

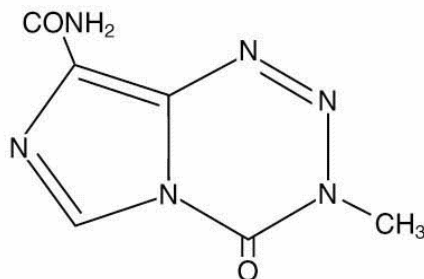
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5 **PRODUCT**
6 **INFORMATION**

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

10
11 **DESCRIPTION**

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



15
16
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 temozolomide.
24 The inactive ingredients for TEMODAR Capsules are lactose anhydrous, colloidal
25 silicon dioxide, sodium starch glycolate, tartaric acid, and stearic acid. Gelatin
26 capsule shells contain titanium dioxide. The capsules are white and imprinted with
27 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 contains pharmaceutical grade shellac, anhydrous
32 ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, purified water,
33 ammonium hydroxide, potassium hydroxide, titanium dioxide, black iron oxide,
34 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.

41

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**).

78

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

84

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

87

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

90

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

98

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

104

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

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

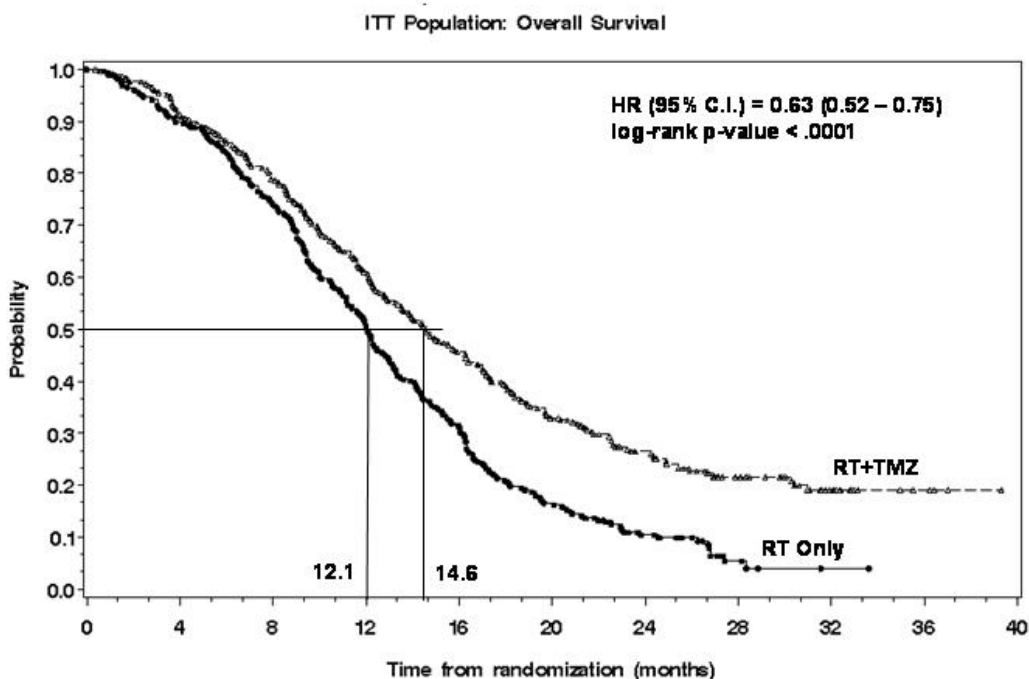
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114 **CLINICAL STUDIES**

115 **Newly Diagnosed Glioblastoma Multiforme** Five hundred and seventy-
116 three patients were randomized to receive either TEMODAR (TMZ) + Radiotherapy
117 (RT) (n= 287) or RT alone (n=286). Patients in the TEMODAR + RT arm received
118 concomitant TEMODAR (75 mg/m²) once daily, starting the first day of RT until the
119 last day of RT, for 42 days (with a maximum of 49 days). This was followed by 6
120 cycles of Temodar alone (150 or 200 mg/m²) on day 1 -5 of every 28-day cycle,
121 starting 4 weeks after the end of RT. Patients in the control arm received RT only. In
122 both arms focal radiation therapy was delivered as 60 Gy/30 fractions. Focal RT
123 includes the tumor bed or resection site with a 2-3 cm margin. Pneumocystis carinii
124 pneumonia (PCP) prophylaxis was required during the TMZ + radiotherapy
125 treatment, regardless of lymphocyte count, and was to continue until recovery of
126 lymphocyte count to less than or equal to grade 1.

127

128 At the time of disease progression, TEMODAR was administered as salvage therapy
129 in 161 patients of the 282 (57 %) in the RT alone arm, and 62 patients of the 277
130 (22%) in the TEMODAR + RT arm.
131 The addition of concomitant and maintenance TEMODAR to radiotherapy in the
132 treatment of patients with newly diagnosed GBM showed a statistically significant
133 improvement overall survival compared radiotherapy alone. (Figure 1) The hazard
134 ratio (HR) for overall survival was 0.63 (95 % CI for HR=0.52-0.75) with a log-rank p
135 <0.0001 in favor of the TEMODAR arm. The median survival was increased by 2 ½
136 months in the TEMODAR arm.
137



138
139 Figure 1 Kaplan-Meier Curves for Overall Survival (ITT Population)

140
141 **Refractory (Anaplastic Astrocytoma)**

142 A single-arm, multicenter study was conducted in 162 patients who had anaplastic
143 astrocytoma at first relapse and who had a baseline Karnofsky performance status
144 of 70 or greater. Patients had previously received radiation therapy and may also
145 have previously received a nitrosourea with or without other chemotherapy. Fifty-four
146 patients had disease progression on prior therapy with both a nitrosourea and
147 procarbazine and their malignancy was considered refractory to chemotherapy
148 (refractory anaplastic astrocytoma population). Median age of this subgroup of 54
149 patients was 42 years (19 to 76). Sixty-five percent were male. Seventy-two percent
150 of patients had a KPS of >80. Sixty-three percent of patients had surgery other than
151 a biopsy at the time of initial diagnosis. Of those patients undergoing resection, 73%



152 underwent a subtotal resection and 27% underwent a gross total resection. Eighteen
153 percent of patients had surgery at the time of first relapse. The median time from
154 initial diagnosis to first relapse was 13.8 months (4.2 to 75.4).

155 TEMODAR Capsules were given for the first 5 consecutive days of a 28-day cycle at
156 a starting dose of 150 mg/m²/day. If the nadir and day of dosing (Day 29, Day 1 of
157 next cycle) absolute neutrophil count was $>1.5 \times 10^9/L$ (1,500/ μ L) and the nadir and
158 Day 29, Day 1 of next cycle, platelet count was $>100 \times 10^9/L$ (100,000/ μ L), the
159 TEMODAR dose was increased to 200 mg/m²/day for the first 5 consecutive days of
160 a 28-day cycle.

161 In the refractory anaplastic astrocytoma population the overall tumor response rate
162 (CR + PR) was 22% (12/54 patients) and the complete response rate was 9% (5/54
163 patients). The median duration of all responses was 50 weeks (range of 16 to 114
164 weeks) and the median duration of complete responses was 64 weeks (range of 52
165 to 114 weeks). In this population, progression-free survival at 6 months was 45%
166 (95% confidence interval 31% to 58%) and progression-free survival at 12 months
167 was 29% (95% confidence interval 16% to 42%). Median progression-free survival
168 was 4.4 months. Overall survival at 6 months was 74% (95% confidence interval
169 62% to 86%) and 12-month overall survival was 65% (95% confidence interval 52%
170 to 78%). Median overall survival was 15.9 months.

171

172 INDICATIONS AND USAGE

173 TEMODAR (temozolomide) Capsules are indicated for the treatment of adult
174 patients with newly diagnosed glioblastoma multiforme concomitantly with
175 radiotherapy and then as maintenance treatment.

176

177 TEMODAR Capsules are indicated for the treatment of adult patients with refractory
178 anaplastic astrocytoma, i.e. patients who have experienced disease progression on
179 a drug regimen containing nitrosurea and procarbazine.

180

181 CONTRAINDICATIONS

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

186

187 WARNINGS

188 Patients treated with TEMODAR Capsules may experience myelosuppression. Prior
189 to dosing, patients must have an absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$ and a
190 platelet count $\geq 100 \times 10^9/L$. A complete blood count should be obtained on Day 22
191 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC
192 is above $1.5 \times 10^9/L$ and platelet count exceeds $100 \times 10^9/L$. Geriatric patients and
193 women have been shown in clinical trials to have a higher risk of developing
194 myelosuppression. Very rare cases of myelodysplastic syndrome and secondary
195 malignancies, including myeloid leukemia have also been observed.

196

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

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

204

205 **Pregnancy:** Temozolomide may cause fetal harm when administered to a pregnant
206 woman. Five consecutive days of oral administration of 75 mg/m²/day in rats and
207 150 mg/m²/day in rabbits during the period of organogenesis (3/8 and 3/4 the
208 maximum recommended human dose, respectively) caused numerous
209 malformations of the external organs, soft tissues, and skeleton in both species.
210 Doses of 150 mg/m²/day in rats and rabbits also caused embryoletality as indicated
211 by increased resorptions. There are no adequate and well-controlled studies in
212 pregnant women. If this drug is used during pregnancy, or if the patient becomes
213 pregnant while taking this drug, the patient should be apprised of the potential
214 hazard to the fetus. Women of childbearing potential should be advised to avoid
215 becoming pregnant during therapy with TEMODAR Capsules.

216

217 **PRECAUTIONS**

218 **Information for Patients:** Nausea and vomiting were among the most frequently
219 occurring adverse events. These were usually either self-limiting or readily controlled
220 with standard antiemetic therapy. Capsules should not be opened. If capsules are
221 accidentally opened or damaged, rigorous precautions should be taken with the
222 capsule contents to avoid inhalation or contact with the skin or mucous membranes.
223 The medication should be kept away from children and pets.

224

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

227

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

231

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

237 In the anaplastic astrocytoma study population, patients 70 years of age or older had
238 a higher incidence of Grade 4 neutropenia and Grade 4 thrombocytopenia (2/8;
239 25%, p=.31 and 2/10; 20%, p=.09, respectively) in the first cycle of therapy than
240 patients under 70 years of age (see **ADVERSE REACTIONS**).

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

243

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

246 For the 28 day treatment cycles, a complete blood count should be obtained on Day
247 22 (21 days after the first dose). Blood counts should be performed weekly until
248 recovery if the ANC falls below $1.5 \times 10^9/L$ and the platelet count falls below $100 \times$
249 $10^9/L$.

250

251 **Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Standard
252 carcinogenicity studies were not conducted with temozolomide. In rats treated with
253 $200 \text{ mg}/\text{m}^2$ temozolomide (equivalent to the maximum recommended daily human
254 dose) on 5 consecutive days every 28 days for 3 cycles, mammary carcinomas were
255 found in both males and females. With 6 cycles of treatment at 25, 50, and 125
256 mg/m^2 (about 1/8 to 1/2 the maximum recommended daily human dose), mammary
257 carcinomas were observed at all doses and fibrosarcomas of the heart, eye, seminal
258 vesicles, salivary glands, abdominal cavity, uterus, and prostate; carcinoma of the
259 seminal vesicles, schwannoma of the heart, optic nerve, and harderian gland; and
260 adenomas of the skin, lung, pituitary, and thyroid were observed at the high dose.

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

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

268

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

270

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

275

276 **Pediatric Use:**

277 TEMODAR effectiveness in children has not been demonstrated. TEMODAR
278 Capsules have been studied in 2 open label Phase 2 studies in pediatric patients
279 (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
280 trial conducted by the Schering Corporation, 29 patients with recurrent brain stem
281 glioma and 34 patients with recurrent high grade astrocytoma were enrolled. All
282 patients had failed surgery and radiation therapy, while 31% also failed
283 chemotherapy. In a second Phase 2 open label study conducted by the Children's
284 Oncology Group (COG), 122 patients were enrolled, including
285 medulloblastoma/PNET(29), high grade astrocytoma (23), low grade astrocytoma
286 (22), brain stem glioma (16), ependymoma (14) other CNS tumors (9) and non-CNS
287 tumors (9). The TEMODAR toxicity profile in children is similar to adults. Table 1
288 shows the adverse events in 122 children in the COG Phase 2 study.

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Table 1

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.

292 **ADVERSE REACTIONS IN ADULTS**
293 **Newly Diagnosed Glioblastoma Multiforme**
294

295 During the concomitant phase (Temodar + radiotherapy), adverse events including
296 thrombocytopenia, nausea, vomiting, anorexia and constipation, were more frequent
297 in the TEMODAR + RT arm the RT arm. The incidence of other adverse events
298 was comparable in the two arms. The most common adverse events across the
299 cumulative TEMODAR experience were alopecia, nausea, vomiting, anorexia,
300 headache, and constipation (see **Table 2**). Forty-nine percent (49%) of patients
301 treated with TEMODAR reported one or more severe or life-threatening events, most
302 commonly fatigue (13%), convulsions (6%), headache (5%) and thrombocytopenia
303 (5%). Overall, the pattern of events during the maintenance phase was consistent
304 with the known safety profile of TEMODAR.
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308**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)

	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.

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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.

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

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

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Table 3
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.

354
355

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%)

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

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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.

364

OVERDOSAGE

365

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

375

376 **DOSAGE AND ADMINISTRATION**

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

382

383 **Patients with newly diagnosed high grade glioma:**

384

Concomitant Phase

385 TEMODAR is administered orally at 75 mg/m² daily for 42 days concomitant with
386 focal radiotherapy (60Gy administered in 30 fractions) followed by maintenance
387 TEMODAR for 6 cycles. Focal RT includes the tumor bed or resection site with a 2-3
388 cm margin. No dose reductions are recommended during the concomitant phase;
389 however, dose interruptions or discontinuation may occur based on toxicity. The
390 TEMODAR dose should be continued throughout the 42 day concomitant period up
391 to 49 days if all of the following conditions are met: absolute neutrophil count $\geq 1.5 \times$
392 10^9 /L platelet count $\geq 100 \times 10^9$ /L common toxicity criteria (CTC) non-
393 hematological toxicity \leq Grade 1 (except for alopecia, nausea and vomiting). During
394 treatment a complete blood count should be obtained weekly. Temozolomide dosing
395 should be interrupted or discontinued during concomitant phase according to the
396 hematological and non-hematological toxicity criteria as noted in **Table 5**. PCP
397 prophylaxis is required during the concomitant administration of Temodar and
398 radiotherapy and should be continued in patients who develop lymphocytopenia until
399 recovery from lymphocytopenia (CTC grade ≤ 1).

400 **Table 5 Temozolomide Dosing Interruption or Discontinuation During**
401 **Concomitant Radiotherapy and Temozolomide¹⁸**
402

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 10⁹/L; platelet count ≥100 x 10⁹/L; CTC non-hematological toxicity ≤Grade 1 (except for alopecia, nausea, vomiting).

TMZ = temozolomide; CTC = Common Toxicity Criteria.

403

404 **Maintenance Phase Cycle 1:**

405 Four weeks after completing the TEMODAR + RT phase, TEMODAR is
406 administered for an additional 6 cycles of maintenance treatment. Dosage in Cycle
407 1 (maintenance) is 150 mg/m² once daily for 5 days followed by 23 days without
408 treatment.

409

410 **Cycles 2-6:**

411 At the start of Cycle 2, the dose is escalated to 200 mg/m², if the CTC non-
412 hematologic toxicity for Cycle 1 is Grade ≤2 (except for alopecia, nausea and
413 vomiting), absolute neutrophil count (ANC) is ≥ 1.5 x 10⁹/L, and the platelet count is
414 ≥ 100 x 10⁹/L. The dose remains at 200 mg/m² per day for the first 5 days of each
415 subsequent cycle except if toxicity occurs. If the dose was not escalated at Cycle 2,
416 escalation should not be done in subsequent cycles.

417

418 **Dose reduction or discontinuation during maintenance:**

419 Dose reductions during the maintenance phase should be applied according to
420 tables 6 and 7.

421 During treatment a complete blood count should be obtained on day 22 (21 days
422 after the first dose of Temodar) or within 48 hours of that day, and weekly until the
423 ANC is above 1.5 x 10⁹/L (1,500/μL) and the platelet count exceeds 100 x 10⁹/L
424 (100,000/μL). The next cycle of TEMODAR should not be started until the ANC and
425 platelet count exceed these levels. Dose reductions during the next cycle should be
426 based on the lowest blood counts and worst non-hematologic toxicity during the
427 previous cycle. Dose reductions or discontinuations during the maintenance phase
428 should be applied according to tables 6 and 7.

429

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432 **Table 6** Temozolomide Dose Levels for Maintenance Treatment
433

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

434
435 **Table 7** Temozolomide Dose Reduction or Discontinuation During Maintenance
436 Treatment
437

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 6.

b: TMZ is to be discontinued if dose reduction to <100 mg/m² 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.

438
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440 **Patients with refractory anaplastic astrocytoma**

441 For adults the initial dose is 150 mg/m² orally once daily for 5 consecutive days per
442 28-day treatment cycle. For adult patients, if both the nadir and day of dosing (Day
443 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
444 29, Day 1 of next cycle platelet counts are $\geq 100 \times 10^9/L$ (100,000/ μ L), the
445 TEMODAR dose may be increased to 200 mg/m²/day for 5 consecutive days per 28-
446 day treatment cycle. During treatment, a complete blood count should be obtained
447 on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly
448 until the ANC is above $1.5 \times 10^9/L$ (1,500/ μ L) and the platelet count exceeds $100 \times$
449 $10^9/L$ (100,000/ μ L). The next cycle of TEMODAR should not be started until the ANC
450 and platelet count exceed these levels. If the ANC falls to $<1.0 \times 10^9/L$ (1,000/ μ L) or
451 the platelet count is $<50 \times 10^9/L$ (50,000/ μ L) during any cycle, the next cycle should
452 be reduced by 50 mg/m², but not below 100 mg/m², the lowest recommended dose
453 (see **Table 8**). TEMODAR therapy can be continued until disease progression. In
454 the clinical trial, treatment could be continued for a maximum of 2 years; but the
455 optimum duration of therapy is not known.

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Table 8 Dosing Modification Table

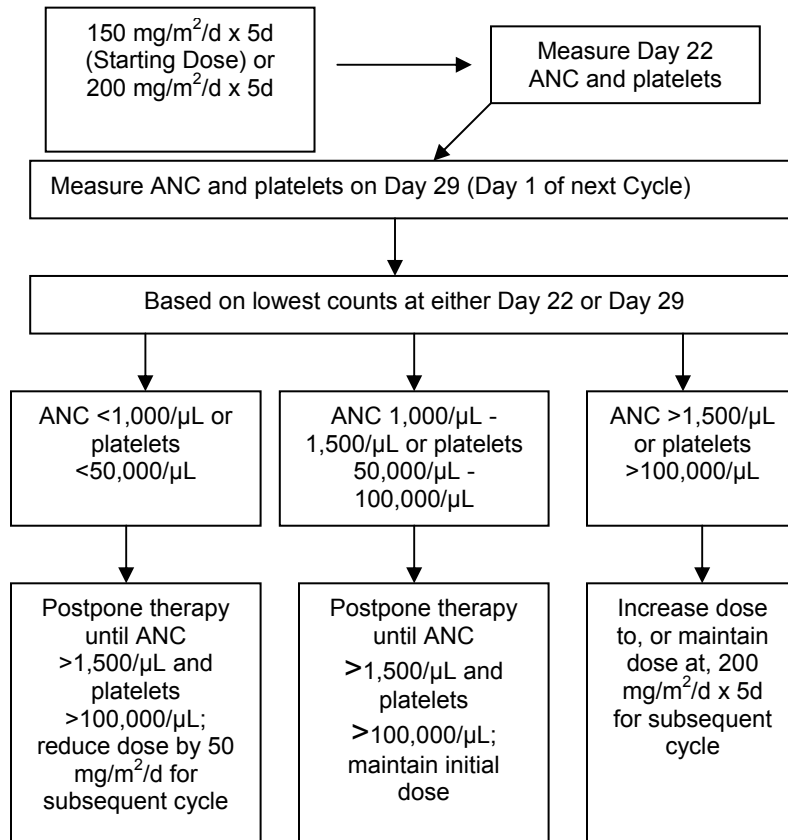


Table 9

Daily Dose Calculations by Body Surface Area (BSA)

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



485

Table 10
Suggested Capsule Combinations Based on Daily Dose in Adults
Number of Daily Capsules by Strength (mg)

Total Daily Dose (mg)	250	100	20	5
75	0	0	3	3
82.5	0	0	4	0
90	0	0	4	2
97.5	0	1	0	0
105	0	1	0	1
112.5	0	1	0	2
120	0	1	1	0
127.5	0	1	1	1
135	0	1	1	3
142.5	0	1	2	0
150	0	1	2	2
157.5	0	1	3	0
165	0	1	3	1
172.5	0	1	3	2
180	0	1	4	0
187.5	0	1	4	1
195	0	1	4	3
200	0	2	0	0
210	0	2	0	2
220	0	2	1	0
225	0	2	1	1
240	0	2	2	0



486

Table 10 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
255	1	0	0	1
260	1	0	0	2
270	1	0	1	0
280	1	0	1	2
285	1	0	1	3
300	0	3	0	0
315	0	3	0	3
320	0	3	1	0
330	1	0	4	0
340	0	3	2	0
345	0	3	2	1
360	0	3	3	0
375	1	1	1	1
380	1	1	1	2
400	0	4	0	0
420	0	4	1	0
440	0	4	2	0
460	1	2	0	2
480	1	2	1	2
500	2	0	0	0

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489 In clinical trials, TEMODAR was administered under both fasting and non-fasting
 490 conditions; however, absorption is affected by food (see **CLINICAL**
 491 **PHARMACOLOGY**) and consistency of administration with respect to food is
 492 recommended. There are no dietary restrictions with TEMODAR. To reduce nausea
 493 and vomiting, TEMODAR should be taken on an empty stomach. Bedtime
 494 administration may be advised. Antiemetic therapy may be administered prior to
 495 and/or following administration of TEMODAR Capsules.

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

498

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

506

507 **HOW SUPPLIED**

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

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

511 5 count - NDC 0085-1248-01

512 20 count - NDC 0085-1248-02



- 513 TEMODAR (temozolomide) Capsules 20 mg: 5 and 20 capsule bottles.
514 5 count - NDC 0085-1244-01
515 20 count - NDC 0085-1244-02
516 TEMODAR (temozolomide) Capsules 100 mg: 5 and 20 capsule bottles.
517 5 count - NDC 0085-1259-01
518 20 count - NDC 0085-1259-02
519 TEMODAR (temozolomide) Capsules 250 mg: 5 and 20 capsule bottles.
520 5 count - NDC 0085-1252-01
521 20 count - NDC 0085-1252-02

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

524 [See USP Controlled Room Temperature]

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Schering Corporation
Kenilworth, NJ 07033 USA

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Rev 3/05

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PHARMACIST:**Tear at perforation and give to patient.****Temodar[®]**
[temozolomide]
Capsules**PHARMACIST
INFORMATION SHEET****IMPORTANT
DISPENSING
INFORMATION****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/m²/day, (a patient with a BSA of 1.84 is 1.84 x 150 = 276, or 275 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.

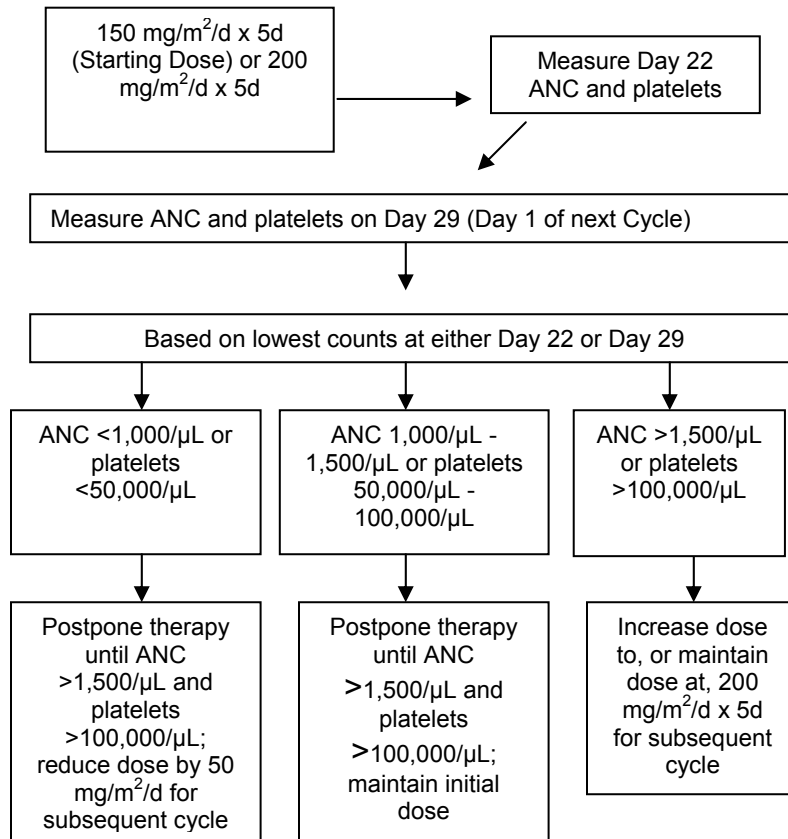
How might the dose of TEMODAR be modified for Refractory Anaplastic Astrocytoma?

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/m² orally once daily for 5



41 consecutive days per 28-day treatment cycle. If both the nadir and day of dosing
 42 (Day 29, Day 1 of next cycle) absolute neutrophil counts (ANC) are $\geq 1.5 \times 10^9/L$
 43 ($1,500/\mu L$) and both the nadir and Day 29, Day 1 of next cycle platelet counts are
 44 $\geq 100 \times 10^9/L$ ($100,000/\mu L$), the TEMODAR dose may be increased to $200 \text{ mg}/\text{m}^2/$
 45 day for 5 consecutive days per 28-day treatment cycle. During treatment, a complete
 46 blood count should be obtained on Day 22 (21 days after the first dose) or within 48
 47 hours of that day, and weekly until the ANC is above $1.5 \times 10^9/L$ ($1,500/\mu L$) and the
 48 platelet count exceeds $100 \times 10^9/L$ ($100,000/\mu L$). The next cycle of TEMODAR
 49 should not be started until the ANC and platelet count exceed these levels. If the
 50 ANC falls to $< 1.0 \times 10^9/L$ ($1,000/\mu L$) or the platelet count is $< 50 \times 10^9/L$ ($50,000/\mu L$)
 51 during any cycle, the next cycle should be reduced by $50 \text{ mg}/\text{m}^2$, but not below 100
 52 mg/m^2 , the lowest recommended dose (see **Table 1** below).

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 54 **TABLE 1**
 55 **Dosing Modification Table for Refractory Anaplastic Astrocytoma**



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

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

83

84

85 Newly Diagnosed Concomitant Phase Treatment Schedule

86 TEMODAR is administered orally at 75 mg/m² daily for 42 days concomitant with
 87 focal radiotherapy (60Gy administered in 30 fractions), followed by maintenance
 88 TEMODAR for 6 cycles. No dose reductions are recommended, however, dose
 89 interruptions may occur based on patient tolerance. The TEMODAR dose can be
 90 continued throughout the 42 day concomitant period up to 49 days if all of the
 91 following conditions are met: absolute neutrophil count $\geq 1.5 \times 10^9$ /L platelet count \geq
 92 100×10^9 /L common toxicity criteria (CTC) non-hematological toxicity \leq Grade 1
 93 (except for alopecia, nausea and vomiting). During treatment a complete blood count
 94 should be obtained weekly. Temozolomide dosing should be interrupted or
 95 discontinued during concomitant phase according to the hematological and non-
 96 hematological toxicity criteria as noted in **Table 2**. PCP prophylaxis is required
 97 during the concomitant administration of Temodar and radiotherapy and should be
 98 continued in patients who develop lymphocytopenia until recovery from
 99 lymphocytopenia (CTC grade ≤ 1).

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

Toxicity	TMZ Interruption ^a	TMZ Discontinuation
Absolute Neutrophil Count	≥ 0.5 and $< 1.5 \times 10^9$ /L	$< 0.5 \times 10^9$ /L
Platelet Count	≥ 10 and $< 100 \times 10^9$ /L	$< 10 \times 10^9$ /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 $\geq 1.5 \times 10^9$ /L; platelet count $\geq 100 \times 10^9$ /L; CTC non-hematological toxicity \leq Grade 1 (except for alopecia, nausea, vomiting).

TMZ = temozolomide; CTC = Common Toxicity Criteria.

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Maintenance Phase Treatment Schedule

106 Four weeks after completing the TEMODAR + RT phase, TEMODAR is
 107 administered for an additional 6 cycles of maintenance treatment. Dosage in Cycle
 108 1 (maintenance) is 150 mg/m² once daily for 5 days followed by 23 days without
 109 treatment. At the start of Cycle 2, the dose is escalated to 200 mg/m², if the CTC
 110 non-hematologic toxicity for Cycle 1 is Grade ≤2 (except for alopecia, nausea and
 111 vomiting), absolute neutrophil count (ANC) is ≥ 1.5 x 10⁹/L, and the platelet count is
 112 ≥ 100 x 10⁹/L. If the dose was not escalated at Cycle 2, escalation should not be
 113 done in subsequent cycles. The dose remains at 200 mg/m² per day for the first 5
 114 days of each subsequent cycle except if toxicity occurs.
 115 During treatment a complete blood count should be obtained on Day 22 (21 days
 116 after the first dose) or within 48 hours of that day, and weekly until the ANC is above
 117 1.5 x 10⁹/L (1,500/μL) and the platelet count exceeds 100 x 10⁹/L (100,000/μL). The
 118 next cycle of TEMODAR should not be started until the ANC and platelet count
 119 exceed these levels. Dose reductions during the next cycle should be based on the
 120 lowest blood counts and worst non-hematologic toxicity during the previous cycle.
 121 Dose reductions or discontinuations during the maintenance phase should be
 122 applied according to tables 3 and 4.

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125
126 **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

127
128 **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/m² 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.

129
130 **How is TEMODAR taken?**



131 Patients should take each day's dose with a full glass of water at the same time
 132 each day. Taking the medication on an empty stomach or at bedtime may help ease
 133 nausea. If patients are also taking anti-nausea or other medications to relieve the
 134 side effects associated with TEMODAR, they should be advised to take these
 135 medications 30 minutes before they take TEMODAR. Temozolomide causes the
 136 rapid appearance of malignant tumors in rats. Patients **SHOULD NOT** open or split
 137 the capsules. If capsules are accidentally opened or damaged, rigorous precautions
 138 should be taken with the capsule contents to avoid inhalation or contact with the skin
 139 or mucous membranes. The medication should be kept away from children and
 140 pets. The TEMODAR capsules should be swallowed whole and **NEVER CHEWED**.

141

142 **What should the patient avoid during treatment with TEMODAR?**

143 There are no dietary restrictions for patients taking TEMODAR. TEMODAR may
 144 affect testicular function, so male patients should exercise adequate birth control
 145 measures. TEMODAR may cause birth defects. Female patients should avoid
 146 becoming pregnant while receiving this drug. Women who are nursing prior to
 147 receiving TEMODAR should discontinue nursing. It is not known whether TEMODAR
 148 is excreted into breast milk.

149

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151 **What are the side effects of TEMODAR?**

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

155

156 **Other commonly reported side effects reported by patients taking TEMODAR**
 157 are fatigue, constipation, and headache.

158

159 **How is TEMODAR supplied?**

160 TEMODAR capsules are available in 250 mg, 100 mg, 20 mg, and 5 mg strengths.
 161 The capsules are white with color-coded printing according to strength.

162

163 <u>TEMODAR Capsule Strength</u>	163 <u>Color</u>
164 5 mg	164 Green Imprint
165 20 mg	165 Brown Imprint
166 100 mg	166 Blue Imprint
167 250 mg	167 Black Imprint

168

169 All capsule strengths are available in 5-count and 20-count packages.

170

171 **How is TEMODAR dispensed?**

172 Each strength of TEMODAR must be dispensed in a separate vial or in its original
 173 glass bottle (one strength per one container). Follow the instructions below:



174 Based on the dose prescribed, determine the number of each strength of TEMODAR
 175 capsules needed for the full 5 day cycle as prescribed by the physician. For
 176 example, 275 mg/day for 5 days would be dispensed as five 250-mg capsules, five
 177 20-mg capsules and five 5-mg capsules. Label each container with the appropriate
 178 number of capsules to be taken each day. Dispense to the patient, making sure
 179 each container lists the strength (mg) per capsule and that he or she understands to
 180 take the appropriate number of capsules of TEMODAR from each bottle or vial to
 181 equal the total daily dose prescribed by the physician.

182

183 **How can TEMODAR be ordered?**

184 TEMODAR can be ordered from your wholesaler. Remember to order enough
 185 TEMODAR for a full five-day cycle. For example, a five-day course of 275 mg/day
 186 would require the following to be ordered:

187 1 5-count package of 250-mg capsules

188 1 5-count package of 20-mg capsules

189 1 5-count package of 5-mg capsules

190

191 <u>TEMODAR Product</u>	<u>NDC Number</u>
192 250-mg capsules (5 count)	0085-1252-01
193 250-mg capsules (20 count)	0085-1252-02
194 100-mg capsules (5 count)	0085-1259-01
195 100-mg capsules (20 count)	0085-1259-02
196 20-mg capsules (5 count)	0085-1244-01
197 20-mg capsules (20 count)	0085-1244-02
198 5-mg capsules (5 count)	0085-1248-01
199 5-mg capsules (20 count)	0085-1248-02

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1 *Temodar*[®]

2 [temozolomide]
3 Capsules

4
5 **Patient Information Sheet**
6 **IMPORTANT INFORMATION**
7 **FOR THE PATIENT**

8 **Patient Package Insert**

9 **TEMODAR[®] (temozolomide) Capsules**

10
11 **What is TEMODAR?**

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

19
20 **Who should not take TEMODAR?**

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

26
27 **How should I take TEMODAR?**

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

42



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

45 Be sure you follow the one that your doctor has prescribed for you. One schedule
46 you may be prescribed is ,TEMODAR for 42 days (up to 49 days) with radiotherapy..

47 Another schedule should be taken for 5 consecutive days only, then you must **STOP**
48 taking TEMODAR for the next 23 days. This total period of 5 days on TEMODAR
49 and 23 days off TEMODAR is called one treatment cycle. Your dose is based on
50 your height and weight, and the number of treatment cycles will depend on how you
51 respond to and tolerate this treatment.

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

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

66
67 Your doctor may have prescribed a treatment regimen that is different from the one
68 discussed in this information sheet. If so, make sure you follow the specific
69 instructions given to you by your doctor. You should talk to your doctor about what to
70 do if you miss a day. If you take more than the prescribed amount of medicine,
71 contact your doctor right away. It is important that you understand your dosage
72 regimen, it is also important that you do not take more than the amount of
73 TEMODAR prescribed for you. Overdoses can lead to serious outcomes including
74 severe low blood counts and possible death.

75 76 **How is TEMODAR supplied?**

77 TEMODAR® (temozolomide) Capsules are white with color-coded printing according
78 to strength, each a different size. The capsules are available in four different
79 strengths.

80

81	<u>TEMODAR Capsule Strength</u>	<u>Color</u>
82	5mg	Green Imprint
83	20mg	Brown Imprint
84	100mg	Blue Imprint
85	250mg	Black Imprint

86



87 **What should I avoid while taking TEMODAR?**

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

90
91 TEMODAR may cause birth defects. Therefore, male or female patients who take
92 TEMODAR should use effective birth control. Female patients should avoid
93 becoming pregnant while receiving this drug. You should not breast-feed an infant
94 while taking TEMODAR. It is not known whether TEMODAR passes into breast
95 milk. Because many drugs do pass into breast milk, there is the possibility of serious
96 harm to nursing infants.

97
98 **What are the possible or reasonably likely side effects of TEMODAR?**

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

102
103 TEMODAR also can reduce the number of certain types of blood cells, which can
104 have serious effects. White blood cells are needed to fight infections. Lowering of
105 white blood cells could result in a serious infection with a potential outcome of death.
106 Platelets are needed in the normal course of blood clotting. Lowering of platelets
107 does not allow your blood to clot normally, which can result in bleeding episodes.
108 Therefore, it is important that your doctor check your blood periodically while you are
109 taking TEMODAR to see if these side effects are occurring. Patients age 70 or older,
110 women, and patients who have had chemotherapy or radiation therapy may be more
111 likely to have their blood cells affected.

112
113 There are other side effects associated with TEMODAR. They are included in a
114 longer, more technical information leaflet written for health care providers that you
115 can get from your doctor or pharmacist.

116
117 **General information about the use of prescription drug products.**

118 Medicines are sometimes prescribed for purposes other than those listed in a
119 Patient Package Insert. You should contact your health care professional regarding
120 any concerns you may have about using TEMODAR. TEMODAR should not be used
121 for a condition for which it was not prescribed, and it should not be given to other
122 persons.

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