DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-029/S-004

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Attention: Mary Jane Nehring
Sr. Director
Marketed Products Support

Dear Ms. Nehring:

Please refer to your supplemental new drug application dated December 4, 2001, received December 5, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Temodar (temozolomide) Capsules.

This "Changes Being Effected" supplemental new drug application provides for an updated package insert with revisions to the ADVERSE REACTIONS section. The revised labeling is the result of the Agency's August 28, 2001 correspondence and review by Schering's Drug Safety Surveillance Group.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in your December 4, 2001 submission. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling included in this submission.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-029/S-004." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Sean Bradley, R.Ph., Regulatory Project Manager, at 301-594-5750.

Sincerely,

{See appended electronic signature page}

/S/

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Richard Pazdur
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REGULATORY PROJECT MANAGER REVIEW

Application Number: 21-029/S004 (FPL)

Name of Drug: Temodar® (temozolomide) Capsules

Sponsor: Schering Corporation

Material Reviewed

Supplement Number	Letter Date	Receipt Date
004 (FPL)	January 15, 2002	January 16, 2002
004 (SLR)	December 4, 2001	December 5, 2001

Background and Summary Description:

Temodar® (temozolomide) Capsules was originally approved on August 11, 1999 for the treatment of adult patients with refractory anaplastic astrocytoma.

S-004 provides an updated package insert with revisions to the ADVERSE REACTIONS section. The revised labeling is the result of the Agency's August 28, 2001 correspondence and review by Schering's Drug Safety Surveillance Group.

S-004 was approved with draft labeling on January 18, 2002. Since it was a CBE, the company had already printed and distributed the new package labeling before the Agency's review was completed. Schering submitted the FPL for S-004 to the Agency for review on January 15, 2002. This labeling was compared to S-004 approved draft labeling and they were identical.

CONCLUSION:

The FPL for supplement S-004 should be approved because it is identical to the approved draft labeling for S-004.

/S/

Sean Bradley, R.Ph./24JAN02
Regulatory Project Manager

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/s/

Sean Bradley
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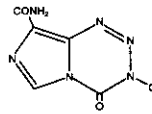
CSO

F-22487825 **PRODUCT INFORMATION**

TEMODAR® (temozolomide) CAPSULES

DESCRIPTION

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



The material is a white to light tan/light pink powder with a molecular formula of $C_6H_6N_8O_2$ and a molecular weight of 194.15. The molecule is stable at acidic pH (<5), and labile at pH >7, hence can be administered orally. The prodrug, temozolomide, is rapidly hydrolysed to the active 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide (MTIC) at neutral and alkaline pH values, with hydrolysis taking place even faster at alkaline pH.

Each capsule contains either 5 mg, 20 mg, 100 mg, or 250 mg of temozolomide. The inactive ingredients for TEMODAR Capsules are lactose anhydrous, colloidal silicon dioxide, sodium starch glycolate, tartaric acid, and stearic acid. Gelatin capsule shells contain titanium dioxide. The capsules are imprinted with pharmaceutical ink.

TEMODAR 5 mg: green imprint contains pharmaceutical grade shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, ammonium hydroxide, titanium dioxide, yellow iron oxide, and FD&C Blue #2 aluminum lake.

TEMODAR 20 mg: brown imprint also contains pharmaceutical grade shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, purified water, ammonium hydroxide, potassium hydroxide, titanium dioxide, black iron oxide, yellow iron oxide, brown iron oxide, and red iron oxide.

TEMODAR 100 mg: blue imprint contains pharmaceutical glaze (modified) in an ethanol/shellac mixture, isopropyl alcohol, n-butyl alcohol, propylene glycol, titanium dioxide, and FD & C Blue #2 aluminum lake.

TEMODAR 250 mg: black, imprint contains pharmaceutical grade shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, purified water, ammonium hydroxide, potassium hydroxide, and black iron oxide.

CLINICAL PHARMACOLOGY

Mechanism of Action: Temozolomide is not directly active but undergoes rapid nonenzymatic conversion at physiologic pH to the reactive compound MTIC. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the O^6 and N^7 positions of guanine.

Pharmacokinetics: Temozolomide is rapidly and completely absorbed after oral administration; peak plasma concentrations occur in 1 hour. Food reduces the rate and extent of temozolomide absorption. Mean peak plasma concentration and AUC decreased by 32% and 9%, respectively, and T_{max} increased 2-fold (from 1.1 to 2.25 hours) when temozolomide was administered after a modified high-fat breakfast. Temozolomide is rapidly eliminated with a mean elimination half-life of 1.8 hours and exhibits linear kinetics over the therapeutic dosing range. 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%.

Metabolism and Elimination: Temozolomide is spontaneously hydrolyzed at physiologic pH to the active species, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC) and to temozolomide acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC) which is known to be an intermediate in purine and nucleic acid biosynthesis and to methylhydrazine, which is believed to be the active alkylating species. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC. Relative to the AUC of temozolomide, the exposure to MTIC and AIC is 2.4% and 23%, respectively. About 38% of the administered temozolomide total radioactive dose is recovered over 7 days; 37.7% in urine and 0.8% in feces. The majority of the recovery of radioactivity in urine is as unchanged temozolomide (5.6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolite(s) (17%). Overall clearance of temozolomide is about 5.5 L/hr/m².

Special Populations: *Age* Population pharmacokinetic analysis indicates that age (range 19 to 78 years) has no influence on the pharmacokinetics of temozolomide. In the anaplastic astrocytoma study population, patients 70 years of age or older had a higher incidence of Grade 4 neutropenia and Grade 4 thrombocytopenia in the first cycle of therapy than patients under 70 years of age (see **PRECAUTIONS**). In the entire safety database, however, there did not appear to be a higher incidence in patients 70 years of age or older (see **ADVERSE REACTIONS**).

Gender Population pharmacokinetic analysis indicates that women have an approximately 5% lower clearance (adjusted for body surface area) for temozolomide than men. Women have higher incidences of Grade 4 neutropenia and thrombocytopenia in the first cycle of therapy than men (see **ADVERSE REACTIONS**).

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

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

Creatinine Clearance Population pharmacokinetic analysis indicates that creatinine clearance over the range of 36-130 mL/min/m² has no effect on the clearance of temozolomide after oral administration. The pharmacokinetics of temozolomide have not been studied in patients with severely impaired renal function (CLcr < 36 mL/min/m²). Caution should be exercised when TEMODAR is administered to patients with severe renal impairment. TEMODAR has not been studied in patients on dialysis.

Hepatically Impaired Patients In a pharmacokinetic study, the pharmacokinetics of temozolomide in patients with mild-to-moderate hepatic impairment (Child's-Pugh Class I - II) were similar to those observed in patients with normal hepatic function. Caution should be exercised when temozolomide is administered to patients with severe hepatic impairment.

Pediatrics Pediatric patients (3 to 17 years of age) and adult patients have similar clearance and half-life values for temozolomide. There is no clinical experience with the use of TEMODAR in children under the age of 3 years.

Drug-Drug Interactions In a multiple-dose study, administration of TEMODAR with ranitidine did not change the C_{max} or AUC values for temozolomide or MTIC.

Population analysis indicates that administration of valproic acid decreases the clearance of temozolomide by about 5% (see **PRECAUTIONS**).

Population analysis failed to demonstrate any influence of coadministered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H_2-receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.

Clinical Studies A single-arm, multicenter study was conducted in 162 patients who had anaplastic astrocytoma at first relapse and who had a baseline Karnofsky performance status of 70 or greater. Patients had previously received radiation therapy and may also have previously received a nitrosourea with or without other chemotherapy. Fifty-four patients had disease progression on prior therapy with both a nitrosourea and procarbazine and their malignancy was considered refractory to chemotherapy (refractory anaplastic astrocytoma population). Median age of this subgroup of 54 patients was 42 years (19 to 76). Sixty-five percent were male. Seventy-two percent of patients had a KPS of ≥80. Sixty-three percent of patients had surgery other than a biopsy at the time of initial diagnosis. Of those patients undergoing resection, 73% underwent a subtotal resection and 27% underwent a gross total resection. Eighteen percent of patients had surgery at the time of first relapse. The median time from initial diagnosis to first relapse was 13.8 months (4.2 to 75.4).

TEMODAR was given for the first 5 consecutive days of a 28-day cycle at a starting dose of 150 mg/m²/day. If the nadir and day of dosing (Day 29, Day 1 of next cycle) absolute neutrophil count was ≥1.5 x 10⁹/L (1,500/μL) and the nadir and Day 29, Day 1 of next cycle, platelet count was ≥100 x 10⁹/L (100,000/μL), the TEMODAR dose was increased to 200 mg/m²/day for the first 5 consecutive days of a 28-day cycle.

In the refractory anaplastic astrocytoma population the overall tumor response rate (CR + PR) was 22% (12/54 patients) and the complete response rate was 9% (5/54 patients). The median duration of all responses was 50 weeks (range of 16 to 114 weeks) and the median duration of complete responses was 64 weeks (range of 52 to 114 weeks). In this population, progression-free survival at 6 months was 45% (95% confidence interval 31% to 58%) and progression-free survival at 12 months was 29% (95% confidence interval 16% to 42%). Median progression-free survival was 4.4 months. Overall survival at 6 months was 74% (95% confidence interval 62% to 86%) and 12-month overall survival was 65% (95% confidence interval 52% to 78%). Median overall survival was 15.9 months.

INDICATIONS AND USAGE

TEMODAR (temozolomide) Capsules are indicated for the treatment of adult patients with refractory anaplastic astrocytoma, ie, patients at first relapse who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine.

This indication is based on the response rate in the indicated population. No results are available from randomized controlled trials in recurrent anaplastic astrocytoma that demonstrate a clinical benefit resulting from treatment, such as improvement in disease-related symptoms, delayed disease progression, or improved survival.

CONTRAINDICATIONS

TEMODAR (temozolomide) Capsules are contraindicated in patients who have a history of hypersensitivity reaction to any of its components. TEMODAR is also contraindicated in patients who have a history of hypersensitivity to DTIC, since both drugs are metabolized to MTIC.

WARNINGS

Patients treated with TEMODAR may experience myelosuppression. Prior to dosing, patients must have an absolute neutrophil count (ANC) ≥1.5 x 10⁹/L and a platelet count ≥100 x 10⁹/L. A complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above 1.5 x 10⁹/L and platelet count exceeds 100 x 10⁹/L. In the clinical trials, if the ANC fell to <1.0 x 10⁹/L or the platelet count was <50 x 10⁹/L during any cycle, the next cycle was reduced by 50 mg/m², but not below 100 mg/m². Patients who do not tolerate 100 mg/m² should not receive TEMODAR. Geriatric patients and women have been shown in clinical trials to have a higher risk of developing myelosuppression. Myelosuppression generally occurred late in the treatment cycle. The median nadirs occurred at 26 days for platelets (range 21 to 40 days) and 28 days for neutrophils (range 1 to 44 days). Only 14% (22/158) of patients had a neutrophil nadir and 20% (32/158) of patients had a platelet nadir which may have delayed the start of the next cycle. Neutrophil and platelet counts returned to normal, on average, within 14 days of nadir counts (see **PRECAUTIONS**).

Pregnancy: Temozolomide may cause fetal harm when administered to a pregnant woman. Five consecutive days of oral administration of 75 mg/m²/day in rats and 150 mg/m²/day in rabbits during the period of organogenesis (3/8 and 3/4 the maximum recommended human dose, respectively) caused numerous malformations of the external organs, soft tissues, and skeleton in both species. Doses of 150 mg/m²/day in rats and rabbits also caused embryolethality as indicated by increased resorptions. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with TEMODAR.

PRECAUTIONS

Information for Patients: In clinical trials, the most frequently occurring adverse effects were nausea and vomiting. These were usually either self-limiting or readily controlled with standard antiemetic therapy. Capsules should not be opened. If capsules are accidentally opened or damaged, rigorous precautions should be taken with the capsule contents to avoid inhalation or contact with the skin or mucous membranes. The medication should be kept away from children and pets.

Drug Interaction: Administration of valproic acid decreases oral clearance of temozolomide by about 5%. The clinical implication of this effect is not known.

Patients with Severe Hepatic or Renal Impairment: Caution should be exercised when TEMODAR is administered to patients with severe hepatic or renal impairment (see **Special Populations**).

Geriatrics: Clinical studies of temozolomide did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Caution should be exercised when treating elderly patients.

In the anaplastic astrocytoma study population, patients 70 years of age or older had a higher incidence of Grade 4 neutropenia and Grade 4 thrombocytopenia (2/8; 25%, p=.31 and 2/10; 20%, p=.09, respectively) in the first cycle of therapy than patients under 70 years of age (see **ADVERSE REACTIONS**).

Laboratory Tests: A complete blood count should be obtained on Day 22 (21 days after the first dose). Blood counts should be performed weekly until recovery if the ANC falls below 1.5 x 10⁹/L and the platelet count falls below 100 x 10⁹/L.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Standard carcinogenicity studies were not conducted with temozolomide. In rats treated with 200 mg/m² temozolomide (equivalent to the maximum recommended daily human dose) on 5 consecutive days every 28 days for 3 cycles, mammary carcinomas were found in both males and females. With 6 cycles of treatment at 25, 50, and 125 mg/m² (about 1/8 to 1/2 the maximum recommended daily human dose), mammary carcinomas were observed at all doses and fibrosarcomas of the heart, eye, seminal vesicles, salivary glands, abdominal cavity, uterus, and prostate; carcinoma of the seminal vesicles, schwannoma of the heart, optic nerve, and harderian gland; and adenomas of the skin, lung, pituitary, and thyroid were observed at the high dose.

Temozolomide was mutagenic *in vitro* in bacteria (Ames assay) and clastogenic in mammalian cells (human peripheral blood lymphocyte assays).

Reproductive function studies have not been conducted with temozolomide. However, multicycle toxicology studies in rats and dogs have demonstrated testicular toxicity (syncytial cells/immature sperm, testicular atrophy) at doses of 50 mg/m² in rats and 125 mg/m² in dogs (1/4 and 5/8, respectively, of the maximum recommended human dose on a body surface area basis).

Pregnancy Category D: See **WARNINGS** section.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from TEMODAR, patients receiving TEMODAR should discontinue nursing.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Tables 1 and **2** show the incidence of adverse events in the 158 patients in the anaplastic astrocytoma study for whom data are available. In the absence of a control group, it is not clear in many cases whether these events should be attributed to temozolomide or the patients' underlying conditions, but nausea, vomiting, fatigue, and hematologic effects appear to be clearly drug related. The most frequently occurring side effects were nausea, vomiting, headache, and fatigue. The adverse events were usually NCI Common Toxicity Criteria (CTC) Grade 1 or 2 (mild to moderate in severity) and were self-limiting, with nausea and vomiting readily controlled with antiemetics. The incidence of severe nausea and vomiting (CTC Grade 3 or 4) was 10% and 6%, respectively. Myelosuppression (thrombocytopenia and neutropenia) was the dose-limiting adverse event. It usually occurred within the first few cycles of therapy and was not cumulative.

Myelosuppression occurred late in the treatment cycle and returned to normal, on average, within 14 days of nadir counts. The median nadirs occurred at 26 days for platelets (range 21 to 40 days) and 28 days for neutrophils (range 1 to 44 days). Only 14% (22/158) of patients had a neutrophil nadir and 20% (32/158) of patients had a platelet nadir which may have delayed the start of the next cycle (see **WARNINGS**). Less than 10% of patients required hospitalization, blood transfusion, or discontinuation of therapy due to myelosuppression.

In clinical trial experience with 110 to 111 women and 169 to 174 men (depending on measurements), there were higher rates of Grade 4 neutropenia (ANC < 500 cells/μL) and thrombocytopenia (< 20,000 cells/μL) in women than men in the first cycle of therapy: (12% versus 5% and 9% versus 3%, respectively).

In the entire safety database for which hematologic data exist (N=932), 7% (4/61) and 9.5% (6/63) of patients over age 70 experienced Grade 4 neutropenia or thrombocytopenia in the first cycle, respectively. For patients less than or equal to age 70, 7% (62/871) and 5.5% (48/879) experienced Grade 4 neutropenia or thrombocytopenia in the first cycle, respectively. Pancytopenia, leukopenia, and anemia have also been reported.

In addition, the following spontaneous adverse experiences have been reported during the marketing surveillance of TEMODAR Capsules: allergic reactions including rare cases of anaphylaxis. Rare cases of erythema multiforme have been reported which resolved after discontinuation of TEMODAR and, in some cases, recurred upon rechallenge.

Table 1

Adverse Events in the Anaplastic Astrocytoma Trial (≥5%)

	No. (%) of TEMODAR Patients (N=158)	
	All Events	Grade 3/4
Any Adverse Event	**153 (97)**	**79 (50)**
Body as a Whole		
Headache	65 (41)	10 (6)
Fatigue	54 (34)	7 (4)
Asthenia	20 (13)	9 (6)
Fever	21 (13)	3 (2)
Back pain	12 (8)	4 (3)
Cardiovascular		
Edema peripheral	17 (11)	1 (1)
Central and Peripheral Nervous System		
Convulsions	36 (23)	8 (5)
Hemiparesis	29 (18)	10 (6)
Dizziness	19 (12)	1 (1)
Coordination abnormal	17 (11)	2 (1)
Amnesia	16 (10)	6 (4)
Insomnia	16 (10)	0
Paresthesia	15 (9)	1 (1)
Somnolence	15 (9)	5 (3)
Paresis	13 (8)	4 (3)

R 2 3 4 5 6 12

F-22487825 **PRODUCT INFORMATION**

TEMODAR®
(temozolomide)
CAPSULES

TEMODAR® (temozolomide) CAPSULES

Table 1 *continued*

Adverse Events in the Anaplastic Astrocytoma Trial (≥5%)

	No. (%) of TEMODAR Patients (N=158)	
	All Events	Grade 3/4
Any Adverse Event	**153 (97)**	**79 (50)**
Central and Peripheral Nervous System		
Urinary incontinence	13 (8)	3 (2)
Ataxia	12 (8)	3 (2)
Dysphasia	11 (7)	1 (1)
Convulsions local	9 (6)	0
Gait abnormal	9 (6)	1 (1)
Confusion	8 (5)	0
Endocrine		
Adrenal hypercorticism	13 (8)	0
Gastrointestinal System		
Nausea	84 (53)	16 (10)
Vomiting	66 (42)	10 (6)
Constipation	52 (33)	1 (1)
Diarrhea	25 (16)	3 (2)
Abdominal pain	14 (9)	2 (1)
Anorexia	14 (9)	1 (1)
Metabolic		
Weight increase	8 (5)	0
Musculoskeletal System		
Myalgia	8 (5)	
Psychiatric Disorders		
Anxiety	11 (7)	1 (1)
Depression	10 (6)	0
Reproductive Disorders		
Breast pain, female	4 (6)	
Resistance Mechanism Disorders		
Infection viral	17 (11)	0
Respiratory System		
Upper respiratory tract infection	13 (8)	0
Pharyngitis	12 (8)	0
Sinusitis	10 (6)	0
Coughing	8 (5)	0
Skin and Appendages		
Rash	13 (8)	0
Pruritus	12 (8)	2 (1)
Urinary System		
Urinary tract infection	12 (8)	0
Micturition increased frequency	9 (6)	0
Vision		
Diplopia	8 (5)	0
Vision Abnormal*	8 (5)	

*Blurred vision, visual deficit, vision changes, vision troubles.

Table 2

Adverse Hematologic Effects (Grade 3 to 4) in the Anaplastic Astrocytoma Trial

	TEMODAR*
Hemoglobin	7/158 (4%)
Neutrophils	20/142 (14%)
Platelets	29/156 (19%)
WBC	18/158 (11%)

*Change from Grade 0 to 2 at baseline to Grade 3 or 4 during treatment.

OVERDOSAGE

Doses of 500, 750, 1,000, and 1,250 mg/m² (total dose per cycle over 5 days) have been evaluated clinically in patients. Dose-limiting toxicity was hematologic and was reported at 1,000 mg/m² and at 1,250 mg/m². Up to 1,000 mg/m² has been taken as a single dose, with only the expected effects of neutropenia and thrombocytopenia resulting. In the event of an overdose, hematologic evaluation is needed. Supportive measures should be provided as necessary.

DOSAGE AND ADMINISTRATION

Dosage of TEMODAR must be adjusted according to nadir neutrophil and platelet counts in the previous cycle and neutrophil and platelet counts at the time of initiating the next cycle. The initial dose is 150 mg/m² orally once daily for 5 consecutive days per 28-day treatment cycle. If both the nadir and day of dosing (Day 29, Day 1 of next cycle) absolute neutrophil counts (ANC) are ≥1.5 x 10^9/L (1,500/µL) and both the nadir and Day 29, Day 1 of next cycle platelet counts are ≥100 x 10^9 /L (100,000/µL), the TEMODAR dose may be increased to 200 mg/m²/day for 5 consecutive days per 28-day treatment cycle. During treatment, a complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above 1.5 x 10^9/L (1,500/µL) and the platelet count exceeds 100 x 10^9/L (100,000/µL). The next cycle of TEMODAR should not be started until the ANC and platelet count exceed these levels. If the ANC falls to <1.0 x 10^9/L (1,000/µL) or the platelet count is <50 x 10^9/L (50,000/µL) during any cycle, the next cycle should be reduced by 50 mg/m², but not below 100 mg/m², the lowest recommended dose (see **Table 3**) (see **WARNINGS**).

TEMODAR therapy can be continued until disease progression. In the clinical trial, treatment could be continued for a maximum of 2 years; but the optimum duration of therapy is not known. For TEMODAR dosage calculations based on body surface area (BSA), see **Table 4**. For suggested capsule combinations based on daily dose, see **Table 5**.

Table 3 Dosing Modification Table

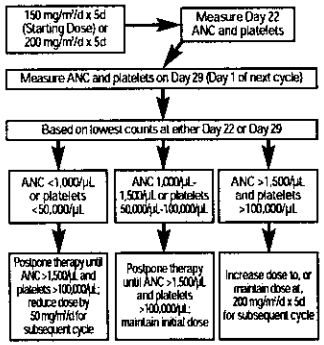


Table 4

Daily Dose Calculations by Body Surface Area (BSA) for 5 consecutive days per 28-day treatment cycle for the initial chemotherapy cycle (150 mg/m²) and for subsequent chemotherapy cycles (200 mg/m²) for patients whose nadir and day of dosing (Day 29, Day 1 of next cycle) absolute neutrophil count (ANC) is >1.5 x 10^9/L (1,500/µL) and whose nadir and Day 29, Day 1 of next cycle platelet count is >100 x 10^9/L (100,000/µL).

Total BSA (m²)	150 mg/m² (mg daily)	200 mg/m² (mg daily)
0.5	75	100
0.6	90	120
0.7	105	140
0.8	120	160
0.9	135	180
1.0	150	200
1.1	165	220
1.2	180	240
1.3	195	260
1.4	210	280
1.5	225	300
1.6	240	320
1.7	255	340
1.8	270	360
1.9	285	380
2.0	300	400
2.1	315	420
2.2	330	440
2.3	345	460
2.4	360	480
2.5	375	500

Table 5

Suggested Capsule Combinations Based on Daily Dose

	Number of Daily Capsules by Strength (mg)			
Total Daily Dose (mg)	250	100	20	5
200	0	2	0	0
205	0	2	0	1
210	0	2	0	2
215	0	2	0	3
220	0	2	1	0
225	0	2	1	1
230	0	2	1	2
235	0	2	1	3
240	0	2	2	0
245	0	2	2	1
250	1	0	0	0
255	1	0	0	1
260	1	0	0	2
265	1	0	0	3
270	1	0	1	0

Table 5 *continued*

Suggested Capsule Combinations Based on Daily Dose

	Number of Daily Capsules by Strength (mg)			
Total Daily Dose (mg)	250	100	20	5
275	1	0	1	1
280	1	0	1	2
285	1	0	1	3
290	1	0	2	0
295	1	0	2	1
300	0	3	0	0
305	0	3	0	1
310	0	3	0	2
315	0	3	0	3
320	0	3	1	0
325	0	3	1	1
330	1	0	4	0
335	1	0	4	1
340	0	3	2	0
345	0	3	2	1
350	1	1	0	0
355	1	1	0	1
360	1	1	0	2
365	1	1	0	3
370	1	1	1	0
375	1	1	1	1
380	1	1	1	2
385	1	1	1	3
390	1	1	2	0
395	1	1	2	1
400	0	4	0	0
405	0	4	0	1
410	0	4	0	2
415	0	4	0	3
420	0	4	1	0
425	0	4	1	1
430	1	1	4	0
435	0	4	1	3
440	0	4	2	0
445	0	4	2	1
450	1	2	0	0
455	1	2	0	1
460	1	2	0	2
465	1	2	0	3
470	1	2	1	0
475	1	2	1	1
480	1	2	1	2
485	1	2	1	3
490	1	2	2	0
495	1	2	2	1
500	2	0	0	0

In the clinical trial, TEMODAR was administered under both fasting and nonfasting conditions; however, absorption is affected by food (see **CLINICAL PHARMACOLOGY**) and consistency of administration with respect to food is recommended. There are no dietary restrictions with temozolomide. To reduce nausea and vomiting, temozolomide should be taken on an empty stomach. Bedtime administration may be advised. Antiemetic therapy may be administered prior to and/or following administration of TEMODAR.

TEMODAR (temozolomide) Capsules should not be opened or chewed. They should be swallowed whole with a glass of water.

Handling and Disposal: Temozolomide causes the rapid appearance of malignant tumors in rats. Capsules should not be opened. If capsules are accidentally opened or damaged, rigorous precautions should be taken with the capsule contents to avoid inhalation or contact with the skin or mucous membranes. Procedures for proper handling and disposal of anticancer drugs should be considered.[1-7] Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

TEMODAR (temozolomide) Capsules are supplied in amber glass bottles with child-resistant polypropylene caps containing the following capsule strengths:

TEMODAR (temozolomide) Capsules 5 mg: 5 and 20 capsule bottles.
5 count - NDC 0085-1248-01
20 count - NDC 0085-1248-02
TEMODAR (temozolomide) Capsules 20 mg: 5 and 20 capsule bottles.
5 count - NDC 0085-1244-01
20 count - NDC 0085-1244-02
TEMODAR (temozolomide) Capsules 100 mg: 5 and 20 capsule bottles.
5 count - NDC 0085-1259-01
20 count - NDC 0085-1259-02
TEMODAR (temozolomide) Capsules 250 mg: 5 and 20 capsule bottles.
5 count - NDC 0085-1252-01
20 count - NDC 0085-1252-02

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

[See USP Controlled Room Temperature]

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs, NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.
2. AMA Council Report, Guidelines for Handling Parenteral Antineoplastics. *JAMA*. 1985;2.53(11):1590-1592.
3. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
4. Clinical Oncological Society of Australia, Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med J Australia*. 1983;1:426-428.
5. Jones RB, et al. Safe Handling Of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. CA - *A Cancer Journal for Clinicians*. 1983;(Sept/Oct):258-263.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm*. 1990;47:1033-1049.
7. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines), *Am J Health-Syst Pharm*. 1996;53:1669-1685.

Schering Corporation
Kenilworth, NJ 07033 USA

Rev. 11/01 B-22487825

REGULATORY PROJECT MANAGER REVIEW

Application Number: 21-029/S004

Name of Drug: Temodar® (temozolomide) Capsules

Sponsor: Schering Corporation

Material Reviewed

Supplement Number	Letter Date	Receipt Date
004 (SLR)	December 4, 2001	December 5, 2001
001 (FA)	September 9, 1999	September 10, 1999

Background and Summary Description:

Temodar® (temozolomide) Capsules was originally approved on August 11, 1999 for the treatment of adult patients with refractory anaplastic astrocytoma.

S-004 provides an updated package insert with revisions to the ADVERSE REACTIONS section. The revised labeling is the result of the Agency's August 28, 2001 correspondence and review by Schering's Drug Safety Surveillance Group.

REVIEW

The package insert from S-004 was compared to the final approved labeling (FA) submitted to the Agency September 9, 1999 and approved October 13, 1999. The following changes are the only changes that were made to the approved product labeling.

Proposed Changes in S-004

The following highlighted text has been added to the **ADVERSE REACTIONS** section starting at the end of paragraph four:

In the entire safety database for which hematologic data exist (N=932), 7% (4/61) and 9.5% (6/63) of patients over age 70 experienced Grade 4 neutropenia or thrombocytopenia in the first cycle, respectively. For patients less than or equal to age 70, 7% (62/871) and 5.5% (48/879) experienced Grade 4 neutropenia or thrombocytopenia in the first cycle, respectively. Pancytopenia, leukopenia, and anemia have also been reported.

In addition, the following spontaneous adverse experiences have been reported during the marketing surveillance of TEMODAR Capsules: allergic reactions including rare cases of anaphylaxis. Rare cases of erythema multiforme have been reported which resolved after discontinuation of TEMODAR and, in some cases, recurred upon rechallenge.

CONCLUSION:

Supplement S-004 should be approved because the changes made were already agreed upon by the Agency on September 14, 2001 (see attached email transmissions). The acceptability of these changes is indicated by the concurrence of the noted reviewers below.

/S/
Sean Bradley, R.Ph./08JAN02
Regulatory Project Manager

This review was reviewed and signed off by:

Concurrence: Dotti Pease/08JAN02
Chief, Project Management Staff

Concurrence: Martin Cohen, M.D./11JAN02
Medical Reviewer

Concurrence: John Johnson, M.D./14JAN02
Medical Team Leader

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-029\S-004

Schering Corporation
2000 Galluping Hill Road
Kenilworth, NJ 07033

Attention: Mary Jane Nehring
Senior Director, Marketed products Support
Worldwide Regulatory Affairs

Dear Ms. Nehring:

We acknowledge receipt of your January 15, 2002 submission containing final printed labeling for your supplemental new drug application for Temodar (temozolomide) Capsules.

We have reviewed this labeling and we find it acceptable.

If you have any questions, call Sean Bradley, R.Ph., Regulatory Project Manager, at 301-594-5750.

Sincerely,

{See appended electronic signature page}

/S/

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Dotti Pease
2/1/02 11:53:53 AM
Signing for Richard Pazdur, M.D.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-029/S-004

CBE-0 SUPPLEMENT

Schering Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033

Attention: Mary Jane Nehring
Senior Director, Marketed Products Support
Worldwide Regulatory Affairs

Dear Ms. Nehring:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Temodar® (temozolomide) Capsules

NDA Number: 21-029

Supplement number: S-004

Date of supplement: December 4, 2001

Date of receipt December 6, 2001

This supplemental application was submitted as a "Supplement - Changes Being Effected." The appropriateness of reporting the proposed change(s) as changes being effected is under review.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 4, 2002, in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Attention: Division Document Room, 3067
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug products, HFD-150
Attention: Document Room 3067
1451 Rockville Pike
Rockville, Maryland 20852

If you have any question, call Sean Bradley, R.Ph., Regulatory Project Manager, at (301) 594-5750

Sincerely yours,

/S/
Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

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

/s/

Sean Bradley
12/20/01 03:04:11 PM
Signing off for Dotti Pease