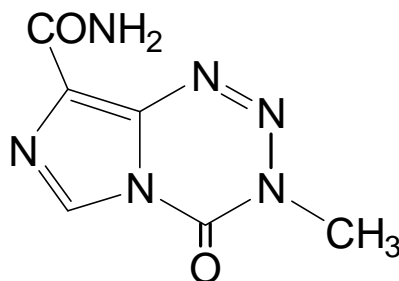


1 **TEMODAR (temozolomide)**
2 **CAPSULES**

3
4 **DESCRIPTION**

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



11
12
13
14 The material is a white to light tan/light pink powder with a molecular formula of C₆H₆N₆O₂ and
15 a molecular weight of 194.15. The molecule is stable at acidic pH (<5), and labile at pH>7,
16 hence can be administered orally. The prodrug, temozolomide, is rapidly hydrolysed to the
17 active 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide (MTIC) at neutral and alkaline pH
18 values, with hydrolysis taking place even faster at alkaline pH.

19
20 Each capsule contains 5 mg, 20 mg, 100 mg, or 250 mg of temozolomide. The inactive
21 ingredients for TEMODAR CAPSULES are lactose anhydrous, colloidal silicon dioxide, sodium
22 starch glycolate, tartaric acid, and stearic acid. Gelatin capsule shells contain titanium dioxide.
23 The capsules are imprinted with pharmaceutical ink.

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

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

31 TEMODAR 100 mg: blue imprint contains pharmaceutical glaze (modified) in an ethanol/shellac
32 mixture, isopropyl alcohol, n-butyl alcohol, propylene glycol, titanium dioxide, and FD & C Blue
33 #2 aluminium lake.

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

37

38 CLINICAL PHARMACOLOGY

39
40 **Mechanism of Action:** Temozolomide is not directly active but undergoes rapid non-enzymatic
41 conversion at physiologic pH to the reactive compound MTIC. The cytotoxicity of MTIC is
42 thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the
43 O⁶ and N⁷ positions of guanine.
44

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

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

66 **Special Populations:**

67
68 **Age:** Population pharmacokinetic analysis indicates that age (range 19-78 years) has no
69 influence on the pharmacokinetics of temozolomide. In the anaplastic astrocytoma study
70 population, patients 70 years of age or older had a higher incidence of Grade 4 neutropenia and
71 Grade 4 thrombocytopenia in the first cycle of therapy than patients under 70 years of age. (See
72 Precautions). In the entire safety database, however, there did not appear to be a higher incidence
73 in patients 70 years of age or older. (See Adverse Reactions).
74

75 **Gender:** Population pharmacokinetic analysis indicates that women have an approximately 5%
76 lower clearance (adjusted for body surface area) for temozolomide than men. Women have
77 higher incidences of Grade 4 neutropenia and thrombocytopenia in the first cycle of therapy than
78 men. (See Adverse Reactions)
79

80 **Race:** The effect of race on the pharmacokinetics of temozolomide has not been studied.
81

82 **Tobacco Use:** Population pharmacokinetic analysis indicates that the oral clearance of
83 temozolomide is similar in smokers and non-smokers.

84

85 **Creatinine Clearance:** Population pharmacokinetic analysis indicates that creatinine clearance
86 over the range of 36-130 ml/min/m² has no effect on the clearance of temozolomide after oral
87 administration. The pharmacokinetics of temozolomide have not been studied in patients with
88 severely impaired renal function (CL_{cr} < 36 ml/min/ m²). Caution should be exercised when
89 TEMODAR is administered to patients with severe renal impairment. TEMODAR has not been
90 studied in patients on dialysis.

91

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

96

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

100

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

103

104 Population analysis indicates that administration of valproic acid decreases the clearance of
105 temozolomide by about 5% (See Precautions).

106

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

110

111 **Clinical Studies:** A single arm, multicenter study was conducted in 162 patients who had
112 anaplastic astrocytoma at first relapse and who had a baseline Karnofsky performance status of
113 70 or greater. Patients had previously received radiation therapy and may also have previously
114 received a nitrosourea with or without other chemotherapy. Fifty-four patients had disease
115 progression on prior therapy with both a nitrosourea and procarbazine and their malignancy was
116 considered refractory to chemotherapy (refractory anaplastic astrocytoma population). Median
117 age of this subgroup of 54 patients was 42 years (19-76). Sixty-five percent were male. Seventy-
118 two percent of patients had a KPS of ≥ 80 . Sixty-three percent of patients had surgery other than
119 a biopsy at the time of initial diagnosis. Of those patients undergoing resection, 73% underwent a
120 subtotal resection and 27% underwent a gross total resection. Eighteen percent of patients had
121 surgery at the time of first relapse. The median time from initial diagnosis to first relapse was
122 13.8 months (4.2-75.4).

123 TEMODAR was given for the first 5 consecutive days of a 28 day cycle at a starting dose of 150
124 mg/m²/day. If the nadir and day of dosing (Day 29, Day 1 of next cycle) absolute neutrophil
125 count was $\leq 1.5 \times 10^9/L$ (1,500/FL) and the nadir and day 29, Day 1 of next cycle, platelet count
126 was $\leq 100 \times 10^9/L$ (100,000/FL), the TEMODAR dose was increased to 200 mg/m²/day for the
127 first 5 consecutive days of a 28 day cycle.

128

129 In the refractory anaplastic astrocytoma population the overall tumor response rate (CR + PR)
130 was 22% (12/54 patients) and the complete response rate was 9% (5/54 patients). The median
131 duration of all responses was 50 weeks (range of 16 to 114 weeks) and the median duration of
132 complete responses was 64 weeks (range of 52 to 114 weeks). In this population, progression-
133 free survival at 6 months was 45% (95% confidence interval 31-58%) and progression-free
134 survival at 12 months was 29% (95% confidence interval 16-42%). Median progression-free
135 survival was 4.4 months. Overall survival at 6 months was 74% (95% confidence interval 62-
136 86%) and 12 month overall survival was 65% (95% confidence interval 52-78%). Median overall
137 survival was 15.9 months.

138

139 **INDICATIONS AND USAGE**

140

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

144

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

149

150 **CONTRAINDICATIONS**

151

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

155

156 **WARNINGS**

157

158 Patients treated with TEMODAR may experience myelosuppression. Prior to dosing patients
159 must have an absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$ and a platelet count $\geq 100 \times 10^9/L$.
160 A complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48
161 hours of that day, and weekly until the ANC is above $1.5 \times 10^9/L$ and platelet count exceeds 100
162 $\times 10^9/L$. In the clinical trials, if the ANC fell to $< 1.0 \times 10^9/L$ or the platelet count was $< 50 \times$
163 $10^9/L$ during any cycle, the next cycle was reduced by 50 mg/m^2 , but not below 100 mg/m^2 .
164 Patients who do not tolerate 100 mg/m^2 should not receive TEMODAR. Geriatric patients and
165 women have been shown in clinical trials to have a higher risk of developing myelosuppression.
166 Myelosuppression generally occurred late in the treatment cycle. The median nadirs occurred at
167 26 days for platelets [range 21-40 days] and 28 days for neutrophils [range 1-44 days]. Only 14%
168 (22/158) of patients had a neutrophil nadir and 20% (32/158) of patients had a platelet nadir
169 which may have delayed the start of the next cycle. Neutrophil and platelet counts returned to
170 normal, on average, within 14 days of nadir counts (**see Precautions**).

171

172 **Pregnancy.** Temozolomide may cause fetal harm when administered to a pregnant woman. Five
173 consecutive days of oral administration of $75 \text{ mg/m}^2/\text{day}$ in rats and $150 \text{ mg/m}^2/\text{day}$ in rabbits
174 during the period of organogenesis (3/8 and 3/4 the maximum recommended human dose,

175 respectively) caused numerous malformations of the external organs, soft tissues and skeleton in
176 both species. Doses of 150 mg/m²/day in rats and rabbits also caused embryoletality as
177 indicated by increased resorptions. There are no adequate and well-controlled studies in
178 pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while
179 taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of
180 childbearing potential should be advised to avoid becoming pregnant during therapy with
181 TEMODAR.

182

183 **PRECAUTIONS**

184

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

191

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

194

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

198

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

203 In the anaplastic astrocytoma study population, patients 70 years of age or older had a higher
204 incidence of Grade 4 neutropenia and Grade 4 thrombocytopenia (2/8; 25%, p=.31 and 2/10;
205 20%, p=.09, respectively) in the first cycle of therapy than patients under 70 years of age. (See
206 Adverse Reactions).

207

208 **Laboratory Tests:** A complete blood count should be obtained on day 22 (21 days after the first
209 dose). Blood counts should be performed weekly until recovery if the ANC falls below 1.5 x
210 10⁹/L and the platelet count falls below 100 x 10⁹/L.

211

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

221
222 Temozolomide was mutagenic *in vitro* in bacteria (Ames assay) and clastogenic in mammalian
223 cells (human peripheral blood lymphocyte assays).
224

225 Reproductive function studies have not been conducted with temozolomide. However, multi-
226 cycle toxicology studies in rats and dogs have demonstrated testicular toxicity (syncytial
227 cells/immature sperm, testicular atrophy) at doses of 50 mg/m² in rats and 125 mg/m² in dogs
228 (1/4 and 5/8 respectively of the maximum recommended human dose on a body surface area
229 basis).
230

231 **Pregnancy Category D. See Warnings Section.**
232

233 **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many
234 drugs are excreted in human milk and because of the potential for serious adverse reactions in
235 nursing infants from TEMODAR, patients receiving TEMODAR should discontinue nursing.
236

237 **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.
238

239 **ADVERSE REACTIONS**

240

241 Tables 1 and 2 show the incidence of adverse events in the 158 patients in the Anaplastic
242 Astrocytoma study for whom data are available. In the absence of a control group, it is not clear
243 in many cases whether these events should be attributed to temozolomide or the patients'
244 underlying conditions, but nausea, vomiting, fatigue and hematologic effects appear to be clearly
245 drug-related. The most frequently occurring side effects were nausea, vomiting, headache and
246 fatigue. The adverse events were usually NCI Common Toxicity Criteria (CTC) Grade 1 or 2
247 (mild to moderate in severity) and were self-limiting, with nausea and vomiting readily
248 controlled with antiemetics. The incidence of severe nausea and vomiting (CTC grade 3 or 4)
249 was 10% and 6%, respectively. Myelosuppression (thrombocytopenia and neutropenia) was the
250 dose-limiting adverse event. It usually occurred within the first few cycles of therapy and was
251 not cumulative.
252

253 Myelosuppression occurred late in the treatment cycle and returned to normal, on average, within
254 14 days of nadir counts. The median nadirs occurred at 26 days for platelets [range 21-40 days]
255 and 28 days for neutrophils [range 1-44 days]. Only 14% (22/158) of patients had a neutrophil
256 nadir and 20% (32/158) of patients had a platelet nadir which may have delayed the start of the
257 next cycle. (See Warnings). Less than 10% of patients required hospitalization, blood transfusion
258 or discontinuation of therapy due to myelosuppression.
259

260 In clinical trial experience with 110-111 women and 169-174 men (depending on
261 measurements), there were higher rates of Grade 4 neutropenia (ANC < 500 cells/FL) and
262 thrombocytopenia (< 20,000 cells/FL) in women than men in the first cycle of therapy: (12%
263 versus 5% and 9% versus 3%, respectively).
264

265 In the entire Safety database for which hematologic data exist (N=932), 7% (4/61) and 9.5%
266 (6/63) of patients over age 70 experienced Grade 4 neutropenia or thrombocytopenia in the first

267 cycle, respectively. For patients less than or equal to age 70, 7% (62/871) and 5.5% (48/879)
268 experienced Grade 4 neutropenia or thrombocytopenia in the first cycle, respectively.
269

Table 1 Adverse Events in the Anaplastic Astrocytoma Trial (\$5%)		
	No. (%) of TEMODAR Patients (N=158)	
	All Events	Grade 3 / 4
Any Adverse Event	153 (97)	79 (50)
Body as a Whole		
Headache	65 (41)	10 (6)
Fatigue	54 (34)	7 (4)
Asthenia	20 (13)	9 (6)
Fever	21 (13)	3 (2)
Back pain	12 (8)	4 (3)
Cardiovascular		
Edema peripheral	17 (11)	1 (1)
Central and Peripheral Nervous System		
Convulsions	36 (23)	8 (5)
Hemiparesis	29 (18)	10 (6)
Dizziness	19 (12)	1 (1)
Coordination abnormal	17 (11)	2 (1)
Amnesia	16 (10)	6 (4)
Insomnia	16 (10)	0
Paresthesia	15 (9)	1 (1)
Somnolence	15 (9)	5 (3)
Paresis	13 (8)	4 (3)
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
Gastro-Intestinal 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
Musculo-Skeletal System		
Myalgia	8 (5)	
Psychiatric Disorders		
Anxiety	11 (7)	1 (1)
Depression	10 (6)	0
Reproductive Disorders		

Table 1 Adverse Events in the Anaplastic Astrocytoma Trial (\$5%)		
	No. (%) of TEMODAR Patients (N=158)	
	All Events	Grade 3 / 4
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

270
271

Table 2 Adverse Hematologic Effects (Grade 3-4) in the Anaplastic Astrocytoma Trial	
	Temodal ^a
Hemoglobin	7/158 (4%)
Neutrophils	20/142 (14%)
Platelets	29/156 (19%)
WBC	18/158 (11%)

a: Change from grade 0-2 at baseline to grade 3 or 4 during treatment.

272
273
274
275
276
277

OVERDOSAGE

278 Doses of 500, 750, 1,000 and 1,250 mg/m² (total dose per cycle over five days) have been
279 evaluated clinically in patients. Dose-limiting toxicity was hematologic and was reported at
280 1,000 mg/m² and at 1,250 mg/m². Up to 1,000 mg/m² has been taken as a single dose, with only
281 the expected effects of neutropenia and thrombocytopenia resulting. In the event of an overdose,
282 hematologic evaluation is needed. Supportive measures should be provided as necessary.
283

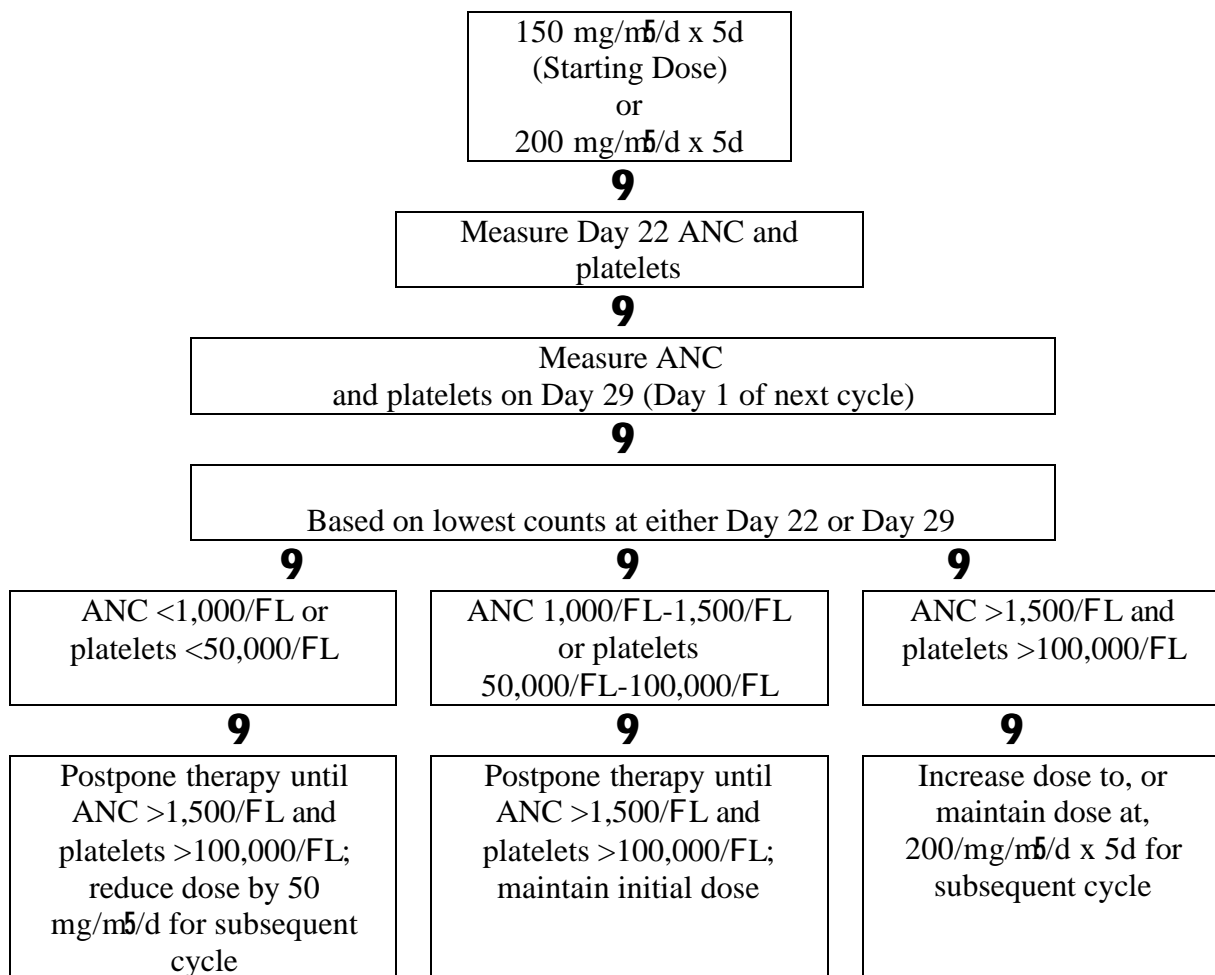
284 **DOSAGE AND ADMINISTRATION**

285
286 Dosage of TEMODAR must be adjusted according to nadir neutrophil and platelet counts in the
287 previous cycle and neutrophil and platelet counts at the time of initiating the next cycle. The
288 initial dose is 150 mg/m² orally once daily for 5 consecutive days per 28 day treatment cycle. If
289 both the nadir and day of dosing (Day 29, Day 1 of next cycle) absolute neutrophil counts (ANC)
290 are $\geq 1.5 \times 10^9/L$ (1,500/ μ L) and both the nadir and day 29, Day 1 of next cycle platelet counts
291 are $\geq 100 \times 10^9/L$ (100,000/ μ L), the TEMODAR dose may be increased to 200 mg/m²/day for 5
292 consecutive days per 28 day treatment cycle. During treatment, a complete blood count should
293 be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly
294 until the ANC is above $1.5 \times 10^9/L$ (1,500/ μ L) and the platelet count exceeds $100 \times 10^9/L$
295 (100,000/ μ L). The next cycle of TEMODAR should not be started until the ANC and platelet
296 count, exceed these levels. If the ANC falls to $< 1.0 \times 10^9/L$ (1,000/ μ L) or the platelet count is
297 $< 50 \times 10^9/L$ (50,000/ μ L) during any cycle, the next cycle should be reduced by 50 mg/m², but
298 not below 100 mg/m², the lowest recommended dose (see Table 3). **(See Warnings).**
299

300 TEMODAR therapy can be continued until disease progression. In the clinical trial, treatment
301 could be continued for a maximum of 2 years; but the optimum duration of therapy is not known.
302 For TEMODAR dosage calculations based on body surface area (BSA), see table 4. For
303 suggested capsule combinations based on daily dose, see table 5.
304

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 310
 311

Table 3 Dosing Modification



312
 313
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324

325

326

327 Table 4. Daily Dose Calculations by Body Surface Area (BSA) for 5 consecutive days per 28
328 day treatment cycle for the initial chemotherapy cycle (150 mg/m²) and for subsequent
329 chemotherapy cycles (200 mg/m²) for patients whose nadir and day of dosing (Day 29, Day 1 of
330 next cycle) absolute neutrophil count (ANC) is >1.5 x 10⁹/L (1,500/FL) and whose nadir and day
331 29, Day 1 of next cycle platelet count is >100 x 10⁹/L (100,000/FL).
332

Total BSA (m ²)	150 mg/m ² (mg daily)	200 mg/m ² (mg daily)
0.5	75	100
0.6	90	120
0.7	105	140
0.8	120	160
0.9	135	180
1.0	150	200
1.1	165	220
1.2	180	240
1.3	195	260
1.4	210	280
1.5	225	300
1.6	240	320
1.7	255	340
1.8	270	360
1.9	285	380
2.0	300	400
2.1	315	420
2.2	330	440
2.3	345	460
2.4	360	480
2.5	375	500

333

334 Table 5. Suggested Capsule Combinations Based on Daily Dose
335

Total Daily Dose (mg)	Number of Daily Capsules by Strength (mg)			
	250	100	20	5
200	0	2	0	0
205	0	2	0	1
210	0	2	0	2
215	0	2	0	3
220	0	2	1	0
225	0	2	1	1
230	0	2	1	2
235	0	2	1	3
240	0	2	2	0
245	0	2	2	1
250	1	0	0	0
255	1	0	0	1
260	1	0	0	2
265	1	0	0	3
270	1	0	1	0
275	1	0	1	1
280	1	0	1	2
285	1	0	1	3
290	1	0	2	0
295	1	0	2	1
300	0	3	0	0
305	0	3	0	1
310	0	3	0	2
315	0	3	0	3
320	0	3	1	0
325	0	3	1	1
330	1	0	4	0
335	1	0	4	1
340	0	3	2	0
345	0	3	2	1
350	1	1	0	0
355	1	1	0	1
360	1	1	0	2
365	1	1	0	3
370	1	1	1	0
375	1	1	1	1
380	1	1	1	2
385	1	1	1	3
390	1	1	2	0
395	1	1	2	1
400	0	4	0	0

405	0	4	0	1
410	0	4	0	2
415	0	4	0	3
420	0	4	1	0
425	0	4	1	1
430	1	1	4	0
435	0	4	1	3
440	0	4	2	0
445	0	4	2	1
450	1	2	0	0
455	1	2	0	1
460	1	2	0	2
465	1	2	0	3
470	1	2	1	0
475	1	2	1	1
480	1	2	1	2
485	1	2	1	3
490	1	2	2	0
495	1	2	2	1
500	2	0	0	0

336

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

343

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

346

347

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

354

355 **How Supplied:**

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

358

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

360 5 count – NDC# 0085-1248-01

361 20 count – NDC# 0085-1248-02

362
363 TEMODAR (temozolomide) Capsules 20 mg: 5 and 20 capsule bottles.
364 5 count – NDC# 0085-1244-01
365 20 count – NDC# 0085-1244-02
366
367 TEMODAR (temozolomide) Capsules 100 mg: 5 and 20 capsule bottles.
368 5 count – NDC# 0085-1259-01
369 20 count – NDC# 0085-1259-02
370
371 TEMODAR (temozolomide) Capsules 250 mg: 5 and 20 capsule bottles.
372 5 count – NDC# 0085-1252-01
373 20 count – NDC# 0085-1252-02
374

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

376 [See USP Controlled Room Temperature]

377
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Patient Package Insert TEMODAR (temozolomide) Capsules

What is TEMODAR?

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

Who should not take TEMODAR?

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

How should I take TEMODAR?

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

Your pharmacist has carefully packaged the TEMODAR capsules for each day of treatment in five separate packets or vials, labeled "Day 1", "Day 2", "Day 3", "Day 4", and "Day 5". On the first day of treatment, you should take all the capsules in the package labeled "Day 1" (as a single dose), on the second day, take all the capsules in the package labeled Day 2 as a single dose, and so on. Don't worry that the capsules that you take on a given day are different sizes or colors. Your doctor and pharmacist have made sure that you will be taking the correct dose on each of the five days of the treatment cycle. If you think your medication has been packaged incorrectly, contact your physician or pharmacist immediately.

Because TEMODAR is a drug you take by mouth, you can take it at home. TEMODAR is usually taken for five days in a row over a 28-day period. This period is called a treatment cycle. That means you will take TEMODAR for five days, have a break from therapy for 23 days, and then take the drug for another five days. The number of treatment cycles will depend on how you respond to and tolerate this treatment.

Your doctor may have prescribed a treatment regimen that is different from the one discussed in this information sheet. If so, make sure you follow the specific instructions given to you by your doctor. You should talk to your doctor about what to do if you miss a day. If you take more than the prescribed amount of medicine, contact your doctor right away.

What should I avoid while taking TEMODAR?

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

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

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

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

TEMODAR also can reduce the number of certain types of blood cells, which can have serious effects. Therefore, it is important that your doctor check your blood periodically while you are taking TEMODAR to see if these side effects are occurring. Patients, age 70 or older, women, and patients who have had chemotherapy or radiation therapy may be more likely to have their blood cells affected.

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

General information about the use of prescription drug products.

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

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Pharmacist Information Sheet

IMPORTANT DISPENSING INFORMATION

For every patient, each day's dose of TEMODAR must be packaged separately so that, patients take the correct daily dose. Please see the dispensing instructions below for more information.

What is TEMODAR?

TEMODAR (temozolomide) is an oral alkylating agent for the treatment of refractory-anaplastic astrocytoma.

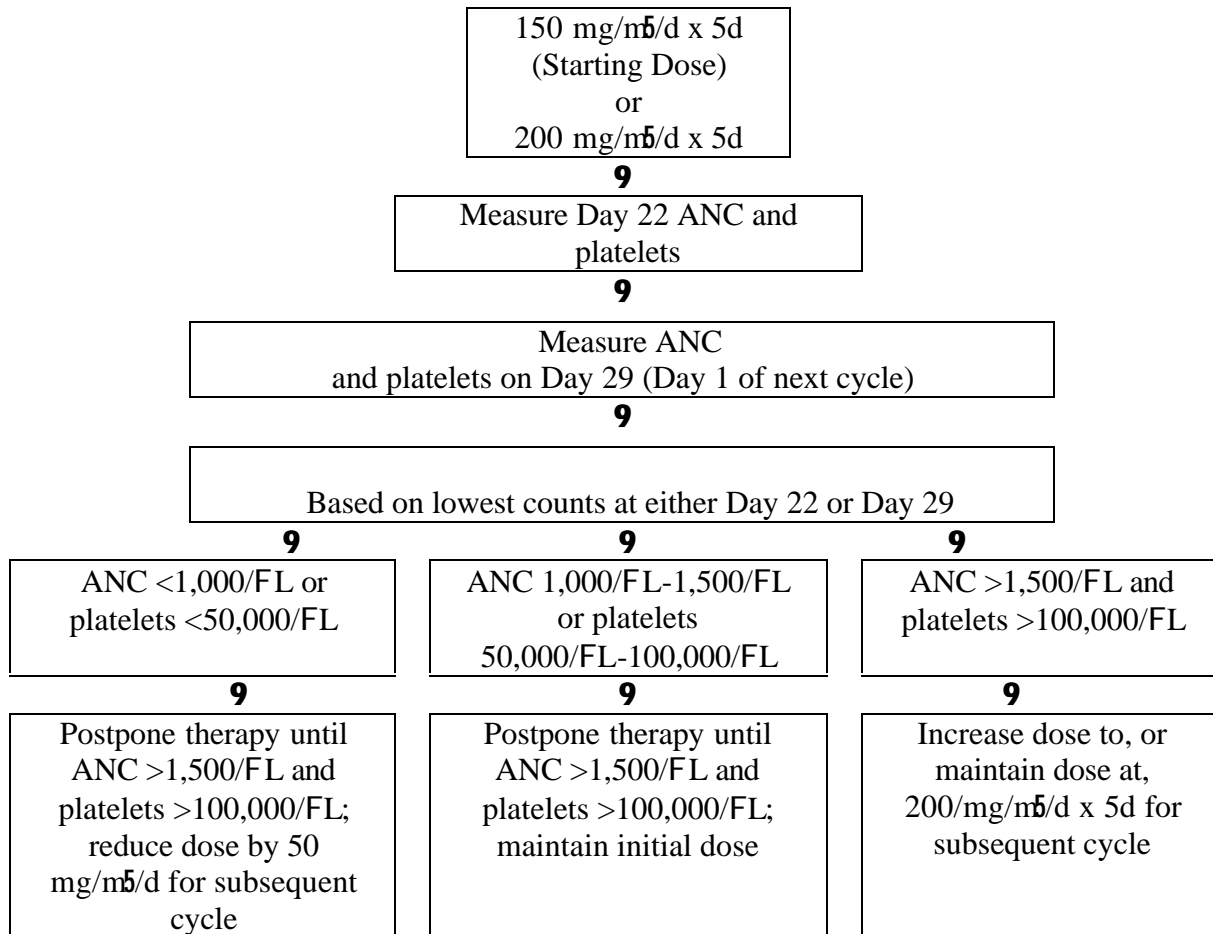
How is TEMODAR dosed?

The daily dose of TEMODAR for a given patient is calculated by the physician, based on the patient's body surface area (BSA). The initial daily dose of TEMODAR in milligrams is the BSA multiplied by 150 ($150 \text{ mg/m}^2/\text{day}$). The resulting dose is then rounded off to the nearest 5 mg. For example, the daily dose for a patient with a BSA of 1.84 is $1.84 \times 150 = 276$, 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?

Dosage of TEMODAR must be adjusted according to nadir neutrophil and platelet counts in the previous cycle and neutrophil and platelet counts at the time of initiating the next cycle. The initial dose is 150 mg/m^2 orally once daily for 5 consecutive days per 28 day treatment cycle. If both the nadir and day of dosing (Day 29, Day 1 of next cycle) absolute neutrophil counts (ANC) are $\geq 1.5 \times 10^9/\text{L}$ ($1,500/\mu\text{L}$) and both the nadir and day 29, Day 1 of next cycle platelet counts are $\geq 100 \times 10^9/\text{L}$ ($100,000/\mu\text{L}$), the TEMODAR dose may be increased to $200 \text{ mg/m}^2/\text{day}$ for 5 consecutive days per 28 day treatment cycle. During treatment, a complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above $1.5 \times 10^9/\text{L}$ ($1,500/\mu\text{L}$) and the platelet count exceeds $100 \times 10^9/\text{L}$ ($100,000/\mu\text{L}$). The next cycle of TEMODAR should not be started until the ANC and platelet count, exceed these levels. If the ANC falls to $< 1.0 \times 10^9/\text{L}$ ($1,000/\mu\text{L}$) or the platelet count is $< 50 \times 10^9/\text{L}$ ($50,000/\mu\text{L}$) during any cycle, the next cycle should be reduced by 50 mg/m^2 , but not below 100 mg/m^2 , the lowest recommended dose (see table below).

Dosing Modification Table



What is the TEMODAR treatment regimen?

TEMODAR is given for five 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.

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 medications 30 minutes before they take TEMODAR. Temozolomide causes the rapid appearance of malignant tumors in rats. Patients **SHOULD NOT** open or split the capsules. If capsules are accidentally opened or damaged, rigorous

precautions should be taken with the capsule contents to avoid inhalation or contact with the skin or mucous membranes. The medication should be kept away from children and pets. The TEMODAR capsules should be swallowed whole and **NEVER CHEWED**.

What should the patient avoid during treatment with TEMODAR?

There are no dietary restrictions for patients taking TEMODAR. There are no known interactions with other medications.

TEMODAR may affect testicular function so male patients should exercise adequate birth control measures. TEMODAR may cause birth defects. Female patients should avoid becoming pregnant while receiving this drug. Women who are nursing prior to receiving TEMODAR should discontinue nursing. It is not known whether TEMODAR is excreted into breast milk.

What are the side effects of TEMODAR?

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

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

How is TEMODAR supplied?

TEMODAR capsules are available in 250mg, 100mg, 20mg, and 5mg strengths. The capsules are color coded according to strength.

TEMODAR Capsule

<u>Strength</u>	<u>Color</u>
5 mg	Green
20 mg	Brown
100 mg	Blue
250 mg	Black

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

How is TEMODAR dispensed?

For a given prescription, each day's dose of TEMODAR must be packaged separately so that, patients take the correct dose each day. Follow the instructions below:

Determine the number of capsules of each strength needed to add up to the daily dose prescribed by the physician (eg, 275 mg/day = 1 x 250mg capsule, 1 x 20mg capsule and 1 x 5mg capsule).

Place one day's supply of TEMODAR in each of five separate packets or vials. In the above prescription for 275 mg/day, each of the five packets or vials should contain 1 x 250mg capsule, 1 x 20mg capsule and 1 x 5mg capsule.

Label the five packages as Day 1, Day 2, Day 3, Day 4, and Day 5, using the labels enclosed.

Dispense to the patient, making sure that he or she understands that each day's dose of TEMODAR is packaged separately.

How can TEMODAR be ordered?

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

- 1 5-count package of 250mg capsules
- 1 5-count package of 20mg capsules
- 1 5-count package of 5mg capsules

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

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