.

At the start of sample analysis, the firm identified a lot of matrix to be used in preparing freshly spiked calibration standards for each batch. Although there was no documentation on each day of spiking to confirm that the pre-identified lot Page 3 of 4 – NDA 22-277 Temodar (Temozolomide)(b) (4) for Injection was used, the analytical procedure forms did specify that human plasma should be used.

b. The analytical procedure for MTIC required that a maximum of (b) (4) samples be extracted at a time. There was no documentation to confirm that the procedure was followed or to identify the samples processed in each subset of samples in a run.

Small processing subsets were required due to stability concerns regarding the MTIC metabolite. Although the firm claimed that the procedure was followed, the source data does

not confirm which samples were processed together and whether a QC was included in each subset. However, one analyst processed all the samples in a run.

c. There was no documentation to confirm that the autosampler injection sequence was verified.

The firm claimed that the sample sequence was checked but not documented in writing.

With respect to items 3a-c, the firm needs to improve their documentation practices to confirm that all aspects of study conduct are carried out appropriately.

Conclusion:

Following the above inspections, DSI recommends that the clinical (Drs. Schwarz and Pallota) and analytical portions of Study P02476 be accepted for review.

DRISK Review

DRISK reviewed the draft TEMODAR (temozolomide) for Injection Patient Package Insert (PPI) submitted by the applicant, and the currently approved TEMODAR (temozolomide) Capsules PPI, part of the Full Prescribing Information (FPI) approved on October 19, 2006. (b) (4) DDOP has requested the Patient Labeling and Education Team review the proposed PPI.

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 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). The draft PPI has an average of 13.9 words per sentence and 23.8% passive sentences.

DRISK identified approximately a dozen items related to readability and discrepancies between the PPI and PI. These issues have been resolved during the labeling revisions conducted in the Division.

DMEPA Review

DMEPA reviewed the PI, carton and container labeling. 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. DMEPA has worked with the Division to address these labeling issues.

DDMAC Review

The DDMAC reviewer noted that not PPI was included in the submission. This has since been addressed. The DDMAC reviewer also recommended that the statement (b) (4) be retained, at least partly, in the highlights section of the label. This has been removed from the highlights, as the DIVISION felt it did not need to be in this section.

13. Labeling

TEMODAR for injection labeling is virtually complete. The DRISK reviewer highlighted several issues that needed resolution, including the need for (b) (4) and increased readability of the PI and especially the PPI. The DMEPA reviewer identified issues with respect to 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. These issues are virtually completely resolved via negotiation with the applicant.

14. Recommendations/Risk Benefit Assessment

The Division recommends NDA 22-277 for approval.

- Risk Benefit Assessment

The product is deemed to be bioequivalent to the oral (capsule) formulation. Therefore, the overall benefit to risk ratio is the same as for the capsule formulation, and is weighted in terms of benefit with respect to the indicated patient populations. The only new concern is the CMC/nonclinical pharmacology/toxicology identification of no-qualified levels of (b) (4). The nonclinical pharmacology/toxicology team recommends a postmarketing requirement to assess the safety of these impurities. The team concurs with this recommendation.

- Recommendation for Postmarketing Risk Management Activities

  NA

- Recommendation for other Postmarketing Study Requirement

1. The study should mimic a single cycle of the approved clinical schedule (daily x 5 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.

The timetable you submitted on November 10, 2008, states that you will conduct this trial according to the following timetable:

Protocol Submission:	January 9, 2009
Trial/Study Start Date:	by approximately March 2, 2009
Final Report Submission:	December 31, 2009

The clinical and nonclinical studies submitted with this NDA did not directly test intravenous exposures of (b) (4) impurities, (b) (4) at levels that are comparable to the proposed clinical formulation. 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. The postmarketing study proposed above could address these concerns.

- Recommended Comments to Applicant

NA

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/s/

Brian Booth
11/20/2008 02:47:14 PM
BIOPHARMACEUTICS