

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 21029**

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**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW

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NDAs: 21-029

Submission Dates: August 12, 1998  
November 6, 1998  
November 18, 1998

Drug Name: Temozolomide (Temodal®)

Dosage Form: 5 mg, 20 mg, 100 mg, and 250 mg Immediate-Release Capsules For Oral Administration

Sponsor: Schering Corporation  
Kenilworth, NJ

Reviewer: Safaa Ibrahim, Ph.D.

Type of Submission: New Drug Application (NME)

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### 1. SYNOPSIS

Temozolomide (Temodal®, SCH 52365) is a cytotoxic alkylating agent of the imidazotetrazine class and is chemically related to the approved chemotherapeutic agent dacarbazine. It is spontaneously hydrolyzed at physiologic pH to the cytotoxic triazine, 3-methyl-(triazene-1-yl)imidazole-4-carboxamide (MTIC). MTIC is also the active metabolite of dacarbazine; however, unlike temozolomide, dacarbazine must be metabolically converted in the liver to MITC. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA at the O<sup>6</sup> and N<sup>7</sup> positions of guanine. The final degradation product of both temozolomide and dacarbazine is 5-aminoimidazole-4-carboxamide (AIC), an intermediate in purine and nucleic acid biosynthesis.

Temodal® is being proposed for the treatment of patients with malignant glioma (glioblastoma multiforme) and anaplastic astrocytoma) at first relapse and as first line treatment for patients with advanced metastatic malignant melanoma. The proposed dose of Temodal® is 200 mg/m<sup>2</sup> once a day for 5 days per 28-day cycle for patients that were previously untreated with chemotherapy. In previously treated patients, the initial dose is 150 mg/m<sup>2</sup> once a day to be increased in the second cycle to 200 mg/m<sup>2</sup> once a day, provided that the absolute neutrophil count is  $\geq 1.5 \times 10^9/L$  and the thrombocyte count is  $\geq 100 \times 10^9/L$  on Day 1 of the next cycle.

A validated assay method was used to analyze temozolomide in plasma and urine. Using this method, the sponsor studied the clinical pharmacology and biopharmaceutics of temozolomide in cancer patients and provided individual study reports of their investigations. The results are summarized as follows:

### 1.1 Clinical Pharmacology and *In Vivo* Metabolism

Temozolomide has a mean apparent volume of distribution of 0.4 L/kg (%CV=13%). It is weekly bound to human plasma proteins; the mean percent bound of drug-related total radioactivity is 15%.

Temozolomide is spontaneously hydrolyzed at physiologic pH to the active metabolite, MTIC and to temozolomide acid metabolite. MTIC is further metabolized to AIC which is known to be an intermediate in the purine and nucleic acid biosynthesis. Cytochrome P450 is believed not to play a role in metabolic conversion of temozolomide.

Plasma concentrations of temozolomide decline rapidly with a mean elimination half-life of 1.8 hours (%CV=6%). Systemic exposure to MTIC and AIC is low with a mean AUC metabolite/parent drug ratio of 2.4% and 23%, respectively.

A total of 38.5% administered radioactive dose is recovered in urine and feces over 7 days (37.7% and 0.8%, respectively). The majority of the dose is recovered in urine as AIC (12%), unchanged temozolomide (5.6%), temozolomide acid metabolite (2.3%), and unidentified polar metabolite(s) (17%).

Population pharmacokinetic analyses of data from the four Phase II studies have revealed the followings:

- Age has no effect on the pharmacokinetics of temozolomide.
- Females tend to have a lower clearance (5 %) than males
- Tobacco use has no effect on the pharmacokinetics of temozolomide.
- No influence of renal impairment ( $CL_{cr} = 36-230 \text{ ml/min/m}^2$ ) has been noted on the pharmacokinetics of temozolomide. The Pharmacokinetics of temozolomide in patients with severe renal dysfunction ( $CL_{cr} < 36 \text{ ml/min/m}^2$ ) have not been studied. Caution should be exercised in patients with severe hepatic dysfunction when they are treated with Temodal®.

In an interim single-dose study, it is shown that patients with mild-to-moderate hepatic dysfunction (Child's-Pugh Class I - II) have similar pharmacokinetics as in patients with normal hepatic function. Dosage adjustment is not recommended in patients with mild-to-moderate hepatically impaired patients. Patients with severe hepatic dysfunction have not been adequately evaluated; only one patient has been studied so far. Caution

should be exercised in patients with severe hepatic dysfunction when they are treated with Temodal®.

At dose levels of 100 and 200 mg/m<sup>2</sup>, pediatric patients (3-17 years of age) have higher C<sub>max</sub> (37% and 17%, respectively) and AUC (40% at both dose levels) than adult patients. However, pediatric and adult patients have similar oral clearance and apparent volume of distribution values. Thus, no dosage adjustment is necessary in pediatric patients of 3-17 years of age.

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, prochlorperazine has 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.

Population analysis of Phase II data in cancer patients has shown that the incidence of neutropenia and thrombocytopenia during the first cycle of temozolomide administration (150 and 200 mg/m<sup>2</sup>/day for 5 days) is 7.4% and 5.3%, respectively. Females have higher incidence of neutropenia and thrombocytopenia than males (11.9% versus 4.7% and 9.1% versus 2.9%, respectively). Elderly patients (≥ 70 years of age) have a higher incidence of neutropenia and thrombocytopenia (25% and 20%, respectively). Higher doses and greater exposure (AUC) are associated with the incidence of neutropenia and thrombocytopenia.

## 1.2 Biopharmaceutics

Temozolomide is rapidly and completely absorbed after oral administration (T<sub>max</sub> = 1 hour). Food reduces both the rate and extent of absorption of temozolomide. Mean C<sub>max</sub> and AUC<sub>0-∞</sub> decreased by 32 % and 9 %, respectively; T<sub>max</sub> increased 2-fold (from 1.1 to 2.25 hours) when temozolomide was administered with food. During clinical trials, patients were fasted overnight and 2 hours before temozolomide administration.

The sponsor is proposing to market temozolomide as 5 mg, 20 mg, 100 mg, and 250 mg immediate-release capsules for oral administration. Capsules are not compositionally proportional. A bioequivalency study has not been conducted since the clinical capsules are the same as the commercial capsules. A dosage strength bioequivalency study has not been conducted. Switchability is not recommended since

capsules are not compositionally proportional.

Dissolution test method for temozolomide capsules (5 mg, 20 mg, 100 mg, and 250 mg) uses USP Apparatus 1 (Basket Stirrer) at 100 rpm and 500 ml of water for the 5 mg capsule and 900 ml of water for the 20, 100, and 250 mg capsules at  $37 \pm 0.5^\circ \text{C}$ . The sponsor proposes dissolution specification of not less than      % dissolved in      minutes.

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## 2. Comments

[To be sent to the firm]

1. The Agency recommends the following dissolution methodology and specification for Temodal<sup>®</sup> capsules (5 mg, 20 mg, 100 mg, and 250 mg):

<u>Apparatus:</u>	USP Apparatus 1 (Basket Stirrer)
<u>Speed:</u>	100 rpm
<u>Medium:</u>	water at $37 \pm 0.5^\circ \text{C}$ (500 ml for the 5 mg capsule and 900 ml for the other strengths)
<u>Specification:</u>	{ <u>    </u> % dissolved in <u>    </u> minutes

2. In Study # H96-034, interim pharmacokinetic data were provided in patients with hepatocellular carcinoma. The sponsor is requested to resubmit the data for review when this study is completed.
3. The sponsor claims that temozolomide does not alter the metabolism of other drugs (i.e., by competitive inhibition); however, *in vitro* inhibition data with human liver microsomes have not been provided to support this claim. The sponsor mentions that since temozolomide is primarily degraded to MTIC by non-enzymatic pH-dependent chemical hydrolysis, *in vitro* inhibition studies with human microsomes were not necessary and thus, not conducted. The non-enzymatic pH-dependent hydrolysis of temozolomide does not preclude the fact that temozolomide may have the potential to inhibit the metabolism of other drugs which are substrates of cytochrome P450 isoenzymes. Therefore, the sponsor should to conduct *in vitro* inhibition studies with human liver microsomes to determine the effect of temozolomide on cytochrome P450 isoenzymes.
4. In future studies, the sponsor is advised to assess the pharmacokinetics of the active species, MTIC, in addition to the parent drug, temozolomide.
5. The sponsor is requested to incorporate the OCPB's pharmacokinetic labeling as outlined in pages # 5-9.

[To the Medical Reviewer]

6. Population analysis of Phase II data has revealed that the incidence of neutropenia and thrombocytopenia is high in elderly patients of  $\geq 70$  years of age (25% and 20%, respectively). Population analysis has also revealed that females have higher incidence of neutropenia and thrombocytopenia than males (11.9% versus 4.7% and 9.1% versus 2.9%, respectively). Therefore, caution should be exercised in elderly patients of  $\geq 70$  years of age and female patients when they are treated with Temodal®.
  7. Patients with severe hepatic and renal dysfunction have not been adequately evaluated. Therefore, caution should be exercised in these patients when they are treated with Temodal®.
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### 3. OCPB's Pharmacokinetic Labeling

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pages of trade

secret and/or

confidential

commercial

information

#### **4. Recommendations**

The NDA submitted for temozolomide capsules has adequately addressed the Office of Clinical Pharmacology and Biopharmaceutics' requirements. The sponsor is requested to adopt the dissolution methodology and specification as outlined in Comment #1, to address Comments # 2-4, and to incorporate the OCPB's pharmacokinetic labeling as outlined on pages 5-9.

Please forward Comments #1-5 and OCPB's pharmacokinetic labeling to the firm.

Comments # 6 and 7 are to the Medical Reviewer.





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## Attachments

<u>Attachment 1</u>	Sponsor's Proposed Labeling
<u>Attachment 2</u>	Sponsor's Individual Study Summaries
<u>Attachment 3</u>	Sponsor's Dissolution Data Summary
<u>Attachment 4</u>	Sponsor's Analytical Summary

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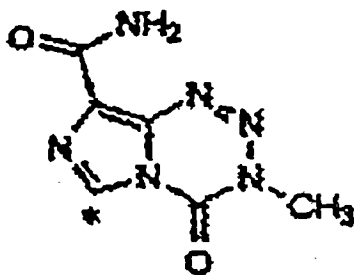
## 6. Background

Temozolomide (Temodal®, SCH 52365) is a cytotoxic alkylating agent related to a series of imidazotetrazinones.

### PHYSICO-CHEMICAL PROPERTIES:

Temozolomide is a white to light tan/light pink powder. It is slightly soluble in aqueous solution (2-4 mg/ml), acetone, acetonitril, and methanol. It is soluble in dimethylsulfoxide (33 mg/ml) and very slightly soluble in ethyl acetate and ethanol (0.4-0.6 mg/ml). It has no pKa because it has no functional groups that can be protonated or deprotonated at pH 1-13. The partition coefficient is 22.4.

### STRUCTURAL FORMULA:



### CHEMICAL FORMULA:

The Chemical name for temozolomide is 8-carbamoyl-3-methylimidazo[5,1-d]-1,2,3,5-tetrazin-4(3H)-one. It has an empirical formula of  $C_6H_6N_6O_2$  and a molecular weight of 194.

### INDICATION AND USAGE:

Temodal® is being proposed for the treatment of patients with malignant glioma ((glioblastoma multiforme and) anaplastic astrocytome) at first relapse and as first line treatment for patients with advanced metastatic malignant melanoma.

HOW IT IS SUPPLIED:

Temodal® will be supplied as immediate-release gelatin capsules containing 5 mg (green imprint), 20 mg (brown imprint), 100 mg (blue imprint), and 250 mg (black imprint) of temozolomide for oral administration.

PROPOSED DOSAGE AND ADMINISTRATION (FIRM'S):

The proposed dose of Temodal® is 200 mg/m<sup>2</sup> once a day for 5 days per 28-day cycle for patients whom were previously untreated with chemotherapy. In previously treated patients, the initial dose is 150 mg/m<sup>2</sup> once a day to be increased in the second cycle to 200 mg/m<sup>2</sup> once a day, providing that the absolute neutrophil count is  $\geq 1.5 \times 10^9/l$  and the thrombocyte count is  $\geq 100 \times 10^9/l$  on the first day of the next cycle.

MANUFACTURER AND MANUFACTURING SITE:

Temodal® will be manufactured and packaged by  
and Schering Corporation, Kenilworth, New Jersey.

APPEARS THIS WAY  
ON ORIGINAL

## Summary of Clinical Pharmacology and Biopharmaceutics

The clinical pharmacology and biopharmaceutics of temozolomide were evaluated in 7 studies conducted in Europe and the United States. In all the studies, the dose of temozolomide was calculated on the basis of milligrams per square meter of body surface area as measured at baseline ( $\text{mg}/\text{m}^2$ ).

### 7. Clinical Pharmacology and In Vivo Metabolism

#### 7.1 Distribution and Protein Binding

##### In Vivo:

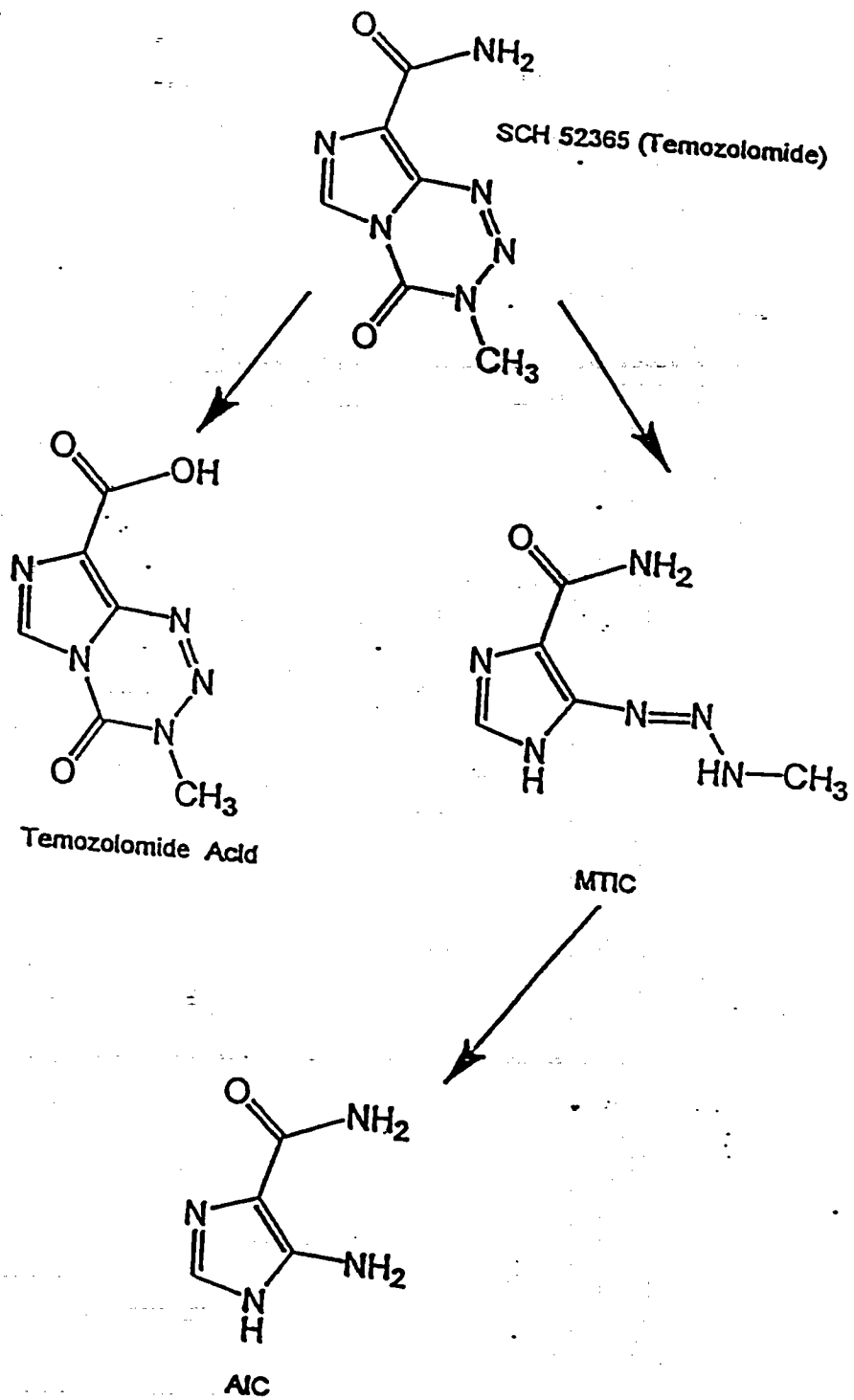
Temozolomide has a mean apparent volume of distribution of 0.4 L/kg (%CV=13%) following daily 200  $\text{mg}/\text{m}^2$  oral doses for five days to six cancer patients [Study # I93-114, Attachment 2, pp. 2].

##### In Vitro:

Because of stability concerns, *in vitro* plasma protein binding studies were performed for the drug-related radioactivity rather than for temozolomide itself [Study # C95-006, Attachment 2, pp. 25]. The percentage of protein-bound of drug-related radioactivity averages 15%.

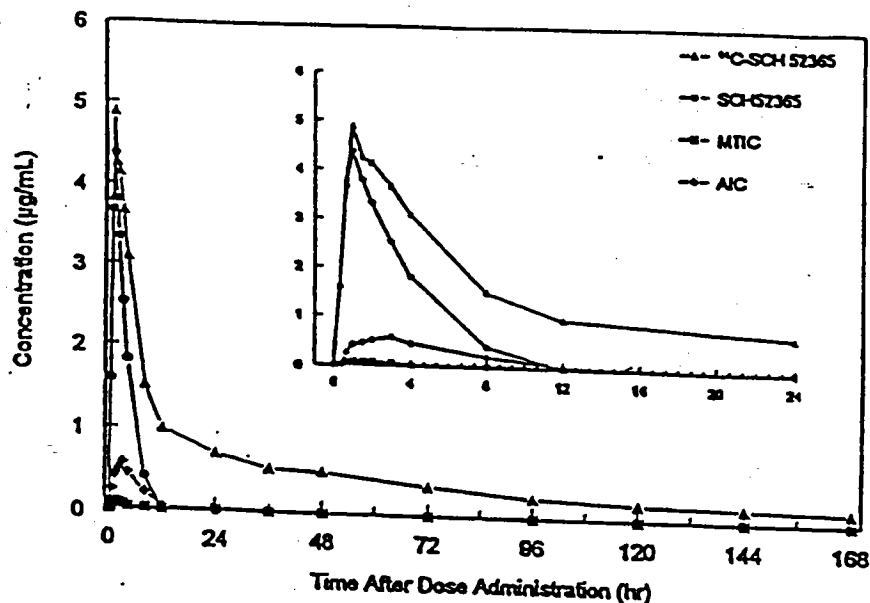
#### 7.2 Metabolism

Temozolomide undergoes spontaneous hydrolysis at physiologic pH to the active metabolite, 3-methyl-(triazene-1-yl)imidazole-4-carboxamide (MTIC) and also to temozolomide acid metabolite (See Figure 1). MTIC is further degraded to 5-aminoimidazole-4-carboxamide (AIC). AIC is known to be an intermediate in purine and nucleic acid biosynthesis. It is believed that cytochrome P450 does not play a role in the hydrolysis of temozolomide (no data provided). It is shown that the majority of radioactivity in plasma is associated with the parent drug, 74 % and 89% at 1 hour and 4 hours, respectively, after oral administration of a 200 mg (70  $\mu\text{Ci}$ ) of  $^{14}\text{C}$ -temozolomide to 6 cancer patients [Study # C95-006, Attachment 2, pp. 25]. Systemic exposure to MTIC and AIC is low (See Figure 2). Mean AUC ratio of metabolite/parent drug is 2.4% (%CV=59%) and 23% (%CV=15%) for MTIC and AIC, respectively. The elimination of MTIC and AIC is paralleled that of temozolomide, suggesting a formation-rate limited elimination for both metabolites. The focus of this NDA is the parent drug, temozolomide.



**Figure 1** Proposed Metabolic/Degradation Pathway for Temozolomide

Figure 2: Mean Plasma Concentration/Time Profiles of Total radioactivity, Temozolomide (SCH 52365), MTIC, and AIC



### 7.3 Excretion

#### Mass-Balance:

Following a single 200 mg (70 µCi) oral dose of <sup>14</sup>C-temozolomide to 6 male cancer patients, the mean recovery of radioactivity over 7 days in urine and feces is 37.7% and 0.8% of the dose, respectively, suggesting that renal excretion is the major pathway of temozolomide elimination [Study # C95-006, Attachment 2, pp. 50]. This incomplete total recovery (~38%) may be likely due to the conversion of temozolomide to AIC, which is known to be incorporated in the biosynthesis of purines and nucleic acids. A portion of the radioactivity may also be eliminated as <sup>14</sup>CO<sub>2</sub>. The majority of the radioactivity is recovered in urine as unchanged temozolomide (5.6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolite(s) (17%).

#### Oral Clearance and Elimination Half-life:

Following daily 200 mg/m<sup>2</sup> oral doses for five days to 6 cancer patients, mean oral clearance of temozolomide and its elimination half-life are 2.5 ml/min/kg (%CV=17%) and 1.8 hours (%CV=6%), respectively [Study # I93-114, Attachment 2, pp. 2].



## 7.4 Single-Dose Kinetics

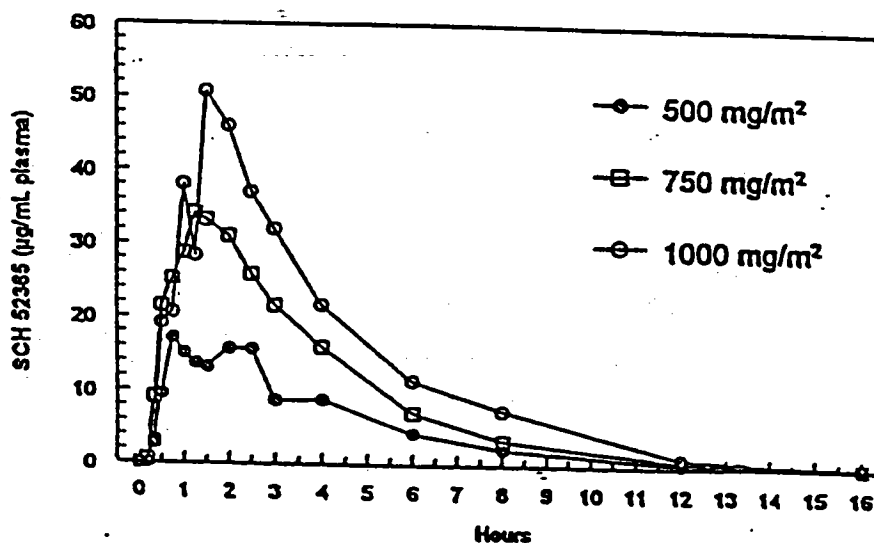
Single-dose kinetics of temozolomide were evaluated in study # C93-196 [Attachment 2, pp. 91] during the first cycle in patients with advanced cancer. Table 1 shows the mean (%CV) pharmacokinetic parameters:

PARAMETER	DOSE		
	500 mg/m <sup>2</sup> (n=3)	750 mg/m <sup>2</sup> (n=6)	1000 mg/m <sup>2</sup> (n=2)
AUC <sub>0-∞</sub> (μg.hr/ml)	75 (14%)	138 (13%)	196
C <sub>max</sub> (μg/ml)	22.8 (17%)	40.8 (15%)	51.6
T <sub>max</sub> (hr)	1.3 (76%)	1.3 (37%)	1.75
t <sub>1/2</sub> (hr)	1.8 (7%)	1.9 (10%)	1.7
CL/F (ml/min/kg)	2.8 (11%)	2.5 (23%)	2.3
CL <sub>r</sub> (ml/min/kg)	0.17 *	0.16 (76%)**	0.19
V <sub>darea</sub> /F (L/kg)	0.43 (15%)	0.40 (21%)	0.35

\*(n=2)

\*\* (n=4)

Figure 3: Mean Plasma temozolomide Concentration/Time Profiles Following Single-Dose oral Administration to Patients with Advanced Cancer



## 7.5 Multiple-Dose Kinetics

Multiple-dose kinetics were examined during the first cycle in two studies [# I93-114 and C94-022, Attachment 2, pp. 2 & 67]. In study I93-114, doses of 100-250 mg/m<sup>2</sup> were administered once a day for 5 consecutive days to patients with advanced cancer. The results are shown in the figures and table below.

Figure 4: Mean Plasma Temozolomide Concentration/Time Profiles on Day 1

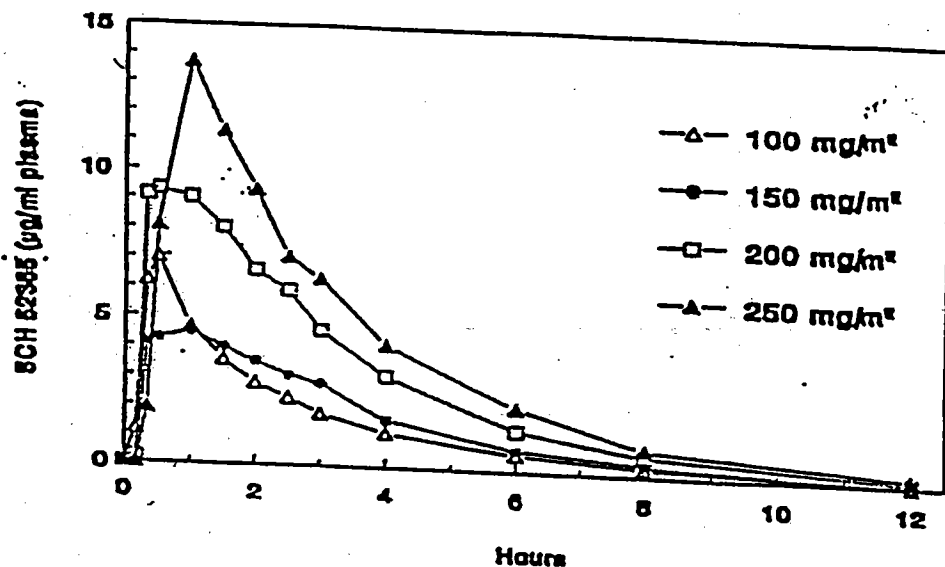


Figure 5: Mean Plasma Temozolomide Concentration/Time Profiles on Day 5

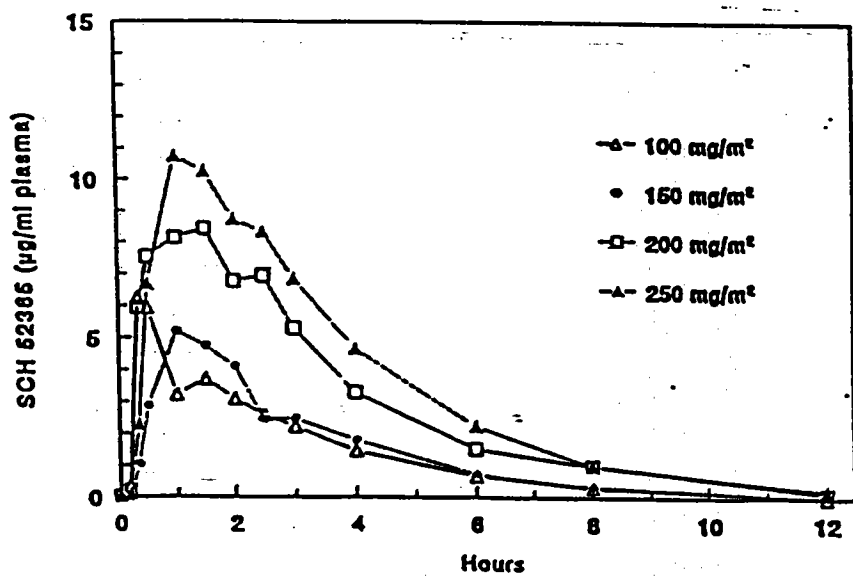


Table 2: Mean (%CV) pharmacokinetic parameters determined for temozolomide on Days 1 and 5

PARAMETER	DOSE			
	100 mg/m <sup>2</sup> (n=3)	150 mg/m <sup>2</sup> (n=3)	200 mg/m <sup>2</sup> (n=6)	250 mg/m <sup>2</sup> (n=3)
AUC <sub>0-24hr</sub> (μg.hr/ml)				
Day 1	15.5 (8%)	17.0 (35%)	33.2 (15%)	43.0 (7%)
Day 5	16.7 (9%)	16.8 (13)	34.5 (15%)	42.6 (3%)
C <sub>max</sub> (μg/ml)				
Day 1	7.0 (21%)	5.8 (56%)	13.9 (46%)	13.7 (17%)
Day 5	6.9 (30%)	5.7 (27%)	12.8 (39%)	12.2 (15%)
T <sub>max</sub> (hr)				
Day 1	0.50 (0%)	0.94 (62%)	0.94 (87%)	1.0 (0%)
Day 5	0.39 (25)	1.17 (25%)	1.25 (55%)	1.3 (78%)
t <sub>1/2</sub> (hr)				
Day 1	1.7 (4%)	1.7 (4%)	1.8 (6%)	1.9 (8%)
Day 5	1.8 (4%)	1.7 (15%)	1.8 (9%)	1.8 (5%)
CL/F (ml/min/kg)				
Day 1	2.5 (10%)	4.1 (45%)	2.5 (17%)	2.4 (5%)
Day 5	2.5 (13%)	3.8 (23%)	2.5 (18%)	2.5 (9%)
CL <sub>r</sub> (ml/min/kg)				
Day 1	0.12 (42%)	0.21 (10%)	0.19 (15%)	0.17 (8%)
Day 5	0.12 (29%)	0.26 (16%)	0.18 (45%)	0.23 (17%)
V <sub>darea</sub> /F (L/kg)				
Day 1	0.37 (9%)	0.63 (49%)	0.39 (13%)	0.40 (4%)
Day 5	0.39 (15%)	0.56 (20%)	0.38 (16%)	0.39 (9%)
R (AUC <sub>0-24hr</sub> ratio of DAY5/Day1)	1.0 (4%)	1.04 (22%)	1.04 (8%)	0.99 (4%)

No accumulation occurs for temozolomide upon once a day administration; the mean AUC<sub>0-24h</sub> ratio (R) is approximately equal one. Oral clearance (CL/F) and apparent volume of distribution (V<sub>darea</sub>/F) do not change across doses or between Days 1 and 5, indicating that temozolomide exhibits both dose- and time-independent kinetics. Interpatient coefficient of variation (%CV) is low (4-56%), except for T<sub>max</sub> (0-87%).

Similar results are obtained in study # C94-022 during the first cycle following daily oral administration of 100 mg/m<sup>2</sup> (n=6), 150 mg/m<sup>2</sup> (n=12), and 200 mg/m<sup>2</sup> (n=6) doses for 5 consecutive days to patients with advanced cancer. The pharmacokinetics of temozolomide are similar in patients who were heavily pre-treated with therapy (chemo- and/or radiation), defined as poor risk group and those who were less heavily pre-treated with therapy, defined as good risk group.

## 7.6 Dose-Proportionality

Dose proportionality was evaluated in one single-dose, parallel-design study involving 11 cancer patients [C93-169, Attachment 2, pp.91] and in two single- and multiple-dose, parallel-design, studies [I93-114 and C94-022, Attachment 2, pp. 2 & 67] involving 15 and 24 cancer patients, respectively. The results of these studies indicate that temozolomide exhibits linear kinetics over the single oral doses of 100-1000 mg/m<sup>2</sup> and over the daily oral doses of 100-250 mg/m<sup>2</sup> administered for 5 consecutive days, which covers the therapeutic dosing range for the drug.

## 7.7 Special Populations

The influence of patient covariates on the pharmacokinetics and pharmacodynamics (PK/PD) of temozolomide was evaluated using a population analysis approach on the data from the four Phase I and Phase II studies [Report # 97206350, Attachment 2, pp.107]. The database consisted of 359 patients with glioblastoma multiforme and anaplastic astrocytoma who were administered temozolomide as 100-200 mg/m<sup>2</sup> daily for 5 days every 28 days or 500-100 mg/m<sup>2</sup> as a single dose every 28 days (Phase I studies) and as 150 mg/m<sup>2</sup> or 200 mg/m<sup>2</sup> daily for 5 days every 28 days (Phase II studies). Phase I studies used an extensive plasma sampling scheme and were used for model building and validation. Phase II studies used a sparse sampling scheme (i.e., prospectively developed) and were used to evaluate the effect of patient covariates on the PK/PD of temozolomide. Patient covariates included age, gender, weight, height, body surface area (BSA), smoking, creatinine clearance as an index of renal function (calculated from serum creatinine and Cockcroft/Gault equation), serum chemistry data as indices of hepatic function (e.g. SGOT, SGPT, alkaline phosphatase, bilirubin, albumin, and total protein), and concomitant medications. A summary of patient demographics are shown in Table 3:

**Table 3 Summary of Demographic Variables of the Patients Included in the Population Pharmacokinetic Analysis.**

Study	N(N <sub>F</sub> )	Age (yr)	Weight (kg)	Height (cm)	BSA (m <sup>2</sup> )	Serum Creatinine (mg/dL)	N <sub>NC</sub>	Smokers (Non-Smokers)
I93-114	15 (4)	25 - 63	57 - 102	155 - 188	1.58 - 2.28	0.70 - 1.07	1	—
I93-114A	15 (6)	27 - 71	51 - 82	157 - 188	1.50 - 2.10	0.59 - 1.37	1	—
C93-169	11 (5)	33 - 73	45 - 97	160 - 188	1.41 - 2.25	0.60 - 1.50	4	—
C94-022	24 (11)	32 - 78	49 - 108	150 - 193	1.41 - 2.26	0.50 - 1.30	6	—
I94-122	117 (45)	24 - 77	50 - 127	154 - 197	1.47 - 2.45	0.40 - 1.45 <sup>c</sup>	0	25( 91) <sup>c</sup>
I94-123	43 (19)	23 - 73	45 - 98	146 - 185	1.45 - 2.18	0.49 - 1.55	0	10( 33)
C94-123	73 (28)	19 - 76	49 - 145	147 - 190	1.43 - 2.51	0.40 - 1.60 <sup>b</sup>	4	14( 59)
C94-091	61 (20)	28 - 72	41 - 137	150 - 193	1.36 - 2.71	0.50 - 1.50 <sup>b</sup>	2	10( 51)
All	359 (138)	19 - 78	41 - 137	146 - 197	1.36 - 2.71	0.40 - 1.60	18	59(234)

Note: N<sub>F</sub>: number of females, N<sub>NC</sub>: number of non-Caucasian  
a: Data not available.  
b: 2 missing values not included.  
c: 1 missing value not included.

### **7.7.1 Age**

Age (range=19-78 years, n=359) has no influence on the pharmacokinetics of temozolomide (p=0.854). No dosage adjustment is necessary in elderly patients.

### **7.7.2 Gender**

Female patients (n=112) tend to have a lower clearance (adjusted to BSA) for temozolomide (about 5.3%) than male patients (n=182) (p=<0.001). This may be not clinically significant and dosage adjustment is not necessary in female patients.

### **7.7.3 Race**

The effect race on the pharmacokinetics of temozolomide has not been studied since most patients enrolled in the pharmacokinetic studies were Caucasians.

### **7.7.4 Tobacco Use**

Oral clearance of temozolomide is similar in smokers (n=59) and non-smokers (n=234); 5.45 L/hr/m<sup>2</sup> and 5.58 L/hr/m<sup>2</sup> (p=0.09), respectively.

### **7.7.5 Creatinine Clearance**

Creatinine clearance (36-230 ml/min/m<sup>2</sup>) has no effect on the oral clearance of temozolomide (adjusted to BSA) (p=0.181).

The pharmacokinetics of temozolomide have not been studied in patients with severe renal function (CLcr < 36 ml/min/ m<sup>2</sup>). Patients with severe renal dysfunction should use temozolomide with caution.

Temozolomide has not studied in patients under dialysis. However, it is predicted that temozolomide may be removed by dialysis; it is a low molecular weight compound (< 500 kDa), low protein-bound, and has a short half-life. Dialysis may be of value in case of overdosage with temozolomide

### **7.7.6 Hepatic Patients**

Population analysis of Phase II data have revealed that no obvious correlation is observed between BSA-adjusted clearance values for temozolomide and any of serum chemistry data (SGOT, SGPT, alkaline phosphatase, bilirubin, albumin, or total protein). In an interim report, the pharmacokinetics of temozolomide and MTIC were determined during the first cycle in 10 patients with advanced hepatocellular carcinoma

following once a day oral administration of 150 mg/m<sup>2</sup> for 5 consecutive days [Study # H96-034, Attachment 2, pp. 137]. Patients were divided into three groups: mild (n=5), moderate (n=4), and severe (n=1) according to Pugh's modification of Child's Classification of severity of liver disease.

Table 4: Mean (%CV) pharmacokinetic parameters of temozolomide and MTIC following oral administration of 150 mg/m<sup>2</sup> of temozolomide in patients with advanced hepatocellular carcinoma:

Parameter	Temozolomide				
	Group I (n=5) Mild	Group II (n=4) Moderate	Group III (n=1) Severe	I95-007 (n=12) Normal	C94-022 (n=12) Normal
AUC <sub>0-∞</sub> (μg.hr/ml)	26 (13%)	21 (16%)	14	24 (22%)	23 (13%)
C <sub>max</sub> (μg/ml)	8.9 (33%)	6.4 (29%)	3.8	8.2 (37%)	7.7 (35%)
T <sub>max</sub> (hr)	1.05 (54%)	1.4 (36%)	1.7	1.8 (97%)	0.85 (60%)
T <sub>1/2</sub> (hr)	1.8 (10%)	1.8 (4%)	1.9	1.8 (19%)	1.8 (7%)
CL/F (ml/min/m <sup>2</sup> )	94 (9%)	125 (15%)	174	194 (27%)*	111 (17%)
V <sub>darea</sub> (L/m <sup>2</sup> )	15 (12%)	19.5 (12%)	29.6	31 (34%)*	18 (18%)
	MTIC				
AUC <sub>0-∞</sub> (ng.hr/ml)	657 (37%)	587 (16%)	501	585 (20%)	
C <sub>max</sub> (ng/ml)	264 (58%)	242 (43%)	123	211 (48%)	
T <sub>max</sub> (hr)	1.0 (59%)	1.2 (38%)	1.2	1.9 (97%)	
T <sub>1/2</sub> (hr)	2.03 (24%)	1.9 (6%)	1.9	1.9 (37%)	
%AUC(MTIC/ Temozolomide)	2.6 (50%)	2.9 (16%)	3.5	2.7 (28%)	

\* (CL/F in ml/min and V<sub>darea</sub> in L)

These interim data reveal that the mild and moderate groups have similar pharmacokinetics for temozolomide and its metabolite, MTIC, to those with normal liver function [Studies # I95-007 and C94-002, Attachment 2, pp. 168 & 67]. In one patient with severe liver function, there is a trend for C<sub>max</sub> and AUC to decrease (50% and 37%, respectively) and CL/F and V<sub>darea</sub>/F to increase (54% and 66%, respectively) compared to patients with normal liver function. Dosage adjustment for Temodal® is not necessary in patients with mild-to-moderate hepatocellular carcinoma. Patients with severe hepatocellular carcinoma have not been adequately evaluated and therefore, Temodal® should be used with caution in these patients.

### 7.7.7 Pediatric Patients

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 2, pp. 151). 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 as 100-240 mg/m<sup>2</sup> daily doses for 5 consecutive days. The pharmacokinetics of temozolomide are similar in good risk and poor risk pediatric patients. The combined data from both groups are shown in Table 5:

Table 5: Mean (%CV) pharmacokinetic parameters determined for temozolomide on Day 5 in Pediatric Patients (Poor Risk and Good Risk Combined):

PARAMETER	DOSE				
	100 mg/m <sup>2</sup> (n=5)	120 mg/m <sup>2</sup> (n=3)	160 mg/m <sup>2</sup> (n=3)	200 mg/m <sup>2</sup> (n=5)	240 mg/m <sup>2</sup> (n=3)
AUC <sub>0-∞</sub> (μg.hr/ml)	24 (11%)	28 (17%)	37 (2%)	48 (17%)	17 (22%)
C <sub>max</sub> (μg/ml)	9.5 (42%)	9.3 (24%)	11 (32%)	15 (24%)	45 (16%)
T <sub>max</sub> (hr)	1.3 (75%)	1.4 (36%)	1.8 (53%)	1.8 (40%)	1.7 (46%)
t <sub>1/2</sub> (hr)	1.7 (11%)	1.7 (9%)	1.7 (8%)	1.7 (4%)	1.4 (22%)
CL/F (ml/min/kg)	2.8 (18%)	2.5 (20%)	2.7 (3%)	2.4 (21%)	3.0 (28%)
CL <sub>r</sub> (ml/min/kg)	0.15 (92%) (n=4)	0.26 (38%)	—	0.18 (83%) (n=3)	0.34 (25%)
V <sub>darea</sub> /F (L/kg)	0.41 (22%)	0.35 (13%)	0.40 (12%)	0.35 (23%)	0.35 (24%)

A cross-study comparison [this study and study # 193-114, Attachment 2, pp. 2] at dose levels of 100 and 200 mg/m<sup>2</sup> on Day 5 reveals that pediatric patients have higher C<sub>max</sub> (37% and 17%, respectively) and AUC (40% at both dose levels) than adult patients. However, pediatric and adult patients have similar clearance and volume of distribution values. Thus, no dosage adjustment is necessary in pediatric patients (3-17 years of age).

## 7.8 Drug Interactions

### 7.8.1 *In Vitro* Drug Interaction Studies

The sponsor claims that temozolomide does not alter the metabolism of other drugs (i.e., by competitive inhibition), however, no *in vitro* inhibition data with human liver microsomes have been provided to support this claim. In the submission of November 18, 1998 [Attachment 2, pp. 166], the sponsor mentions that since temozolomide is primarily degraded to MTIC by non-enzymatic pH-dependent chemical hydrolysis, *in vitro* inhibition studies with human microsomes were not necessary and thus, not conducted (see Comment #3).

### 7.8.2 *In Vivo* Drug Interaction Studies

**Ranitidine:** In a two-way crossover study, the effect of ranitidine on the pharmacokinetics of temozolomide and MTIC were evaluated during the first cycle after oral

administration of 150 mg/m<sup>2</sup> of temozolomide once a day for 5 days to 12 patients with advanced cancer [Study # I95-007, Attachment 2, pp. 168]. Ranitidine was administered orally as 150 mg every 12 hours, either on Days 1 and 2 or on Days 4 and 5 of the first cycle. The results indicate that the increase of pH by 0.8-2.5 units due to the coadministration of ranitidine does not have an effect on the oral bioavailability of temozolomide. Concomitant administration of ranitidine does not also have an effect on the pharmacokinetics of either temozolomide or its metabolite, MTIC.

Additionally, population analysis [Report # 97206350, Attachment 2, pp. 107] with a data base of 290 patients has shown that the pharmacokinetics of temozolomide are not influenced by most commonly administered drugs such as dexamethasone (n=143), phenytoin (n=96), phenobarbital (n=29), carbamazepine (n=68), H<sub>2</sub>-receptor antagonists (n=100), ondansetron (n=181), and prochlorperazine (n=18). Administration of valproic acid decreases oral clearance of temozolomide by 4.7% (p=0.019, n=39), the clinical implication of this effect is unknown.

## 7.9. Population Pharmacokinetic/Pharmacodynamic Analysis

The most common adverse events occurred with temozolomide administration during the clinical program were nausea, vomiting, headache, fatigue, and constipation. Hematologic toxicities included neutropenia, thrombocytopenia, anemia, leukopenia, and pancytopenia were also occurred. Population analysis of Phase II studies [Report # 97206350, Attachment 2, pp. 107] with a database of 270 patients (169 males and 101 females) shows that the incidence of neutropenia (nadir neutrophil count <0.5 x 10<sup>3</sup> /μL) is 7.4% in the first cycle of treatment. Females have a greater incidence of neutropenia than males (11.9% versus 4.7%, p=0.029). Patients of ≥70 years of age have the highest incidence of neutropenia (25%, 2/8 patients). Temozolomide dose is significantly related to the incidence of neutropenia; 2.3% in patients receiving 150 mg/m<sup>2</sup>/day versus 12.4% in patients receiving 200 mg/m<sup>2</sup>/day (p=0.001). Greater AUC is associated with the incidence of neutropenia; (36 μg.hr/ml versus 32 μg.hr/ml, p=0.003). Similar results are obtained for the incidence of thrombocytopenia. With a database of 284 patients (174 males and 110 females), the incidence of thrombocytopenia (nadir platelet count <20 x 10<sup>3</sup> /μL) is 5.3%. Females have a greater incidence of thrombocytopenia than males (9.1% versus 2.9%, p=0.024). Patients of ≥70 years of age have the highest incidence of thrombo-cytopenia (20%, 2/10 patients). Temozolomide dose is related to the incidence of thrombocytopenia; 3.6% in patients receiving 150 mg/m<sup>2</sup>/day versus 6.9% in patients receiving 200 mg/m<sup>2</sup>/day (p=0.164). Greater AUC is associated with the incidence of thrombocytopenia; (35 μg.hr/ml versus 32 μg.hr/ml, p=0.071).

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## Biopharmaceutics

### 8.1 Absorption

Temozolomide is rapidly and completely absorbed reaching peak plasma concentrations in 1.0 hour under fasting conditions following oral administration of 200 mg/m<sup>2</sup> dose to 6 cancer patients [Study # 193-114, Attachment 2, pp. 2].

### 8.2 Bioavailability

The absolute and relative bioavailabilities of temozolomide have not been determined. The absolute bioavailability in rats and dogs averages 100%.

### 8.3 Effect of Food

The effect of food on the absorption of temozolomide was evaluated in 12 cancer patients, as part of a phase I study [#193-114A, Attachment 2, pp. 15] following 200 mg/m<sup>2</sup> orally once a day for 5 consecutive days. On Days 1 and 2 of the first cycle, patients were randomized to receive temozolomide either after an overnight fast or after a standard breakfast (1 fried egg, 2 strips of bacon, 2 slices of toast, 2 parts of butter, 8 oz. of whole milk, 587 cal.) in a two-way crossover design. Results are shown in the table below.

Table 6 Mean (%CV) pharmacokinetic parameters of temozolomide following 200 mg/m<sup>2</sup> oral daily doses for 5 days before and after food intake in patients with advanced cancer (n=12)

Parameter	Fasted	Fed	90% Confidence Interval*
C <sub>max</sub> (µg/mL)	9.5 (18%)	6.5 (27%)	58-79%
AUC <sub>0-24hr</sub> (µg.hr/mL)	30.8 (14%)	28.1 (16%)	84-98%
T <sub>max</sub> (hr)	1.07 (40%)	2.25 (48%)	—
t <sub>1/2</sub> (hr)	1.8 (9%)	1.9 (12%)	—

\* (90% confidence interval based on log-transformed data,  $\alpha = 0.05$ )

Food reduces both the rate and extent of absorption of temozolomide. Mean C<sub>max</sub> and AUC<sub>0-24hr</sub> decreased by 32% and 9%, respectively, and T<sub>max</sub> increased 2-fold when temozolomide was administered with food. During clinical trials, patients were fasted

overnight and 2 hours before administration of temozolomide. It is recommended that Temodal® be administered under fasting conditions.

#### 8.4 Bioequivalence

No bioequivalence studies were required to be conducted for temozolomide since the final to-be-marketed capsules (5 mg, 10 mg, 100 mg, and 250 mg) were identical in composition to those used in clinical trials. The sponsor has not conducted a dosage strength proportionality study as capsule strengths are not compositionally proportional.

### 9. Formulations

The composition of the proposed market formulations for Temodal® capsules (5 mg, 20 mg, 100 mg, and 250 mg) are shown below.

#### Drug Product Composition and Dosage Form (5 mg strength)

Ingredient	mg/capsule
✓ Temozolomide (SCH 52365)	
✓ Lactose Anhydrous NF	
✓ Sodium Starch Glycolate NF	
✓ Colloidal Silicon Dioxide NF	
✓ Tartaric Acid NF	
✓ Stearic Acid NF	
Total	

Capsule #3 White Opaque Branded with Green Ink

#### Drug Product Composition and Dosage Form (20 mg strength)

Ingredient	mg/capsule
✓ Temozolomide (SCH 52365)	
✓ Lactose Anhydrous NF	
✓ Sodium Starch Glycolate NF	
✓ Colloidal Silicon Dioxide NF	
✓ Tartaric Acid NF	
✓ Stearic Acid NF	
Total	

Capsule #2 White Opaque Branded with Brown Ink

**Drug Product Composition and Dosage Form (100 mg strength)**

<b>Ingredient</b>	<b>mg/capsule</b>
• Temozolomide (SCH 52365)	
Lactose Anhydrous NF	
Sodium Starch Glycolate NF	
Colloidal Silicon Dioxide NF	
Tartaric Acid NF	
Stearic Acid NF	
<b>Total</b>	
<b>Capsule #1 White Opaque Branded with Blue Ink</b>	

**Drug Product Composition and Dosage Form (250 mg strength)**

<b>Ingredient</b>	<b>mg/capsule</b>
• Temozolomide (SCH 52365)	
Lactose Anhydrous NF	
Sodium Starch Glycolate NF	
Colloidal Silicon Dioxide NF	
Tartaric Acid NF	
Stearic Acid NF	
<b>Total</b>	
<b>Capsule #0 White Opaque Branded with Black Ink</b>	

**Capsules are not compositionally proportional. Same formulations were used in the entire development program for temozolomide.**

## 10. *IN Vitro* Dissolution

*In vitro* dissolution testing of temozolomide capsules was performed using USP Apparatus 1 (basket stirrer) at a rotation speed of 100 rpm in water at  $37 \pm 0.5^\circ \text{C}$  as the dissolution medium. Five hundred ml of water was used for the 5 mg capsule and 900 ml was used for the 20, 100 and 250 mg capsules. Dissolution data for temozolomide are not available in different pH range media. Stability data (below) show that temozolomide is stable in acid pH (<5) and labile at pH > 7. The sponsor did not provide any justification for choosing water as the dissolution medium.

Dissolution data (Range, mean, % CV, n=12 units) were submitted [See Attachment 3, pp. 182). Rapid dissolution is observed, mean % of temozolomide dissolved in water in 30 minutes ranges from 101-103% for the 5 mg capsule, 99-104% for the 20 mg capsule, 96-104% for the 100 mg capsule, and 85-99% for the 250 mg capsule. The sponsor proposes a specification of % dissolved in minutes for all capsule strengths (See Comment #1).

## 11. Analytical

**Attachment 1**

**Sponsor's Proposed Labeling**

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confidential

commercial

information

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW

NDA: 21-029  
Submission Date: June 24, 1999  
Drug Name: Temozolomide (Temodal®)  
Sponsor: Schering Corporation  
Kenilworth, NJ  
Reviewer: Safaa Ibrahim, Ph.D.  
Submission Type: Review of a Phase IV Protocol and  
Clinical Responses

JUL 30 1999  
30 1999

This submission contains a Phase IV clinical protocol for the study of temozolomide in patients with newly diagnosed anaplastic astrocytoma and responses to the FDA's clinical questions that were included in the approvable letter of February 12, 1999. The study is designed as a three-arm study comparing radiation plus temozolomide with radiation plus BCNU and radiation plus combination of BCNU and temozolomide.

**Recommendation**

No clinical pharmacology issues are to be addressed in this submission and therefore, no action is necessary.

*ISI*  
Team Leader: *7/30/99* Atiqur Rahman, Ph.D.  
Division of Pharmaceutical Evaluation I

*ISI*  
Reviewer: Safaa S. Ibrahim, Ph.D.  
Division of Pharmaceutical Evaluation I

cc: IND 21-029  
HFD-150/Division file  
~~HFD-150/Conn~~, Johnson, Cohen  
HFD-150/ HFD-850/Lesko  
HFD-860/Mehta, Rahman, Ibrahim  
CDR/Biopharm