

Clinical Pharmacology and Biopharmaceutics Review

NDA	21,029/(b) (4) 005
Date of Submission	September 12, 2002
Drug Name	Temodar
Generic	temozolomide
Dosage Form	oral capsule
Strength	5, 20, 100, 250 mg
Sponsor	Schering Corporation 2000 Galloping Hill Road Kenilworth, NJ 07033
Reviewer	Anne Zajicek, M.D., Pharm.D.
Team Leader	N.A.M. Atiqur Rahman
Type of Submission	NDA-Supplement

Executive Summary: Temozolomide is an oral alkylating agent which was approved in 1999 for treatment of adults with refractory anaplastic astrocytoma. A written request was issued for a pediatric study by the Food and Drug Administration on Jan 25, 2001 and amended on August 24, 2001. Three studies are submitted in response to the written request; the Clinical Pharmacology and Biopharmaceutics section of the application was previously submitted with the original NDA. Nineteen children, age 3-17 years with primary brain tumors, were randomized to temozolomide 100, 120, 160, 200 or 240 mg/m² taken orally daily for five days. Pharmacokinetic sampling took place on day 5. Results showed maximum concentration (C_{max}) and area under the concentration time curve (AUC) to be somewhat higher in children than in adults given the same dose, indicating either increased bioavailability or lower clearance in children; these results, however, are difficult to interpret due to the small numbers of patients studied. There was proportionality between dose and area under the concentration-time curve, and there was no apparent relationship between clearance and age.

Comments: The previously submitted pediatric pharmacokinetic study is adequate for the purposes of the Written Request and the Clinical Pharmacology and Biopharmaceutics review. The remaining question is how very young children took the oral capsule formulation. In future submissions, we recommend plasma MTIC concentration measurements, since it is the active species.

Labeling comments:

(b) (4)

Recommendation: No action is indicated.

Anne Zajicek, M.D, Pharm.D,
Clinical Pharmacology Reviewer

N.A.M. Atiqur Rahman, Ph.D.
Team Leader

CC: NDA 22,029/ (b) (4) 005

HFD-150/ Division File

HFD-150/JohnsonJ, FarrellA, ShapiroA

HFD-860/MehtaM, SahajwallaC, RahmanNAM, ZajicekA, LazorJ, SelenA, MarroumP

CDR/Biopharm

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III. List of Abbreviations

AUC: area under the concentration vs. time curve
AUC_{0-∞}: area under the concentration-time curve extrapolated from time 0 to infinity
BSA: body surface area
C_{max}: peak plasma concentration of the drug
CL: clearance
CL/F: apparent oral clearance
CV: coefficient of variation
CYP450: cytochrome P-450
Hr, hrs: hours
Kg, kg: kilograms
K_i: constant of inhibition
L: liter
LOD: lower limit of detection
LOQ: lower limit of quantification
M², m²: square meters, meters squared
Min, min: minutes
ml, mL: milliliter
μg/L: micrograms per liter
μM: micromolar, micromoles per liter
NDA: New Drug Application
ng/ml: nanograms per milliliter
PD: pharmacodynamics
PK: pharmacokinetics
PPK: population pharmacokinetics
sNDA: supplemental NDA
T_{1/2}, t_{1/2}: half-life
T_{max}: time to reach maximal concentration
V: volume of distribution
V_z/F: apparent volume of distribution

Background

Temozolomide (Temodar, SCH 52365) is a cytotoxic alkylating agent of the imidazotetrazine class and is chemically related to the 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 MTIC. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA at the O⁶ and N⁷ 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.

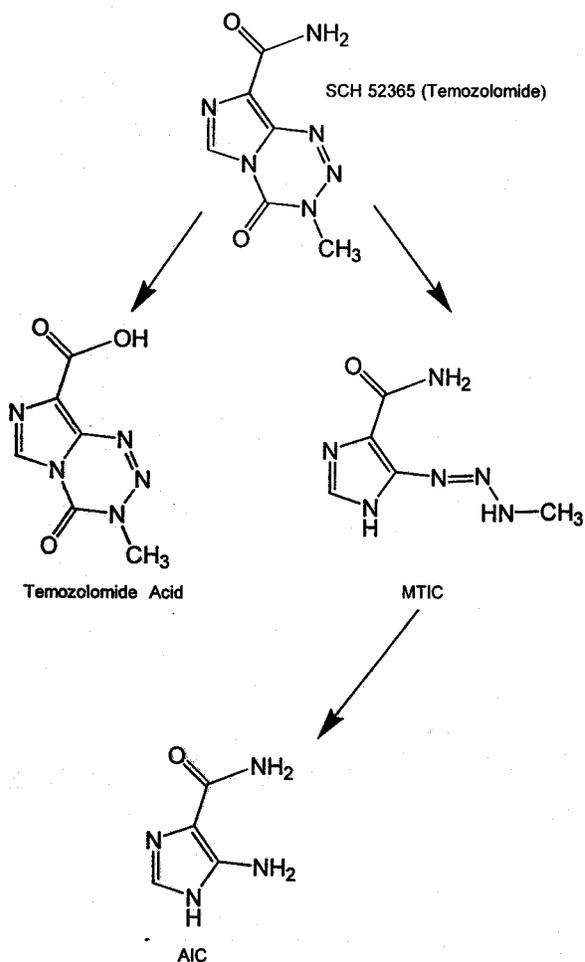


Figure 1. Structure of temozolomide and metabolites

Question-Based Review

A. What is known about the pharmacokinetics of temozolomide in adults ?

Mass balance: 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%).

Absorption: Temozolomide is reported to be rapidly and completely absorbed, with t_{max} occurring at about one hour. Food reduces both the rate and extent of absorption.

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

Clearance: 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%). Apparent oral clearance is 2.5 ml/min/kg, or approximately 100 ml/min/m². Systemic exposure to MTIC and AIC is low with a mean AUC metabolite/parent drug ratio of 2.4% and 23%, respectively.

Special populations:

Hepatic impairment: In an interim single-dose study, it is shown that patients with mild-to-moderate hepatic dysfunction (Child-Pugh Class I - II) have pharmacokinetics that are similar to patients with normal hepatic function. Dosage adjustment is not recommended in patients with mild to moderate hepatic impairment. 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.

Drug-drug interactions: 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, H₂-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.

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 ml/min/m²) has been noted on the pharmacokinetics of temozolomide. The pharmacokinetics of temozolomide in patients with severe renal dysfunction (CL_{Cr} < 36 ml/min/m²) have not been studied.

D. Is there a relationship between age and clearance ?

(b) (4)



E. Assay issues

The assay presented in this submission measures the temozolomide parent compound only, and not the active metabolite MTIC. It would be preferable in the future if the applicant reported both temozolomide and MTIC concentrations and pharmacokinetic parameters.

Appendix 1. Clinical Pharmacology and Biopharmaceutics Review of the original NDA

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW

<u>NDA:</u>	21-029
<u>Submission Dates:</u>	August 12, 1998 November 6, 1998 November 18, 1998
<u>Drug Name:</u>	Temozolomide (Temodal®)
<u>Dosage Form:</u>	5 mg, 20 mg, 100 mg, and 250 mg Immediate-Release Capsules For Oral Administration
<u>Sponsor:</u>	Schering Corporation Kenilworth, NJ
<u>Reviewer:</u>	Sophia Abraham, Ph.D.
<u>Type of Submission:</u>	New Drug Application (NME)

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 O⁶ and N⁷ 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.

(b) (4)

A validated high-performance liquid chromatography with UV detection (HPLC-UV) 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^2 , pediatric patients (3-17 years of age) have higher C_{max} (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. (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, carbama-zepine, H_2 -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 $\text{mg/m}^2/\text{day}$ 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 ($T_{max} \approx 1$ hour). Food reduces both the rate and extent of absorption of temozolomide. Mean C_{max} and $AUC_{0-\infty}$ decreased by 32 % and 9 %, respectively; T_{max} 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. (b) (4)

(b) (4) 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. (b) (4)

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 $37 \pm 0.5^\circ C$. The sponsor proposes dissolution specification of not less than (b) (4) % dissolved in 30 minutes.

2. Comments

[To be sent to the firm]

1. The Agency recommends the following dissolution methodology and specification for Temodal® 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 $37 \pm 0.5^\circ C$ (500 ml for the 5 mg capsule and 900 ml for the other strengths)
<u>Specification:</u>	(b) (4) % dissolved in 30 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. (b) (4)

(b) (4) 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.  (b) (4)

[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 ≥ 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 ≥ 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®.

 (b) (4)

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, (b) (4)

Please forward Comments #1-5 (b) (4) to the firm.

Comments # 6 and 7 are to the Medical Reviewer.

Reviewer: Sophia Abraham, Ph.D.
Division of Pharmaceutical Evaluation I

ClinPharm/Biopharm Briefing on January 11, 1999: (Attendees: Drs.: Williams, Lesko, Huang, Chen, Selen, Mehta, Abraham)

RD/FT _____

Team Leader: Atiqur Rahman, Ph.D.
Division of Pharmaceutical Evaluation I

cc: NDA 21-029
HFD-150/Division file
HFD-150/Guinn, Johnson, Cohen
HFD-860/Mehta, Rahman, Abraham
CDR/Biopharm

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Attachments

<u>Attachment 1</u>	(b) (4)
<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

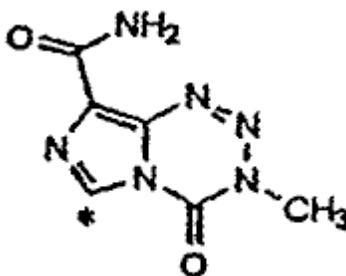
6. Background

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 dimethyl-sulfoxide (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-methylimidazol[5,1-d]-1,2,3,5-tetrazin-4(3H)-one. It has an empirical formula of C₆H₆N₆O₂ and a molecular weight of 194.

(b) (4)

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.

(b) (4)

MANUFACTURER AND MANUFACTURING SITE:

Temodal[®] will be manufactured and packaged by (b) (4) Schering Corporation, Kenilworth, New Jersey.

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 (mg/m^2).

2. 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 mg/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-(triazen-1-yl)imidazole-4-carboxamide (MTIC) and also to temozolomide acid metabolite (See Figure 1). MTIC is further degraded to 5-amino-imidazole-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 μ Ci) of 14 C-temozo-lomide 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 Tomozolomide

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 μ Ci) oral dose of 14 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 (\approx 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 14 CO₂. 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/m² 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 ² (n=3)	750 mg/m ² (n=6)	1000 mg/m ² (n=2)
AUC _{0-∞} (μ g.hr/ml)	75 (14%)	138 (13%)	196
Cmax (μ g/ml)	22.8 (17%)	40.8 (15%)	51.6
Tmax (hr)	1.3 (76%)	1.3 (37%)	1.75
t _{1/2} (hr)	1.8 (7%)	1.9 (10%)	1.7
CL/F (ml/min/kg)	2.8 (11%)	2.5 (23%)	2.3
CLr (ml/min/kg)	0.17 *	0.16 (76%)**	0.19
Vdarea/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/m² 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 ² (n=3)	150 mg/m ² (n=3)	200 mg/m ² (n=6)	250 mg/m ² (n=3)
AUC _{0-24hr} (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%)
Cmax (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%)
Tmax (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 _{1/2} (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%)
CLr (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%)
Vdarea/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 _{0-24hr} 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_{0-24h} ratio (R) is approximately equal one. Oral clearance (CL/F) and apparent volume of distribution (Vdarea/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 Tmax (0-87%).

Similar results are obtained in study # C94-022 during the first cycle following daily oral administration of 100 mg/m² (n=6), 150 mg/m² (n=12), and 200 mg/m² (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/m² and over the daily oral doses of 100-250 mg/m² 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/m² daily for 5 days every 28 days or 500-100 mg/m² as a single dose every 28 days (Phase I studies) and as 150 mg/m² or 200 mg/m² 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:

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/m² and 5.58 L/hr/m² (p=0.09), respectively.

7.7.5 Creatinine Clearance

Creatinine clearance (36-230 ml/min/m²) 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 (CL_{cr} < 36 ml/min/ m²). 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/m² 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/m² of temozolomide in patients with advanced hepatocellular carcinoma:

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

These interim data reveal that the mild and moderate groups have similar pharmaco-kinetics 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_{max} and AUC to decrease (50% and 37%, respectively) and CL/F and V_{darea}/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/m² daily doses for 5 consecutive days.

(b) (4)

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

(b) (4)

(b) (4)

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 pharmaco-kinetics of temozolomide and MTIC were evaluated during the first cycle after oral administration of 150 mg/m² of temozolomide once a day for 5 days to 12 patients with advanced cancer [Study # 195-

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), H₂-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 $<0.5 \times 10^3 /\mu\text{L}$) 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/m²/day versus 12.4% in patients receiving 200 mg/m²/day (p=0.001). Greater AUC is associated with the incidence of neutropenia; (36 $\mu\text{g}\cdot\text{hr}/\text{ml}$ versus 32 $\mu\text{g}\cdot\text{hr}/\text{ml}$, 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 $<20 \times 10^3 /\mu\text{L}$) 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/m²/day versus 6.9% in patients receiving 200 mg/m²/day (p=0.164). Greater AUC is associated with the incidence of thrombocytopenia; (35 $\mu\text{g}\cdot\text{hr}/\text{ml}$ versus 32 $\mu\text{g}\cdot\text{hr}/\text{ml}$, p=0.071).

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/m² dose to 6 cancer patients [Study # I93-114, Attachment 2, pp. 2].

8.2 Bioavailability

The absolute and relative bioavailabilities of temozolomide have not been determined. In a published article by Newlands et. al. (Br. J. cancer, 65, 286-291, 1992), it is reported that the mean absolute bioavailability in 5 cancer patients 109%.

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/m² 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/m²

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 _{max} (µg/mL)	9.5 (18%)	6.5 (27%)	58-79%
AUC _{0-24hr} (µg.hr/mL)	30.8 (14%)	28.1 (16%)	84-98%
T _{max} (hr)	1.07 (40%)	2.25 (48%)	---
t _{1/2} (hr)	1.8 (9%)	1.9 (12%)	---

[#] (90% confidence interval based on log-transformed data, α =0.05)

Food reduces both the rate and extent of absorption of temozolomide. Mean C_{max} and AUC_{0-∞} decreased by 32% and 9%, respectively; and T_{max} 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. (b) (4)

9. Formulations

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

(b) (4). 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±0.5° 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].

(b) (4)
The sponsor proposes a specification of (b) (4) % dissolved in 30 minutes for all capsule strengths (See Comment #1).

11. Analytical

Temozolomide concentrations were quantitated in plasma and urine samples using an HPLC method with UV detection [See Attachment 4, pp. 187]. The method involves (b) (4)

(b) (4) The method was adequately validated with respect to accuracy, precision, linearity, reproducibility, sensitivity and selectivity over the range of 0.1-20 µg/ml and 0.5–200 µg/ml, in plasma and urine, respectively. The limit of quantitation is 0.1 µg/ml in plasma and 0.5-1 µg/ml in urine. Temozolomide active metabolite, MTIC, concentrations were measured in the plasma using also HPLC method with UV detection. The method was adequately validated respect to accuracy, precision, linearity, reproducibility, sensitivity and selectivity over the ranges of 10-2000 ng/ml. The limit of quantitation is 10-25 µg/ml.

Temozolomide was unstable in human plasma at 37° C and 4° C, but stable in acidified (pH ≤ 4) human plasma for at least 24 hr at 25° C and for 30 days at -20° C. MTIC was unstable (t½ of 25 to 50 min) at 25° C in human plasma or in human plasma adjusted to pH 12. However, MTIC in human plasma was relatively stable at 4° C for 1 hr.

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