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**PRODUCT
INFORMATION**

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TEMODAR[®] (temozolomide) CAPSULES

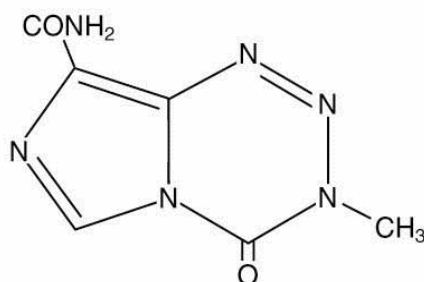
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DESCRIPTION

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

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

21 Each capsule contains either 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, or 250 mg of
22 temozolomide. The inactive ingredients for TEMODAR Capsules are lactose
23 anhydrous, colloidal silicon dioxide, sodium starch glycolate, tartaric acid, and
24 stearic acid. The 5 mg, 20 mg, 100 mg, and 250 mg gelatin capsule shells contain
25 titanium dioxide. The capsules are white and imprinted with pharmaceutical ink. The
26 body of the capsules for the 140 mg and 180 mg strengths is made of gelatin, and is
27 opaque white. The cap is also made of gelatin, and the colors vary based on the
28 dosage strength.

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

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

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

39 *TEMODAR 140 mg*: The blue cap contains gelatin, sodium lauryl sulfate, FD&C Blue
40 #2, and titanium dioxide. The capsule body and cap are imprinted with
41 pharmaceutical branding ink, which contains shellac, dehydrated alcohol, isopropyl
42 alcohol, butyl alcohol, propylene glycol, purified water, strong ammonia solution,
43 potassium hydroxide, and ferric oxide.

44 *TEMODAR 180 mg*: The red cap contains gelatin, sodium lauryl sulfate, titanium
45 dioxide, iron oxide red and iron oxide yellow. The capsule body and cap are
46 imprinted with pharmaceutical branding ink, which contains shellac, dehydrated
47 alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, purified water, strong
48 ammonia solution, potassium hydroxide, and ferric oxide.

49
50 *TEMODAR 250 mg*: black imprint contains pharmaceutical grade shellac, anhydrous
51 ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, purified water,
52 ammonium hydroxide, potassium hydroxide, and black iron oxide.

53

54 **CLINICAL PHARMACOLOGY**

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

59

60 **Pharmacokinetics:** Temozolomide is rapidly and completely absorbed after oral
61 administration; peak plasma concentrations occur in 1 hour. Food reduces the rate
62 and extent of temozolomide absorption. Mean peak plasma concentration and AUC
63 decreased by 32% and 9%, respectively, and T_{max} increased 2-fold (from 1.1 to 2.25
64 hours) when temozolomide was administered after a modified high-fat breakfast.
65 Temozolomide is rapidly eliminated with a mean elimination half-life of 1.8 hours and
66 exhibits linear kinetics over the therapeutic dosing range. Temozolomide has a
67 mean apparent volume of distribution of 0.4 L/kg (%CV=13%). It is weakly bound to
68 human plasma proteins; the mean percent bound of drug-related total radioactivity is
69 15%.

70

71 **Metabolism and Elimination:** Temozolomide is spontaneously hydrolyzed at
72 physiologic pH to the active species, 3-methyl-(triazene-1-yl)imidazole-4-car-
73 boxamide (MTIC) and to temozolomide acid metabolite. MTIC is further hydrolyzed
74 to 5-amino-imidazole-4-carboxamide (AIC) which is known to be an intermediate in
75 purine and nucleic acid biosynthesis and to methylhydrazine, which is believed to be
76 the active alkylating species. Cytochrome P450 enzymes play only a minor role in
77 the metabolism of temozolomide and MTIC. Relative to the AUC of temozolomide,
78 the exposure to MTIC and AIC is 2.4% and 23%, respectively. About 38% of the
79 administered temozolomide total radioactive dose is recovered over 7 days; 37.7%
80 in urine and 0.8% in feces. The majority of the recovery of radioactivity in urine is as
81 unchanged temozolomide (5.6%), AIC (12%), temozolomide acid metabolite (2.3%),

82 and unidentified polar metabolite(s) (17%). Overall clearance of temozolomide is
83 about 5.5 L/hr/m².

84

85 **Special Populations:** *Age* Population pharmacokinetic analysis indicates that age
86 (range 19 to 78 years) has no influence on the pharmacokinetics of temozolomide.
87 In the anaplastic astrocytoma study population, patients 70 years of age or older had
88 a higher incidence of Grade 4 neutropenia and Grade 4 thrombocytopenia in the first
89 cycle of therapy than patients under 70 years of age (see **PRECAUTIONS**).

90

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

96

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

99

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

102

103 *Creatinine Clearance* Population pharmacokinetic analysis indicates that creatinine
104 clearance over the range of 36-130 mL/min/m² has no effect on the clearance of
105 temozolomide after oral administration. The pharmacokinetics of temozolomide have
106 not been studied in patients with severely impaired renal function (CL_{Cr} <36
107 mL/min/m²). Caution should be exercised when TEMODAR Capsules are
108 administered to patients with severe renal impairment. TEMODAR has not been
109 studied in patients on dialysis.

110

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

116

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

121 Population analysis failed to demonstrate any influence of coadministered
122 dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H₂-
123 receptor antagonists, or phenobarbital on the clearance of orally administered
124 temozolomide.

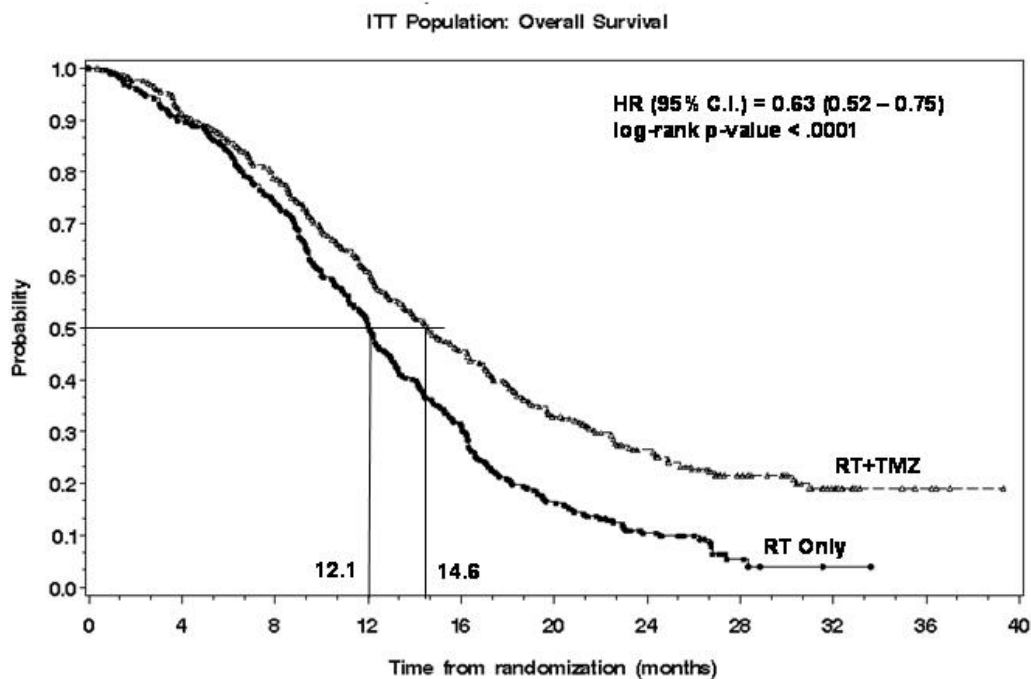
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126 **CLINICAL STUDIES**

127 **Newly Diagnosed Glioblastoma Multiforme** Five hundred and seventy-
 128 three patients were randomized to receive either TEMODAR (TMZ) + Radiotherapy
 129 (RT) (n= 287) or RT alone (n=286). Patients in the TEMODAR + RT arm received
 130 concomitant TEMODAR (75 mg/m²) once daily, starting the first day of RT until the
 131 last day of RT, for 42 days (with a maximum of 49 days). This was followed by 6
 132 cycles of TEMODAR alone (150 or 200 mg/m²) on Day 1-5 of every 28-day cycle,
 133 starting 4 weeks after the end of RT. Patients in the control arm received RT only. In
 134 both arms, focal radiation therapy was delivered as 60 Gy/30 fractions. Focal RT
 135 includes the tumor bed or resection site with a 2-3 cm margin. *Pneumocystis carinii*
 136 pneumonia (PCP) prophylaxis was required during the TMZ + radiotherapy
 137 treatment, regardless of lymphocyte count, and was to continue until recovery of
 138 lymphocyte count to less than or equal to Grade 1.
 139

140 At the time of disease progression, TEMODAR was administered as salvage therapy
 141 in 161 patients of the 282 (57%) in the RT alone arm, and 62 patients of the 277
 142 (22%) in the TEMODAR + RT arm.

143 The addition of concomitant and maintenance TEMODAR to radiotherapy in the
 144 treatment of patients with newly diagnosed GBM showed a statistically significant
 145 improvement in overall survival compared to radiotherapy alone (Figure 1). The
 146 hazard ratio (HR) for overall survival was 0.63 (95% CI for HR=0.52-0.75) with a log-
 147 rank p <0.0001 in favor of the TEMODAR arm. The median survival was increased
 148 by 2 ½ months in the TEMODAR arm.
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150
 151

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

152

153 Refractory (Anaplastic Astrocytoma)

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

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

173 In the refractory anaplastic astrocytoma population, the overall tumor response rate
174 (CR + PR) was 22% (12/54 patients) and the complete response rate was 9% (5/54
175 patients). The median duration of all responses was 50 weeks (range of 16 to 114
176 weeks) and the median duration of complete responses was 64 weeks (range of 52
177 to 114 weeks). In this population, progression-free survival at 6 months was 45%
178 (95% confidence interval 31% to 58%) and progression-free survival at 12 months
179 was 29% (95% confidence interval 16% to 42%). Median progression-free survival
180 was 4.4 months. Overall survival at 6 months was 74% (95% confidence interval
181 62% to 86%) and 12-month overall survival was 65% (95% confidence interval 52%
182 to 78%). Median overall survival was 15.9 months.

183

184 INDICATIONS AND USAGE

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

188

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

192

193 CONTRAINDICATIONS

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



198

199 **WARNINGS**

200 Patients treated with TEMODAR Capsules may experience myelosuppression. Prior
201 to dosing, patients must have an absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$ and a
202 platelet count $\geq 100 \times 10^9/L$. A complete blood count should be obtained on Day 22
203 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC
204 is above $1.5 \times 10^9/L$ and platelet count exceeds $100 \times 10^9/L$. Geriatric patients and
205 women have been shown in clinical trials to have a higher risk of developing
206 myelosuppression. Very rare cases of myelodysplastic syndrome and secondary
207 malignancies, including myeloid leukemia, have also been observed.

208

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

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

216

217 **Pregnancy:** Temozolomide may cause fetal harm when administered to a pregnant
218 woman. Five consecutive days of oral administration of $75 \text{ mg/m}^2/\text{day}$ in rats and
219 $150 \text{ mg/m}^2/\text{day}$ in rabbits during the period of organogenesis ($3/8$ and $3/4$ the
220 maximum recommended human dose, respectively) caused numerous
221 malformations of the external organs, soft tissues, and skeleton in both species.
222 Doses of $150 \text{ mg/m}^2/\text{day}$ in rats and rabbits also caused embryoletality as indicated
223 by increased resorptions. There are no adequate and well-controlled studies in
224 pregnant women. If this drug is used during pregnancy, or if the patient becomes
225 pregnant while taking this drug, the patient should be apprised of the potential
226 hazard to the fetus. Women of childbearing potential should be advised to avoid
227 becoming pregnant during therapy with TEMODAR Capsules.

228

229 **PRECAUTIONS**

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

236

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

239

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

243



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

249 In the anaplastic astrocytoma study population, patients 70 years of age or older had
250 a higher incidence of Grade 4 neutropenia and Grade 4 thrombocytopenia (2/8;
251 25%, p=0.31 and 2/10; 20%, p=0.09, respectively) in the first cycle of therapy than
252 patients under 70 years of age (see **ADVERSE REACTIONS**).

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

255
256 **Laboratory Tests:** For the concomitant treatment phase with RT, a complete blood
257 count should be obtained weekly.

258 For the 28 day treatment cycles, a complete blood count should be obtained on Day
259 22 (21 days after the first dose). Blood counts should be performed weekly until
260 recovery if the ANC falls below $1.5 \times 10^9/L$ and the platelet count falls below $100 \times$
261 $10^9/L$.

262
263 **Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Standard
264 carcinogenicity studies were not conducted with temozolomide. In rats treated with
265 200 mg/m^2 temozolomide (equivalent to the maximum recommended daily human
266 dose) on 5 consecutive days every 28 days for 3 cycles, mammary carcinomas were
267 found in both males and females. With 6 cycles of treatment at 25, 50, and 125
268 mg/m^2 (about 1/8 to 1/2 the maximum recommended daily human dose), mammary
269 carcinomas were observed at all doses and fibrosarcomas of the heart, eye, seminal
270 vesicles, salivary glands, abdominal cavity, uterus, and prostate; carcinoma of the
271 seminal vesicles, schwannoma of the heart, optic nerve, and harderian gland; and
272 adenomas of the skin, lung, pituitary, and thyroid were observed at the high dose.

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

275 Reproductive function studies have not been conducted with temozolomide.
276 However, multicycle toxicology studies in rats and dogs have demonstrated
277 testicular toxicity (syncytial cells/immature sperm, testicular atrophy) at doses of 50
278 mg/m^2 in rats and 125 mg/m^2 in dogs (1/4 and 5/8, respectively, of the maximum
279 recommended human dose on a body surface area basis).

280
281 **Pregnancy Category D:** See **WARNINGS** section.

282
283 **Nursing Mothers:** It is not known whether this drug is excreted in human milk.
284 Because many drugs are excreted in human milk and because of the potential for
285 serious adverse reactions in nursing infants from TEMODAR Capsules, patients
286 receiving TEMODAR should discontinue nursing.

287
288 **Pediatric Use:** TEMODAR effectiveness in children has not been demonstrated.
289 TEMODAR Capsules have been studied in 2 open label Phase 2 studies in pediatric

290 patients (age 3-18 years) at a dose of 160-200 mg/m² 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%)		
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, Ewing's
 sarcoma, pineoblastoma, alveolar soft part
 sarcoma, neurofibrosarcoma, optic glioma, and
 osteosarcoma.

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ADVERSE REACTIONS IN ADULTS

Newly Diagnosed Glioblastoma Multiforme

During the concomitant phase (Temodar + radiotherapy), adverse events including thrombocytopenia, nausea, vomiting, anorexia, and constipation, were more

312 frequent in the TEMODAR + RT arm. The incidence of other adverse events was
313 comparable in the two arms. The most common adverse events across the
314 cumulative TEMODAR experience were alopecia, nausea, vomiting, anorexia,
315 headache, and constipation (see **Table 2**). Forty-nine percent (49%) of patients
316 treated with TEMODAR reported one or more severe or life-threatening events, most
317 commonly fatigue (13%), convulsions (6%), headache (5%), and thrombocytopenia
318 (5%). Overall, the pattern of events during the maintenance phase was consistent
319 with the known safety profile of TEMODAR.

320 **Table 2** Number (%) of Patients with Adverse Events: All and Severe/Life
 321 **Threatening (Incidence of 5% or Greater)**
 322

	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.

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/ μ L) and thrombocytopenia (< 20,000 cells/ μ L) 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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 367

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.

368
369

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.

370
371

372 In addition, the following spontaneous adverse experiences have been reported
373 during the marketing surveillance of TEMODAR Capsules: allergic reactions,
374 including rare cases of anaphylaxis. Rare cases of erythema multiforme have been
375 reported which resolved after discontinuation of TEMODAR and, in some cases,
376 recurred upon rechallenge. Rare cases of opportunistic infections including
377 *Pneumocystis carinii* pneumonia (PCP) have also been reported. ¹

378

OVERDOSAGE

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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 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

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

389

390 **DOSAGE AND ADMINISTRATION**

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

396

397 **Patients with Newly Diagnosed High Grade Glioma:** 398 **Concomitant Phase**

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

414 **Table 5 Temozolomide Dosing Interruption or Discontinuation During**
415 **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 are 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.

416

417 **Maintenance Phase Cycle 1:**

418 Four weeks after completing the TEMODAR + RT phase, TEMODAR is
 419 administered for an additional 6 cycles of maintenance treatment. Dosage in Cycle
 420 1 (maintenance) is 150 mg/m² once daily for 5 days followed by 23 days without
 421 treatment.

422

423 **Cycles 2-6:**

424 At the start of Cycle 2, the dose is escalated to 200 mg/m², if the CTC non-
 425 hematologic toxicity for Cycle 1 is Grade ≤2 (except for alopecia, nausea, and
 426 vomiting), absolute neutrophil count (ANC) is ≥ 1.5 x 10⁹/L, and the platelet count is
 427 ≥ 100 x 10⁹/L. The dose remains at 200 mg/m² per day for the first 5 days of each
 428 subsequent cycle except if toxicity occurs. If the dose was not escalated at Cycle 2,
 429 escalation should not be done in subsequent cycles.

430

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

432 Dose reductions during the maintenance phase should be applied according to
 433 Tables 6 and 7.

434 During treatment, a complete blood count should be obtained on Day 22 (21 days
 435 after the first dose of TEMODAR) or within 48 hours of that day, and weekly until the
 436 ANC is above 1.5 x 10⁹/L (1,500/μL) and the platelet count exceeds 100 x 10⁹/L
 437 (100,000/μL). The next cycle of TEMODAR should not be started until the ANC and
 438 platelet count exceed these levels. Dose reductions during the next cycle should be
 439 based on the lowest blood counts and worst non-hematologic toxicity during the
 440 previous cycle. Dose reductions or discontinuations during the maintenance phase
 441 should be applied according to Tables 6 and 7.

442

443 **Table 6** Temozolomide Dose Levels for Maintenance Treatment

444

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

445

446 **Table 7** Temozolomide Dose Reduction or Discontinuation During Maintenance
 447 Treatment
 448

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 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.

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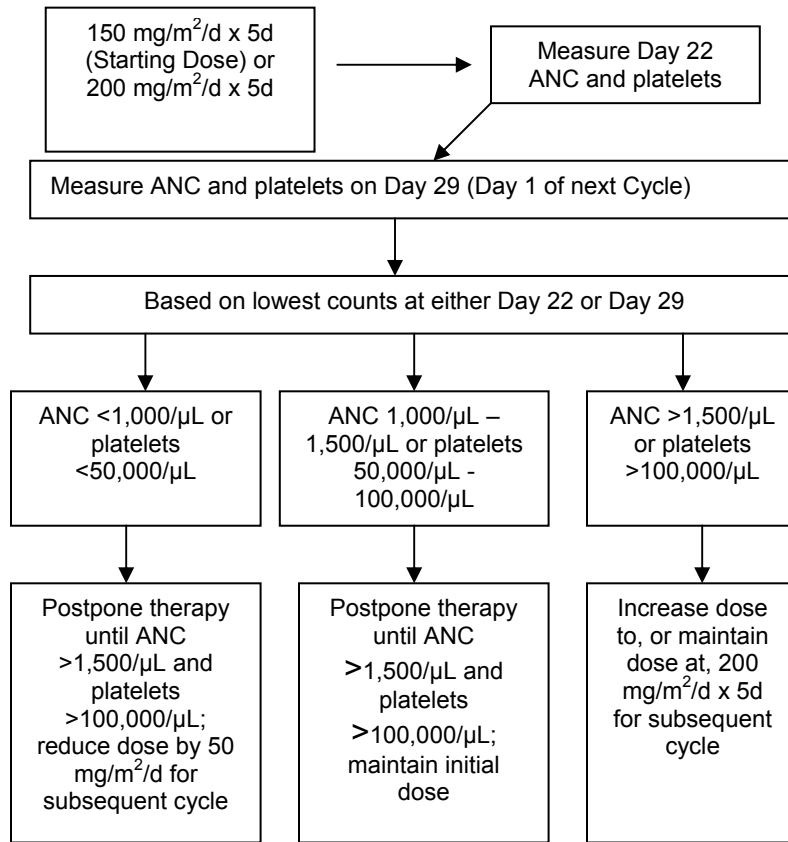
450

451 **Patients with Refractory Anaplastic Astrocytoma**

452 For adults the initial dose is 150 mg/m² orally once daily for 5 consecutive days per
 453 28-day treatment cycle. For adult patients, if both the nadir and day of dosing (Day
 454 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
 455 29, Day 1 of next cycle platelet counts are $\geq 100 \times 10^9/L$ (100,000/ μ L), the
 456 TEMODAR dose may be increased to 200 mg/m²/day for 5 consecutive days per 28-
 457 day treatment cycle. During treatment, a complete blood count should be obtained
 458 on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly
 459 until the ANC is above $1.5 \times 10^9/L$ (1,500/ μ L) and the platelet count exceeds $100 \times$
 460 $10^9/L$ (100,000/ μ L). The next cycle of TEMODAR should not be started until the ANC
 461 and platelet count exceed these levels. If the ANC falls to $<1.0 \times 10^9/L$ (1,000/ μ L) or
 462 the platelet count is $<50 \times 10^9/L$ (50,000/ μ L) during any cycle, the next cycle should
 463 be reduced by 50 mg/m², but not below 100 mg/m², the lowest recommended dose
 464 (see **Table 8**). TEMODAR therapy can be continued until disease progression. In
 465 the clinical trial, treatment could be continued for a maximum of 2 years; but the
 466 optimum duration of therapy is not known.

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Table 8 Dosing Modification Table



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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

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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

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

499
500

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

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

510

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

518

519 **HOW SUPPLIED**

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

522 TEMODAR (temozolomide) Capsules 5 mg:

523 5 count - NDC 0085-1248-01 20 count - NDC 0085-1248-02

524 TEMODAR (temozolomide) Capsules 20 mg: 5 count - NDC 0085-1244-01 20
 525 count - NDC 0085-1244-02

526 TEMODAR (temozolomide) Capsules 100 mg: 5 count - NDC 0085-1259-01 20
 527 count - NDC 0085-1259-02

528 TEMODAR (temozolomide) Capsules 140 mg:

529 5 count - NDC 0085-1425-01 14 count – NDC 0085-1425-02

530 TEMODAR (temozolomide) Capsules 180 mg:

531 5 count - NDC 0085-1430-01 14 count – NDC 0085-1430-02

532 TEMODAR (temozolomide) Capsules 250 mg:

533 5 count - NDC 0085-1252-01 20 count - NDC 0085-1252-02

534

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

536 [See USP Controlled Room Temperature]

537

538 **REFERENCES**

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 Kenilworth, NJ 07033 USA



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566



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. Your doctor has prescribed TEMODAR (temozolomide) as part of
14 your cancer treatment. TEMODAR is a drug you take by mouth that interferes with
15 cell growth, especially in cells that are growing rapidly, such as cancerous cells.
16 TEMODAR has been shown to help slow the growth of certain cancerous tumors.
17 When given to patients with brain cancer, TEMODAR has been shown to reduce the
18 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, you may
25 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 do
34 not take a second dose. New capsules should not be taken until the next planned
35 dose. The medicine is used best by your body if you take it at the same time every
36 day in relation to a meal. To reduce nausea, try to take TEMODAR on an empty
37 stomach or at bedtime. Your doctor may also have prescribed anti-nausea or other
38 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 healthcare provider each time you start
62 a new cycle. Sometimes the dose or the mix of capsules you need to take will
63 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 Your doctor may have prescribed a treatment regimen that is different from those
67 discussed in this information sheet. If so, make sure you follow the specific
68 instructions given to you by your doctor. You should talk to your doctor about what to
69 do if you miss a day. If you take more than the prescribed amount of medicine,
70 contact your doctor right away. It is important that you understand your dosage
71 regimen, it is also important that you do not take more than the amount of
72 TEMODAR prescribed for you. Overdoses can lead to serious outcomes including
73 severe low blood counts and possible death.



74 **How is TEMODAR supplied?**

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

80

81	TEMODAR Capsule Strength	Color
82	5mg	Green Imprint
83	20mg	Brown Imprint
84	100mg	Blue Imprint
85	140mg	Blue Cap
86	180mg	Orange Cap
87	250mg	Black Imprint

88

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

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

92

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

99

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

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

105

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

115

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



119

120 **General information about the use of prescription drug products.**

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

126

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129 Rev. 6/06

130



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/m²/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.

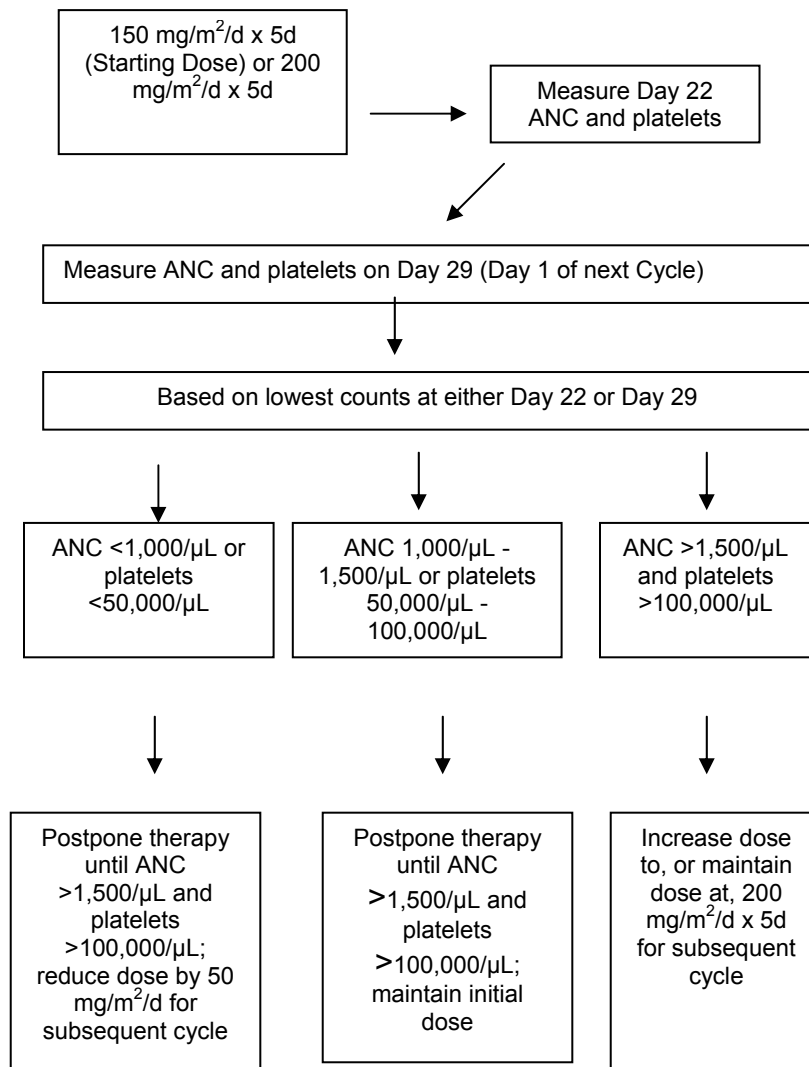
How might the dose of TEMODAR be modified for Refractory Anaplastic Astrocytoma?

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/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).

53
 54 **TABLE 1**
 55 **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/m² 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 $\geq 1.5 \times 10^9/L$ platelet count $\geq 100 \times 10^9 /L$ common toxicity criteria (CTC) non-hematological toxicity \leq 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 $< 1.5 \times 10^9/L$	$< 0.5 \times 10^9/L$
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

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/m² once daily for 5 days followed by 23 days without



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

112 During treatment a complete blood count should be obtained on Day 22 (21 days
 113 after the first dose) or within 48 hours of that day, and weekly until the ANC is above
 114 1.5 x 10⁹/L (1,500/μL) and the platelet count exceeds 100 x 10⁹/L (100,000/μL). The
 115 next cycle of TEMODAR should not be started until the ANC and platelet count
 116 exceed these levels. Dose reductions during the next cycle should be based on the
 117 lowest blood counts and worst non-hematologic toxicity during the previous cycle.
 118 Dose reductions or discontinuations during the maintenance phase should be
 119 applied according to Tables 3 and 4.
 120
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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

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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.

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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 anti-nausea or other medications to relieve the side effects associated with TEMODAR, they should be advised to take these



130 medications 30 minutes before they take TEMODAR. Temozolomide causes the
 131 rapid appearance of malignant tumors in rats. Patients **SHOULD NOT** open or split
 132 the capsules. If capsules are accidentally opened or damaged, rigorous precautions
 133 should be taken with the capsule contents to avoid inhalation or contact with the skin
 134 or mucous membranes. The medication should be kept away from children and pets.
 135 The TEMODAR capsules should be swallowed whole and **NEVER CHEWED**.

136

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

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

144

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

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

149

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

152

153 **How is TEMODAR supplied?**

154 TEMODAR capsules are available in 5mg, 20 mg, 100 mg, 140 mg, 180 mg, and
 155 250 mg strengths. The 5 mg, 20 mg, 100 mg, and 250 mg capsules contain a white
 156 capsule body with a white cap. The 140 mg and 180 mg capsules contain a white
 157 capsule body with a color cap. Each capsule contains color-coded printing according
 158 to strength.

159 **TEMODAR Capsule Strength**

Color

160	5 mg	Green Imprint
161	20 mg	Brown Imprint
162	100 mg	Blue Imprint
163	140 mg	Blue Cap
164	180 mg	Red Cap
165	250 mg	Black Imprint

166

167 The 5 mg, 20 mg, 100 mg, and 250 mg capsule strengths are available in 5-count
 168 and 20-count packages. The 140 mg and 180 mg capsule strengths are available in
 169 5-count and 14-count.



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

182

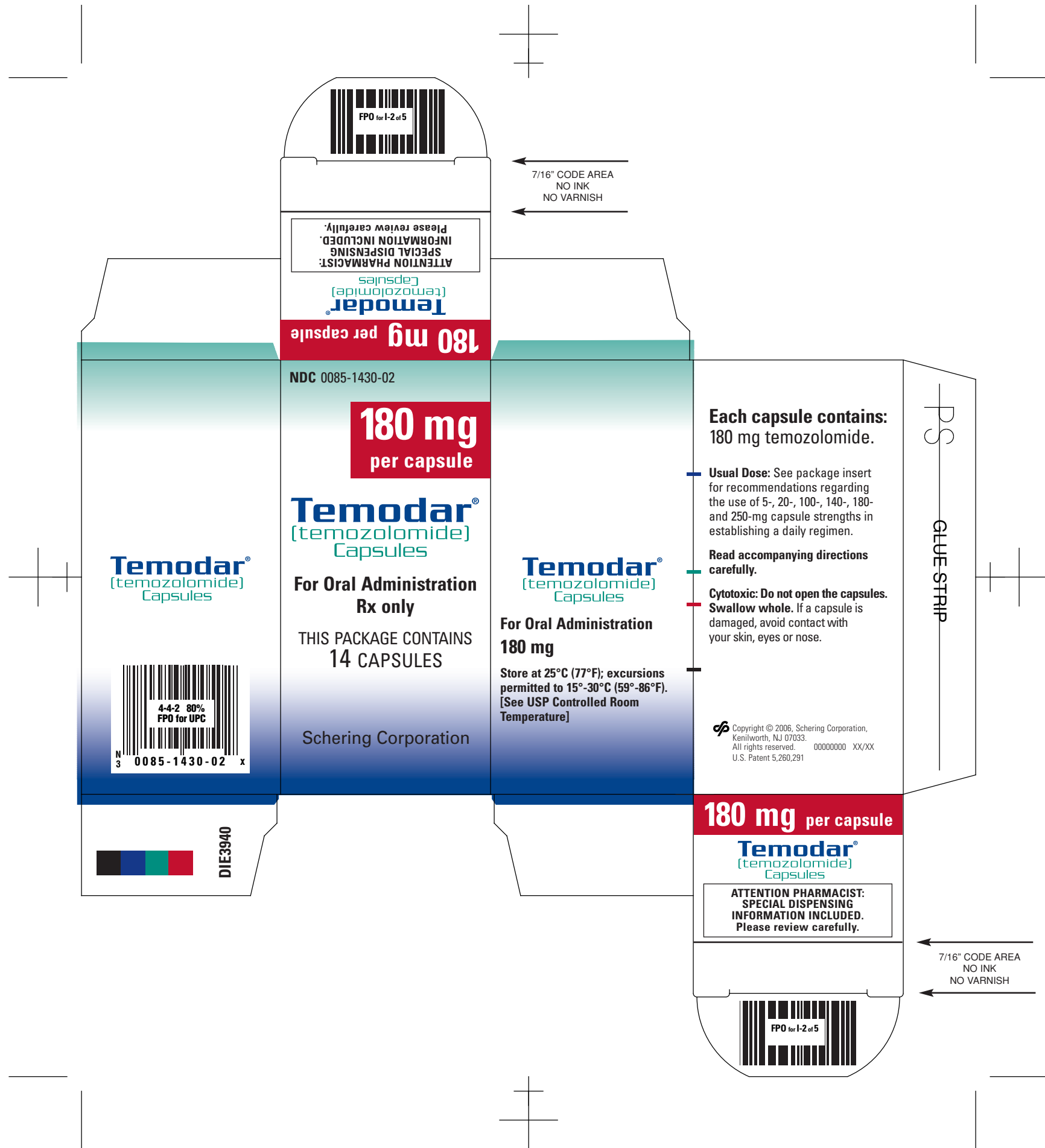
183 **How can TEMODAR be ordered?** TEMODAR can be ordered from your
184 wholesaler. [It is important to understand if TEMODAR is being used as part of a 42](#)
185 [day regimen or as part of a five-day course.](#) Remember to order enough TEMODAR
186 for the appropriate cycle.187 [For example:](#)188 • [a 5-day course of 360 mg/day would require the following to be ordered:](#)189 [two-5 count packages of 180 mg capsules](#)190 • [a 42-day course of 140 mg/day would require the following to be ordered:](#)191 [three-14 count packages of 140 mg capsules](#)192 [For example of other dosing regimens, please refer to the full Prescribing](#)
193 [Information \(Table 10\)](#)





194

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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PMS 187	



FPO for 1-2 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

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

180 mg per capsule

Temodar®
(temozolomide)
Capsules

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Please review carefully.

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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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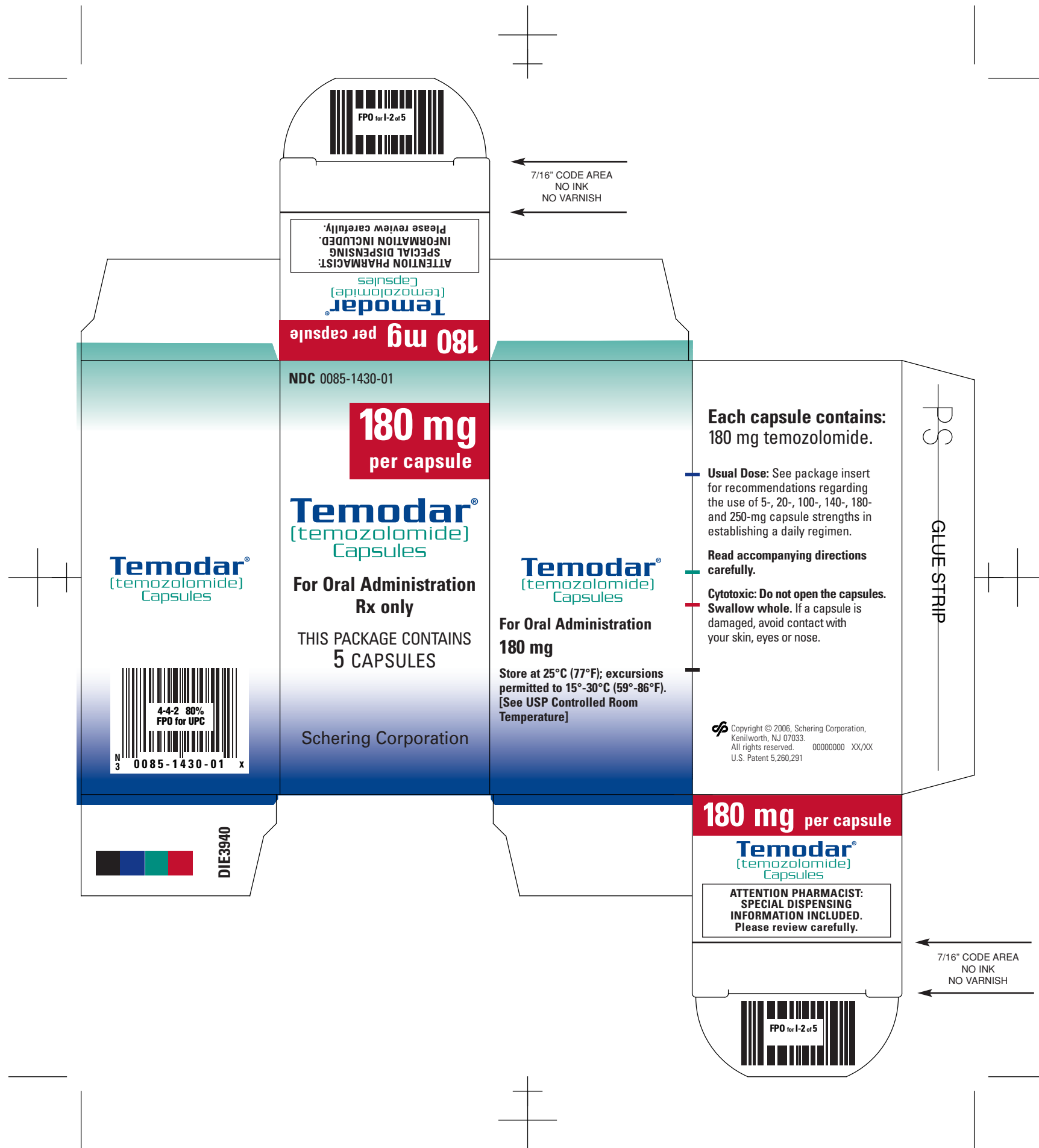






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ATTENTION PHARMACIST:
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Please review carefully.

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

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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U.S. Patent 5,260,291

180 mg per capsule

Temodar®
(temozolomide)
Capsules

ATTENTION PHARMACIST:
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Please review carefully.

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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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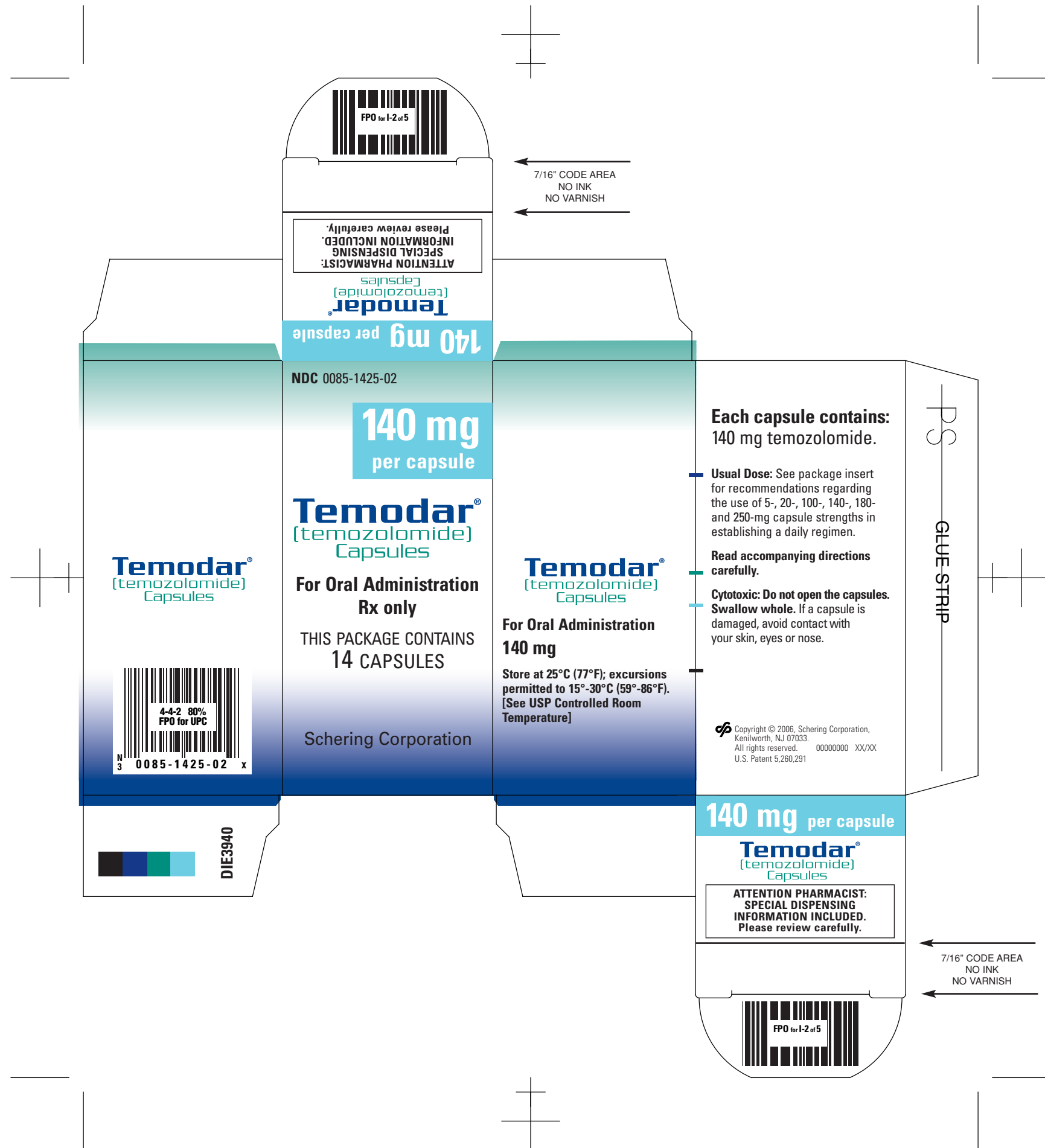
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140 mg per capsule
Temodar®
(temozolomide)
Capsules

NDC 0085-1425-02

140 mg
per capsule

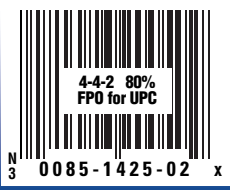
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(temozolomide)
Capsules

For Oral Administration
Rx only

THIS PACKAGE CONTAINS
14 CAPSULES

Schering Corporation

Temodar®
(temozolomide)
Capsules



4-4-2 80%
FPO for UPC

N 0085-1425-02 x
3

DIE3940



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.

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

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PS
GLUE STRIP

140 mg per capsule

Temodar®
(temozolomide)
Capsules

ATTENTION PHARMACIST:
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Please review carefully.

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NO VARNISH



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PMS 3288	
PMS 305	

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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NO VARNISH

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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 0085-1425-01 x
3

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

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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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