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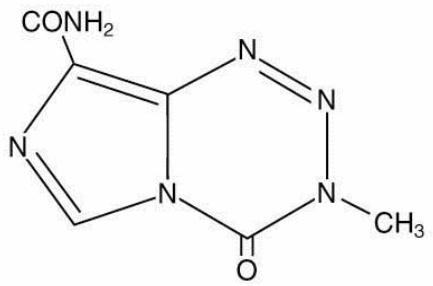
F-XXXXXXXX

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 $C_6H_6N_6O_2$ and a molecular weight of 194.15. The molecule is stable at acidic pH (<5), and labile at pH >7, hence TEMODAR can be administered orally. The prodrug, temozolomide, is rapidly hydrolyzed 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, 140 mg, 180 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. The 5 mg, 20 mg, 100 mg, and 250 mg gelatin capsule shells contain titanium dioxide. The capsules are white and imprinted with pharmaceutical ink. The body of the capsules for the 140 mg and 180 mg strengths is made of gelatin, and is opaque white. The cap is also made of gelatin, and the colors vary based on the dosage strength.

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 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.

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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 140 mg: The blue cap contains gelatin, sodium lauryl sulfate, FD&C Blue #2, and titanium dioxide. The capsule body and cap are imprinted with pharmaceutical branding ink, which contains shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, purified water, strong ammonia solution, potassium hydroxide, and ferric oxide.
TEMODAR 180 mg: The red cap contains gelatin, sodium lauryl sulfate, titanium dioxide, iron oxide red and iron oxide yellow. The capsule body and cap are imprinted with pharmaceutical branding ink, which contains shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, purified water, strong ammonia solution, potassium hydroxide, and ferric oxide.

TEMODAR 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%),

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and unidentified polar metabolite(s) (17%). Overall clearance of temozolomide is about 5.5 L/hr/m^2.

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**).

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/m^2 has no effect on the clearance of temozolomide after oral administration. The pharmacokinetics of temozolomide have not been studied in patients with severely impaired renal function (CLcr <36 mL/min/m^2). Caution should be exercised when TEMODAR Capsules are 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.

Drug-Drug Interactions In a multiple-dose study, administration of TEMODAR Capsules 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

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Newly Diagnosed Glioblastoma Multiforme Five hundred and seventy-three patients were randomized to receive either TEMODAR (TMZ) + Radiotherapy (RT) (n= 287) or RT alone (n=286). Patients in the TEMODAR + RT arm received concomitant TEMODAR (75 mg/m^2) once daily, starting the first day of RT until the last day of RT, for 42 days (with a maximum of 49 days). This was followed by 6 cycles of TEMODAR alone (150 or 200 mg/m^2) on Day 1-5 of every 28-day cycle, starting 4 weeks after the end of RT. Patients in the control arm received RT only. In both arms, focal radiation therapy was delivered as 60 Gy/30 fractions. Focal RT includes the tumor bed or resection site with a 2-3 cm margin. *Pneumocystis carinii* pneumonia (PCP) prophylaxis was required during the TMZ + radiotherapy treatment, regardless of lymphocyte count, and was to continue until recovery of lymphocyte count to less than or equal to Grade 1.

At the time of disease progression, TEMODAR was administered as salvage therapy in 161 patients of the 282 (57%) in the RT alone arm, and 62 patients of the 277 (22%) in the TEMODAR + RT arm.
The addition of concomitant and maintenance TEMODAR to radiotherapy in the treatment of patients with newly diagnosed GBM showed a statistically significant improvement in overall survival compared to radiotherapy alone (Figure 1). The hazard ratio (HR) for overall survival was 0.63 (95% CI for HR=0.52-0.75) with a log-rank p <0.0001 in favor of the TEMODAR arm. The median survival was increased by 2 ½ months in the TEMODAR arm.

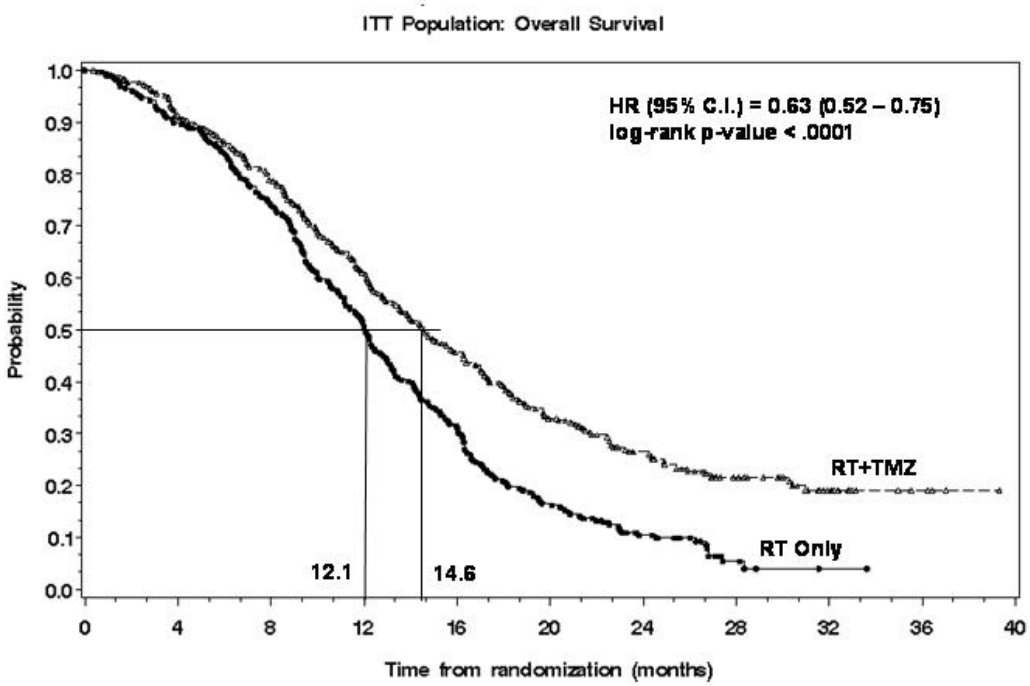

Figure 1 Kaplan-Meier Curves for Overall Survival (ITT Population)

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Refractory (Anaplastic Astrocytoma)

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 Capsules were given for the first 5 consecutive days of a 28-day cycle at a starting dose of 150 mg/m^2/day. If the nadir and day of dosing (Day 29, Day 1 of next cycle) absolute neutrophil count was >1.5 x 10^9/L (1,500/µL) and the nadir and Day 29, Day 1 of next cycle, platelet count was >100 x 10^9/L (100,000/µL), the TEMODAR dose was increased to 200 mg/m^2/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 newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment.

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

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.

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WARNINGS

Patients treated with TEMODAR Capsules may experience myelosuppression. Prior to dosing, patients must have an absolute neutrophil count (ANC) $\geq$1.5 x 10^9/L and a platelet count $\geq$100 x 10^9/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 10^9/L and platelet count exceeds 100 x 10^9/L.Geriatric patients and women have been shown in clinical trials to have a higher risk of developing myelosuppression. Very rare cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukemia, have also been observed.

For treatment of newly diagnosed glioblastoma multiforme: Prophylaxis against *Pneumocystis carinii* pneumonia is required for all patients receiving concomitant TEMODAR and radiotherapy for the 42 day regimen.

There may be a higher occurrence of PCP when temozolomide is administered during a longer dosing regimen. However, all patients receiving temozolomide, particularly patients receiving steroids, should be observed closely for the development of PCP regardless of the regimen.

Pregnancy: Temozolomide may cause fetal harm when administered to a pregnant woman. Five consecutive days of oral administration of 75 mg/m^2/day in rats and 150 mg/m^2/day in rabbits during the period of organogenesis (3/8 and 3/4 the maximum recommended human dose, respectively) caused numerous malformations of the external organs, soft tissues, and skeleton in both species. Doses of 150 mg/m^2/day in rats and rabbits also caused 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 Capsules.

PRECAUTIONS

Information for Patients: Nausea and vomiting were among the most frequently occurring adverse events. 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 Capsules are administered to patients with severe hepatic or renal impairment (see **Special Populations**).

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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=0.31 and 2/10; 20%, p=0.09, respectively) in the first cycle of therapy than patients under 70 years of age (see **ADVERSE REACTIONS**).

In newly diagnosed patients with glioblastoma multiforme, the adverse event profile was similar in younger patients (<65 years) vs older (≥65 years).

Laboratory Tests: For the concomitant treatment phase with RT, a complete blood count should be obtained weekly.

For the 28 day treatment cycles**,** 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 10^9/L and the platelet count falls below 100 x 10^9/L.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Standard carcinogenicity studies were not conducted with temozolomide. In rats treated with 200 mg/m^2 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/m^2 (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/m^2 in rats and 125 mg/m^2 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 Capsules, patients receiving TEMODAR should discontinue nursing.

Pediatric Use: TEMODAR effectiveness in children has not been demonstrated. TEMODAR Capsules have been studied in 2 open label Phase 2 studies in pediatric

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290 patients (age 3-18 years) at a dose of 160-200 mg/m^2 daily for 5 days every 28
291 days. In one trial conducted by the Schering Corporation, 29 patients with recurrent
292 brain stem glioma and 34 patients with recurrent high grade astrocytoma were
293 enrolled. All patients had failed surgery and radiation therapy, while 31% also failed
294 chemotherapy. In a second Phase 2 open label study conducted by the Children's
295 Oncology Group (COG), 122 patients were enrolled, including
296 medulloblastoma/PNET(29), high grade astrocytoma (23), low grade astrocytoma
297 (22), brain stem glioma (16), ependymoma (14), other CNS tumors (9), and non-
298 CNS tumors (9). The TEMODAR toxicity profile in children is similar to adults.
299 Table 1 shows the adverse events in 122 children in the COG Phase 2 study.
300
301 **Table 1**
302

Adverse Events Reported in Pediatric Cooperative Group Trial (≥10%)		
	No. (%) of TEMODAR Patients (N=122)[a]	
Body System/Organ Class Adverse Event	**All Events**	**Gr 3/4**
Subjects Reporting an AE	**107 (88)**	**69 (57)**
Body as a Whole		
Central and Peripheral Nervous System		
Central cerebral CNS cortex	22 (18)	13 (11)
Gastrointestinal System		
Nausea	56 (46)	5 (4)
Vomiting	62 (51)	4 (3)
Platelet, Bleeding and Clotting		
Thrombocytopenia	71 (58)	31 (25)
Red Blood Cell Disorders		
Decreased Hemoglobin	62 (51)	7 (6)
White Cell and RES Disorders		
Decreased WBC	71 (58)	21 (17)
Lymphopenia	73 (60)	48 (39)
Neutropenia	62 (51)	24 (20)

a: These various tumors included the following: PNET-medulloblastoma, glioblastoma, low grade astrocytoma, brain stem tumor, ependymoma, mixed glioma, oligodendroglioma, neuroblastoma, Ewing's sarcoma, pineoblastoma, alveolar soft part sarcoma, neurofibrosarcoma, optic glioma, and osteosarcoma.

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306 **ADVERSE REACTIONS IN ADULTS**
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308 **Newly Diagnosed Glioblastoma Multiforme**
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310 During the concomitant phase (Temodar + radiotherapy), adverse events including
311 thrombocytopenia, nausea, vomiting, anorexia, and constipation, were more

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frequent in the TEMODAR + RT arm. The incidence of other adverse events was comparable in the two arms. The most common adverse events across the cumulative TEMODAR experience were alopecia, nausea, vomiting, anorexia, headache, and constipation (see **Table 2**). Forty-nine percent (49%) of patients treated with TEMODAR reported one or more severe or life-threatening events, most commonly fatigue (13%), convulsions (6%), headache (5%), and thrombocytopenia (5%). Overall, the pattern of events during the maintenance phase was consistent with the known safety profile of TEMODAR.

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Table 2 Number (%) of Patients with Adverse Events: All and Severe/Life Threatening (Incidence of 5% or Greater)

	Concomitant Phase RT Alone (n=285)		Concomitant Phase RT+TMZ (n=288)*		Maintenance Phase TMZ (n=224)	
	All	Grade ≥ 3	All	Grade ≥ 3	All	Grade ≥ 3
Subjects Reporting any Adverse Event	**258 (91)**	**74 (26)**	**266 (92)**	**80 (28)**	**206 (92)**	**82 (37)**
Body as a Whole - General Disorders						
Anorexia	25 (9)	1 (<1)	56 (19)	2 (1)	61 (27)	3 (1)
Dizziness	10 (4)	0	12 (4)	2 (1)	12 (5)	0
Fatigue	139 (49)	15 (5)	156 (54)	19 (7)	137 (61)	20 (9)
Headache	49 (17)	11 (4)	56 (19)	5 (2)	51 (23)	9 (4)
Weakness	9 (3)	3 (1)	10 (3)	5 (2)	16 (7)	4 (2)
Central and Peripheral Nervous System Disorders						
Confusion	12 (4)	6 (2)	11 (4)	4 (1)	12 (5)	4 (2)
Convulsions	20 (7)	9 (3)	17 (6)	10 (3)	25 (11)	7 (3)
Memory Impairment	12 (4)	1 (<1)	8 (3)	1 (<1)	16 (7)	2 (1)
Disorders of the Eye						
Vision Blurred	25 (9)	4 (1)	26 (9)	2 (1)	17 (8)	0
Disorders of the Immune System						
Allergic Reaction	7 (2)	1 (<1)	13 (5)	0	6 (3)	0
Gastro-Intestinal System Disorders						
Abdominal Pain	2 (1)	0	7 (2)	1 (<1)	11 (5)	1 (<1)
Constipation	18 (6)	0	53 (18)	3 (1)	49 (22)	0
Diarrhea	9 (3)	0	18 (6)	0	23 (10)	2 (1)
Nausea	45 (16)	1 (<1)	105 (36)	2 (1)	110 (49)	3 (1)
Stomatitis	14 (5)	1 (<1)	19 (7)	0	20 (9)	3 (1)
Vomiting	16 (6)	1 (<1)	57 (20)	1 (<1)	66 (29)	4 (2)
Injury and Poisoning						
Radiation Injury NOS	11 (4)	1 (<1)	20 (7)	0	5 (2)	0
Musculo-Skeletal System Disorders						
Arthralgia	2 (1)	0	7 (2)	1 (<1)	14 (6)	0
Platelet, Bleeding and Clotting Disorders						
Thrombocytopenia	3 (1)	0	11 (4)	8 (3)	19 (8)	8 (4)
Psychiatric Disorders						
Insomnia	9 (3)	1 (<1)	14 (5)	0	9 (4)	0
Respiratory System Disorders						
Coughing	3 (1)	0	15 (5)	2 (1)	19 (8)	1 (<1)
Dyspnea	9 (3)	4 (1)	11 (4)	5 (2)	12 (5)	1 (<1)

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	Concomitant Phase RT Alone (n=285)		Concomitant Phase RT+TMZ (n=288)*		Maintenance Phase TMZ (n=224)	
	All	Grade ≥ 3	All	Grade ≥ 3	All	Grade ≥ 3
Skin and Subcutaneous Tissue Disorders						
Alopecia	179 (63)	0	199 (69)	0	124 (55)	0
Dry Skin	6 (2)	0	7 (2)	0	11 (5)	1 (<1)
Erythema	15 (5)	0	14 (5)	0	2 (1)	0
Pruritus	4 (1)	0	11 (4)	0	11 (5)	0
Rash	42 (15)	0	56 (19)	3 (1)	29 (13)	3 (1)
Special Senses Other, Disorders						
Taste Perversion	6 (2)	0	18 (6)	0	11 (5)	0

*One patient who was randomized to RT only arm received RT + temozolomide

RT+TMZ=radiotherapy plus temozolomide; LT=life threatening; SGPT = serum glutamic pyruvic transaminase (=alanine aminotransferase [ALT]); NOS=not otherwise specified.

Note: Grade 5 (fatal) adverse events are included in the Grade ≥ 3 column.

Myelosuppression, (neutropenia and thrombocytopenia), which are known dose limiting toxicities for most cytotoxic agents, including TEMODAR, were observed. When laboratory abnormalities and adverse events were combined, Grade 3 or Grade 4 neutrophil abnormalities including neutropenic events were observed in 8% of the patients and Grade 3 or Grade 4 platelet abnormalities, including thrombocytopenic events were observed in 14% of the patients treated with TEMODAR.

Refractory Anaplastic Astrocytoma

Tables 3 and **4** 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. Less than 10% of patients required hospitalization, blood transfusion, or discontinuation of therapy due to myelosuppression.

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356 In clinical trial experience with 110 to 111 women and 169 to 174 men (depending
357 on measurements), there were higher rates of Grade 4 neutropenia (ANC < 500
358 cells/μL) and thrombocytopenia (< 20,000 cells/μL) in women than men in the first
359 cycle of therapy (12% versus 5% and 9% versus 3%, respectively).
360 In the entire safety database for which hematologic data exist (N=932), 7% (4/61)
361 and 9.5% (6/63) of patients over age 70 experienced Grade 4 neutropenia or
362 thrombocytopenia in the first cycle, respectively. For patients less than or equal to
363 age 70, 7% (62/871) and 5.5% (48/879) experienced Grade 4 neutropenia or
364 thrombocytopenia in the first cycle, respectively. Pancytopenia, leukopenia, and
365 anemia have also been reported.
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Table 3

Adverse Events in the Anaplastic Astrocytoma Trial in Adults(>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)
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

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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 4 Adverse Hematologic Effects (Grade 3 to 4) in the Anaplastic Astrocytoma Trial in Adults	
	TEMODAR[a]
Hemoglobin	7/158 (4%)
Lymphopenia	83/152 (55%)
Neutrophils	20/142 (14%)
Platelets	29/156 (19%)
WBC	18/158 (11%)

[a]Change from Grade 0 to 2 at baseline to Grade 3 or 4 during treatment.

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. Rare cases of opportunistic infections including *Pneumocystis carinii* pneumonia (PCP) have also been reported. .

OVERDOSAGE

Doses of 500, 750, 1,000, and 1,250 mg/m ^{2} (total dose per cycle over 5 days) have been evaluated clinically in patients. Dose-limiting toxicity was hematologic and was reported with any dose but is expected to be more severe at higher doses. An overdose of 2,000 mg per day for 5 days was taken by one patient and the adverse events reported were pancytopenia, pyrexia, multi-organ failure, and death. There are reports of patients who have taken more than 5 days of treatment (up to 64 days) with adverse events reported including bone marrow suppression, which in some cases was severe and prolonged, and infections and resulted in death. In the

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event of an overdose, hematologic evaluation is needed. Supportive measures should be provided as necessary.

DOSAGE AND ADMINISTRATION

Dosage of TEMODAR Capsules must be adjusted according to nadir neutrophil and platelet counts in the previous cycle and the neutrophil and platelet counts at the time of initiating the next cycle. For TEMODAR dosage calculations based on body surface area (BSA) see **Table 9**. For suggested capsule combinations on a daily dose see **Table 10**.

Patients with Newly Diagnosed High Grade Glioma:
Concomitant Phase

TEMODAR is administered orally at 75 mg/m^2 daily for 42 days concomitant with focal radiotherapy (60Gy administered in 30 fractions) followed by maintenance TEMODAR for 6 cycles. Focal RT includes the tumor bed or resection site with a 2-3 cm margin. No dose reductions are recommended during the concomitant phase; however, dose interruptions or discontinuation may occur based on toxicity. The TEMODAR dose should be continued throughout the 42 day concomitant period up to 49 days if all of the following conditions are met: absolute neutrophil count ≥ 1.5 x 10^9 /L platelet count ≥ 100 x 10^9/L common toxicity criteria (CTC) non-hematological toxicity ≤Grade 1 (except for alopecia, nausea, and vomiting). During treatment, a complete blood count should be obtained weekly. Temozolomide dosing should be interrupted or discontinued during concomitant phase according to the hematological and non-hematological toxicity criteria as noted in **Table 5.** PCP prophylaxis is required during the concomitant administration of TEMODAR and radiotherapy and should be continued in patients who develop lymphocytopenia until recovery from lymphocytopenia (CTC grade ≤ 1).

Table 5 Temozolomide Dosing Interruption or Discontinuation During Concomitant Radiotherapy and Temozolomide

Toxicity	TMZ Interruption[a]	TMZ Discontinuation
Absolute Neutrophil Count	≥0.5 and <1.5 x 10^9/L	<0.5 x 10^9/L
Platelet Count	≥10 and <100 x 10^9/L	<10 x 10^9/L
CTC Non-hematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 2	CTC Grade 3 or 4

a: Treatment with concomitant TMZ could be continued when all of the following conditions are met: absolute neutrophil count ≥1.5 x 10^9/L; platelet count ≥100 x 10^9/L; CTC non-hematological toxicity ≤Grade 1 (except for alopecia, nausea, vomiting).

TMZ = temozolomide; CTC = Common Toxicity Criteria.

Maintenance Phase Cycle 1:

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Four weeks after completing the TEMODAR + RT phase, TEMODAR is administered for an additional 6 cycles of maintenance treatment. Dosage in Cycle 1 (maintenance) is 150 mg/m^2 once daily for 5 days followed by 23 days without treatment.

Cycles 2-6:
At the start of Cycle 2, the dose is escalated to 200 mg/m^2, if the CTC non-hematologic toxicity for Cycle 1 is Grade ≤2 (except for alopecia, nausea, and vomiting), absolute neutrophil count (ANC) is ≥ 1.5 x 10^9/L, and the platelet count is ≥ 100 x 10^9/L. The dose remains at 200 mg/m^2 per day for the first 5 days of each subsequent cycle except if toxicity occurs. If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles.

Dose reduction or discontinuation during maintenance:
Dose reductions during the maintenance phase should be applied according to Tables **6** and **7**.
During treatment, a complete blood count should be obtained on Day 22 (21 days after the first dose of TEMODAR) 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. Dose reductions during the next cycle should be based on the lowest blood counts and worst non-hematologic toxicity during the previous cycle. Dose reductions or discontinuations during the maintenance phase should be applied according to Tables **6 and 7**.

Table 6 Temozolomide Dose Levels for Maintenance Treatment

Dose Level	Dose (mg/m^2/day)	Remarks
–1	100	Reduction for prior toxicity
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2-6 in absence of toxicity

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Table 7 Temozolomide Dose Reduction or Discontinuation During Maintenance Treatment

Toxicity	Reduce TMZ by 1 Dose Level[a]	Discontinue TMZ
Absolute Neutrophil Count	$<1.0 \times 10^9$/L	See footnote b
Platelet Count	$<50 \times 10^9$/L	See footnote b
CTC Non-hematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4[b]

a: TMZ dose levels are listed in Table 6.

b: TMZ is to be discontinued if dose reduction to <100 mg/m^2 is required or if the same Grade 3 non-hematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction.

TMZ = temozolomide; CTC = Common Toxicity Criteria.

Patients with Refractory Anaplastic Astrocytoma

For adults the initial dose is 150 mg/m^2 orally once daily for 5 consecutive days per 28-day treatment cycle. For adult patients, if both the nadir and day of dosing (Day 29, Day 1 of next cycle) ANC are $\geq 1.5 \times 10^9$/L (1,500/µL) and both the nadir and Day 29, Day 1 of next cycle platelet counts are $\geq 100 \times 10^9$/L (100,000/µL), the TEMODAR dose may be increased to 200 mg/m^2/day for 5 consecutive days per 28-day treatment cycle. During treatment, a complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above 1.5×10^9/L (1,500/µL) and the platelet count exceeds 100×10^9/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 $<1.0 \times 10^9$/L (1,000/µL) or the platelet count is $<50 \times 10^9$/L (50,000/µL) during any cycle, the next cycle should be reduced by 50 mg/m^2, but not below 100 mg/m^2, the lowest recommended dose (see **Table 8**). 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.

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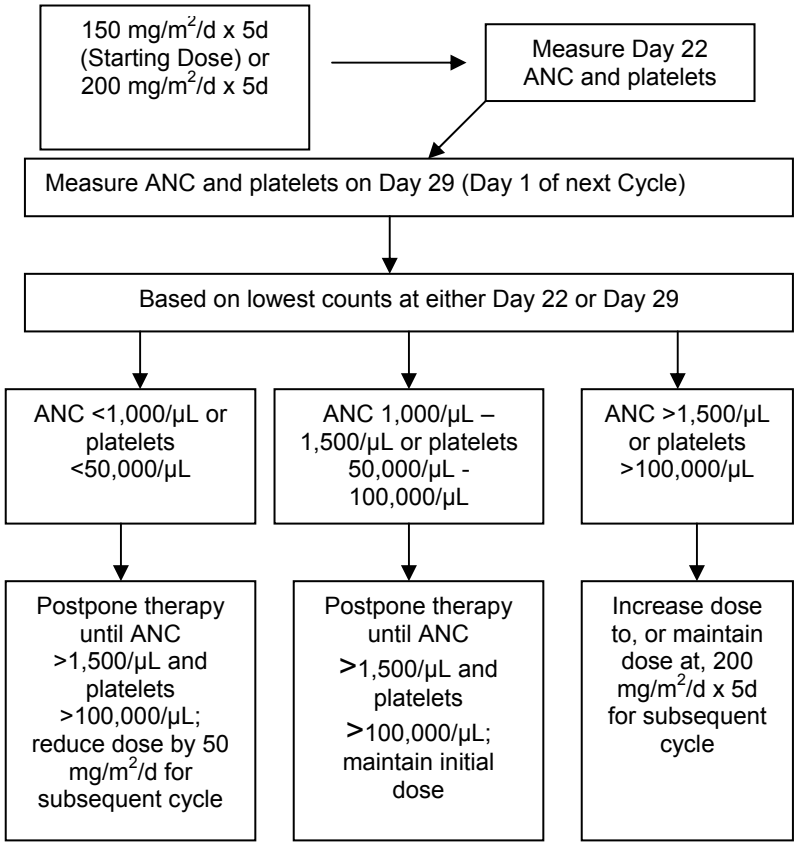
Table 8 Dosing Modification Table



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492
493 **Table 9**
494 Daily Dose Calculations by Body Surface Area (BSA)
495

Total BSA (m^2)	75 mg/m^2 (mg daily)	150 mg/m^2 (mg daily)	200 mg/m^2 (mg daily)
1.0	75	150	200
1.1	82.5	165	220
1.2	90	180	240
1.3	97.5	195	260
1.4	105	210	280
1.5	112.5	225	300
1.6	120	240	320
1.7	127.5	255	340
1.8	135	270	360
1.9	142.5	285	380
2.0	150	300	400
2.1	157.5	315	420
2.2	165	330	440
2.3	172.5	345	460
2.4	180	360	480
2.5	187.5	375	500

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497
498

Table 10

Suggested Capsule Combinations Based on Daily Dose in Adults

Number of Daily Capsules by Strength (mg)

Total Daily Dose (mg)	250 mg	180 mg	140 mg	100 mg	20 mg	5 mg
75	0	0	0	0	3	3
82.5	0	0	0	0	4	0
90	0	0	0	0	4	2
97.5	0	0	0	1	0	0
105	0	0	0	1	0	1
112.5	0	0	0	1	0	2
120	0	0	0	1	1	0
127.5	0	0	0	1	1	1
135	0	0	0	1	1	3
142.5	0	0	1	0	0	0
150	0	0	1	0	0	2
157.5	0	0	1	0	1	0
165	0	0	1	0	1	1

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172.5	0	0	1	0	1	2
180	0	1	0	0	0	0
187.5	0	1	0	0	0	1
195	0	1	0	0	0	3
200	0	1	0	0	1	0
210	0	0	0	2	0	2
220	0	0	0	2	1	0
225	0	0	0	2	1	1
240	0	0	1	1	0	0
255	1	0	0	0	0	1
260	1	0	0	0	0	2
270	1	0	0	0	2	0
280	0	0	2	0	0	0
285	0	0	2	0	0	1
300	0	0	0	3	0	0
315	0	0	0	3	0	3
320	0	1	1	0	0	0
330	0	1	1	0	0	2
340	0	1	1	0	1	0
345	0	1	1	0	1	1
360	0	2	0	0	0	0
375	0	2	0	0	0	3
380	0	1	0	2	0	0
400	0	0	0	4	0	0
420	0	0	3	0	0	0
440	0	0	3	0	1	0
460	0	2	0	1	0	0
480	0	1	0	3	0	0
500	2	0	0	0	0	0

In clinical trials, TEMODAR was administered under both fasting and non-fasting 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 TEMODAR. To reduce nausea and vomiting, TEMODAR 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 Capsules.
TEMODAR (temozolomide) Capsules should not be opened or chewed. They should be swallowed whole with a glass of water.

Handling and Disposal: TEMODAR 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.

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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 count - NDC 0085-1248-01 20 count - NDC 0085-1248-02
TEMODAR (temozolomide) Capsules 20 mg: 5 count - NDC 0085-1244-01 20 count - NDC 0085-1244-02
TEMODAR (temozolomide) Capsules 100 mg: 5 count - NDC 0085-1259-01 20 count - NDC 0085-1259-02
TEMODAR (temozolomide) Capsules 140 mg:
5 count - NDC 0085-1425-01 14 count – NDC 0085-1425-02
TEMODAR (temozolomide) Capsules 180 mg:
5 count - NDC 0085-1430-01 14 count – NDC 0085-1430-02
TEMODAR (temozolomide) Capsules 250 mg:
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]

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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.
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7. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines), *Am J Health-Syst Pharm*. 1996;53:1669-1685.

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Temodar®

[temozolomide]
Capsules

Patient Information Sheet
IMPORTANT INFORMATION
FOR THE PATIENT

Patient Package Insert

TEMODAR® (temozolomide) Capsules

What is TEMODAR?
TEMODAR (temozolomide) is used to treat certain cancerous tumors in the brain of adult patients. Your doctor has prescribed TEMODAR (temozolomide) as part of your cancer treatment. TEMODAR is a drug you take by mouth that interferes with cell growth, especially in cells that are growing rapidly, such as cancerous cells. TEMODAR has been shown to help slow the growth of certain cancerous tumors. When given to patients with brain cancer, TEMODAR has been shown to reduce the size of the tumor in some patients.

Who should not take TEMODAR?
You should not take TEMODAR Capsules if you have had an allergic reaction to DTIC-Dome (dacarbazine), a different treatment for cancer. If you have had an allergic reaction before to drugs such as DTIC-Dome, be sure to tell your doctor before taking TEMODAR. If you are allergic to drugs similar to TEMODAR, you may also have an allergic reaction to TEMODAR.

How should I take TEMODAR?
Take each day's dose of capsules at one time, with a full glass of water. **DO NOT** open or split the capsules. If the capsules are accidentally opened or damaged, you should be extremely careful to avoid inhaling the powder in the capsules or getting it on your skin or mucous membranes (eg, in nose or mouth). Flush the area with water if contact occurs. The medication should be kept away from children and pets. They should be swallowed whole and **NEVER CHEWED**. If capsules are vomited do not take a second dose. New capsules should not be taken until the next planned dose. The medicine is used best by your body if you take it at the same time every day in relation to a meal. To reduce nausea, try to take TEMODAR on an empty stomach or at bedtime. Your doctor may also have prescribed antinausea or other medications to relieve the side effects associated with TEMODAR. Antinausea medications should be taken as directed by your doctor. It is important that you continue to see your doctor regularly to check your progress. Your doctor can uncover side effects of treatment that you might not notice.

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Because TEMODAR (temozolomide) Capsules is a drug you take by mouth, you can take it at home. There are two different dosing schedules for taking TEMODAR.

Be sure you follow the one that your doctor has prescribed for you. One schedule you may be prescribed is, TEMODAR for 42 days (up to 49 days) with radiotherapy. Another schedule should be taken for 5 consecutive days only, then you must **STOP** taking TEMODAR for the next 23 days. This total period of 5 days on TEMODAR and 23 days off TEMODAR is called one treatment cycle. Your dose is based on your height and weight, and the number of treatment cycles will depend on how you respond to and tolerate this treatment.

TEMODAR comes in different strength capsules (shown on the outer label in mg). Each strength has a different color band. Depending on the dose of TEMODAR that your doctor prescribes, you may have to take several capsules on each dosing day of a treatment cycle (Day 1 through Day 5, followed by 23 days with no capsules) or the 42 days (up to 49 days) of consecutive treatment schedule with radiotherapy.

- Be sure you understand exactly how many capsules you need to take of each strength. Ask your doctor or pharmacist to write down the number of each strength (include color) that you need to take each dosing day.
- Be sure you know exactly which days are your dosing days.
- Be sure to review the dose with your healthcare provider each time you start a new cycle. Sometimes the dose or the mix of capsules you need to take will be different from the last cycle.
- Once you take the medicine home, if you are confused or unsure about how to take your dose, contact your doctor or pharmacist immediately.

Your doctor may have prescribed a treatment regimen that is different from those discussed in this information sheet. If so, make sure you follow the specific instructions given to you by your doctor. You should talk to your doctor about what to do if you miss a day. If you take more than the prescribed amount of medicine, contact your doctor right away. It is important that you understand your dosage regimen, it is also important that you do not take more than the amount of TEMODAR prescribed for you. Overdoses can lead to serious outcomes including severe low blood counts and possible death.

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How is TEMODAR supplied?

The 5mg, 20 mg, 100 mg and 250 mg TEMODAR® (temozolomide) Capsules contain a white capsule body with a white cap. The 140 mg and 180 mg capsules contain a white capsule body with a color cap. Each capsule contains color-coded printing according to strength, each a different size. The capsules are available in six different strengths.

TEMODAR Capsule Strength	Color
5mg	Green Imprint
20mg	Brown Imprint
100mg	Blue Imprint
140mg	Blue Cap
180mg	Orange Cap
250mg	Black Imprint

What should I avoid while taking TEMODAR?

There are no limitations on what you may eat or drink while taking TEMODAR. However, to ease nausea, try to take TEMODAR on an empty stomach.

TEMODAR may cause birth defects. Therefore, male or female patients who take TEMODAR should use effective birth control. Female patients should avoid becoming pregnant while receiving this drug. You should not breast feed an infant while taking TEMODAR. It is not known whether TEMODAR passes into breast milk. Because many drugs do pass into breast milk, there is the possibility of serious harm to nursing infants.

What are the possible or reasonably likely side effects of TEMODAR?

Nausea and vomiting are the most common side effects associated with TEMODAR. Your doctor can prescribe medicines that may help reduce some of these. Other common side effects include headache, feeling tired, loss of appetite, hair loss and constipation.

TEMODAR also can reduce the number of certain types of blood cells, which can have serious effects. White blood cells are needed to fight infections. Lowering of white blood cells, could result in a serious infection with a potential outcome of death. Platelets are needed in the normal course of blood clotting. Lowering of platelets does not allow your blood to clot normally, which can result in bleeding episodes. Therefore, it is important that your doctor check your blood periodically while you are taking TEMODAR to see if these side effects are occurring. Patients age 70 or older, women, and patients who have had chemotherapy or radiation therapy may be more likely to have their blood cells affected.

There are other side effects associated with TEMODAR. They are included in a longer, more technical information leaflet written for healthcare providers that you can get from your doctor or pharmacist.

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General information about the use of prescription drug products.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Package Insert. You should contact your healthcare professional regarding any concerns you may have about using TEMODAR. TEMODAR should not be used for a condition for which it was not prescribed, and it should not be given to other persons.

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PHARMACIST:

Tear at perforation and give to patient.

Temodar®
[temozolomide]
Capsules

PHARMACIST
INFORMATION SHEET

IMPORTANT
DISPENSING
INFORMATION

PHARMACIST INFORMATION SHEET

IMPORTANT DISPENSING INFORMATION

For every patient, TEMODAR must be dispensed in a separate vial or in its original glass bottle making sure each container lists the strength per capsule and that patients take the appropriate number of capsules from each bottle or vial.
Please see the dispensing instructions below for more information.

What is TEMODAR?

TEMODAR® (temozolomide) is an oral alkylating agent for the treatment of newly diagnosed glioblastoma multiforme and refractory anaplastic astrocytoma.

How is TEMODAR dosed?

The daily dose of TEMODAR Capsules for a given patient is calculated by the physician, based on the patient's body surface area (BSA). The resulting dose is then rounded off to the nearest 5 mg. An example of the dosing may be as follows: the initial daily dose of TEMODAR in milligrams is the BSA multiplied by mg/m^2/day, (a patient with a BSA of 1.84 is 1.84 x 75 mg= 138, or 140 mg/day . The dose for subsequent cycles may be adjusted according to nadir neutrophil and platelet counts in the previous cycle and at the time of initiating the next cycle.

How might the dose of TEMODAR be modified for Refractory Anaplastic Astrocytoma?

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/m^2 orally once daily for 5

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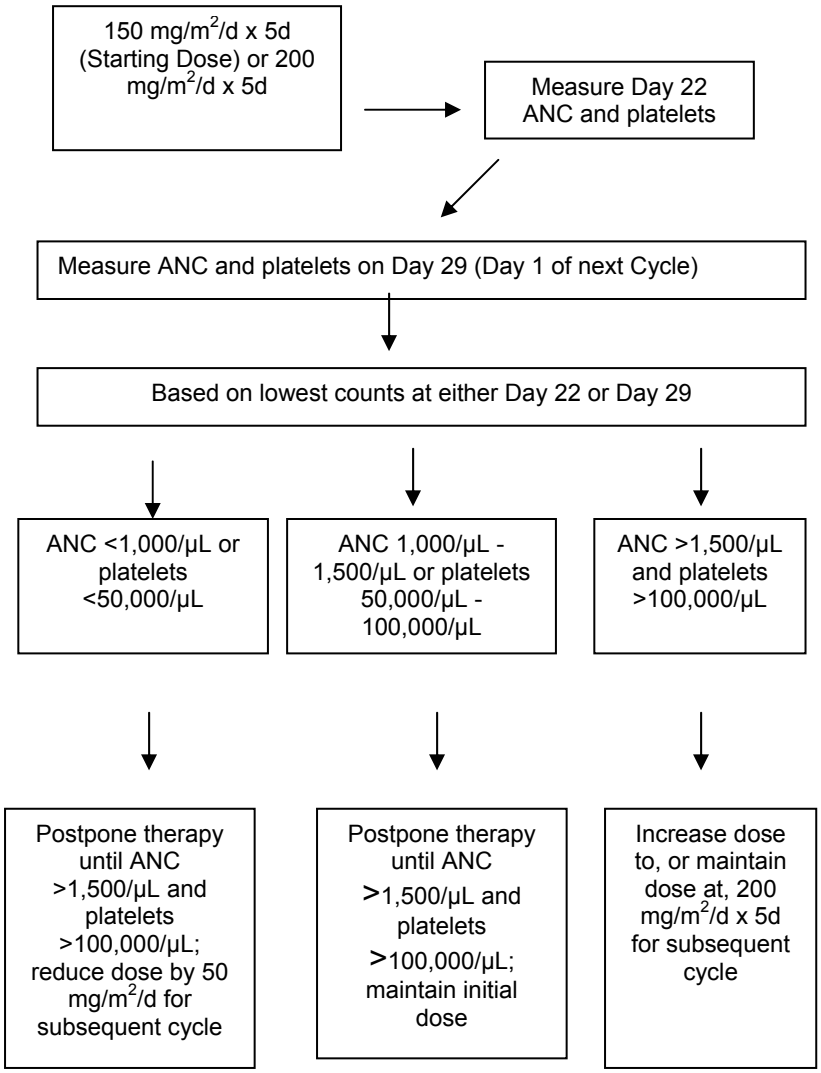
consecutive days per 28-day treatment cycle. If both the nadir and day of dosing (Day 29, Day 1 of next cycle) absolute neutrophil counts (ANC) are ≥1.5 x 10^9/L (1,500/μL) and both the nadir and Day 29, Day 1 of next cycle platelet counts are ≥100 x 10^9/L (100,000/μL), the TEMODAR dose may be increased to 200 mg/m^2/day for 5 consecutive days per 28-day treatment cycle. During treatment, a complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above 1.5 x 10^9/L (1,500/μL) and the platelet count exceeds 100 x 10^9/L (100,000/μL). The next cycle of 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/m^2, but not below 100 mg/m^2, the lowest recommended dose (see **Table 1** below).

TABLE 1

Dosing Modification Table for Refractory Anaplastic Astrocytoma



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What is the TEMODAR® (temozolomide) Capsules treatment regimen?

TEMODAR is given for 5 consecutive days on a 28-day cycle. Patients should continue taking TEMODAR until their physician determines that their disease has progressed, up to 2 years, or until unacceptable side effects or toxicities occur. Physicians may alter the treatment regimen for a given patient.

Newly Diagnosed Concomitant Phase Treatment Schedule

TEMODAR is administered orally at 75 mg/m^2 daily for 42 days concomitant with focal radiotherapy (60Gy administered in 30 fractions), followed by maintenance TEMODAR for 6 cycles. No dose reductions are recommended, however, dose interruptions may occur based on patient tolerance. The TEMODAR dose can be continued throughout the 42 day concomitant period up to 49 days if all of the following conditions are met: absolute neutrophil count ≥ 1.5 x 10^9/L platelet count ≥ 100 x10^9 /L common toxicity criteria (CTC) non-hematological toxicity ≤Grade 1 (except for alopecia, nausea and vomiting). During treatment a complete blood count should be obtained weekly. Temozolomide dosing should be interrupted or discontinued during concomitant phase according to the hematological and non-hematological toxicity criteria as noted in **Table 2.** PCP prophylaxis is required during the concomitant administration of Temodar and radiotherapy and should be continued in patients who develop lymphocytopenia until recovery from lymphocytopenia (CTC grade ≤ 1).

Table 2 Temozolomide Dosing Interruption or Discontinuation During Concomitant Radiotherapy and Temozolomide

Toxicity	TMZ Interruption[a]	TMZ Discontinuation
Absolute Neutrophil Count	≥0.5 and <1.5 x 10^9/L	<0.5 x 10^9/L
Platelet Count	≥10 and <100 x 10^9/L	<10 x 10^9/L
CTC Non-hematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 2	CTC Grade 3 or 4

a: Treatment with concomitant TMZ could be continued when all of the following conditions were met: absolute neutrophil count ≥1.5 x 10^9/L; platelet count ≥100 x 10^9/L; CTC non-hematological toxicity ≤Grade 1 (except for alopecia, nausea, vomiting).

TMZ = temozolomide; CTC = Common Toxicity Criteria.

Maintenance Phase Treatment Schedule

Four weeks after completing the TEMODAR + RT phase, TEMODAR is administered for an additional 6 cycles of maintenance treatment. Dosage in Cycle 1 (maintenance) is 150 mg/m^2 once daily for 5 days followed by 23 days without

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treatment. At the start of Cycle 2, the dose is escalated to 200 mg/m^2, if the CTC non-hematologic toxicity for Cycle 1 is Grade ≤2 (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is ≥ 1.5 x 10^9/L, and the platelet count is ≥ 100 x 10^9/L. If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles. The dose remains at 200 mg/m^2 per day for the first 5 days of each subsequent cycle except if toxicity occurs.

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. Dose reductions during the next cycle should be based on the lowest blood counts and worst non-hematologic toxicity during the previous cycle. Dose reductions or discontinuations during the maintenance phase should be applied according to Tables **3 and 4**.

Table 3 Temozolomide Dose Levels for Maintenance Treatment

Dose Level	Dose (mg/m^2/day)	Remarks
–1	100	Reduction for prior toxicity
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2-6 in absence of toxicity

Table 4 Temozolomide Dose Reduction or Discontinuation During Maintenance Treatment

Toxicity	Reduce TMZ by 1 Dose Level[a]	Discontinue TMZ
Absolute Neutrophil Count	<1.0 x 10^9/L	See footnote b
Platelet Count	<50 x 10^9/L	See footnote b
CTC Non-hematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4[b]

a: TMZ dose levels are listed in Table 3

b: TMZ is to be discontinued if dose reduction to <100 mg/m^2 is required or if the same Grade 3 non-hematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction.

TMZ = temozolomide; CTC = Common Toxicity Criteria.

How is TEMODAR taken?

Patients should take each day's dose with a full glass of water at the same time each day. Taking the medication on an empty stomach or at bedtime may help ease nausea. If patients are also taking antinausea or other medications to relieve the side effects associated with TEMODAR, they should be advised to take these

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medications 30 minutes before they take TEMODAR. Temozolomide causes the rapid appearance of malignant tumors in rats. Patients **SHOULD NOT** open or split the capsules. 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. The TEMODAR capsules should be swallowed whole and **NEVER CHEWED**.

What should the patient avoid during treatment with TEMODAR?
There are no dietary restrictions for patients taking TEMODAR. TEMODAR may affect testicular function, so male patients should exercise adequate birth control measures. TEMODAR may cause birth defects. Female patients should avoid becoming pregnant while receiving this drug. Women who are nursing prior to receiving TEMODAR should discontinue nursing. It is not known whether TEMODAR is excreted into breast milk.

What are the side effects of TEMODAR?
Nausea and vomiting are the most common side effects associated with TEMODAR. Noncumulative myelosuppression is the dose-limiting toxicity. Patients should be evaluated periodically by their physician to monitor blood counts.

Other commonly reported side effects reported by patients taking TEMODAR are fatigue, constipation, alopecia, anorexia, and headache.

How is TEMODAR supplied?
TEMODAR capsules are available in 5mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg strengths. The 5 mg, 20 mg, 100 mg, and 250 mg capsules contain a white capsule body with a white cap. The 140 mg and 180 mg capsules contain a white capsule body with a color cap. Each capsule contains color-coded printing according to strength.

TEMODAR Capsule Strength	Color
5 mg	Green Imprint
20 mg	Brown Imprint
100 mg	Blue Imprint
140 mg	Blue Cap
180 mg	Red Cap
250 mg	Black Imprint

The 5 mg, 20 mg, 100 mg, and 250 mg capsule strengths are available in 5-count and 20-count packages. The 140 mg and 180 mg capsule strengths are available in 5-count and 14-count.

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How is TEMODAR dispensed?
Each strength of TEMODAR must be dispensed in a separate vial or in its original glass bottle (one strength per one container). Follow the instructions below:
Based on the dose prescribed, determine the number of each strength of TEMODAR capsules needed for the full 42 or 5 day cycle as prescribed by the physician. For example, in a 5 day cycle, 275 mg/day would be dispensed as five 250-mg capsules, five 20-mg capsules and five 5-mg capsules. Label each container with the appropriate number of capsules to be taken each day. Dispense to the patient, making sure each container lists the strength (mg) per capsule and that he or she understands to take the appropriate number of capsules of TEMODAR from each bottle or vial to equal the total daily dose prescribed by the physician.

How can TEMODAR be ordered? TEMODAR can be ordered from your wholesaler. It is important to understand if TEMODAR is being used as part of a 42 day regimen or as part of a five-day course. Remember to order enough TEMODAR for the appropriate cycle.
For example:

- a 5-day course of 360 mg/day would require the following to be ordered: two-5 count packages of 180 mg capsules
- a 42-day course of 140 mg/day would require the following to be ordered: three-14 count packages of 140 mg capsules

For example of other dosing regimens, please refer to the full Prescribing Information (Table 10)

TEMODAR Product	NDC Number
250-mg capsules (5 count)	0085-1252-01
250-mg capsules (20 count)	0085-1252-02
180 mg capsules (5 count)	0085-1430-01
180 mg capsules (14 count)	0085-1430-02
140 mg capsules (5 count)	0085-1425-01
140 mg capsules (14 count)	0085-1425-02
100-mg capsules (5 count)	0085-1259-01
100-mg capsules (20 count)	0085-1259-02
20-mg capsules (5 count)	0085-1244-01
20-mg capsules (20 count)	0085-1244-02
5-mg capsules (5 count)	0085-1248-01
5-mg capsules (20 count)	0085-1248-02

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FPO for I-2 of 5

7/16" CODE AREA
NO INK
NO VARNISH

ATTENTION PHARMACIST:
SPECIAL DISPENSING
INFORMATION INCLUDED.
Please review carefully.

Temodar®
[temozolomide]
Capsules

180 mg per capsule

NDC 0085-1430-02

180 mg
per capsule

Temodar®
[temozolomide]
Capsules

For Oral Administration
Rx only

THIS PACKAGE CONTAINS
14 CAPSULES

Schering Corporation

Temodar®
[temozolomide]
Capsules

4-4-2 80%
FPO for UPC
N 3 0085-1430-02 x

DIE3940

Temodar®
[temozolomide]
Capsules

For Oral Administration
180 mg

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature]

Each capsule contains:
180 mg temozolomide.

Usual Dose: See package insert for recommendations regarding the use of 5-, 20-, 100-, 140-, 180- and 250-mg capsule strengths in establishing a daily regimen.

Read accompanying directions carefully.

Cytotoxic: Do not open the capsules. Swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

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U.S. Patent 5,260,291

GLUE STRIP

180 mg per capsule

Temodar®
[temozolomide]
Capsules

ATTENTION PHARMACIST:
SPECIAL DISPENSING
INFORMATION INCLUDED.
Please review carefully.

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NO VARNISH

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PANTONE COLORS
BLACK
PMS 2748
PMS 3288
PMS 187

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For current labeling information, please visit https://www.fda.gov/drugsatfda

NO COLOR

RSS LIMITED BARCODE (.010) FPO

Dispense in tight, light-resistant containers as defined in USP/NF.

Usual Dose: See package insert for recommendations regarding the use of 5-, 20-, 100-, 140-, 180-, and 250-mg capsule strengths in establishing a daily regimen.

Each capsule contains:
180 mg temozolomide.

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

NDC 0085-XXXX-01

180 mg PER CAPSULE

Temodar®
(temozolomide)
Capsules

THIS PACKAGE CONTAINS 5 CAPSULES

For Oral Administration
Rx only

Cytotoxic
Read accompanying directions carefully.

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FPO for 1-2 of 5

7/16" CODE AREA
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NO VARNISH

ATTENTION PHARMACIST:
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INFORMATION INCLUDED.
Please review carefully.

Temodar®
[temozolomide]
Capsules

180 mg per capsule

NDC 0085-1430-01

180 mg
per capsule

Temodar®
[temozolomide]
Capsules

For Oral Administration
Rx only

THIS PACKAGE CONTAINS
5 CAPSULES

Schering Corporation

Temodar®
[temozolomide]
Capsules

4-4-2 80%
FPO for UPC

N 3 0085-1430-01 x

DIE3940

Temodar®
[temozolomide]
Capsules

For Oral Administration
180 mg

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature]

Each capsule contains:
180 mg temozolomide.

Usual Dose: See package insert for recommendations regarding the use of 5-, 20-, 100-, 140-, 180- and 250-mg capsule strengths in establishing a daily regimen.

Read accompanying directions carefully.

Cytotoxic: Do not open the capsules. Swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

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Kenilworth, NJ 07033.
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U.S. Patent 5,260,291

GLUE STRIP

180 mg per capsule

Temodar®
[temozolomide]
Capsules

ATTENTION PHARMACIST:
SPECIAL DISPENSING
INFORMATION INCLUDED.
Please review carefully.

7/16" CODE AREA
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CODE AREA
NO COLOR

RSS LIMITED
BARCODE (.010)
FPO

Dispense in tight, light-resistant containers as defined in USP/NF.

Usual Dose: See package insert for recommendations regarding the use of 5-, 20-, 100-, 140-, 180-, and 250-mg capsule strengths in establishing a daily regimen

Each capsule contains:
140 mg temozolomide.

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

NDC 0085-XXXX-01 **140 mg PER CAPSULE**

Temodar®
(temozolomide) Capsules

THIS PACKAGE CONTAINS 14 CAPSULES

For Oral Administration
Rx only

Cytotoxic
Read accompanying directions carefully.

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NO VARNISH

ATTENTION PHARMACIST:
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Please review carefully.

Temodar®
(temozolomide)
Capsules

140 mg per capsule

NDC 0085-1425-02

140 mg
per capsule

Temodar®
(temozolomide)
Capsules

For Oral Administration
Rx only

THIS PACKAGE CONTAINS
14 CAPSULES

Schering Corporation

Temodar®
(temozolomide)
Capsules

4-4-2 80%
FPO for UPC
N 3 0085-1425-02 x

DIE3940

Temodar®
(temozolomide)
Capsules

For Oral Administration
140 mg

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature]

Each capsule contains:
140 mg temozolomide.

Usual Dose: See package insert for recommendations regarding the use of 5-, 20-, 100-, 140-, 180- and 250-mg capsule strengths in establishing a daily regimen.

Read accompanying directions carefully.

Cytotoxic: Do not open the capsules. Swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

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U.S. Patent 5,260,291

PS
GLUE STRIP

140 mg per capsule

Temodar®
(temozolomide)
Capsules

ATTENTION PHARMACIST:
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INFORMATION INCLUDED.
Please review carefully.

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NO INK
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PANTONE COLORS
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NO COLOR

RSS LIMITED BARCODE (.010) FPO

Dispense in tight, light-resistant containers as defined in USP/NF.

Usual Dose: See package insert for recommendations regarding the use of 5-, 20-, 100-, 140-, 180-, and 250-mg capsule strengths in establishing a daily regimen

Each capsule contains:
140 mg temozolomide.

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

NDC 0085-XXXX-01

140 mg PER CAPSULE

Temodar®
(temozolomide)
Capsules

THIS PACKAGE CONTAINS 5 CAPSULES

For Oral Administration
Rx only

Cytotoxic
Read accompanying directions carefully.

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CODE AREA
NO COLOR

CODE AREA
NO COLOR

PANTONE COLORS
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PMS 2748
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PMS 305

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FPO for I-2 of 5

7/16" CODE AREA
NO INK
NO VARNISH

ATTENTION PHARMACIST:
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INFORMATION INCLUDED.
Please review carefully.

Temodar®
(temozolomide)
Capsules

140 mg per capsule

NDC 0085-1425-01

140 mg
per capsule

Temodar®
(temozolomide)
Capsules

For Oral Administration
Rx only

THIS PACKAGE CONTAINS
5 CAPSULES

Schering Corporation

Temodar®
(temozolomide)
Capsules

4-4-2 80%
FPO for UPC
N 3 0085-1425-01 x

DIE3940

Temodar®
(temozolomide)
Capsules

For Oral Administration
140 mg

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature]

Each capsule contains:
140 mg temozolomide.

Usual Dose: See package insert for recommendations regarding the use of 5-, 20-, 100-, 140-, 180- and 250-mg capsule strengths in establishing a daily regimen.

Read accompanying directions carefully.

Cytotoxic: Do not open the capsules. Swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

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U.S. Patent 5,260,291

PS
GLUE STRIP

140 mg per capsule

Temodar®
(temozolomide)
Capsules

ATTENTION PHARMACIST:
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OVERLAP AREA-NO PRINT-NO COLOR

CODE AREA
NO COLOR

RSS LIMITED
BARCODE (.010)
FPO

Dispense in tight, light-resistant containers as defined in USP/NF.

Usual Dose: See package insert for recommendations regarding the use of 5-, 20-, 100-, 140-, 180-, and 250-mg capsule strengths in establishing a daily regimen

Each capsule contains:
180 mg temozolomide.

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

NDC 0085-XXXX-01

180 mg PER CAPSULE

Temodar®
(temozolomide)
Capsules

THIS PACKAGE CONTAINS 14 CAPSULES

For Oral Administration
Rx only

Cytotoxic
Read accompanying directions carefully.

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CODE AREA
NO COLOR

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PMS 3288	
PMS 187	