

# **Supplemental NDA 21-029/S005 New Drug Application**

## **TEMODAR Capsules (Temozolomide)**

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## Executive Summary Section

# Clinical Review for NDA 21-029

### Executive Summary

This multidisciplinary medical-statistical review addresses a supplement to NDA 21-029/S-005 (b) (4)

The current supplement presents the results of two Phase 1 and one Phase 2, open-label, multicenter studies of Temodar administered to this patient population. Phase 1 Study 193-125 was a dose escalation study in 27 pediatric patients with advanced non-CNS and CNS cancers. Phase 1 Study 193-125 Extended was actually a Phase 2 Study in 63 pediatric patients with recurrent brain stem glioma and high grade astrocytoma.

Phase 2 study H97-017 was a Cooperative Group-Sponsored Study in 122 pediatric patients with various recurrent CNS tumors. The primary objective for the Phase 2 study was assessment of the response rate of Temodar in patients with recurrent CNS tumors.

Submission of results of these studies meets the FDA Written Request for pediatric studies. On this basis Pediatric Exclusivity has been granted.

(b) (4)

TEMODAR is approved by the FDA for “the treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients at first relapse who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine.”

## **I. Recommendations**

### **A. Recommendation** (b) (4)

(b) (4)

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(b) (4)  
Safety results from the clinical studies in children will be added to the Pediatric subsection of the PRECAUTIONS section of the label.

### **B. Recommendation on Phase 4 Studies and/or Risk Management Steps**

(b) (4), there are no recommended Phase 4 studies of the use of Temodar in pediatric patients with recurrent brain tumors.

## **II. Summary of Clinical Findings**

### **A. Brief Overview of Clinical Program**

Temozolomide (TEMODAR) Capsules was granted marketing accelerated approval in the United States (NDA 21-029) for treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients at first relapse who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine. Approval was based on the complete response rate and duration in a single-arm, multicenter study.

The primary source for this sNDA review consisted of data submitted to the original NDA 21-029 from Phase 1 Study 193-125 in pediatric patients with advanced cancers, and previously unsubmitted Phase 1 Study 193-125/Extended study of Temozolomide in pediatric patients with recurrent cancers, and previously unsubmitted Phase 2 Study H97-017 in children and adolescents with recurrent CNS tumors.

(b) (4)

### **B. Efficacy**

Temodar Capsules have been studied in 2 open-label Phase 1 Studies (Study 193-125 and Study 193-125/Extended), and Phase 2 Study H97-017 in children and adolescents with recurrent non-CNS and CNS tumors. The primary endpoint for the Phase 2 Study and for the Extended Phase 1 Study was tumor response rate. Assessment of the response was a secondary endpoint for the initial Phase 1 Study.

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(b) (4)

#### C. Safety

Safety was assessed at a doses of 100-240mg/m<sup>2</sup> daily for 5 days every 28 days, in 204 pediatric patients with recurrent primary brain tumors and some non-CNS tumors. The toxicity profile in children was similar to that of the adult patients. The most common adverse events were dizziness, neuropathy, paresthesia, nausea, vomiting and constipation.

#### D. Dosing

##### Study 193-125 Dose Escalation Part.

Twenty seven pediatric patients with advanced cancers, most with primary CNS tumors (high-grade astrocytoma or brain stem glioma), participated in this study. The ages of the patients ranged from 3 to 17 years, with the majority of the patients between 6 and 12 years of age. Patients were stratified for previous treatment with either nitrosurea therapy or craniospinal irradiation (poor risk) versus no such previous treatment (good risk). Patients were randomized to one of the Temodar dose levels (100, 120, 160 or 240mg/m<sup>2</sup>) given daily for 5 days every 28 days.

##### Study 193-125 /Extended.

In Extension Part of Study 193-125, 63 pediatric patients with recurrent CNS tumors (brain stem glioma or high-grade astrocytoma) received Temodar daily for 5 days every 28 days. The ages of the patients ranged from 4 to 15 years. Patients were given either 160mg/m<sup>2</sup>/day if they had prior therapy, or 200mg/m<sup>2</sup>/day if no prior therapy was received.

##### Study H97-017.

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One hundred twenty two pediatric patients with recurrent CNS tumors (113 patients), and tumor histology categorized by the sponsor as “Other” (9 patients) were enrolled in this Phase 2 Study. Category “other” includes: neuroblastoma, osteosarcoma, Ewing’s sarcoma, malignant meningioma, and alveolar soft part sarcoma.

The ages of the patients ranged from 1 to 23 years. Temodar was administered at the dose of 180mg/m<sup>2</sup>/day to patients previously treated with cranio-spinal irradiation, and 200mg/m<sup>2</sup>/day to patients who did not receive radiation treatment.

#### **E. Special Populations**

Both Phase 1 Studies (Study 193-125 and Study 193-125 Extended) and Phase 2 Study H97-017 were conducted solely in children and adolescents with recurrent CNS tumors and a few non-CNS tumors. Patients range in age from 1 to 23 years old. The majority of patients were between 3 to 17 years.

### **Clinical Review**

#### **I. Introduction and Background**

Central nervous system (CNS) tumors are among the most serious and devastating of malignant diseases in children, being associated with significant morbidity and mortality despite aggressive treatment. Tumors of the central nervous system are the most common solid malignancy in childhood and account for approximately 20% of all neoplasms in children. Primitive neuroectodermal tumors (PNET), such as medulloblastoma is the most common malignant brain tumors in children that accounts for approximately 30% of all infratentorial tumors. Malignant gliomas of childhood, including anaplastic astrocytomas (AA) and glioblastoma multiforme (GBM), constitute approximately 25% of all brain neoplasms. Other tumor histologies include low-grade astrocytomas (18%), ependymoma (15%), craniopharyngioma (5%), and germ cell tumors (5%).

The majority of pediatric patients have suboptimal response to any treatment, including surgery, radiation therapy, and chemotherapy treatment. The standard care for primary disease has been surgery and radiation. The use of adjuvant chemotherapy is still controversial for low- and high-grade malignant gliomas. For the treatment of PNET the addition of chemotherapy has become part of the current standard. The most commonly used chemotherapeutic agents are BCNU, cisplatin, vincristine, high-dose methotrexate, and etoposide.

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The best survival results are achieved in patients with medulloblastoma (MB). In large multicenter trials in which adjuvant therapy in patients with newly diagnosed PNET has been investigated, the 5-year survival ranges from 40 to 75%. Local and metastatic recurrences occur in 30 to 40% of patients with MB. In this subgroup of patients the median survival time after progression is 5 months (<1-41 months).

Survival expectations in patients with GBM at the time of the initial relapse are poor, only 25% of patients survived 4-6 months. In recurrent disease, no standard of care for malignant gliomas of different histology exists.

The search for effective chemotherapy for children with recurrent high-grade malignant glioma is one of the priorities in oncology. It is important to find an agent that is not only effective, but has an acceptable safety profile, does not adversely impact patients' quality of life, and is easy to administer.

As indicated by the sponsor, Temozolomide is an alkylating agent that has demonstrated antitumor activity and a well-tolerated safety profile in Phase I and II trials in adult and pediatric patients with various advanced cancers, including recurrent malignant glioma. It is rapidly and completely absorbed following oral administration and undergoes spontaneous hydrolysis at physiologic pH to an active metabolite, MTIC. The cytotoxicity of MTIC is thought to be due to alkylation at the O-6 position of guanine with additional alkylation at the N-7 position. The final degradation product, AIC, is an intermediate in the biosynthetic pathway to purines and, ultimately, to nucleic acids.

(b) (4)

In adult clinical studies, temozolomide was relatively well tolerated, side effects were usually mild to moderate in severity and most frequently included nausea, vomiting, headache, fatigue, and constipation. Myelosuppression was the most common dose-limiting adverse event (AE).

Temozolomide Capsules was approved (as Temodar) in 1999 for "the

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treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients at first relapse who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine.”

**A. Drug Established and Proposed Trade Name, Drug Class, Sponsor’s Proposed Indication(s), Dose, Regimens, Age Groups**

Established Name: Temozolomide

Proprietary Name: TEMODAR

Applicant: Schering-Plough Research Institute (SPRI)

Drug Class: Antineoplastic

Indication: Temodar Capsules was approved for “the treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients at first relapse who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine.”

(b) (4)

**B. State of Armamentarium for Indication(s)**

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TEMODAR is approved by the FDA “the treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients at first relapse who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine.”

(b) (4)

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#### C. Important Milestones in Product Development

1998 - A multicenter open-label phase 2 study of temozolomide (SCH 52365) in the treatment of patients with anaplastic astrocytoma at first relapse was completed. This was a study C/194-123 which encompassed the period from February 16, 1995 to April 1, 1998. The primary objectives of this study were to determine progression-free survival at 6 months and safety. Secondary objectives were to determine overall survival, objective response, health-related quality of life and population pharmacokinetics.

1998 - A summary report of one of the Phase 1 Study (193-125), was submitted to the original NDA (Section 6B). This report included pharmacokinetics and dose determination data on 27 pediatric patients with recurrent non-CNS and CNS tumors, as well as safety reports (Section 8H).

1999 - NDA 21-029 (Relapsed Anaplastic Astrocytoma in adults) was submitted to the FDA for review.

1999 - Temozolomide (TEMODAR) Capsules was granted marketing accelerated approval in the United States (NDA 21-029) for treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients at first relapse who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine. Approval was based on the complete response rate and duration in a single-arm, multicenter study.

2001 - The FDA issued a formal Written Request for studies that will investigate the potential use of TEMODAR in the treatment of children with various cancers. Two types of studies were requested:

Study 1: A summary report of the Phase 1 information in pediatric subjects (data previously submitted to the NDA). This report included pharmacokinetics and dose determination in more than 18 subjects covering the age group from 3 to 17 years.

Study 2: Phase 2 pilot studies: Enrollment of more than 14 patients with recurrent Central Nervous System (CNS) tumors in each to the following studies: a two-arm Phase 2 Study and a six-arm Phase 2 pilot study. The tumor histologies covered by these two studies included: high grade astrocytoma (grade 3 and 4 astrocytoma, glioblastoma multiforme, anaplastic astrocytoma, brain stem glioma, low-grade astrocytoma, ependymoma, medulloblastoma/PNET, other CNS tumors.

2002 - Pediatric Exclusivity Board granted Pediatric Exclusivity to TEMODAR (b) (4)

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#### D. Other Relevant Information

TEMODAR is approved in the US for the following indication:

TEMODAR is indicated for “the treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients at first relapse who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine.”

(b) (4)

#### E. Important Issues with Pharmacologically Related Agents

Alkylating agents, particularly the nitrosoureas (BCNU and CCNU) are the most commonly used chemotherapeutic agents in treatment of malignant gliomas. These drugs have been used as single agents or in combination with other drugs, such as procarbazine or vincristine. The benefit of these drugs in the treatment of malignant gliomas is often short-lived or not apparent.

Drug delivery may be difficult because many of the commonly used chemotherapy agents have physical characteristics unfavorable to pass through the blood-brain barrier.

The most consistently noted toxicities of nitrosoureas is delayed myelosuppression, which reaches a nadir 4 to 6 weeks after treatment and can delay subsequent cycles of chemotherapy by 6 to 8 weeks (De Vita, 1993). High dose systemic BCNU is associated with hepatic necrosis, encephalopathy, and cardiac necrosis (Phillips et al., 1983). The major dose-limiting toxicity is pulmonary, predominantly fibrosis (O'Driscoll et al., 1990).

Most adverse events related to Temozolomide are usually mild or moderate, including nausea, vomiting, headache, lymphopenia and thrombocytopenia, and either resolved spontaneously or were readily controlled with the symptomatic treatment.

## II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Temozolomide is a marketed drug; the chemistry and manufacturing controls have been previously reviewed and approved. No new information with regard to chemistry, toxicology and microbiology was submitted with this NDA. This review is a combined medical and statistical review. Please see biopharmaceutical review below.

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### III. Human Pharmacokinetics and Pharmacodynamics

#### A. Pharmacokinetics

Nineteen pediatric patients (3-17 years of age) with advanced cancer were included in the pharmacokinetic portion of a rising dose, open-labeled Phase I study (Study #193-125, Attachment 1). Patients were stratified for previous treatment with either nitrosurea therapy or cerebrospinal irradiation (poor risk) versus no such previous treatment (good risk). Temozolomide was administered orally 100-240 mg/m<sup>2</sup> /day for 5 consecutive days. (b) (4)

(b) (4)

Coadministration of ranitidine has no effect on the oral bioavailability and pharmacokinetics of temozolomide. Additionally, population pharmacokinetic analysis reveals that the use of commonly administered drugs such as dexamethasone, phenytoin, phenobarbital, carbamazepine, H<sub>2</sub>-receptor antagonists, ondansetron, and prochlorperazine have no effect on the oral clearance of temozolomide. Administration of valproic acid decreases oral clearance of temozolomide by 4.7% (p=0.019); the clinical implication of this effect is unknown.

#### B. Pharmacodynamics

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### IV. Description of Clinical Data and Sources

#### A. Overall Data

The current supplemental NDA (sNDA) in children is being provided in response to a Written Request for pediatric studies from the FDA in a letter dated January 9, 2001 and an amended letter dated August 24, 2001.

The primary source for this sNDA review consisted of data submitted to the sNDA 21-029 on Phase 1 Study 193-125 in pediatric patients with advanced cancers, Phase 1 Study 193-125/Extended study of Temozolomide in pediatric patients with advanced cancers, and Phase 2 Study H97-017 in children and adolescents with recurrent CNS tumors.

#### B. Tables Listing the Clinical Trials

**Table 1: Tables Listing the Clinical Trials of TMZ in Children.**

Phase/Study/Number	TMZ-treated Patients Evaluated for Safety and Efficacy
<b>SPRI-Sponsored</b>	
Phase I: 193-125 Dose Escalation	27
Phase I: 193-125 Extension	55
<b>Cooperative Group-Sponsored</b>	
Phase II: H97-017	122
<b>TOTAL</b>	<b>204</b>

*Reviewer Comments: A summary report of the Phase I information (Study 1, 193-125), was submitted to the original NDA in 1998. This report included pharmacokinetics and*

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*dose determination data on 27 pediatric patients with recurrent non-CNS and CNS tumors.*

### C. Postmarketing Experience

TEMODAR (Temozolomide) capsules was approved in 1999. As of February 20, 2003, AERS database contains 581 reports of all adverse events (AE's), including 30 AE's for children age 0-16 years. It should be noted that many of these reports may be duplicated. The top ten most frequently reported AE's in children are presented in the Table below.

**Table 2: Most common adverse events (>5%) in children reported to FDA (N=30)**

Preferred Term	N	% of total
Pyrexia	6	20
Headache	5	16.7
Thrombocytopenia	5	16.7
Vomiting	5	16.7
Aplastic anemia	3	10.0
Neutropenia	3	10.0
Sedation	3	10.0
Bone marrow depression	2	6.7
Candida infection	2	6.7
Confusion	2	6.7

### D. Literature Review

The sponsor's literature review appears to be adequate.

## V. Clinical Review Methods

### A. How the Review was Conducted

The review centers on the data from two Phase 1 studies (Study 193-125 in pediatric patients with advanced cancers, Study 193-125/Extended study of Temozolomide in pediatric patients with advanced cancers) and one Phase 2 Study (H97-017) in children and adolescents with recurrent CNS tumors.

Data submitted from Study 193-125/Extended and from Study H97-017 were the primary data submitted in this sNDA.

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A summary report of Study 193-125, was submitted to the original NDA in 1998. This report included pharmacokinetics and dose determination data on 27 pediatric patients with recurrent non-CNS and CNS tumors.

Data on a total of 204 pediatric patients with recurrent non-CNS and CNS tumors were considered sufficient for an efficacy conclusion.

All of the following documents from the NDA components were submitted in electronic form for all three studies:

- Initial submission of protocols for the 3 studies
- Protocol amendments
- Labeling
- Application Summary
- Pediatric Pharmacokinetics and Bioavailability
- Clinical Data
- Statistical Section
- Case Report Tabulation
- Case Report Form

Statistical review included analyses using the SAS datasets.

#### **B. Overview of Materials Consulted in Review**

Data submitted under sNDA 21-029 included data from two Phase 1 studies, one Phase 2 study, clinical reports from these studies, and labeling.

#### **C. Overview of Methods Used to Evaluate Data Quality and Integrity**

The primary data were analyzed for consistency with the study reports and with selected patient narratives. DSI audit was not conducted.

#### **D. Were Trials Conducted in Accordance with Accepted Ethical Standards**

The studies were conducted under US IND 44,162 in full compliance with the principles of the declaration of Helsinki, including the current amendments, or with the laws and regulations of the country in which studies were conducted. Prior to initiation of the studies, the protocols, and the patient informed consent were reviewed and approved by the ethics committees or institutional review boards of the centers of the study. Subsequent protocol amendments were also submitted, reviewed and approved before implementation.

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### E. Evaluation of Financial Disclosure

A complete Financial Disclosure (FD) FDA Form 3454 is submitted with attached list of principal investigators. Information regarding FD was properly collected by SPRI.

In summary: No principal investigators are full or part-time employee of SPRI. No disclosable financial information was reported by any of the investigators from US and non-US centers participating in trials.

## VI. Integrated Review of Efficacy

### A. Brief Statement of Conclusions

The efficacy analyses were based on the data from the following sources:

(1) Phase 1 study I93-125 which was submitted as two study reports, a DLT/MTD/PK dose escalation part in 27 pediatric patients with advanced cancer and an extension part in 63 pediatric subjects (55 patients enrolled to the extension part plus data from 8 subjects previously enrolled in the dose escalation part of I93-125) with brain stem glioma (BSG) or high grade astrocytoma (HGA).

The primary objectives for each study were evaluation of pharmacokinetics with MTD determined, safety profile assessment, and to determine the efficacy, defined as response rate (complete and partial).

The secondary objectives of Study I93-125 Extension were to determine the progression free survival and to assess overall survival in two arms of BSG and HGA.

(b) (4)

(2) Phase 2 study H97-017 was a Cooperative Group-Sponsored Study in 122 pediatric patients with various CNS tumors. The primary objective for the Phase 2 study included evaluation of the anti-tumor effect of Temodar in patients with recurrent CNS tumors.

All patients were stratified based on previous treatment to a "good" and "poor" risk: prior nitrosourea therapy or craniospinal radiation therapy (XRT) – poor risk group, and patients who did not receive prior nitrosourea therapy or (XRT) – good risk group.

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(b) (4)

#### **B. General Approach to Review of the Efficacy of the Drug**

The review focused on the supplemental NDA data submitted by Schering-Plough Research Institute on a total of 204 pediatric patients with recurrent non-CNS and CNS tumors. Submitted efficacy information for each patient was reviewed.

#### **C. Detailed Review of Trials by Indication**

The primary objectives of the Phase 1 study 193-125 were DLT and MTD determination and pharmacokinetic assessment. Response rate was used as a surrogate endpoint to determine efficacy. Twenty seven pediatric patients with advanced cancers were enrolled in this study.

The primary objectives of the Study 193-125 Extended were to determine the efficacy, defined as response rate (complete and partial) and safety of temozolomide. Sixty three pediatric patients with recurrent CNS tumors participated in this trial. Number of patients in the 193-125 Extended Study includes 55 children enrolled to the extension part plus data from 8 subjects previously enrolled in the dose escalation part of 193-125 with brain stem glioma (BSG) or high grade astrocytoma (HGA).

Secondary objectives of the study were to determine progression free survival and overall survival in these two patient population.

The objectives of the Phase 2 study H97-017 were to determine the response rate of temozolomide administered orally at 200 mg/m<sup>2</sup>/day or 180 mg/m<sup>2</sup>/day (patients previously treated with craniospinal irradiation) once a day for Day 1 to 5 per cycle.

Further assessment of the Temozolomide toxicity was also included in the study objectives. One hundred and twenty two pediatric patients were enrolled into this study.

#### **Phase 1 Study 193-125**

There was a total of 27 children in this study (19 subjects were in the arm of Good Risk and 8 subjects were in the arm of Poor Risk). The majority of patients (93%) were

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Caucasian; 56% of subjects were female. Patients with the following diagnoses were included in the study: BSG, HGA, medulloblastoma, Ewing's sarcoma, hepatocellular carcinoma, malignant melanoma, pancreatic tumor, and meningioma.

**Statistical Reviewer Comment:**

(b) (4)

[Redacted]

[Redacted]

[Redacted]

Study 193-125 Extended

Number of patients in the 193-125 Extended Study included 55 children enrolled to the extension part plus data from 8 children previously enrolled in the dose escalation part of 193-125 with BSG or HGA.

**Statistical Reviewer Comment:** *The efficacy population consisted of 29 subjects with BSG and 34 subjects with HGA. This included 8 of 10 subjects with BSG who had previously been treated in the Phase 1 dose escalation portion.*

(b) (4)

[Redacted]

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### Study H97-017

There were 122 children in the Phase 2 Study, 114 with recurrent CNS tumors and 9 with non-CNS tumors. Histological tumor subtypes are presented in the Table below.

**Table 3: Tumor Characteristics – Histological Type**

Tumor Type	Number of Patients /Number of Responses (CR or PR)
Medulloblastoma/PNET	29 / (1 CR + 3 PR)
HGA	23 / (1 PR)
LGA	22 / (1 PR)
BSG	16 / 0
Ependymoma	14 / 0
Malignant Meningioma	1 / 0
Other CNS Tumors *	9 / 0
<b>TOTAL</b>	<b>114 / (1 CR + 5 PR)</b>

\* oligodendroglioma, mixed glioma and optic glioma

**Statistical Reviewer Comment:** One hundred and twenty two pediatric patients were enrolled into the study. Of these patients, 114 had response evaluations. Eight children were not evaluable for response for the following reasons: (1) the subjects did not have measurable disease (n=1); (2) the subjects never received TMZ (n=5); or (3) TMZ was stopped prematurely, prior to the subjects being evaluable for response (n=2).

(b) (4)

### **D. Efficacy Conclusions**

(b) (4)

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(b) (4)

## VII. Integrated Review of Safety

### A. Brief Statement of Conclusions

Temodar safety has been studied in 204 children with advanced CNS and non-CNS tumors (27 patients in Study 193-125, 55 patients in Study 193-125 Extended, and 122 patients in Study H97-017).

Vomiting and headache (78% and 41%, respectively) were the most common adverse events (AE's) observed in a pediatric patients in both parts of Study 193-125. Grade 3 toxicity was described in only 4% of patients in Study 193-125, and in 27% of patients in Study 193-125 Extended.

In the Study H97-017, the most common AE's were hematologic in nature (lymphopenia and leucopenia were described in 60% and 58%, respectively). Grade 3 lymphopenia and leucopenia were noticed in 60% and 58%, respectively, and Grade 4 toxicities occurred in 16% of patients.

In conclusion: Temozolomide has a well-defined and acceptable safety profile as demonstrated in 204 pediatric patients with advanced CNS and non-CNS tumors. Toxicities demonstrated with the use of Temodar are consistent with the safety experience in the adult population.

### B. Description of Patient Exposure

The safety review is based on the analysis of data submitted by the sponsor in sNDA 21-029/S001, including electronic copies of case report forms, deaths forms, and information included in the Clinical Data Section.

A total of 204 pediatric patients with advanced CNS and non-CNS tumors were treated with Temodar. The drug was administered in two Phase 1 Studies to 27 patients with advanced solid tumors (Study 193-125), and 55 patients with CNS tumors (Study 193-125 Extended). The patient population receiving Temodar in Phase 2 Study (H97-017) consisted of children with different histological subtypes of CNS tumors.

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#### Patient exposure in Study 193-125.

In the Phase 1 Dose Escalation study 193-125, the highest dose in the good risk treatment arm (n=19 patients) was determined to be 1200 mg/m<sup>2</sup> TMZ and the MTD was determined to be 1000 mg/m<sup>2</sup> TMZ, administered in divided doses as a 5 day regimen every 28 days. In the poor risk treatment arm, a total of 8 subjects were enrolled, however, DLT and MTD was not determined. Due to limited and slow enrollment, there was an early closure of this arm. None of the evaluable subjects at the 500 and 600 mg/m<sup>2</sup> dose levels experienced DLT.

*Reviewer Comment: All patients (a total of 27 children evaluable for safety) were stratified to the “good” and “poor” risk patients based on the previously received treatment. Good risk group included patients who did not receive prior nitrosourea therapy or craniospinal XRT. Poor risk group included patients who received prior nitrosourea therapy or craniospinal XRT.*

#### Patient exposure in Study 193-125 Extended.

In the Phase 1 Extension study 193-125, safety data are provided for subjects with brainstem glioma (BSG, n=29) or high grade astrocytoma (HGA, n=34) who received TMZ at 160 mg/m<sup>2</sup>/day (prior chemotherapy and a history of prolonged CTC Grade 4 thrombocytopenia greater than 14 days) or 200 mg/m<sup>2</sup>/day (no prior history of chemotherapy or Grade 4 thrombocytopenia) for Days 1 to 5 out of every 28 day cycle. This study includes safety data from 8 BSG subjects enrolled into the dose escalation part of 193-125 who met the inclusion criteria for the extension part of the study.

#### Patient exposure in Study H97-017.

In study H97-017, 122 subjects with a variety of CNS tumors were treated with TMZ 200 mg/m<sup>2</sup>/day or 180 mg/m<sup>2</sup>/day (subjects previously treated with craniospinal irradiation) once a day for Days 1 to 5 per cycle.

### **C. Methods and Specific Findings of Safety Review**

The safety review was conducted using the information included in the Clinical Data Section, as well as electronically submitted Death Report Form of CRF, and forms for Adverse Events Reporting.

### **D. Adequacy of Safety Testing**

The safety assessment appears adequate and was carried out on all 204 patients and included extent of exposure, deaths during the study, deaths within the first 28 days

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after discontinuation of the study drug, discontinuation due to Adverse Events, SAE's and AE's. Grade 3 or 4 laboratory abnormalities listed as AE's were used to summarize laboratory abnormalities.

Study Evaluation Guide for Phase 1 and Phase 2 Studies appear adequate for these patient populations'.

#### **E. Summary of Critical Safety Findings and Limitations of Data**

##### Study 193-125 and Study 193-125 Extended.

##### 1. Deaths on Study.

A total of 15 patients died within 30 days of their last dose of study medication. All but one of these deaths were due to disease progression or disease-related complications. For one patient, no reason was given as the cause of death; this subject had discontinued, following 2 cycles of TMZ, due to disease progression 2 weeks prior to death.

*Reviewer Comment: Summaries for patients who died within 30 days of their last dose of study medication are provided in the Clinical Uncontrolled Study Section.*

##### 2. Discontinuation due to Adverse Events.

No patients discontinued from the study due to adverse events.

##### 3. Adverse Events (AE) and Serious Adverse Events (SAE).

Adverse events were identified by the sponsor as those signs/symptoms or concurrent illnesses that are undesirable occurring during study participation. All adverse events were to be recorded in the patient's medical records and on the CRF. Treatment-emergent adverse events were those that began during treatment or up to 30 days after treatment ended, or that began prior to the start of treatment and worsened in severity while on treatment regardless of relationship to treatment.

An adverse event considered serious by SPRI was defined as one that suggested a significant hazard, contraindication, side effect or precaution. This included, but was not limited to, any event that:

- resulted in death;
- was immediately life-threatening;
- resulted in hospitalization or prolongs an existing hospitalization except for hospitalizations for transfusions, study procedures or administration of TMZ;
- resulted in permanent, persistent, or significant disability;
- resulted in end-organ toxicity;

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- was an overdose, either intentional or inadvertent;
- was a congenital anomaly.

The most commonly reported AEs in the BSG arm were vomiting (48%), headache (34%), thrombocytopenia, ataxia, constipation, and neuropathy (each 28%). In HGA subjects the most commonly reported ADEs were headache (65%), vomiting (56%), thrombocytopenia (41%), and dysphagia (35%). Nausea and vomiting were mild to moderate in most subjects and were readily controlled with standard antiemetics. Non-hematologic abnormalities also consisted of 1 report of elevated SGPT and 2 reports of increased total bilirubin; these were not felt to be clinically significant and there were no discontinuations due to these laboratory abnormalities.

Hematologic abnormalities (Grade 3 or 4) included lymphopenia 70% (44 of 63 subjects), neutropenia 38% (24 of 63 subjects), and thrombocytopenia 40% (25 of 63 subjects). In subjects with myelotoxicity, most findings were not clinically significant and few resulted in hospitalizations or transfusions. None resulted in discontinuation from the study. Less than 10% of all cycles had to be dose-reduced, primarily due to neutropenia/thrombocytopenia.

Serious adverse events (SAEs) were reported for 47 patients and were primarily hospitalizations. No unusual or unexpected events were reported. Most of the SAEs were consistent with either progression of the disease or due to known toxicities of TMZ (ie, neutropenia/thrombocytopenia).

#### Study H97-017.

##### 1. Deaths on Study.

The Demographics Table L-1 lists 19 deaths within 30 days of last Temodar dose. Case report forms available for 16 of the deaths. None of the 16 deaths appears to be related to Temodar.

##### 2. Discontinuation due to Adverse Events.

There is no information available on discontinuations due to adverse events for this study.

##### 3. Adverse Events (AE) and Serious Adverse Events (SAE).

Treatment-emergent adverse events (AEs) occurred in 88% of all patients. Decreased hemoglobin, decreased WBC, lymphopenia, neutropenia, thrombocytopenia, and vomiting occurred in over 50% of subjects. The majority of AEs were mild to moderate in severity. Of the subjects who reported an AE, 30% (37/122) of subjects reported at

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least one Grade 3 (severe) AE and 26% (32/122) of subjects reported at least one Grade 4 (life-threatening) AE.

The most common severe AE was lymphopenia, occurring in 26% (32/122) of subjects. Thrombocytopenia was the most common life-threatening AE, occurring in 16% (19/122) of subjects. Treatment-related AEs occurred in 78% of all subjects. The majority of related AEs were mild to moderate in severity; 22% of subjects report Grade 3 AEs and 21% of subjects reported Grade 4 AEs. The most commonly occurring treatment-emergent AEs were nausea (38%), vomiting (42%) and various hematologic AEs.

There are 3 SAE records in the SPRI database: 1) death 17 days following 4 cycles of TMZ that was considered unrelated by the investigator to TMZ administration; 2) disease progression after receiving 2 cycles of TMZ (followed by death) that was considered unrelated by the investigator to TMZ administration, and 3) pancreatitis that SPRI considered unrelated to TMZ administration.

### **VIII. Dosing, Regimen, and Administration Issues**

Phase 1 Study 193-125 was a dose escalation trial for determining the MTD. Patient population included children and adolescents with recurrent CNS and non-CNS malignancies.

All patients were stratified based on previous treatment to a “good” and “poor” risk: prior nitrosourea therapy or craniospinal radiation therapy (XRT) – poor risk group, and patients who did not receive prior nitrosourea therapy or (XRT) – good risk group.

In the “good” risk group the DLT and MTD were established. In the “poor” risk arm DLT and MTD were not established due to slow and limited patients accrual to this group.

Phase 1 Study 193-125 Extended was really a Phase 2 Study. Temodar dose was 200mg/m<sup>2</sup>/day in good risk patients and 160mg/m<sup>2</sup>/day in poor risk patients once a day for 5 days every 28 days.

Phase 2 Study (H97-017) was non-randomized, uncontrolled, open-label study to determine the efficacy of temozolomide administered orally at 200 mg/m<sup>2</sup>/day or 180 mg/m<sup>2</sup>/day to patients previously treated with craniospinal radiation once a day for Days 1 to 5 per cycle.

Temozolomide appears to be well-tolerated at doses 200mg/m<sup>2</sup> and 180mg/m<sup>2</sup> in pediatric patients previously not treated and patients treated with CSI, respectively.

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#### **IX. Use in Special Populations**

##### **A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation**

We agree with the Applicant that there are insufficient numbers of patients to permit analysis.

##### **B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy**

###### Study 193-125 and Study 193-125 Extended.

The combined incidence for children with at least one Grade 3 or 4 AE in the age groups of 2 to <12 and 12 to <16 years was similar for the BSG (75% and 80%) and HGA (67% and 75%) subjects. For the age group 16 years and older, only HGA subjects (n=6) were in this category; the combined incidence of Grade 3 and 4 AEs was 100%.

The incidence of the most common AEs for BSG and HGA patients, vomiting, headache, and thrombocytopenia, were different across the age groups within each arm; this is most likely a consequence of the small number of subjects in these groups.

*Reviewer Comment: Due to the small number of patients in these groups, a discussion of individual AE differences has not been made. A summary presentation of AEs by race is not provided in this study report e as the majority of subjects were Caucasian (57/63, 90%). There were only 2 patients each in the categories of Black, Asian, or Other. There was no efficacy analysis done for subgroups.*

###### Study H97-017.

In general, the distribution of treatment-emergent AEs across the age subgroups (<2 years of age, n=2; 2 to <12 years of age, n=65; 12 to <16 years of age, n=31; and 16 years of age and older, n=24) was similar to the distribution of AEs for all groups combined.

Subgroup analysis of subjects by gender and race are not provided for this study report.

##### **C. Evaluation of Pediatric Program**

This supplemental application satisfactory fulfilled the Written Request requirements stated in the FDA letter of 09 January 2001 and amended in the FDA letter of August

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24, 2001 in which Phase 1 and Phase 2 pediatric studies were requested. Pediatric Exclusivity has been granted.

(b) (4)

Safety data will be added to the label in the pediatric subsection of the PRECAUTIONS section.

#### **D. Comments on Data Available or Needed in Other Populations**

Studies of Temodar in children with impaired hepatic function or decreased renal function were not conducted.

### **X. Conclusions and Recommendations**

#### **A. Conclusions**

Temodar data were submitted from two Phase 1 trials in children with recurrent non-CNS and CNS tumors, and data from the Phase 2 trial conducted in children with recurrent CNS tumors of various histological subtypes and a few non-CNS tumors.

Temodar was previously approved by the FDA for “the treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients at first relapse who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine.” The approval was based on the overall response rate (CR+PR) of 22%, and the complete response rate (CR) of 9%. Complete response median duration was 64 months (range 52-114 weeks).

(b) (4)

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(b) (4)

#### **B. Recommendations**

(b) (4)

Safety results from the clinical studies in children will be added to the Pediatric subsection of the PRECAUTIONS section of the label.

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### XI. Appendix

#### Protocols Synopses.

**Title of Study:** A Phase I/Phase 1 Extended Study Of SCH 52365 In Pediatric Patients With Advanced Cancer (Protocol No. I93-125)

**Investigator(s):** Multicenter

**Study Center(s):** Multicenter: 15 Centers in England and France

**Publication(s):** None

**Studied Period:** 10 JAN 1995 to 30 SEP 1999

**Clinical Phase:** 1

**Objective(s):**

- The primary objectives of the study were to determine the efficacy, defined as response rate (complete and partial) and safety of temozolomide (TMZ; SCH 52365) administered orally, once a day for 5 days repeated every 28 days in pediatric patients with relapsed supratentorial or cerebellar high grade astrocytoma (HGA) or diffuse intrinsic brainstem glioma (BSG).
- Secondary objectives of the study were a) to determine the progression free survival in these two patient populations and b) to assess overall survival in these two patient populations.

**Methodology:** Multicenter, open-label, uncontrolled study. TMZ was given PO once a day on Days 1-5; starting dose: 200 mg/m<sup>2</sup>/day (no prior chemotherapy), 160 mg/m<sup>2</sup>/day in Cycle 1 (prior chemotherapy and a history of prolonged CTC Grade 4 thrombocytopenia greater than 14 days - If no hematologic toxicity reported during Cycle 1, then Cycle 2 could be administered at 200 mg/m<sup>2</sup>/day). Cycles were to be repeated every 28 days. Independent central review of all pathology and radiology was prospectively defined. Gd-MRI scans, neurologic examinations, and clinical assessments were performed at specified intervals. Hematologic and non-hematologic toxicity were graded using the Common Toxicity Criteria (CTC). Abnormal laboratory values that caused hospitalization, transfusion, or discontinuation were recorded as adverse events (AEs).

**Number of Subjects:** 63 subjects (34 with High-Grade Astrocytoma, Arm A; 29 with Brainstem Glioma, Arm B).

**Diagnosis and Criteria for Inclusion:** The following criteria for inclusion are for subjects enrolled into the Phase 1 extension portion of this trial. Criteria for the inclusion used for the 8 brain stem glioma subjects enrolled under the dose escalation portion of the study can be found in Protocol **Section 4.1**.

- Eligible patients (male or female patients of any race, <18 years of age), with a life expectancy of >9 weeks, must have had relapsed supratentorial or cerebellar high grade anaplastic astrocytoma (WHO Grade III) or glioblastoma multiforme (WHO Grade IV) (Arm A) or diffuse intrinsic brainstem glioma (Arm B) in whom no effective therapies were available. Histologies were to be reviewed by central independent pathological review within 2 weeks of enrollment. Diffuse intrinsic tumors of the brainstem were eligible on radiological and clinical criteria. Relapsed disease was defined as either the appearance of one or more new lesions at sites consistent with the natural history of the disease or disease progression in a pre-existing, previously treated lesion. Patients with HGA must have shown unequivocal evidence of relapse as demonstrated by two gadolinium-enhanced magnetic resonance imaging (Gd-MRI) or contrast-enhanced computerized axial tomography (CT) scans after failing standard radiation therapy.
- Patients must have been previously treated with standard radiation therapy.
- Patients must have had completion of radiation therapy greater than or equal to 6 weeks from date of relapse for HGA and greater than or equal to 8 weeks from date of relapse for brainstem glioma.
- Patients must have had measurable disease with an enhancing bidimensional lesion demonstrated on Gd-MRI within 14 days of starting SCH 52365 (baseline MRI). The minimum size for a lesion to be considered measurable must have been 8 mm x 8 mm. Patients with debulking surgery at the time of relapse must have had a Gd-MRI within 72 hours after surgery, and this was to be the baseline MRI of the study. If a baseline scan could not be performed within 72 hours after surgery, a period of at least 4 weeks after surgery must have

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elapsed before a further scan could be accepted as a baseline evaluation and no additional oncology therapy (except for steroids) were to be allowed during that period of time.

- Patients must have been administered TMZ within 4 weeks inclusive of date of relapse or within 3 weeks, inclusive, of date of surgery, if surgery was performed after the diagnosis of relapse. If a patient could not start treatment with TMZ within 3 weeks of surgery inclusive, the patient case was to be discussed with the SPRI Project Physician/Director or designee before allowing the patient on study.
- Patients must have been on a non-increasing dose of steroids for 7 days prior to administration of TMZ.
- Patients may have previously received one, but no more than one, prior chemotherapeutic regimen. This can include exposure to nitrosourea.
- Patients may not have had prior craniospinal irradiation (CSI) or bone marrow transplant or high dose therapy with peripheral blood stem cell rescue.
- Common Toxicity Criteria (CTC) Performance Status of 0, 1 or 2 (Protocol **Appendix C**. A Performance Status of 3 was acceptable for brainstem glioma patients (Arm B) only. Patients with a CTC Grade 4 performance status could have been eligible for enrollment only if due to immobilization (confined to wheel chair) and only for brainstem glioma patients after prior authorization from SPRI Project Physician/Director or designee.
- Laboratory values (performed 14 days prior to administration of TMZ):
  - Absolute neutrophil count (ANC) greater than or equal to  $1.0 \times 10^9/L$
  - Platelet count greater than or equal to  $100 \times 10^9/L$
  - Hemoglobin greater than or equal to 9 gm/dL
  - Urea and serum creatinine less than or equal to 1.5 x the upper limit of laboratory normal for that age group
  - Serum total bilirubin within the upper limit of laboratory normal
  - SGOT or SGPT less than or equal to 2 times upper limit of laboratory normal
  - Alkaline phosphatase <2 times upper limit of laboratory normal

**Duration of Treatment:** Until unacceptable toxicity, disease progression, or a maximum of 2 years.

**Criteria for Evaluation:** 1) Overall Response: Subjects were to be evaluated for overall tumor response during each cycle (objective response from Gd-MRI scans according to a modified WHO Reporting of Response if MRI has been performed or clinical assessment). To assess all tumor sites, Gd-MRI was to be performed on the last day of Cycles 2, 3, 6, 9, and 12 or within one week prior to that day. Gd-MRI was to be used throughout the study, and performed at the same institution. Copies of scans were made available for central review at a committee of the UKCCSG and the SFOP. Comparison of objective assessments, excluding progressive disease, were to be based upon major changes in tumor size on the MRI compared to the baseline MRI. Determination of progressive disease was to be based on comparison to the previous scan with the smallest measurements. If a response (complete or partial) was documented, then radiologic studies to assess all tumor sites were to be repeated 4 weeks from the date of the overall response (CR or PR) was initially determined or within one week of that day. 2) Progression-Free and Overall Survival: secondary endpoints such as progression free survival (time from date of first dose of TMZ to the date of progression or death, whichever came first) and overall survival were to be reported.

**Statistical Methods:** 30 HGA subjects were to be enrolled onto Arm A to allow for 25 evaluable subjects to be part of the efficacy analysis. HGA Subjects from the original Phase 1 dose escalation part of this study were not included in the analysis for Arm A due to the wide TMZ dose range given these subjects as part of the dose escalation study. 30 BSG subjects were to be enrolled to allow for 25 evaluable subjects to be part of Arm B. The total of 25 evaluable BSG subjects included data from 8 eligible Phase 1 subjects from the original Phase 1 portion of this study. For the primary efficacy measurement, the number of subjects that responded were to be tabulated and the response rate with 95% confidence interval was to be provided for each histology. The secondary efficacy analyses were Progression-Free Survival (PFS) and Overall Survival (OS). PFS was measured from the date of first study drug to the date of progression or death, whichever came first. Overall survival (OS) was measured from date of first study drug to date of death or last evaluation. The product limit method (Kaplan-Meier [K-M]) was used to estimate PFS and OS. Median PFS, OS, and K-M estimates were to be provided.

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### Protocol Amendments:

#### **Amendment No. 1**

- Clarifications to language in the Introduction.
- Alteration of dose levels to 80% of adult dose level from same as adult dose levels. Deletion of starting dose of 50 mg/m<sup>2</sup>/day (Dose Level 1).
- Changes in definitions to MTD, DLT, and DLT stopping rules.
- Addition of History and PE, Weight and Vital Signs, PK, Hematologic Tests, Serum Chemistries, and Evaluable Lesion Assessments at Cycle 1 day of dosing.
- Deletion of SPRI End Organ Toxicity Grading Scale for use in SAE grading.
- Clarifications and changes to Pharmacokinetic methods.

#### **Amendment No. 2**

- Changes to Rationale for Study and Study Design with new data from adult studies.
- Updating of Appendix A for SAEs.

#### **Amendment No. 3**

- Amended inclusion criteria to reflect time from prior radiation therapy to subjects based on prior nitrosourea or CSI.

#### **Amendment No. 4**

- Added that performance status of 3 was acceptable for brain stem glioma subjects only.
- Added Grade 4 thrombocytopenia to definition of DLT.
- Added definition of AE grading if not defined by CTC criteria.
- Added definition of finalization of database as when all subject have completed 6 cycles or have withdrawn from study.

#### **Amendment No. 5**

- Addition of a Phase 1 extension study to examine the safety and efficacy in a population of subjects with brain stem glioma or high-grade astrocytoma (30 subjects per arm).

#### **Amendment No. 6**

- Deleted exclusion criteria for subjects with mixed histology WHO Grade 3 or 4 tumors (eg, oligoastrocytoma or ganglioglioma).

#### **Amendment No. 7**

- Changed maximum duration of TMZ treatment from 1 year to 2 years.

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**Title of Study:** A Phase 2 Study of Temodal® (SCH 52365; Temozolomide, IND # 52797) in Children and Adolescents With Recurrent Central Nervous System (CNS) Tumors (Protocol No. H97-017)

**Investigator(s):** Multicenter Study

**Center(s):** Multicenter

**Studied Period:** 23 Jan 1998 to 26 JUL 2000

**Clinical Phase:** 2

**Objective(s):**

The objectives of the study were to: 1). Determine the response rate to temozolomide (TMZ) in several strata of recurrent CNS tumors of childhood. The target tumors were: High Grade Astrocytomas/Gliomas (Grade 3 astrocytoma, Grade 4 astrocytoma, anaplastic astrocytoma or glioblastoma multiforme), Low Grade Astrocytomas/Gliomas (Grade 1 astrocytoma, Grade 2 astrocytoma, pilocytic astrocytoma or low grade astrocytoma), CNS Primitive Neuroectodermal Tumor (PNET)/medulloblastoma, Ependymoma, Brainstem glioma, and Other CNS tumors.

2). Further assess the toxicity of TMZ in a larger group of subjects treated at the maximally tolerated dose (MTD).

**Methodology:** This was a non-randomized, uncontrolled, multi-center, open-label, multiple dose study in children with recurrent CNS tumors designed to determine the efficacy and safety of temozolomide administered orally at 200 mg/m<sup>2</sup>/day (subjects without prior craniospinal irradiation [CSI]) or 180 mg/m<sup>2</sup>/day (subjects with prior CSI) once a day on Days 1-5 of each 28 day cycle. The target tumors included the following: Astrocytomas/Gliomas; CNS Primitive Neuroectodermal Tumor/Medulloblastoma; Ependymoma; Brainstem Glioma; and Other CNS Tumors. Subjects were stratified for response rate analysis based on these disease groups. New courses of temozolomide began on Day 28 following the previous cycle. Subjects were enrolled using a two-stage design, enrolling 10 subjects at each of two stages. Following two cycles, subjects were evaluated for response, using the same imaging modality as at enrollment. Subjects were registered on study at the CCG Operations Center before beginning treatment. Eligibility criteria were met within two weeks of study entry. The documentation of measurable disease was obtained within two weeks of study entry. Subjects who benefited from TMZ (stable disease, partial, or complete response) following 2 cycles of treatment may have continued to receive the drug until progression or a total of 12 cycles had been given.

**Number of Subjects:** 122 subjects were enrolled to this study; 63% of subjects were male, 94% were Caucasian, and 83% had received prior radiation therapy.

**Diagnosis and Criteria for Inclusion:** The significant criteria for inclusion were as follows: a). Subjects must have been no greater than 21 years of age when originally diagnosed with the malignancy to be treated on this protocol. b). Subjects must have had histologic verification of the malignancy at original diagnosis (excluding brain stem tumors). Eligible histologies included the following: High Grade Astrocytomas/Gliomas (Grade 3 astrocytoma, Grade 4 astrocytoma, anaplastic astrocytoma or glioblastoma multiforme), Low Grade Astrocytomas/Gliomas (Grade 1 astrocytoma, Grade 2 astrocytoma, pilocytic astrocytoma or low grade astrocytoma), CNS Primitive Neuroectodermal Tumor/medulloblastoma, Ependymoma, Brainstem glioma, and Other CNS tumors. c). Subjects must have had measurable disease, documented by radiographic, or histologic criteria (for bone marrow), and have relapsed or become refractory to conventional therapy. d). Subjects must have had a performance status of 0, 1, or 2. e). All subjects must have had adequate bone marrow function.

**Dose, Mode of Administration, Batch No(s):** Temozolomide, 180 mg/m<sup>2</sup>/day or 200 mg/m<sup>2</sup>/day for Days 1 to 5 of each cycle. Batch numbers are available at the COG administrative center.

**Duration of Treatment:** Temozolomide was administered for two cycles; subjects were then evaluated for response. If they had stable disease (SD) or were in response (complete response [CR] or partial response [PR]), they could have received temozolomide until evidence of disease progression or for a total of 12 cycles.

**Criteria for Evaluation:** Subjects who received 5 days of therapy with TMZ and were observed for at least 14 days after the start of treatment without other anticancer therapy were considered evaluable for response. The best response obtained during treatment was used to quantify the best response to therapy. The same method (MRI scan with and without gadolinium enhancement or CT scan with and without contrast) used to quantify tumor status prior to starting this study was used to measure tumor status after treatment.

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**Statistical Methods:** The primary endpoint in this trial was the response rate (complete or partial response), based on objective criteria (CR, PR, SD, or progressive disease [PD]). For the purposes of response rate determination, each disease category was considered separately. For each stratum, this trial was designed to determine TMZ to have insufficient activity for further investigation with a probability of 0.05 if the true response rate is 30%. For each stratum, this trial was designed to determine TMZ to be of sufficient activity to warrant further investigation with a probability of 0.07 if the true response rate is 5%.

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