CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-277

MEDICAL REVIEW(S)

Application Type	NDA 22-277
Submission Number	N
Submission Code	000
Letter Date	1/23/08
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Reviewer Name	Martin H. Cohen, M.D.
Review Completion Date	June 1, 2008
Established Name	Temodar® Capsules, (b) (4) for Injection
Trade Name	Temozolomide
Therapeutic Class	Alkylating agent
Sponsor	Schering-Plough Research Inst.
Priority Designation	S

Dosage Form And Strengths

- TEMODAR® (temozolomide) is available in 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg capsules for oral administration.
- TEMODAR® (temozolomide) is available as 100 mg/vial powder for injection.

Formulation

Each capsule contains either 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, or 250 mg of temozolomide. The inactive ingredients for temozolomide capsules are: lactose anhydrous, colloidal silicon dioxide, sodium starch glycolate, tartaric acid, and stearic acid. The body of the capsules are made of gelatin, and are opaque white. The cap is also made of gelatin, and the colors vary based on the dosage strength. The capsule body and cap are imprinted with pharmaceutical branding ink, which contains shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, purified water, strong ammonia solution, potassium hydroxide, and ferric oxide.

TEMODAR 5 mg: The green cap contains gelatin, titanium dioxide, iron oxide yellow, sodium lauryl sulfate, and FD&C Blue #2.
TEMODAR 20 mg: The yellow cap contains gelatin, sodium lauryl sulfate, and iron oxide yellow.
TEMODAR 100 mg: The pink cap contains gelatin, titanium dioxide, sodium lauryl sulfate, and iron oxide red.
TEMODAR 140 mg: The blue cap contains gelatin, sodium lauryl sulfate, and FD&C Blue #2.
TEMODAR 180 mg: The orange cap contains gelatin, iron oxide red, iron oxide yellow, titanium dioxide, and sodium lauryl sulfate.

TEMODAR 250 mg: The white cap contains gelatin, titanium dioxide, and sodium lauryl sulfate.

Temodar (b) (4) for Injection
Each vial contains 100 mg of temozolomide lyophilized powder. The inactive ingredients for Temodar (b) (4) for Injection are: mannitol, L-threonine, polysorbate-80, sodium citrate dihydrate, and hydrochloric acid.

Dosing Regimen

Patients with newly diagnosed high grade glioma:
Concomitant Phase

Temozolomide is administered orally at 75 mg/m^2 daily for 42 days concomitant with radiotherapy (60Gy administered in 30 fractions) followed by (b) (4) temozolomide for 6 cycles. No dose reductions are recommended, however, dose interruptions may occur based on (b) (4). The temozolomide dose (b) (4) be continued throughout the 42 day concomitant period up to 49 days if all of the following conditions are met: absolute neutrophil count ≥ 1.5 x 10^9 /L platelet count ≥ 100 x10^9/L common toxicity criteria (CTC) non-hematological toxicity ≤Grade 1 (except for alopecia, nausea and vomiting). During treatment a complete blood count should be obtained weekly. Temozolomide dosing should be interrupted or discontinued during concomitant phase according to the hematological and non-hematological toxicity (b) (4)

(b) (4) Phase

Four weeks after completing the Temozolomide + RT phase, temozolomide is administered for an additional 6 cycles of (b) (4) treatment. Dosage in Cycle 1 (b) (4) is 150 mg/m^2 once daily for 5 days followed by 23 days without treatment. At the start of Cycle 2, the dose (b) escalated to 200 mg/m^2 , if the CTC non-hematologic toxicity for Cycle 1 is Grade ≤2 (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is ≥ 1.5 x 10^9/L, and the platelet count is ≥100 x 10^9/L. If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles. The dose remains at 200 mg/m^2 per day for the first 5 days of each subsequent cycle except if toxicity occurs.

Patients with recurrent and refractory high grade glioma

For adults the initial dose is 150 mg/m^2 orally once daily for 5 consecutive days per 28-day treatment cycle. For adult patients, if both the nadir and day of dosing (Day 29, Day 1 of next cycle) ANC are >1.5 x 10^9/L (1,500/μL) and both the nadir and Day 29, Day 1 of next cycle platelet counts are >100 x 10^9/L (100,000/μL), the temozolomide dose may be increased to 200 mg/m^2/day for 5 consecutive days per 28-day treatment cycle. During treatment, a complete blood count should be obtained on Day 22 (21 days after

the first dose) or within 48 hours of that day, and weekly until the ANC is above 1.5 x 10^9/L (1,500/μL) and the platelet count exceeds 100 x 10^9/L (100,000/μL). The next cycle of temozolomide should not be started until the ANC and platelet count exceed these levels. If the ANC falls to <1.0 x 10^9/L (1,000/μL) or the platelet count is <50 x 10^9/L (50,000/μL) during any cycle, the next cycle should be reduced by 50 mg/m^2, but not below 100 mg/m^2, the lowest recommended dose. Temozolomide therapy can be continued until disease progression, but optimum duration of therapy is not known.

INDICATIONS AND USAGE

Newly Diagnosed Glioblastoma Multiforme

TEMODAR® (temozolomide) is indicated for the treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment.

Refractory Anaplastic Astrocytoma

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.

Intended Population

See indication

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1. EXECUTIVE 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 (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.

1.1 Recommendation On Regulatory Action

The DODP medical reviewer recommends that the intravenous TMZ formulation be registered.

1.2 Recommendation On Postmarketing Actions

Continue post-marketing surveillance.

1.2.1 Risk Management Activity

Continue post-marketing surveillance of AE's

1.2.2 Required Phase 4 Commitments

No new phase 4 commitments are required.

1.2.3 Other Phase 4 Requests

None.

1.3 SUMMARY OF CLINICAL FINDINGS

1.3.1 Product Development Rationale

Temozolomide (TMZ, SCH 52365) is an orally administered cytotoxic alkylating agent that is a 3-methyl analog of mitozolomide, and is a pro-drug of the cytotoxic 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC). TMZ capsules have been licensed in over 80 countries (TMZ is licensed under the trade name Temodar® in the United States [US] and under Temodal® in the European Union [EU] and Japan). In the US, TMZ is approved for adult patients with newly diagnosed GBM concomitantly with radiotherapy (RT) and then as maintenance treatment, and for adult patients with refractory anaplastic astrocytoma (AA), ie, patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine. TMZ is currently approved in the EU for the treatment of patients with newly diagnosed glioblastoma multiforme (GBM) in a combination treatment with radiation and subsequently as monotherapy treatment, and malignant glioma, such as GBM or AA, showing recurrence or progression after standard therapy. In Japan, TMZ is licensed for adult subjects with malignant glioma. Outside of the EU, Japan, and the US, TMZ is also approved for metastatic melanoma in over 20 countries.

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.

On 01 APR 1999, Schering-Plough first proposed an IV TMZ development program to the FDA. This proposal included a bridging toxicology program, coupled with demonstration of bioequivalence (BE) of the IV and oral formulations of TMZ, in addition to a small clinical safety study. Over the years, additional communication followed where the Agency recommended that strict BE needed to be established for both maximum observed plasma drug concentration (Cmax) and area under the plasma concentration-time curve (AUC) and that the proposed toxicology program

was adequate (11 May 1999). On 20 May 1999, the Agency communicated that BE needed to be established for both TMZ and the active metabolite, MTIC. Although there was discussion about the need for a small efficacy and phase I safety trial, on 06 Mar 2001 the Agency indicated the efficacy trial would not be needed. On 30 Jun 2005, the Agency indicated as long as BE was demonstrated for both TMZ and MTIC for the IV formulation compared to the oral formulation with respect to both AUC and Cmax in an adequate number of patients there would be no need to conduct a separate small phase I safety study. Based on this advice, Schering-Plough embarked on the bioequivalence program as described below.

A clinical program was designed to establish that the pharmacokinetic (PK) profiles (Cmax and AUC) of TMZ and MTIC following the IV administration are bioequivalent to those following oral administration of TMZ and to adequately assess local tolerability at the injection site.

The approved initial TMZ dose and schedule in patients with refractory AA is 150 mg/m2/day for the first 5 consecutive days of a 28-day cycle. If both the nadir and day of dosing (Day 29, Day 1 of next cycle) absolute neutrophil count (ANC) are ≥1.5 x 109/L (1500/μL) and platelet counts are ≥100 x 109/L (100,000/μL), the oral TMZ dose may be increased to 200 mg/m2/day for the 5 day treatment cycle.

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).

Since the two IV BA/BE studies allowed subjects with primary brain tumors who had either received prior chemotherapy or who had not received prior chemotherapy to be enrolled, the dosing regimen in these studies was modified to accommodate both populations, ie, TMZ doses of 200 mg/m2/day for the three non-PK days (Days 1, 2, and 5); and 150 mg/m2/day on both PK days. Subjects were randomized to receive IV on Day 3 and oral on Day 4 or oral on Day 3 and IV on Day 4 according to a random code. The use of a single dose of IV TMZ and 4 oral doses of TMZ was selected to minimize subject inconvenience and because BE of the two formulations had yet to be confirmed. Data from the pilot study P02466 was used to optimize the IV infusion duration and sample size for the pivotal BE trial.

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 studies do not raise any new safety concerns and local tolerability was acceptable.

1.3.2 Efficacy

No efficacy data for the IV TMZ formulation is available.

1.3.3 Safety

These two TMZ studies do not raise any new safety concerns and local tolerability was acceptable.

1.3.4 Dosing Regimen and Administration

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 according to a random code. TMZ doses were 200 mg/m2/day for the three non-PK days (Days 1, 2, and 5); and 150 mg/m2/day on both PK days.

1.3.5 Drug-Drug Interactions

No new information is available.

1.3.6 Special Populations

No new information is available.

Pregnancy: Category D:

Temozolomide may cause fetal harm when administered to a pregnant woman. Five consecutive days of oral administration of 75 mg/m^2/day in rats and 150 mg/m^2/day in rabbits during the period of organogenesis (3/8 and 3/4 the maximum recommended human dose, respectively) caused numerous malformations of the external organs, soft tissues, and skeleton in both species. Doses of 150 mg/m^2/day in rats and rabbits also caused embryo lethality as indicated by increased resorptions. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants patients receiving temozolomide should discontinue nursing.

Pediatric Use: No new information is available.

Race: The effect of race on the pharmacokinetics of temozolomide has not been studied.

Tobacco Use: Population pharmacokinetic analysis indicates that the oral clearance of temozolomide is similar in smokers and nonsmokers.

Renal Impairment: Population pharmacokinetic analysis indicates that creatinine clearance over the range of 36-130 mL/min/m^2 has no effect on the clearance of temozolomide after oral administration. The pharmacokinetics of temozolomide have not been studied in patients with severely impaired renal function (CLcr <36 mL/min/m^2). Caution should be exercised when Temozolomide is administered to patients with severe renal impairment. Temozolomide has not been studied in patients on dialysis.

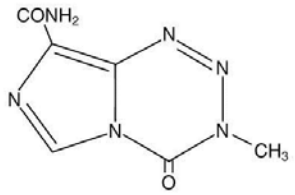
Hepatic Impairment: The pharmacokinetics of temozolomide in patients with mild-to-moderate hepatic impairment (Child's-Pugh Class I -II) were similar to those observed in patients with normal hepatic function. Caution should be exercised when temozolomide is administered to patients with severe hepatic impairment.

2.0 INTRODUCTION AND BACKGROUND

2.1 Product Information

TEMOZOLOMIDE Capsules for oral administration contain temozolomide, an imidazotetrazine derivative. The chemical name of temozolomide is 3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]-*a*s-tetrazine-8-carboxamide. The structural formula is shown in Figure 1:

Figure 1: Temozolomide structure



The material is a white to light tan/light pink powder with a molecular formula of $C_6H_6N_6O_2$ and a molecular weight of 194.15. The molecule is stable at acidic pH (<5), and labile at pH >7, hence temozolomide can be administered orally. The prodrug, temozolomide, is rapidly hydrolysed to the active 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide (MTIC) at neutral and alkaline pH values, with hydrolysis taking place even faster at alkaline pH.

2.2 Currently Available Treatment For Indication(s)

Nitrosoureas (carmustine [BCNU] and lomustine [CCNU]), procarbazine, vincristine, platinum analogs, etoposide

2.3 Availability Of Proposed Active Ingredient In The United States

Temozolomide is approved and available in the United States.

2.4 Important Issues With Pharmacologically Related Products

None

2.5 Presubmission Regulatory Activity

On 01 Apr 1999, Schering-Plough first proposed an IV TMZ development program to the FDA. This proposal included a bridging toxicology program, coupled with demonstration of bioequivalence (BE) of the IV and oral formulations of TMZ, in addition to a small clinical safety study. Over the years, additional communication followed where the Agency recommended that strict BE needed to be established for both maximum observed plasma drug concentration (Cmax) and area under the plasma concentration-time curve (AUC) and that the proposed toxicology program was adequate (11 May 1999). On 20 MAY 1999, the Agency communicated that BE needed to be established for both TMZ and the active metabolite, MTIC. Although there was discussion about the need for a small efficacy and phase I safety trial, on 06 Mar 2001 the Agency indicated the efficacy trial would not be needed. On 30 Jun 2005, the Agency indicated as long as BE was demonstrated for both TMZ and MTIC for the IV formulation compared to the oral formulation with respect to both AUC and Cmax in an adequate number of patients there would be no need to conduct a separate small phase I safety study.

2.6 Other Relevant Background Information

Temozolomide is approved in 73 markets worldwide. The approved indications include relapsed glioblastoma multiforme (GBM), relapsed anaplastic astrocytoma (AA), and metastatic malignant melanoma in specific countries.

To support the development plan and approval of the IV formulation of TMZ, local tolerability toxicology studies were conducted. The results of the local irritation studies demonstrated that the irritation is short-lived, is not associated with significant local tissue damage at the site of injection, and is due to the slightly acidic pH (pH = 4) necessary for this formulation. No new toxicology concerns were raised by these studies, and the risk to benefit was considered favorable for the IV formulation.

3.0 Significant Findings From Other Review Disciplines

3.1 CMC (And Product Microbiology. If Applicable)

See CMC review

Request for Categorical Exclusion from Environmental Assessment is included in this sNDA.

3.2 Animal Pharmacology/Toxicology

None. See original approved NDA

4.0 DATA SOURCES. REVIEW STRATEGY. AND DATA INTEGRITY

4.1 Sources Of Clinical Data

No efficacy data for the IV TMZ formulation is available.

4.2 Tables of Clinical Studies

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.

4.3 Review Strategy

No efficacy review was conducted. Except for local skin reactions it was not possible to compare the safety of IV and oral TMZ as IV TMZ was given for only 1 day of a 5 day treatment schedule.

4.4 Data Quality and Integrity

Satisfactory

4.5 Compliance With Good Clinical Practices

Trials were conducted in accordance with principles set forth in the World Medical Association Declaration of Helsinki or the laws and regulations of the country, whichever provided the greatest protection of the subject. Before patient randomization, informed consent had to be given according to the International Conference on Harmonization (ICH) Good Clinical Practice: Consolidated Guidance and any applicable local regulations. All institutions were subject to the Quality Control Procedure of the Brain Tumor Group

4.6 Financial Disclosures

No new information

5.0 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Preclinical studies demonstrated complete (approximately 100%) bioavailability of TMZ when administered orally to rats and dogs. Using a different IV formulation (drug in solution in dimethyl sulfoxide), Newlands et al, demonstrated that the absolute bioavailability of TMZ in five human patients was, on average, 109%.(11) Collectively, these preclinical and clinical data indicate that TMZ is completely bioavailable. This allowed abbreviated nonclinical and clinical programs to register the IV formulation.

The clinical program to register the IV formulation consists of two studies. The Phase 1, fixed-sequence, pilot bioavailability study in 13 subjects with primary CNS malignancies demonstrated that exposure to TMZ and MTIC after oral dosing with the approved capsule formulations and IV infusion over 1 hour met the criteria for BE, as measured by AUC. Mean absolute oral BA for TMZ was estimated to be 96% (90% CI was 89 to 103%).

To design the pivotal IV/oral BE study, a population PK model was developed to describe the PK profiles of TMZ and MTIC following oral administration of TMZ. Based on the oral model, an IV population PK model was developed and Monte Carlo simulations were performed to virtually conduct crossover BE clinical trials comparing the oral and IV TMZ and MTIC PK profiles. Based on these simulations, the duration of the IV infusion was optimized to infuse TMZ over 1.5 hours and the number of subjects needed for the pivotal trial was estimated to be approximately 20.

The pivotal crossover study was conducted in 22 subjects with primary CNS malignancies to demonstrate the BE of IV TMZ to the approved oral formulation of TMZ. In this study the IV formulation met the criteria for bioequivalence, as compared to the oral formulation, with the 90% CIs of the treatment AUC and Cmax ratio estimates for both TMZ and MTIC within the BE range of 80% to 125%.

The absorption, metabolism, and elimination of oral TMZ have been defined in the original marketing application submitted to the EMEA in January 1998 and to the FDA in August 1998. Temozolomide is rapidly and completely absorbed and undergoes non-enzymatic hydrolysis at physiologic pH to its active metabolite 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC). The cytotoxicity of MTIC is thought to be due primarily to alkylation of DNA. Temozolomide readily crosses the blood-brain barrier. Data from a single patient demonstrated that the AUC of temozolomide in cerebral spinal fluid (CSF) is approximately 30% of the AUC in plasma. Subsequent studies have shown temozolomide concentrations in the CSF of approximately 20% to 40% of that found in plasma. Preferential penetration of temozolomide into GBM has been confirmed using positron emission tomography scanning in four patients administered

^{11}C-temozolomide; both uncorrected and perfusion-corrected ^{11}C-temozolomide concentrations were greater in the gliomas than in the normal contralateral brain.

5.2 Pharmacodynamics

No new data are available and therefore no changes of the label are required.

5.3 Exposure-Response Relationships

No new data are available and therefore no changes of the label are required.

6.0 INTEGRATED REVIEW OF EFFICACY

There were no new efficacy studies conducted for this application.

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6.1 Indication

The application is adequate to support registration of TMZ IV formulation for the approved indications

6.1.1 Methods

Not relevant.

6.1.2 General Discussion of Endpoints

Efficacy endpoints were not evaluated.

6.1.3 Study Design

No efficacy study was conducted.

6.1.4 Efficacy Findings

None

6.1.5 Clinical Microbiology

Not applicable

6.1.6 Efficacy Conclusions

None

7.0 INTEGRATED REVIEW OF SAFETY

7.1 Overview

TMZ is an orally administered, cytotoxic alkylating agent that has demonstrated clinical antitumor activity in newly diagnosed GBM and refractory AA. Extensive safety information is available for the oral TMZ formulation as this drug has been approved in over 80 countries since 1999. To support the development plan of the IV formulation of TMZ, local tolerability toxicology studies were conducted. Results of these studies demonstrated that local irritation is short-lived, is not associated with significant local tissue damage at the site of injection, and is due to the slightly acidic pH (pH = 4) necessary for this formulation. No new toxicology concerns were raised by these studies, and the risk to benefit was considered favorable for the IV formulation.

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 generally mild and transient local reactions associated with the IV route of administration.

Both the pilot and pivotal studies used a dosing regimen similar to that which formed the basis of approval for refractory AA utilizing the oral formulation. Study subjects received a 5-day treatment sequence. On Days 1, 2, and 5, all subjects received TMZ (200 mg/m2/day) as an oral dose. Subjects were randomized to receive TMZ 150 mg/m2/day IV on Day 3 and oral on Day 4, or TMZ 150 mg/m2/day oral on Day 3 and IV on Day 4. The study design was similar for both trials with the exception of a difference in sample size (13 subjects in the pilot study versus 22 subjects in the pivotal study) and mode of administration (IV TMZ as a 1-hour infusion in the pilot study, and as a 1.5-hour infusion in the pivotal study).

Subjects were followed for 23 days after treatment ended for safety evaluation. As part of this evaluation, physical examinations, periodic clinical laboratory evaluations, adverse event (AE) assessment, IV injection site assessment for local tolerability, Karnofsky Performance scores (KPS), electrocardiograms (ECGs), and vital signs were recorded.

Local Reactions and Local Tolerability

Most injection-site reactions were mild and transient in all but one subject who had infusion-site pain reported as of moderate severity but had no tenderness at the IV site, and no clinical evidence of erythema, swelling, induration, or palpable venous cord. Local tolerability was acceptable with only 5 out of 35 subjects having local irritations following the onset of IV treatment. Even though there were reports of tender IV site, erythema and some degree of swelling in the IV injection site, there were no reports of induration, palpable venous cords, or vein thrombosis at the IV site. There were no long term effects of the reported local AEs.

7.1 Methods And Findings

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.

The treatment-emergent adverse events (TEAEs) observed in the pilot and the pivotal study were consistent with those reported previously with oral TMZ in brain tumor patients.

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.

7.1.1 Deaths

There were no deaths reported during the 5-day drug treatment period or the 23-day follow up period for both studies. However, there was one death in the pilot study due to generalized seizure leading to cardio-respiratory arrest reported within 30 days after the study follow-up period ended that was considered unrelated to TMZ by the investigator

7.1.2 Other Serious Adverse Events

There were four serious adverse events (SAEs) reported during the conduct of the pilot and pivotal studies. Two subjects each experienced the SAE of convulsions in the pilot study within 30 days after the study follow-up period ended; both had a history of seizures. In the pivotal study, one subject experienced hydrocephalus on Day 9 (4 days after the last day of study drug administration) and appendicitis on Day 22 (17 days after the last day of study drug administration).

In the pilot study, only one subject had a severe TEAE. This subject had severe nausea and vomiting reported on Day 7, which was considered to be probably related to treatment by the investigator. These AEs resolved without intervention. No other subjects had severe or life-threatening TEAEs during treatment or within 30 days after treatment ended. However, severe and life-threatening AEs were reported in two subjects in the pilot study more than 30 days after treatment ended. One subject experienced lifethreatening convulsion and life-threatening cardiorespiratory arrest 46 days after treatment ended (this subject died) and one subject experienced severe convulsion 32 days after treatment ended. The investigator considered these events unlikely related to study medication. In the pivotal study, four subjects reported 12 severe or life-threatening TEAEs; these AEs included headache, hematologic TEAEs (which are the known dose-limiting toxicity for TMZ), hydrocephalus and appendicitis

(both occurring in the same subject and deemed unrelated to TMZ), and convulsions (which was consistent with the subject's underlying disease and deemed unrelated to TMZ). There were no severe or life-threatening TEAEs reported on Day 3 or Day 4, and none of these severe or life-threatening TEAEs raised a new signal for TMZ.

Myelosuppression was frequent. In the refractory AA population receiving oral TMZ, laboratory changes from Grade 0 to 2 at baseline to Grade 3 or 4 during treatment include lymphopenia (55%), platelets (19%); neutrophils (14%), white blood cells (11%), and hemoglobin (4%). As expected, similar observations have been seen within the BA/BE studies. In the pivotal study, there were no instances of infections or bleeding with the exception of epistaxis/hematoma in one subject with severe thrombocytopenia who was also on anticoagulation, and one subject with Grade 4 thrombocytopenia with reported petechiae and hematoma who required platelet transfusion. In the pilot study, lymphopenia was observed in 4 subjects. Of these, 2 subjects developed lymphopenia (Grade 2) during the study; in both subjects the lymphopenia recovered to baseline values by the end of study. In the pivotal study, 2 subjects developed Grade 1 lymphopenia during the study. In addition, 5 other subjects presented with lymphopenia at baseline which either improved during the study or remained stable. There were no reports of opportunistic infections.

7.1.3 Dropouts and Other Significant Adverse Events

No new information

7.1.4 Other Search Strategies

Not applicable

7.1.5 Common Adverse Events

Table 1 summarizes common TEAEs.

Table 1: TEAEs Excluding Infusion Related AEs

	Number (%) of Subjects

Adverse Event	Pilot Study (P02466) All Combined (n=13)	Pivotal Study (P02467) All Combined (n=22)
Subjects Reporting Any Adverse Eventa	8 (62)	21 (95)
Headache	5 (38)	9 (41)
Nausea	4 (31)	9 (41)
Constipation	1 (8)	6 (27)
Anemia	-	5 (23)
Vomiting	2(15)	5 (23)
Leukopenia	-	4 (18)
Dizziness	1 (8)	4 (18)
Neutropenia	-	3 (14)
Thrombocytopenia	-	3 (14)
Hematoma	-	2 (9)
Petechiae	-	2 (9)
Convulsion	-	2 (9)
Alanine aminotransferase Increased	2 (15)	-
Hypotension	2 (15)b	-

a: A subject may have reported more than 1 adverse event.
b: Both subjects had a transient episode which resolved without intervention and both were on concomitant medications associated with hypotension.

To assess AEs that occurred on the two PK days, **Table 2** presents the TEAEs in the pivotal study for Days 3 and 4 of treatment pooled by route of administration. All subjects who received oral TMZ on Day 3/4 comprise the Pooled Data Oral group, and all subjects who received IV TMZ on Day 3/4 comprise the Pooled Data IV group; therefore, the Pooled Data Oral and IV group is comprised of all subjects who received oral TMZ and IV TMZ on Day 3/4. A total of 14 subjects (64%) experienced TEAEs in the pivotal study that were not related to injection- and infusion-site reactions on Day 3/4 only, with 8 subjects (36%) in the Pooled Data Oral group and 10 subjects (45%) in the Pooled Data IV group experiencing TEAEs that were not related to injection- and infusion-site reactions on Day 3/4 only (**Table 2**). All TEAEs are known to be associated with TMZ or are consistent with the patient population or underlying disease, and there are no differences of more than one subject between IV and oral days of dosing.

Table 2: TEAEs Pooled by Route of Administration (Oral Day 3/4 and IV Day 3/4)

Adverse Events	Number (%) of Subjects, Day 3 and Day 4 Only *a*

	Method of Administration		
	Pooled Data Oral (n=22)	**Pooled Data IV (n=22)**	**Pooled Data Oral/IV (n=22)**
Subjects Reporting Any Adverse Event	**8 (36)**	**10 (45)**	**14 (64)**
Headache	3 (14)	4 (18)	6 (27)
Dizziness	2 (9)	1 (5)	3 (14)
Nausea	1 (5)	2 (9)	3 (14)
Vomiting	1 (5)	2 (9)	3 (14)
Burning Sensation *b*	0	1 (5)	1 (5)
Constipation	0	1 (5)	1 (5)
Dyspepsia	1 (5)	0	1 (5)
Epistaxis	0	1 (5)	1 (5)
Feeling Hot	0	1 (5)	1 (5)
Flushing	0	1 (5)	1 (5)
Pain in Extremity	1 (5)	0	1 (5)
Prostatism	1 (5)	0	1 (5)
Pruritus *c*	0	1 (5)	1 (5)
Toothache	0	1 (5)	1 (5)
Vessel Puncture Site Reaction *d*	1 (5)	0	1 (5)

BSOC = Body System Organ Class; IV = intravenous(ly); TEAE = treatment-emergent adverse event; TMZ = temozolomide.
a: Captures only TEAEs that were not previously reported on Days 1 and 2.
b: Subject No. 111 (Sequence A) reported facial burning on Day 3, beginning 5 minutes after the IV TMZ infusion began. It was reported under the Nervous System Disorders BSOC but was actually a skin and subcutaneous tissue disorder.
c: Subject No. 116 had pruritus reported at the infusion site on the IV dosing day (Day 4 IV); it was categorized under the BSOC Skin and Subcutaneous Tissue Disorders although it is listed as a nonlocal reaction
d Subject No. 102 had vessel puncture site reaction, which resulted from a pharmacokinetic blood draw on the non-IV dosing day (Day 3 oral) and was categorized under the BSOC Skin and Subcutaneous Tissue Disorders

7.1.6 Less Common Adverse Events

Not applicable

7.1.7 Laboratory Findings

No new information

7.1.8 Vital Signs

No new information

7.1.9 Electrocardiograms (ECGs)

No new information

7.1.10 Immunogenicity

Not applicable

7.1.11 Human Carcinogenicity

Not applicable

7.1.12 Special Safety Studies

No new information

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Not applicable

7.1.14 Human Reproduction and Pregnancy Data

No new information

7.1.15 Assessment of Effect on Growth

No new information

7.1.16 Overdose Experience

No new information

7.1.17 Postmarketing Experience

The following spontaneous adverse experiences have been reported during the marketing surveillance of temozolomide capsules: allergic reactions, including cases of anaphylaxis, erythema multiforme, and opportunistic infections including *Pneumocystis carinii* pneumonia (PCP). Myelodysplastic syndrome and secondary malignancies, including myeloid leukemia have also been observed.

7.2 Adequacy Of Patient Exposure And Safety Assessments

Temozolomide was first approved in the United States on April 11,1999. Considerable safety data is available.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

No new information.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No secondary data sources were used.

7.2.3 Adequacy of Overall Clinical Experience

Adequate.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Preclinical testing was adequate

7.2.5 Adequacy of Routine Clinical Testing

Adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No new data.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

No recommendations for further study.

7.2.8 Assessment of Quality and Completeness of Data

Data quality and completeness were adequate

7.2.9 Additional Submissions. Including Safety Update

None

7.3 Summary Of Selected Drug- Related Adverse Events, Important Limitations Of Data And Conclusions

The pilot and pivotal studies, which form the basis of this application, demonstrated that the IV TMZ formulation met the criteria for bioequivalence, as compared with the oral formulation. These studies include safety data which are consistent with the observations made using the 5 consecutive days out of a 28-day cycle dosing regimen with oral TMZ in brain tumor patients, with the exception of local injection-site reactions related to the route of administration which were mostly mild and transient demonstrating an acceptable local tolerability. The IV formulation provides the benefit of a treatment option for the patients with life-threatening disease for whom TMZ is indicated, but who have medical circumstances that preclude use of an oral formulation or make an IV formulation preferable (for example: patients with brain stem involvement who may have impaired swallowing, patients with nausea and vomiting associated with increased intracranial pressure, or patients unable to swallow capsules).

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Pooling was not done

7.4.2 Explorations for Predictive Factors

Adverse reactions were dose and time dependent and were consistent with those seen for other cytotoxic alkylating agents.

7.4.3 Causality Determination

Causality was addressed appropriately.

8.0 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen And Administration

In the TMZ daily x 5 schedule IV TMZ can replace oral TMZ on a mg to mg basis.

8.2 Drug-Drug Interactions

There are no important drug-drug interactions. Phase 1 studies are required when temozolomide is to be combined with other cancer chemotherapy and/or radiation therapy.

8.3 Special Populations

No new information.

8.4 Pediatrics

No new information

8.5 Advisory Committee Meeting

No ODAC meeting is planned

8.6 Literature Review

None

8.7 Postmarketing Risk Management Plan

No specific recommendations for post-marketing risk management activities are required.

8.8 Other Relevant Materials

None

9.0 0VERALL ASSESSMENT

9.1 Conclusions

The FDA medical reviewer concurs with the applicants conclusions regarding the BE of IV and oral TMZ.

9.2 Recommendation On Regulatory Action

The DODP medical reviewer recommends registration of the TMZ IV formulation.

9.3 Recommendation On Postmarketing Actions

9.3.1 Risk Management Activity

No specific recommendations are made.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

None

9.4 Labeling Review

Ongoing

9.5 Comments To Applicant

None

10.0 APPENDICES

None

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

/s/

Martin Cohen
11/10/2008 10:40:29 AM
MEDICAL OFFICER