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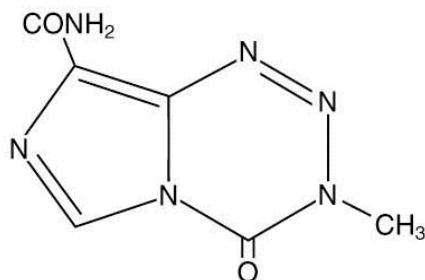
6 **TEMODAR®**
7 **(temozolomide)**
8 **CAPSULES**

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10 **DESCRIPTION**

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

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17 The material is a white to light tan/light pink powder with a molecular formula of
18 C₆H₆N₆O₂ and a molecular weight of 194.15. The molecule is stable at acidic pH
19 (<5), and labile at pH >7, hence TEMODAR can be administered orally. The
20 prodrug, temozolomide, is rapidly hydrolysed to the active 5-(3-methyltriazen-1-yl)
21 imidazole-4-carboxamide (MTIC) at neutral and alkaline pH values, with hydrolysis
22 taking place even faster at alkaline pH.

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

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

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

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



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

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42 **CLINICAL PHARMACOLOGY**

43 **Mechanism of Action:** Temozolomide is not directly active but undergoes rapid
44 nonenzymatic conversion at physiologic pH to the reactive compound MTIC. The
45 cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Alkylation
46 (methylation) occurs mainly at the O⁶ and N⁷ positions of guanine.

47

48 **Pharmacokinetics:** Temozolomide is rapidly and completely absorbed after oral
49 administration; peak plasma concentrations occur in 1 hour. Food reduces the rate
50 and extent of temozolomide absorption. Mean peak plasma concentration and AUC
51 decreased by 32% and 9%, respectively, and T_{max} increased 2-fold (from 1.1 to 2.25
52 hours) when temozolomide was administered after a modified high-fat breakfast.
53 Temozolomide is rapidly eliminated with a mean elimination half-life of 1.8 hours and
54 exhibits linear kinetics over the therapeutic dosing range. Temozolomide has a
55 mean apparent volume of distribution of 0.4 L/kg (%CV=13%). It is weakly bound to
56 human plasma proteins; the mean percent bound of drug-related total radioactivity is
57 15%.

58

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

72

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

80

81 **Gender Population** pharmacokinetic analysis indicates that women have an
82 approximately 5% lower clearance (adjusted for body surface area) for
83 temozolomide than men. Women have higher incidences of Grade 4 neutropenia



84 and thrombocytopenia in the first cycle of therapy than men (see **ADVERSE**
85 **REACTIONS**).

86
87 *Race* The effect of race on the pharmacokinetics of temozolomide has not been
88 studied.

89
90 *Tobacco Use Population* pharmacokinetic analysis indicates that the oral clearance
91 of temozolomide is similar in smokers and nonsmokers.

92
93 *Creatinine Clearance Population* pharmacokinetic analysis indicates that creatinine
94 clearance over the range of 36-130 mL/min/m² has no effect on the clearance of
95 temozolomide after oral administration. The pharmacokinetics of temozolomide have
96 not been studied in patients with severely impaired renal function (CL_{cr} <36
97 mL/min/m²). Caution should be exercised when TEMODAR Capsules are
98 administered to patients with severe renal impairment. TEMODAR has not been
99 studied in patients on dialysis.

100
101 *Hepatically Impaired Patients* In a pharmacokinetic study, the pharmacokinetics of
102 temozolomide in patients with mild-to-moderate hepatic impairment (Child's-Pugh
103 Class I - II) were similar to those observed in patients with normal hepatic function.
104 Caution should be exercised when temozolomide is administered to patients with
105 severe hepatic impairment.

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108 *Drug-Drug Interactions* In a multiple-dose study, administration of TEMODAR
109 Capsules with ranitidine did not change the C_{max} or AUC values for temozolomide or
110 MTIC. Population analysis indicates that administration of valproic acid decreases
111 the clearance of temozolomide by about 5% (see **PRECAUTIONS**).

112 Population analysis failed to demonstrate any influence of coadministered
113 dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H₂-
114 receptor antagonists, or phenobarbital on the clearance of orally administered
115 temozolomide.

116
117 *Clinical Studies* A single-arm, multicenter study was conducted in 162 patients who
118 had anaplastic astrocytoma at first relapse and who had a baseline Karnofsky
119 performance status of 70 or greater. Patients had previously received radiation
120 therapy and may also have previously received a nitrosourea with or without other
121 chemotherapy. Fifty-four patients had disease progression on prior therapy with both
122 a nitrosourea and procarbazine and their malignancy was considered refractory to
123 chemotherapy (refractory anaplastic astrocytoma population). Median age of this
124 subgroup of 54 patients was 42 years (19 to 76). Sixty-five percent were male.
125 Seventy-two percent of patients had a KPS of ≥80. Sixty-three percent of patients
126 had surgery other than a biopsy at the time of initial diagnosis. Of those patients
127 undergoing resection, 73% underwent a subtotal resection and 27% underwent a
128 gross total resection. Eighteen percent of patients had surgery at the time of first



129 relapse. The median time from initial diagnosis to first relapse was 13.8 months (4.2
130 to 75.4).

131 TEMODAR Capsules were given for the first 5 consecutive days of a 28-day
132 cycle at a starting dose of 150 mg/m²/day. If the nadir and day of dosing (Day 29,
133 Day 1 of next cycle) absolute neutrophil count was $\geq 1.5 \times 10^9/L$ (1,500/ μ L) and the
134 nadir and Day 29, Day 1 of next cycle, platelet count was $\geq 100 \times 10^9/L$ (100,000/ μ L),
135 the TEMODAR dose was increased to 200 mg/m²/day for the first 5 consecutive
136 days of a 28-day cycle.

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

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148 INDICATIONS AND USAGE

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

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

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159 CONTRAINDICATIONS

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

164

165 WARNINGS

166 Patients treated with TEMODAR Capsules may experience
167 myelosuppression. Prior to dosing, patients must have an absolute neutrophil count
168 (ANC) $\geq 1.5 \times 10^9/L$ and a platelet count $\geq 100 \times 10^9/L$. A complete blood count
169 should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that
170 day, and weekly until the ANC is above $1.5 \times 10^9/L$ and platelet count exceeds 100
171 $\times 10^9/L$. In the clinical trials, if the ANC fell to $< 1.0 \times 10^9/L$ or the platelet count was
172 $< 50 \times 10^9/L$ during any cycle, the next cycle was reduced by 50 mg/m² but not below
173 100 mg/m². Patients who do not tolerate 100 mg/m² should not receive TEMODAR
174 Capsules. Geriatric patients and women have been shown in clinical trials to have a



175 higher risk of developing myelosuppression. Myelosuppression generally occurred
176 late in the treatment cycle. The median nadirs occurred at 26 days for platelets
177 (range 21 to 40 days) and 28 days for neutrophils (range 1 to 44 days). Only 14%
178 (22/158) of patients had a neutrophil nadir and 20% (32/158) of patients had a
179 platelet nadir which may have delayed the start of the next cycle. Neutrophil and
180 platelet counts returned to normal, on average, within 14 days of nadir counts (see
181 **PRECAUTIONS**).

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183 **Pregnancy:** Temozolomide may cause fetal harm when administered to a pregnant
184 woman. Five consecutive days of oral administration of 75 mg/m²/day in rats and
185 150 mg/m²/day in rabbits during the period of organogenesis (3/8 and 3/4 the
186 maximum recommended human dose, respectively) caused numerous
187 malformations of the external organs, soft tissues, and skeleton in both species.
188 Doses of 150 mg/m²/day in rats and rabbits also caused embryoletality as indicated
189 by increased resorptions. There are no adequate and well-controlled studies in
190 pregnant women. If this drug is used during pregnancy, or if the patient becomes
191 pregnant while taking this drug, the patient should be apprised of the potential
192 hazard to the fetus. Women of childbearing potential should be advised to avoid
193 becoming pregnant during therapy with TEMODAR Capsules.

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PRECAUTIONS

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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.

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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.

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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**).



219 **Laboratory Tests:** A complete blood count should be obtained on Day 22 (21 days
220 after the first dose). Blood counts should be performed weekly until recovery if the
221 ANC falls below $1.5 \times 10^9/L$ and the platelet count falls below $100 \times 10^9/L$.
222

223 **Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Standard
224 carcinogenicity studies were not conducted with temozolomide. In rats treated with
225 $200 \text{ mg}/\text{m}^2$ temozolomide (equivalent to the maximum recommended daily human
226 dose) on 5 consecutive days every 28 days for 3 cycles, mammary carcinomas were
227 found in both males and females. With 6 cycles of treatment at 25, 50, and 125
228 mg/m^2 (about 1/8 to 1/2 the maximum recommended daily human dose), mammary
229 carcinomas were observed at all doses and fibrosarcomas of the heart, eye, seminal
230 vesicles, salivary glands, abdominal cavity, uterus, and prostate; carcinoma of the
231 seminal vesicles, schwannoma of the heart, optic nerve, and harderian gland; and
232 adenomas of the skin, lung, pituitary, and thyroid were observed at the high dose.

233 Temozolomide was mutagenic *in vitro* in bacteria (Ames assay) and
234 clastogenic in mammalian cells (human peripheral blood lymphocyte assays).
235

236 Reproductive function studies have not been conducted with temozolomide.
237 However, multicycle toxicology studies in rats and dogs have demonstrated
238 testicular toxicity (syncytial cells/immature sperm, testicular atrophy) at doses of 50
239 mg/m^2 in rats and $125 \text{ mg}/\text{m}^2$ in dogs (1/4 and 5/8, respectively, of the maximum
240 recommended human dose on a body surface area basis).
241

241 **Pregnancy Category D:** See **WARNINGS** section.
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243 **Nursing Mothers:** It is not known whether this drug is excreted in human milk.
244 Because many drugs are excreted in human milk and because of the potential for
245 serious adverse reactions in nursing infants from TEMODAR Capsules, patients
246 receiving TEMODAR should discontinue nursing.
247

248 **Pediatric Use:**

249 TEMODAR effectiveness in children has not been demonstrated. TEMODAR
250 Capsules have been studied in 2 open label Phase 2 studies in pediatric patients
251 (age 3-18 years) at a dose of $160\text{-}200 \text{ mg}/\text{m}^2$ daily for 5 days every 28 days. In one
252 trial conducted by the Schering Corporation, 29 patients with recurrent brain stem
253 glioma and 34 patients with recurrent high grade astrocytoma were enrolled. All
254 patients had failed surgery and radiation therapy, while 31% also failed
255 chemotherapy. In a second Phase 2 open label study conducted by the Children's
256 Oncology Group (COG), 122 patients were enrolled, including
257 medulloblastoma/PNET(29), high grade astrocytoma (23), low grade astrocytoma
258 (22), brain stem glioma (16), ependymoma (14) other CNS tumors (9) and non-CNS
259 tumors (9). The TEMODAR toxicity profile in children is similar to adults. Table 1
260 shows the adverse events in 122 children in the COG Phase 2 study.
261

262 **Table 1**

Adverse Events Reported in Pediatric Cooperative Group Trial ($\geq 10\%$)

No. (%) of TEMODAR
Patients (N=122)^a



Adverse Events Reported in Pediatric Cooperative Group Trial (≥10%)		
Body System/Organ Class Adverse Event	No. (%) of TEMODAR Patients (N=122)^a	
	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, Ewings sarcoma, pineoblastoma, alveolar soft part sarcoma, neurofibrosarcoma, optic glioma, and osteosarcoma.

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ADVERSE REACTIONS IN ADULTS

Tables 2 and 3 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



284 **WARNINGS**). Less than 10% of patients required hospitalization, blood transfusion,
285 or discontinuation of therapy due to myelosuppression.

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

290 In the entire safety database for which hematologic data exist (N=932), 7%
291 (4/61) and 9.5% (6/63) of patients over age 70 experienced Grade 4 neutropenia or
292 thrombocytopenia in the first cycle, respectively. For patients less than or equal to
293 age 70, 7% (62/871) and 5.5% (48/879) experienced Grade 4 neutropenia or
294 thrombocytopenia in the first cycle, respectively. Pancytopenia, leukopenia, and
295 anemia have also been reported.

296 In addition, the following spontaneous adverse experiences have been
297 reported during the marketing surveillance of TEMODAR Capsules: allergic
298 reactions including rare cases of anaphylaxis. Rare cases of erythema multiforme
299 have been reported which resolved after discontinuation of TEMODAR and, in some
300 cases, recurred upon rechallenge.
301

Table 2
Adverse Events in the Anaplastic Astrocytoma Trial in Adults(>5%)

Any Adverse Event	No. (%) of TEMODAR Patients (N=158)	
	All Events	Grade 3/4
	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
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.

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

^aChange from Grade 0 to 2 at baseline to Grade 3 or 4 during treatment.

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OVERDOSAGE

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DOSAGE AND ADMINISTRATION

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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 of TEMODAR Capsules 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.

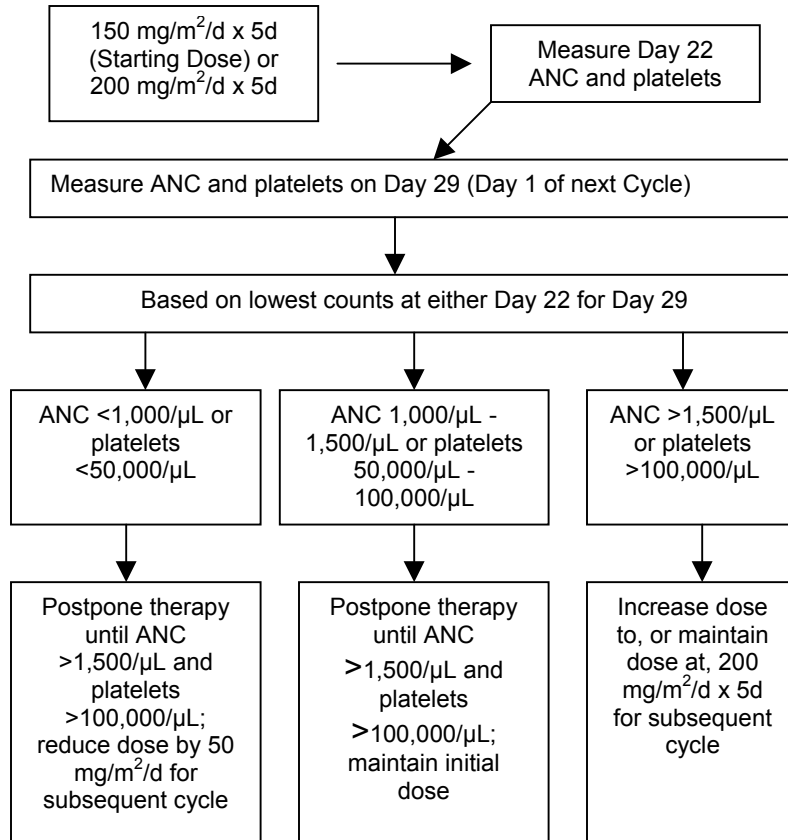
For adults the initial dose is 150 mg/m² orally once daily for 5 consecutive days per 28-day treatment cycle. For adult patients, if both the nadir and day of dosing (Day 29, Day 1 of next cycle) ANC are $\geq 1.5 \times 10^9/L$ (1,500/ μ L) and both the nadir and Day 29, Day 1 of next cycle platelet counts are $\geq 100 \times 10^9/L$ (100,000/ μ L), 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 $1.5 \times 10^9/L$ (1,500/ μ L) and the platelet count exceeds $100 \times 10^9/L$ (100,000/ μ L). 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/ μ L) or the platelet count is $<50 \times 10^9/L$ (50,000/ μ L) 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 4**) (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 5**. For suggested capsule combinations based on daily dose, see **Table 6**.



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Table 4 Dosing Modification Table in Adults



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Table 5
Adult 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 Adult patients whose nadir and day of dosing (Day 29, Day 1 of next cycle) absolute neutrophil count (ANC) is >1.5 x 10⁹/L (1,500/μL) and whose nadir and Day 29, Day 1 of next cycle platelet count is >100 x 10⁹/L (100,000/μL).

Total BSA (m ²)	150 mg/m ² (mg daily)	200 mg/m ² (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

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Table 6
Suggested Capsule Combinations Based on Daily Dose in Adults
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
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



374

Table 6 continued

Suggested Capsule Combinations Based on Daily Dose in Adults				
Number of Daily Capsules by Strength (mg)				
Total Daily Dose (mg)	250	100	20	5
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

375

376

377

378 TEMODAR Capsules were administered under both fasting and non-fasting
 379 conditions; however, absorption is affected by food (see **CLINICAL**
 380 **PHARMACOLOGY**) and consistency of administration with respect to food is
 381 recommended. There are no dietary restrictions with temozolomide. To reduce
 382 nausea and vomiting, temozolomide should be taken on an empty stomach. Bedtime



383 administration may be advised. Antiemetic therapy may be administered prior to
384 and/or following administration of TEMODAR Capsules.

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

387

388 **Handling and Disposal:** Temozolomide causes the rapid appearance of malignant
389 tumors in rats. Capsules should not be opened. If capsules are accidentally opened
390 or damaged, rigorous precautions should be taken with the capsule contents to
391 avoid inhalation or contact with the skin or mucous membranes. Procedures for
392 proper handling and disposal of anticancer drugs should be considered¹⁻⁷. Several
393 guidelines on this subject have been published. There is no general agreement that
394 all of the procedures recommended in the guidelines are necessary or appropriate.

395

396 HOW SUPPLIED

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

399 TEMODAR (temozolomide) Capsules 5 mg: 5 and 20 capsule bottles.

400 5 count - NDC 0085-1248-01

401 20 count - NDC 0085-1248-02

402 TEMODAR (temozolomide) Capsules 20 mg: 5 and 20 capsule bottles.

403 5 count - NDC 0085-1244-01

404 20 count - NDC 0085-1244-02

405 TEMODAR (temozolomide) Capsules 100 mg: 5 and 20 capsule bottles.

406 5 count - NDC 0085-1259-01

407 20 count - NDC 0085-1259-02

408 TEMODAR (temozolomide) Capsules 250 mg: 5 and 20 capsule bottles.

409 5 count - NDC 0085-1252-01

410 20 count - NDC 0085-1252-02

411

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

413 [See USP Controlled Room Temperature]

414

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