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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TEMODAR safely and effectively. See full prescribing information for TEMODAR.

TEMODAR® (temozolomide) Capsules
TEMODAR® (temozolomide) for Injection
administered via intravenous infusion
Initial U.S. Approval: 1999

----------RECENT MAJOR CHANGES----------
Warnings and Precautions, Hepatotoxicity (5.5) 05/2014

----------INDICATIONS AND USAGE----------
TEMODAR is an alkylating drug indicated for the treatment of adult patients with:
- Newly diagnosed glioblastoma multiforme (GBM) concomitantly with radiotherapy and then as maintenance treatment. (1.1)
- Refractory anaplastic astrocytoma patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine. (1.2)

---------- DOSAGE AND ADMINISTRATION ----------
- Newly Diagnosed GBM: 75 mg/m^2 for 42 days concomitant with focal radiotherapy followed by initial maintenance dose of 150 mg/m^2 once daily for Days 1-5 of a 28-day cycle of TEMODAR for 6 cycles. (2.1)
- Refractory Anaplastic Astrocytoma: Initial dose 150 mg/m^2 once daily for 5 consecutive days per 28-day treatment cycle. (2.1)
- The recommended dose for TEMODAR as an intravenous infusion over 90 minutes is the same as the dose for the oral capsule formulation. Bioequivalence has been established only when TEMODAR for Injection was given over 90 minutes. (2.1, 12.3)

---------- DOSAGE FORMS AND STRENGTHS ----------
- 5-mg, 20-mg, 100-mg, 140-mg, 180-mg, and 250-mg capsules. (3)
- 100-mg powder for injection. (3)

----------CONTRAINDICATIONS----------
- Known hypersensitivity to any TEMODAR component or to dacarbazine (DTIC). (4.1)

---------- WARNINGS AND PRECAUTIONS----------
- Myelosuppression — monitor Absolute Neutrophil Count (ANC) and platelet count prior to dosing and throughout treatment. Geriatric patients and women have a higher risk of developing myelosuppression. (5.1)
- Cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukemia, have been observed. (5.2)
- *Pneumocystis* pneumonia (PCP) – PCP prophylaxis required for all patients receiving concomitant TEMODAR and radiotherapy for the 42-day regimen for the treatment of newly diagnosed glioblastoma multiforme. (5.3)
- All patients, particularly those receiving steroids, should be observed closely for the development of lymphopenia and PCP. (5.4)
- Complete blood counts should be obtained throughout the treatment course as specified. (5.4)
- Hepatotoxicity – fatal and severe hepatotoxicity have been reported. Perform liver function tests at baseline, midway through the first cycle, prior to each subsequent cycle, and approximately two to four weeks after the last dose of TEMODAR. (5.5)
- Fetal harm can occur when administered to a pregnant woman. Women should be advised to avoid becoming pregnant when receiving TEMODAR. (5.6)
- As bioequivalence has been established only when given over 90 minutes, infusion over a shorter or longer period of time may result in suboptimal dosing; the possibility of an increase in infusion-related adverse reactions cannot be ruled out. (5.7)

---------- ADVERSE REACTIONS ----------
- The most common adverse reactions (≥10% incidence) are: alopecia, fatigue, nausea, vomiting, headache, constipation, anorexia, convulsions, rash, hemiparesis, diarrhea, asthenia, fever, dizziness, coordination abnormal, viral infection, amnesia, and insomnia. (6.1)
- The most common Grade 3 to 4 hematologic laboratory abnormalities (≥10% incidence) that have developed during treatment with temozolomide are: lymphopenia, thrombocytopenia, neutropenia, and leukopenia. (6.1)
- Allergic reactions have also been reported. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
- Valproic acid: decreases oral clearance of temozolomide. (7.1)

---------- USE IN SPECIFIC POPULATIONS ----------
- Nursing mothers: Not recommended. (8.3)
- Pediatric use: No established use. (8.4)
- Hepatic/Renal Impairment: Caution should be exercised when TEMODAR is administered to patients with severe renal or hepatic impairment. (8.6, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 05/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Newly Diagnosed Glioblastoma Multiforme

TEMODAR® (temozolomide) is indicated for the treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment.

1.2 Refractory Anaplastic Astrocytoma

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing and Dose Modification Guidelines

The recommended dose for TEMODAR as an intravenous infusion over 90 minutes is the same as the dose for the oral capsule formulation. Bioequivalence has been established only when TEMODAR for Injection was given over 90 minutes *[see Clinical Pharmacology (12.3)]*. Dosage of TEMODAR must be adjusted according to nadir neutrophil and platelet counts in the previous cycle and the neutrophil and platelet counts at the time of initiating the next cycle. For TEMODAR dosage calculations based on body surface area (BSA) see **Table 5**. For suggested capsule combinations on a daily dose see **Table 6**.

Patients with Newly Diagnosed High Grade Glioma: *Concomitant Phase:* TEMODAR is administered at 75 mg/m^2 daily for 42 days concomitant with focal radiotherapy (60 Gy administered in 30 fractions) followed by maintenance TEMODAR for 6 cycles. Focal RT includes the tumor bed or resection site with a 2- to 3-cm margin. No dose reductions are recommended during the concomitant phase; however, dose interruptions or discontinuation may occur based on toxicity. The TEMODAR dose should be continued throughout the 42-day concomitant period up to 49 days if all of the following conditions are met: absolute neutrophil count greater than or equal to 1.5 x 10^9/L, platelet count greater than or equal to 100 x 10^9/L, common toxicity criteria (CTC) nonhematological toxicity less than or equal to 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 nonhematological toxicity criteria as noted in **Table 1**. *Pneumocystis* pneumonia (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 less than or equal to 1).

TABLE 1: Temozolomide Dosing Interruption or Discontinuation During Concomitant Radiotherapy and Temozolomide

Toxicity	TMZ Interruption*	TMZ Discontinuation
Absolute Neutrophil Count	greater than or equal to 0.5 and less than 1.5 x 10^9/L	less than 0.5 x 10^9/L
Platelet Count	greater than or equal to 10 and less than 100 x 10^9/L	less than 10 x 10^9/L
CTC Nonhematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 2	CTC Grade 3 or 4

*Treatment with concomitant TMZ could be continued when all of the following conditions were met: absolute neutrophil count greater than or equal to 1.5 x 10^9/L; platelet count greater than or equal to 100 x 10^9/L; CTC nonhematological toxicity less than or equal to Grade 1 (except for alopecia, nausea, vomiting).
TMZ=temozolomide; CTC=Common Toxicity Criteria.

Maintenance Phase:

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

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

Dose Reduction or Discontinuation During Maintenance: Dose reductions during the maintenance phase should be applied according to **Tables 2** and **3**.

During treatment, a complete blood count should be obtained on Day 22 (21 days after the first dose of TEMODAR) or within 48 hours of that day, and weekly until the ANC is above 1.5 x 10^9/L (1500/µL) and the platelet count exceeds 100 x 10^9/L (100,000/µL). The next cycle of TEMODAR should not be started until the ANC and platelet count exceed these levels. Dose reductions during the next cycle should be based on the lowest blood counts and worst nonhematologic toxicity during the previous cycle. Dose reductions or discontinuations during the maintenance phase should be applied according to **Tables 2** and **3**.

TABLE 2: 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 3: Temozolomide Dose Reduction or Discontinuation During Maintenance Treatment

Toxicity	Reduce TMZ by 1 Dose Level*	Discontinue TMZ
Absolute Neutrophil Count	less than 1.0 x 10^9/L	See footnote†
Platelet Count	less than 50 x 10^9/L	See footnote†
CTC Nonhematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4†

*TMZ dose levels are listed in **Table 2**.
†TMZ is to be discontinued if dose reduction to less than 100 mg/m^2 is required or if the same Grade 3 nonhematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction.
TMZ=temozolomide; CTC=Common Toxicity Criteria.

Patients with Refractory Anaplastic Astrocytoma: For adults the initial dose is 150 mg/m^2 once daily for 5 consecutive days per 28-day treatment cycle. For adult patients, if both the nadir and day of dosing (Day 29, Day 1 of next cycle) ANC are greater than or equal to 1.5 x 10^9/L (1500/µL) and both the nadir and Day 29, Day 1 of next cycle platelet counts are greater than or equal to 100 x 10^9/L (100,000/µL), the TEMODAR dose may be increased to 200 mg/m^2/day for 5 consecutive days per 28-day treatment cycle. During treatment, a complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above 1.5 x 10^9/L (1500/µL) and the platelet count exceeds 100 x 10^9/L (100,000/µL). The next cycle of TEMODAR should not be started until the ANC and platelet count exceed these levels. If the ANC falls to less than 1.0 x 10^9/L (1000/µL) or the platelet count is less than 50 x 10^9/L (50,000/µL) during any cycle, the next cycle should be reduced by 50 mg/m^2, but not below 100 mg/m^2, the lowest recommended dose (see **Table 4**). TEMODAR therapy can be continued until disease progression. In the clinical trial, treatment could be continued for a maximum of 2 years, but the optimum duration of therapy is not known.

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TABLE 4: Dosing Modification Table

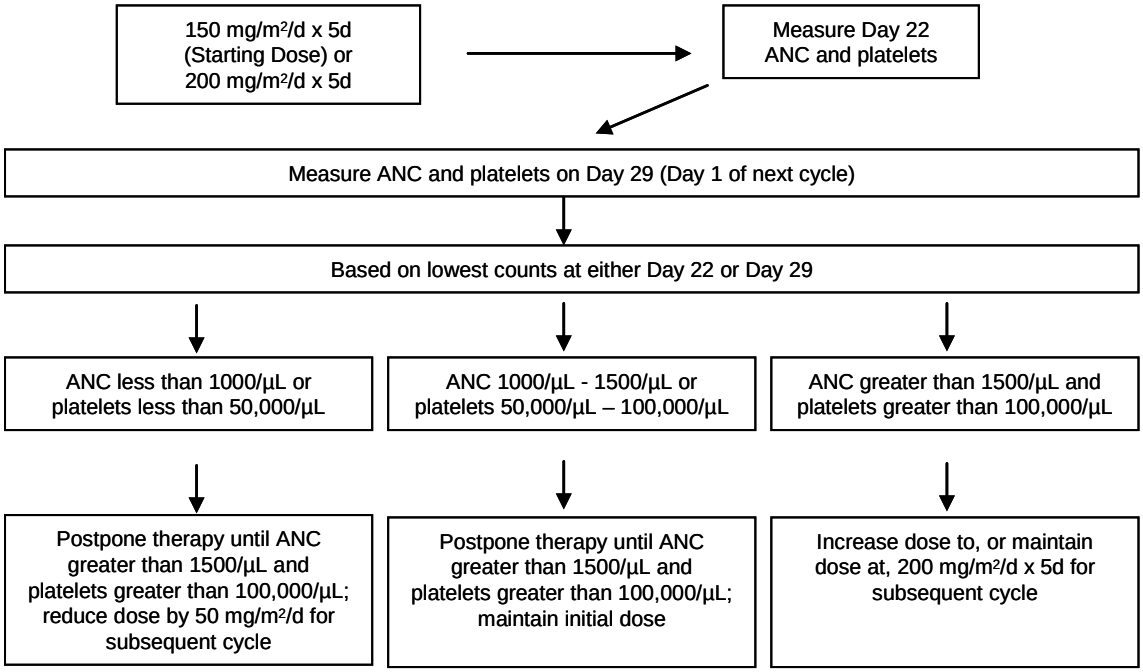

TABLE 5: Daily Dose Calculations by Body Surface Area (BSA)

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

TABLE 6: 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

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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	1	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

2.2 Preparation and Administration

TEMODAR Capsules: In clinical trials, TEMODAR was administered under both fasting and nonfasting conditions; however, absorption is affected by food *[see Clinical Pharmacology (12.3)],* and consistency of administration with respect to food is recommended. There are no dietary restrictions with TEMODAR. To reduce nausea and vomiting, TEMODAR should be taken on an empty stomach. Bedtime administration may be advised. Antiemetic therapy may be administered prior to and/or following administration of TEMODAR.

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

If capsules are accidentally opened or damaged, precautions should be taken to avoid inhalation or contact with the skin or mucous membranes *[see How Supplied/Storage and Handling (16.1)].*

TEMODAR for Injection: Each vial of TEMODAR for Injection contains sterile and pyrogen-free temozolomide lyophilized powder. When reconstituted with 41 mL Sterile Water for Injection, the resulting solution will contain 2.5 mg/mL temozolomide. Bring the vial to room temperature prior to reconstitution with Sterile Water for Injection. The vials should be gently swirled and not shaken. Vials should be inspected, and any vial containing visible particulate matter should not be used. Do not further dilute the reconstituted solution. After reconstitution, store at room temperature (25°C [77°F]). Reconstituted product must be used within 14 hours, including infusion time.

Using aseptic technique, withdraw up to 40 mL from each vial to make up the total dose based on **Table 5** above and transfer into an empty 250 mL infusion bag {2}. TEMODAR for Injection should be infused intravenously using a pump over a period of 90 minutes. TEMODAR for Injection should be administered only by intravenous infusion. Flush the lines before and after each TEMODAR infusion.

TEMODAR for Injection may be administered in the same intravenous line with 0.9% Sodium Chloride injection only.

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Because no data are available on the compatibility of TEMODAR for Injection with other intravenous substances or additives, other medications should not be infused simultaneously through the same intravenous line.

3 DOSAGE FORMS AND STRENGTHS

- TEMODAR (temozolomide) Capsules for oral administration
  - 5-mg capsules have opaque white bodies with green caps. The capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR."
  - 20-mg capsules have opaque white bodies with yellow caps. The capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR."
  - 100-mg capsules have opaque white bodies with pink caps. The capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR."
  - 140-mg capsules have opaque white bodies with blue caps. The capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR."
  - 180-mg capsules have opaque white bodies with orange caps. The capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR."
  - 250-mg capsules have opaque white bodies with white caps. The capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR."
- TEMODAR (temozolomide) is available as 100-mg/vial powder for injection. The lyophilized powder is white to light tan/light pink.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

TEMODAR (temozolomide) is contraindicated in patients who have a history of hypersensitivity reaction (such as urticaria, allergic reaction including anaphylaxis, toxic epidermal necrolysis, and Stevens-Johnson syndrome) to any of its components. TEMODAR is also contraindicated in patients who have a history of hypersensitivity to dacarbazine (DTIC), since both drugs are metabolized to 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide (MTIC).

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Patients treated with TEMODAR may experience myelosuppression, including prolonged pancytopenia, which may result in aplastic anemia, which in some cases has resulted in a fatal outcome. In some cases, exposure to concomitant medications associated with aplastic anemia, including carbamazepine, phenytoin, and sulfamethoxazole/trimethoprim, complicates assessment. Prior to dosing, patients must have an absolute neutrophil count (ANC) greater than or equal to 1.5 x 10^9/L and a platelet count greater than or equal to 100 x 10^9/L. A complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above 1.5 x 10^9/L and platelet count exceeds 100 x 10^9/L. Geriatric patients and women have been shown in clinical trials to have a higher risk of developing myelosuppression.

5.2 Myelodysplastic Syndrome

Cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukemia, have been observed.

5.3 *Pneumocystis* Pneumonia

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

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

5.4 Laboratory Tests

For the concomitant treatment phase with RT, a complete blood count should be obtained prior to initiation of treatment and weekly during treatment.

For the 28-day treatment cycles, a complete blood count should be obtained prior to treatment on Day 1 and on Day 22 (21 days after the first dose) of each cycle. Blood counts should be performed weekly until recovery if the ANC falls below 1.5 x 10^9/L and the platelet count falls below 100 x 10^9/L *[see Recommended Dosing and Dose Modification Guidelines (2.1)]*.

5.5 Hepatotoxicity

Fatal and severe hepatotoxicity have been reported in patients receiving TEMODAR. Perform liver function tests at baseline, midway through the first cycle, prior to each subsequent cycle, and approximately two to four weeks after the last dose of TEMODAR.

5.6 Use in Pregnancy

TEMODAR can cause fetal harm when administered to a pregnant woman. Administration of TEMODAR to rats and rabbits during organogenesis at 0.38 and 0.75 times the maximum recommended human dose (75 and 150 mg/m^2), respectively, caused numerous fetal malformations of the external organs, soft tissues, and skeleton in both species *[see Use in Specific Populations (8.1)]*.

5.7 Infusion Time

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As bioequivalence has been established only when TEMODAR for Injection was given over 90 minutes, infusion over a shorter or longer period of time may result in suboptimal dosing. Additionally, the possibility of an increase in infusion-related adverse reactions cannot be ruled out.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Newly Diagnosed Glioblastoma Multiforme: During the concomitant phase (TEMODAR+radiotherapy), adverse reactions including thrombocytopenia, nausea, vomiting, anorexia, and constipation were more frequent in the TEMODAR+RT arm. The incidence of other adverse reactions was comparable in the two arms. The most common adverse reactions across the cumulative TEMODAR experience were alopecia, nausea, vomiting, anorexia, headache, and constipation (see **Table 7**). Forty-nine percent (49%) of patients treated with TEMODAR reported one or more severe or life-threatening reactions, most commonly fatigue (13%), convulsions (6%), headache (5%), and thrombocytopenia (5%). Overall, the pattern of reactions during the maintenance phase was consistent with the known safety profile of TEMODAR.

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TABLE 7: Number (%) of Patients with Adverse Reactions: All and Severe/Life Threatening (Incidence of 5% or Greater)

	Concomitant Phase RT Alone (n=285)				Concomitant Phase RT+TMZ (n=288)*				Maintenance Phase TMZ (n=224)			
	All		Grade ≥3		All		Grade ≥3		All		Grade ≥3	
Subjects Reporting any Adverse Reaction	**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	
Gastrointestinal 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	
Musculoskeletal 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)
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; NOS=not otherwise specified.
Note: Grade 5 (fatal) adverse reactions are included in the Grade ≥3 column.

Myelosuppression (neutropenia and thrombocytopenia), which is a known dose-limiting toxicity for most cytotoxic agents, including TEMODAR, was observed. When laboratory abnormalities and adverse reactions were combined, Grade 3 or Grade 4

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neutrophil abnormalities including neutropenic reactions were observed in 8% of the patients, and Grade 3 or Grade 4 platelet abnormalities, including thrombocytopenic reactions, were observed in 14% of the patients treated with TEMODAR.

Refractory Anaplastic Astrocytoma: **Tables 8** and **9** show the incidence of adverse reactions 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 reactions 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 adverse reactions were nausea, vomiting, headache, and fatigue. The adverse reactions 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 reaction. 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: 21-40 days) and 28 days for neutrophils (range: 1-44 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.

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

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

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TABLE 8: Adverse Reactions in the Anaplastic Astrocytoma Trial in Adults (≥5%)

	No. (%) of TEMODAR Patients (N=158)	
	All Reactions	**Grade 3/4**
Any Adverse Reaction	**153 (97)**	**79 (50)**
Body as a Whole		
Headache	65 (41)	10 (6)
Fatigue	54 (34)	7 (4)
Asthenia	20 (13)	9 (6)
Fever	21 (13)	3 (2)
Back pain	12 (8)	4 (3)
Cardiovascular		
Edema peripheral	17 (11)	1 (1)
Central and Peripheral Nervous System		
Convulsions	36 (23)	8 (5)
Hemiparesis	29 (18)	10 (6)
Dizziness	19 (12)	1 (1)
Coordination abnormal	17 (11)	2 (1)
Amnesia	16 (10)	6 (4)
Insomnia	16 (10)	0
Paresthesia	15 (9)	1 (1)
Somnolence	15 (9)	5 (3)
Paresis	13 (8)	4 (3)
Urinary incontinence	13 (8)	3 (2)
Ataxia	12 (8)	3 (2)
Dysphasia	11 (7)	1 (1)
Convulsions local	9 (6)	0
Gait abnormal	9 (6)	1 (1)
Confusion	8 (5)	0
Endocrine		
Adrenal hypercorticism	13 (8)	0
Gastrointestinal System		
Nausea	84 (53)	16 (10)
Vomiting	66 (42)	10 (6)
Constipation	52 (33)	1 (1)
Diarrhea	25 (16)	3 (2)
Abdominal pain	14 (9)	2 (1)
Anorexia	14 (9)	1 (1)
Metabolic		
Weight increase	8 (5)	0
Musculoskeletal System		
Myalgia	8 (5)	
Psychiatric Disorders		
Anxiety	11 (7)	1 (1)
Depression	10 (6)	0
Reproductive Disorders		
Breast pain, female	4 (6)	
Resistance Mechanism Disorders		
Infection viral	17 (11)	0
Respiratory System		
Upper respiratory tract infection	13 (8)	0
Pharyngitis	12 (8)	0
Sinusitis	10 (6)	0
Coughing	8 (5)	0
Skin and Appendages		
Rash	13 (8)	0
Pruritus	12 (8)	2 (1)
Urinary System		
Urinary tract infection	12 (8)	0
Micturition increased frequency	9 (6)	0
Vision		
Diplopia	8 (5)	0
Vision abnormal*	8 (5)	

*Blurred vision; visual deficit; vision changes; vision troubles

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TABLE 9: Adverse Hematologic Effects (Grade 3 to 4) in the Anaplastic Astrocytoma Trial in Adults

	TEMODAR*
Hemoglobin	7/158 (4%)
Lymphopenia	83/152 (55%)
Neutrophils	20/142 (14%)
Platelets	29/156 (19%)
WBC	18/158 (11%)

*Change from Grade 0 to 2 at baseline to Grade 3 or 4 during treatment.

TEMODAR for injection delivers equivalent temozolomide dose and exposure to both temozolomide and 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide (MTIC) as the corresponding TEMODAR capsules. Adverse reactions probably related to treatment that were reported from the 2 studies with the intravenous formulation (n=35) that were not reported in studies using the TEMODAR capsules were: pain, irritation, pruritus, warmth, swelling, and erythema at infusion site as well as the following adverse reactions: petechiae and hematoma.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of TEMODAR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the drug exposure.

Dermatologic disorders: Toxic epidermal necrolysis and Stevens-Johnson syndrome

Immune system disorders: Allergic reactions, including anaphylaxis. Erythema multiforme, which resolved after discontinuation of TEMODAR and, in some cases, recurred upon rechallenge.

Hematopoietic disorders: Prolonged pancytopenia, which may result in aplastic anemia and fatal outcomes *[see Warnings and Precautions (5.1)]*.

Hepatobiliary disorders: Fatal and severe hepatotoxicity, elevation of liver enzymes, hyperbilirubinemia, cholestasis, and hepatitis *[see Warnings and Precautions (5.5)]*.

Infections and infestations: Opportunistic infections including *Pneumocystis* pneumonia (PCP) *[see Warnings and Precautions (5.3)]*.

Pulmonary disorders: Interstitial pneumonitis, pneumonitis, alveolitis, and pulmonary fibrosis.

7 DRUG INTERACTIONS

7.1 Valproic Acid

Administration of valproic acid decreases oral clearance of temozolomide by about 5%. The clinical implication of this effect is not known *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D. See Warnings and Precautions section.

TEMODAR can cause fetal harm when administered to a pregnant woman. Five consecutive days of oral temozolomide administration of 0.38 and 0.75 times the highest recommended human dose (75 and 150 mg/m^2) in rats and rabbits, respectively, during the period of organogenesis caused numerous malformations of the external and internal soft tissues and skeleton in both species. Doses equivalent to 0.75 times the highest recommended human dose (150 mg/m^2) caused embryolethality in rats and rabbits as indicated by increased resorptions. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with TEMODAR.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants and tumorigenicity shown for temozolomide in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of TEMODAR to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. TEMODAR Capsules have been studied in 2 open-label studies in pediatric patients (aged 3-18 years) at a dose of 160 to 200 mg/m^2 daily for 5 days every 28 days. In one trial, 29 patients with recurrent brain stem glioma and 34 patients with recurrent high grade astrocytoma were enrolled. All patients had recurrence following surgery and radiation therapy, while 31% also had disease progression following chemotherapy. In a second study conducted by the Children's Oncology Group (COG), 122 patients were enrolled, including patients with medulloblastoma/PNET (29), high grade astrocytoma (23), low grade astrocytoma (22), brain stem glioma (16), ependymoma (14), other CNS tumors (9), and non-CNS tumors (9). The TEMODAR toxicity profile in pediatric patients is similar to adults. **Table 10** shows the adverse reactions in 122 children in the COG study.

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TABLE 10: Adverse Reactions Reported in the Pediatric Cooperative Group Trial (≥10%)

	No. (%) of TEMODAR Patients (N=122)*	
Body System/Organ Class Adverse Reaction	**All Reactions**	**Grade 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)

*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.

8.5 Geriatric Use

Clinical studies of temozolomide did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

In the anaplastic astrocytoma study population, patients 70 years of age or older had a higher incidence of Grade 4 neutropenia and Grade 4 thrombocytopenia (2/8; 25%, *P*=0.31 and 2/10; 20%, *P*=0.09, respectively) in the first cycle of therapy than patients under 70 years of age *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)].*

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

8.6 Renal Impairment

Caution should be exercised when TEMODAR is administered to patients with severe renal impairment *[see Clinical Pharmacology (12.3)].*

8.7 Hepatic Impairment

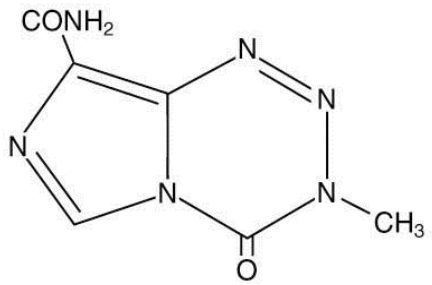
Caution should be exercised when TEMODAR is administered to patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)].*

10 OVERDOSAGE

Doses of 500, 750, 1000, and 1250 mg/m^2 (total dose per cycle over 5 days) have been evaluated clinically in patients. Dose-limiting toxicity was hematologic and was reported with any dose but is expected to be more severe at higher doses. An overdose of 2000 mg per day for 5 days was taken by one patient and the adverse reactions 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 reactions reported including bone marrow suppression, which in some cases was severe and prolonged, and infections and resulted in death. In the event of an overdose, hematologic evaluation is needed. Supportive measures should be provided as necessary.

11 DESCRIPTION

TEMODAR contains temozolomide, an imidazotetrazine derivative. The chemical name of temozolomide is 3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]-*as*-tetrazine-8-carboxamide. The structural formula is:



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The material is a white to light tan/light pink powder with a molecular formula of $C_6H_6N_6O_2$ and a molecular weight of 194.15. The molecule is stable at acidic pH (<5) and labile at pH >7; hence TEMODAR can be administered orally and intravenously. The prodrug, temozolomide, is rapidly hydrolyzed to the active 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide (MTIC) at neutral and alkaline pH values, with hydrolysis taking place even faster at alkaline pH.

TEMODAR Capsules:

Each capsule for oral use contains either 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, or 250 mg of temozolomide.

The inactive ingredients for TEMODAR Capsules are as follows:

TEMODAR 5 mg: lactose anhydrous (132.8 mg), colloidal silicon dioxide (0.2 mg), sodium starch glycolate (7.5 mg), tartaric acid (1.5 mg), and stearic acid (3 mg).

TEMODAR 20 mg: lactose anhydrous (182.2 mg), colloidal silicon dioxide (0.2 mg), sodium starch glycolate (11 mg), tartaric acid (2.2 mg), and stearic acid (4.4 mg).

TEMODAR 100 mg: lactose anhydrous (175.7 mg), colloidal silicon dioxide (0.3 mg), sodium starch glycolate (15 mg), tartaric acid (3 mg), and stearic acid (6 mg).

TEMODAR 140 mg: lactose anhydrous (246 mg), colloidal silicon dioxide (0.4 mg), sodium starch glycolate (21 mg), tartaric acid (4.2 mg), and stearic acid (8.4 mg).

TEMODAR 180 mg: lactose anhydrous (316.3 mg), colloidal silicon dioxide (0.5 mg), sodium starch glycolate (27 mg), tartaric acid (5.4 mg), and stearic acid (10.8 mg).

TEMODAR 250 mg: lactose anhydrous (154.3 mg), colloidal silicon dioxide (0.7 mg), sodium starch glycolate (22.5 mg), tartaric acid (9 mg), and stearic acid (13.5 mg).

The body of the capsules is made of gelatin, and is opaque white. The cap is also made of gelatin, and the colors vary based on the dosage strength. The capsule body and cap are imprinted with pharmaceutical branding ink, which contains shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, purified water, strong ammonia solution, potassium hydroxide, and ferric oxide.

TEMODAR 5 mg: The green cap contains gelatin, titanium dioxide, iron oxide yellow, sodium lauryl sulfate, and FD&C Blue #2.

TEMODAR 20 mg: The yellow cap contains gelatin, sodium lauryl sulfate, and iron oxide yellow.

TEMODAR 100 mg: The pink cap contains gelatin, titanium dioxide, sodium lauryl sulfate, and iron oxide red.

TEMODAR 140 mg: The blue cap contains gelatin, sodium lauryl sulfate, and FD&C Blue #2.

TEMODAR 180 mg: The orange cap contains gelatin, iron oxide red, iron oxide yellow, titanium dioxide, and sodium lauryl sulfate.

TEMODAR 250 mg: The white cap contains gelatin, titanium dioxide, and sodium lauryl sulfate.

TEMODAR for Injection: Each vial contains 100 mg of sterile and pyrogen-free temozolomide lyophilized powder for intravenous injection. The inactive ingredients are: mannitol (600 mg), L-threonine (160 mg), polysorbate 80 (120 mg), sodium citrate dihydrate (235 mg), and hydrochloric acid (160 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Temozolomide is not directly active but undergoes rapid nonenzymatic conversion at physiologic pH to the reactive compound 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide (MTIC). The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the O^6 and N^7 positions of guanine.

12.3 Pharmacokinetics

Absorption: Temozolomide is rapidly and completely absorbed after oral administration with a peak plasma concentration (C_{max}) achieved in a median T_{max} of 1 hour. Food reduces the rate and extent of temozolomide absorption. Mean peak plasma concentration and AUC decreased by 32% and 9%, respectively, and median T_{max} increased by 2-fold (from 1-2.25 hours) when temozolomide was administered after a modified high-fat breakfast.

A pharmacokinetic study comparing oral and intravenous temozolomide in 19 patients with primary CNS malignancies showed that 150 mg/m^2 TEMODAR for injection administered over 90 minutes is bioequivalent to 150 mg/m^2 TEMODAR oral capsules with respect to both C_{max} and AUC of temozolomide and MTIC. Following a single 90-minute intravenous infusion of 150 mg/m^2, the geometric mean C_{max} values for temozolomide and MTIC were 7.3 mcg/mL and 276 ng/mL, respectively. Following a single oral dose of 150 mg/m^2, the geometric mean C_{max} values for temozolomide and MTIC were 7.5 mcg/mL and 282 ng/mL, respectively. Following a single 90-minute intravenous infusion of 150 mg/m^2, the geometric mean AUC values for temozolomide and MTIC were 24.6 mcg·hr/mL and 891 ng·hr/mL, respectively. Following a single oral dose of 150 mg/m^2, the geometric mean AUC values for temozolomide and MTIC were 23.4 mcg·hr/mL and 864 ng·hr/mL, respectively.

Distribution: Temozolomide has a mean apparent volume of distribution of 0.4 L/kg (%CV=13%). It is weakly bound to human plasma proteins; the mean percent bound of drug-related total radioactivity is 15%.

Metabolism and Elimination: Temozolomide is spontaneously hydrolyzed at physiologic pH to the active species, MTIC and to temozolomide acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC), which is known to be an intermediate in purine and nucleic acid biosynthesis, and to methylhydrazine, which is believed to be the active alkylating species. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC. Relative to the AUC of temozolomide, the exposure to MTIC and AIC is 2.4% and 23%, respectively.

Excretion: About 38% of the administered temozolomide total radioactive dose is recovered over 7 days: 37.7% in urine and 0.8% in feces. The majority of the recovery of radioactivity in urine is unchanged temozolomide (5.6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolite(s) (17%). Overall clearance of temozolomide is about 5.5 L/hr/m^2. Temozolomide is rapidly eliminated, with a mean elimination half-life of 1.8 hours, and exhibits linear kinetics over the therapeutic dosing range of 75 to 250 mg/m^2/day.

Effect of Age: A population pharmacokinetic analysis indicated that age (range: 19-78 years) has no influence on the pharmacokinetics of temozolomide.

Effect of Gender: A population pharmacokinetic analysis indicated that women have an approximately 5% lower clearance (adjusted for body surface area) for temozolomide than men.

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Effect of Race: The effect of race on the pharmacokinetics of temozolomide has not been studied.

Tobacco Use: A population pharmacokinetic analysis indicated that the oral clearance of temozolomide is similar in smokers and nonsmokers.

Effect of Renal Impairment: A population pharmacokinetic analysis indicated that creatinine clearance over the range of 36 to 130 mL/min/m^2 has no effect on the clearance of temozolomide after oral administration. The pharmacokinetics of temozolomide have not been studied in patients with severely impaired renal function (CLcr <36 mL/min/m^2). Caution should be exercised when TEMODAR is administered to patients with severe renal impairment *[see Use in Special Populations (8.6)]*. TEMODAR has not been studied in patients on dialysis.

Effect of Hepatic Impairment: A study showed that the pharmacokinetics of temozolomide in patients with mild-to-moderate hepatic impairment (Child-Pugh Class I - II) were similar to those observed in patients with normal hepatic function. Caution should be exercised when temozolomide is administered to patients with severe hepatic impairment *[see Use in Specific Populations (8.7)]*.

Effect of Other Drugs on Temozolomide Pharmacokinetics: In a multiple-dose study, administration of TEMODAR Capsules with ranitidine did not change the C_{max} or AUC values for temozolomide or MTIC.

A population analysis indicated that administration of valproic acid decreases the clearance of temozolomide by about 5% *[see Drug Interactions (7.1)]*.

A population analysis did not demonstrate any influence of coadministered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H_2-receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Temozolomide is carcinogenic in rats at doses less than the maximum recommended human dose. Temozolomide induced mammary carcinomas in both males and females at doses 0.13 to 0.63 times the maximum human dose (25-125 mg/m^2) when administered orally on 5 consecutive days every 28 days for 6 cycles. Temozolomide also induced fibrosarcomas of the heart, eye, seminal vesicles, salivary glands, abdominal cavity, uterus, and prostate, carcinomas of the seminal vesicles, schwannomas of the heart, optic nerve, and harderian gland, and adenomas of the skin, lung, pituitary, and thyroid at doses 0.5 times the maximum daily dose. Mammary tumors were also induced following 3 cycles of temozolomide at the maximum recommended daily dose.

Temozolomide is a mutagen and a clastogen. In a reverse bacterial mutagenesis assay (Ames assay), temozolomide increased revertant frequency in the absence and presence of metabolic activation. Temozolomide was clastogenic in human lymphocytes in the presence and absence of metabolic activation.

Temozolomide impairs male fertility. Temozolomide caused syncytial cells/immature sperm formation at 0.25 and 0.63 times the maximum recommended human dose (50 and 125 mg/m^2) in rats and dogs, respectively, and testicular atrophy in dogs at 0.63 times the maximum recommended human dose (125 mg/m^2).

13.2 Animal Toxicology and/or Pharmacology

Toxicology studies in rats and dogs identified a low incidence of hemorrhage, degeneration, and necrosis of the retina at temozolomide doses equal to or greater than 0.63 times the maximum recommended human dose (125 mg/m^2). These changes were most commonly seen at doses where mortality was observed.

14 CLINICAL STUDIES

14.1 Newly Diagnosed Glioblastoma Multiforme

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

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

The addition of concomitant and maintenance TEMODAR to radiotherapy in the treatment of patients with newly diagnosed GBM showed a statistically significant improvement in overall survival compared to radiotherapy alone (**Figure 1**). The hazard ratio (HR) for overall survival was 0.63 (95% CI for HR=0.52-0.75) with a log-rank *P*<0.0001 in favor of the TEMODAR arm. The median survival was increased by 2.5 months in the TEMODAR arm.

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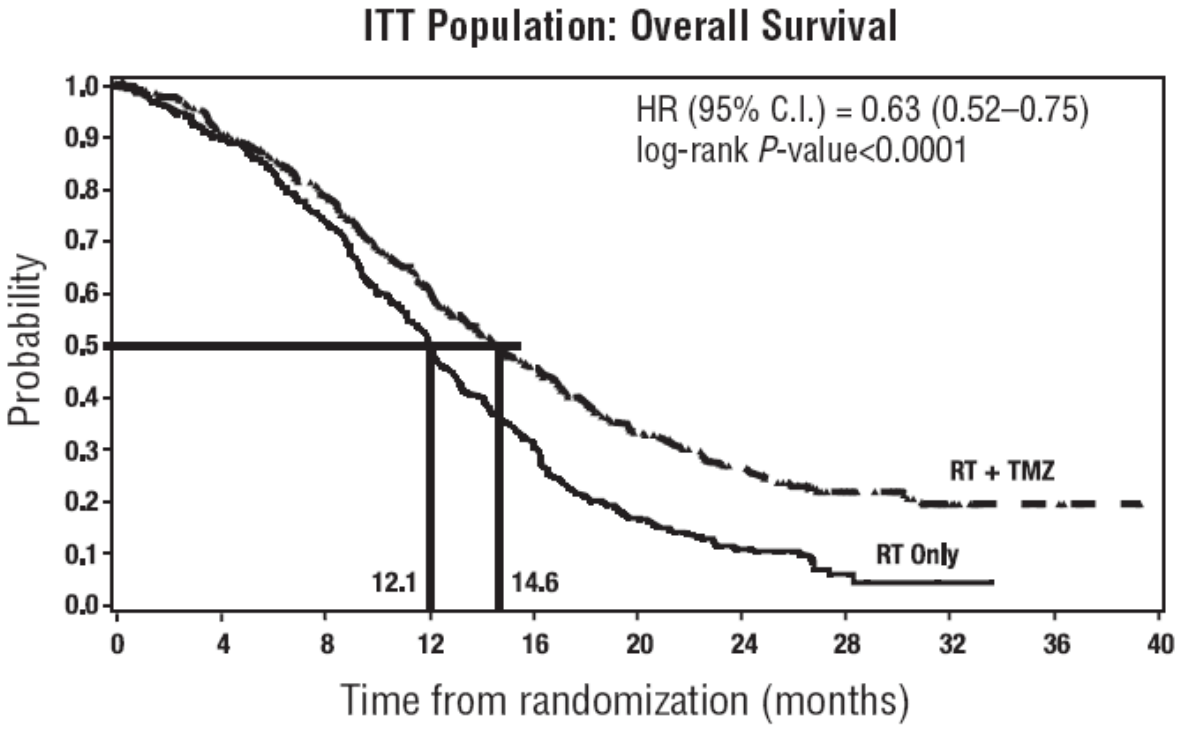
FIGURE 1: Kaplan-Meier Curves for Overall Survival (ITT Population)



14.2 Refractory Anaplastic Astrocytoma

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

TEMODAR Capsules were given for the first 5 consecutive days of a 28-day cycle at a starting dose of 150 mg/m^2/day. If the nadir and day of dosing (Day 29, Day 1 of next cycle) absolute neutrophil count was greater than or equal to 1.5 x 10^9/L (1500/µL) and the nadir and Day 29, Day 1 of next cycle platelet count was greater than or equal to 100 x 10^9/L (100,000/µL), the TEMODAR dose was increased to 200 mg/m^2/day for the first 5 consecutive days of a 28-day cycle.

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

15 REFERENCES

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3. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.[3]
4. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Safe Handling and Disposal

Care should be exercised in the handling and preparation of TEMODAR. Vials and capsules should not be opened. If vials or capsules are accidentally opened or damaged, rigorous precautions should be taken with the contents to avoid inhalation or contact with the skin or mucous membranes. The use of gloves and safety glasses is recommended to avoid exposure in case of breakage

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of the vial or capsules. Procedures for proper handling and disposal of anticancer drugs should be considered {1-4}. Several guidelines on this subject have been published.

16.2 How Supplied

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

TEMODAR Capsules 5 mg: have opaque white bodies with green caps. The capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR".

They are supplied as follows:

Bottles:

5-count – NDC 0085-3004-02
14-count – NDC 0085-3004-01

Sachets:

5-count – NDC 0085-3004-03
14-count – NDC 0085-3004-04

TEMODAR Capsules 20 mg: have opaque white bodies with yellow caps. The capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR".

They are supplied as follows:

Bottles:

5-count – NDC 0085-1519-02
14-count – NDC 0085-1519-01

Sachets:

5-count – NDC 0085-1519-03
14-count – NDC 0085-1519-04

TEMODAR Capsules 100 mg: have opaque white bodies with pink caps. The capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR".

They are supplied as follows:

Bottles:

5-count – NDC 0085-1366-02
14-count – NDC 0085-1366-01

Sachets:

5-count – NDC 0085-1366-03
14-count – NDC 0085-1366-04

TEMODAR Capsules 140 mg: have opaque white bodies with blue caps. The capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR".

They are supplied as follows:

Bottles:

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

Sachets:

5-count – NDC 0085-1425-03
14-count – NDC 0085-1425-04

TEMODAR Capsules 180 mg: have opaque white bodies with orange caps. The capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR".

They are supplied as follows:

Bottles:

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

Sachets:

5-count – NDC 0085-1430-03
14-count – NDC 0085-1430-04

TEMODAR Capsules 250 mg: have opaque white bodies with white caps. The capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR".

They are supplied as follows:

Bottles:

5-count – NDC 0085-1417-01

Sachets:

5-count – NDC 0085-1417-02

TEMODAR for Injection: TEMODAR (temozolomide) for Injection is supplied in single-use glass vials containing 100 mg temozolomide. The lyophilized powder is white to light tan/light pink.

TEMODAR for Injection 100 mg:

NDC 0085-1381-01

16.3 Storage

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

Store TEMODAR for Injection refrigerated at 2-8°C (36-46°F). After reconstitution, store reconstituted product at room temperature (25°C [77°F]). Reconstituted product must be used within 14 hours, including infusion time.

17 PATIENT COUNSELING INFORMATION

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See FDA-Approved Patient Labeling (Patient Information).

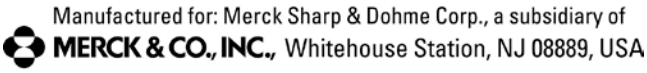
17.1 Information for the Patient

Physicians should discuss the following with their patients:

- Nausea and vomiting are the most frequently occurring adverse reactions. Nausea and vomiting are usually either self-limiting or readily controlled with standard antiemetic therapy.
- Capsules should not be opened. If capsules are accidentally opened or damaged, rigorous precautions should be taken with the capsule contents to avoid inhalation or contact with the skin or mucous membranes.
- The medication should be kept away from children and pets.

TEMODAR Capsules

TEMODAR for Injection



Manufactured by:
Baxter Oncology GmbH, Halle 33790, Germany

For patent information: www.merck.com/product/patent/home.html

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Patient Information

TEMODAR® (těm-ō-dăr)
(temozolomide)
Capsules

TEMODAR® (těm-ō-dăr)
(temozolomide)
for Injection

What is the most important information I should know about TEMODAR?

- **TEMODAR may cause birth defects**. Male and female patients who take TEMODAR should use effective birth control. Female patients and female partners of male patients should avoid becoming pregnant while taking TEMODAR.

See the section "What are the possible side effects of TEMODAR?" for more information about side effects.

What is TEMODAR?
TEMODAR (temozolomide) is a prescription medicine used to treat adults with certain brain cancer tumors. TEMODAR blocks cell growth, especially cells that grow fast, such as cancer cells. TEMODAR may decrease the size of certain brain tumors in some patients.

It is not known if TEMODAR is safe and effective in children.

Who should not take TEMODAR?
Do not take TEMODAR if you:

- have had an allergic reaction to dacarbazine (DTIC), another cancer medicine.
- have had a red itchy rash, or a severe allergic reaction, such as trouble breathing, swelling of the face, throat, or tongue, or severe skin reaction to TEMODAR or any of the ingredients in TEMODAR. If you are not sure, ask your doctor. See the end of the leaflet for a list of ingredients in TEMODAR.

What should I tell my doctor before taking TEMODAR?

Tell your doctor about all your medical conditions, including if you:

- are allergic to dacarbazine (DTIC) or have had a severe allergic reaction to TEMODAR. See "Who should not take TEMODAR?"
- have kidney problems
- have liver problems
- are pregnant. See "What is the most important information I should know about TEMODAR?"
- are breast-feeding. It is not known whether TEMODAR passes into breast milk. You and your doctor should decide if you will breast-feed or take TEMODAR. You should not do both without talking with your doctor.

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Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Especially tell your doctor if you take a medicine that contains valproic acid (Stavzor®, Depakene®).

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I take TEMODAR?

TEMODAR may be taken by mouth as a capsule at home, or you may receive TEMODAR by injection into a vein (intravenous). Your doctor will decide the best way for you to take TEMODAR.

There are two common dosing schedules for taking TEMODAR.

- Some people take TEMODAR for 42 days in a row (possibly 49 days depending on side effects) with radiation treatment. This is one cycle of treatment. After this, you may have "maintenance" treatment. Your doctor may prescribe 6 more cycles of TEMODAR. For each of these cycles, you take TEMODAR one time each day for 5 days in a row and then you stop taking it for the next 23 days. This is a 28-day maintenance treatment cycle.
- Another way to take TEMODAR is to take it one time each day for 5 days in a row only, and then you stop taking it for the next 23 days. This is one cycle of treatment (28 days). Your doctor will watch your progress on TEMODAR and decide how long you should take it. You might take TEMODAR until your tumor gets worse or for possibly up to 2 years.
- Your dose is based on your height and weight, and the number of treatment cycles will depend on how you respond to and tolerate this treatment.
- Your doctor may modify your schedule based on how you tolerate the treatment.
- If your doctor prescribes a treatment regimen that is different from the information in this leaflet, make sure you follow the specific instructions given to you by your doctor.

TEMODAR Capsules:

- Take TEMODAR Capsules exactly as prescribed.
- TEMODAR Capsules come in different strengths. Each strength has a different color cap. Your doctor may prescribe more than one strength of TEMODAR Capsules for you, so it is important that you understand how to take your medicine the right way. Be sure that you understand exactly how many capsules you need to take on each day of your treatment, and what strengths to take. This may be different whenever you start a new cycle.
- Talk to your doctor before you take your dose if you are not sure how much to take. This will help to prevent taking too much TEMODAR and decrease your chances of getting serious side effects.
- Take each day's dose of TEMODAR Capsules at one time, with a full glass of water.
- **Swallow TEMODAR Capsules whole. Do not chew, open, or split the capsules.**
- If TEMODAR Capsules are accidentally opened or damaged, be careful not to breathe in (inhale) the powder from the capsules or get the powder on your skin or mucous membranes (for example, in your nose or mouth). If contact with any of these areas happens, flush the area with water.

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- If you vomit TEMODAR Capsules, do not take any more capsules. Wait and take your next planned dose.
- The medicine is used best by your body if you take it at the same time every day in relation to a meal.
- To lessen nausea, try to take TEMODAR on an empty stomach or at bedtime. Your doctor may prescribe medicine to prevent or treat nausea, or other medicines to lessen side effects with TEMODAR.
- See your doctor regularly to check your progress. Your doctor will check you for side effects that you might not notice.
- If you miss a dose of TEMODAR, talk with your doctor for instructions about when to take your next dose of TEMODAR.
- Call your doctor right away if you take more than the prescribed amount of TEMODAR. It is important that you do not take more than the amount of TEMODAR prescribed for you.

TEMODAR for Injection:

- You will receive TEMODAR as an infusion directly into your vein. Your treatment will take about 90 minutes.
- Your doctor may prescribe medicine to prevent or treat nausea, or other medicines to relieve side effects with TEMODAR.

What should I avoid while taking TEMODAR?

- Female patients and female partners of male patients should avoid becoming pregnant while taking TEMODAR. See "What is the most important information I should know about TEMODAR?"

What are the possible side effects of TEMODAR?

TEMODAR can cause serious side effects.

- See "What is the most important information I should know about TEMODAR?"
- **Decreased blood cells**. TEMODAR affects cells that grow rapidly, including bone marrow cells. This can cause you to have a decrease in blood cells. Your doctor can monitor your blood for these effects.
    - White blood cells are needed to fight infections. Neutrophils are a type of white blood cell that help prevent bacterial infections. Decreased neutrophils can lead to serious infections that can lead to death. Other white blood cells called lymphocytes may also be decreased.
    - Platelets are blood cells needed for normal blood clotting. Low platelet counts can lead to bleeding. Tell your doctor about any unusual bruising or bleeding.

Your doctor will check your blood regularly while you are taking TEMODAR to see if these side effects are happening. Your doctor may need to change the dose of TEMODAR or when you get it depending on your blood cell counts. People who are age 70 or older and women may be more likely to have their blood cells affected.

- ***Pneumocystis* pneumonia (PCP).** PCP is an infection that people can get when their immune system is weak. TEMODAR decreases white blood cells, which makes your immune system weaker and can increase your risk of getting PCP. **All patients** taking TEMODAR will be watched carefully by their doctor for this infection, especially patients who take steroids. Tell your doctor if you have any of the following

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signs and symptoms of PCP infection: shortness of breath and/or fever, chills, dry cough.

- **Secondary cancers.** Blood problems such as myelodysplastic syndrome and secondary cancers, such as a certain kind of leukemia, can happen in people who take TEMODAR. Your doctor will watch you for this.
- **Convulsions.** Convulsions may be severe or life-threatening in people who take TEMODAR.
- **Liver side effects** have been reported, which very rarely included death.

Common side effects with TEMODAR include:

- nausea and vomiting. Your doctor can prescribe medicines that may help reduce these symptoms.
- headache
- feeling tired
- loss of appetite
- hair loss
- constipation
- bruising
- rash
- paralysis on one side of the body
- diarrhea
- weakness
- fever
- dizziness
- coordination problems
- viral infection
- sleep problems
- memory loss
- pain, irritation, itching, warmth, swelling or redness at the site of infusion
- bruising or small red or purple spots under the skin

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all the possible side effects with TEMODAR. For more information, ask your doctor or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TEMODAR Capsules?

- Store TEMODAR Capsules at 77°F (controlled room temperature). Storage at 59°F to 86°F (15°C to 30°C) is permitted occasionally.
- **Keep TEMODAR Capsules out of the reach of children and pets.**

General information about TEMODAR.
Medicines are sometimes prescribed for purposes other than those listed in the Patient Information leaflet. Do not use TEMODAR for a condition for which it was not prescribed. Do not give TEMODAR to other people, even if they have the same symptoms that you have. It may harm them.

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This leaflet summarizes the most important information about TEMODAR. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about TEMODAR that is written for health professionals.

For more information, go to www.TEMODAR.com or call 1-877-888-4231.

How are TEMODAR Capsules supplied?
TEMODAR Capsules contain a white capsule body with a color cap and the colors vary based on the dosage strength. The capsules are available in six different strengths.

TEMODAR Capsule Strength	Color
5 mg	Green Cap
20 mg	Yellow Cap
100 mg	Pink Cap
140 mg	Blue Cap
180 mg	Orange Cap
250 mg	White Cap

What are the ingredients in TEMODAR?
TEMODAR Capsules:
Active ingredient: temozolomide.

Inactive ingredients: lactose anhydrous, colloidal silicon dioxide, sodium starch glycolate, tartaric acid, stearic acid.

The body of the capsules is made of gelatin and is opaque white. The cap is also made of gelatin, and the colors vary based on the dosage strength. The capsule body and cap are imprinted with pharmaceutical branding ink, which contains shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, purified water, strong ammonia, potassium hydroxide, and ferric oxide.

TEMODAR 5 mg: The green cap contains gelatin, titanium dioxide, iron oxide yellow, sodium lauryl sulfate, and FD&C Blue #2.

TEMODAR 20 mg: The yellow cap contains gelatin, sodium lauryl sulfate, and iron oxide yellow.

TEMODAR 100 mg: The pink cap contains gelatin, titanium dioxide, sodium lauryl sulfate, and iron oxide red.

TEMODAR 140 mg: The blue cap contains gelatin, sodium lauryl sulfate, and FD&C Blue #2.

TEMODAR 180 mg: The orange cap contains gelatin, iron oxide red, iron oxide yellow, titanium dioxide, and sodium lauryl sulfate.

TEMODAR 250 mg: The white cap contains gelatin, titanium dioxide, and sodium lauryl sulfate.

TEMODAR for Injection:
Active ingredient: temozolomide.

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Inactive ingredients: mannitol, L-threonine, polysorbate 80, sodium citrate dihydrate, and hydrochloric acid.

TEMODAR Capsules

Manufactured by: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

TEMODAR for Injection

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Manufactured by:
Baxter Oncology GmbH, Halle 33790, Germany

For patent information: www.merck.com/product/patent/home.html

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