

TEMODAR (temozolomide) Capsules

PHARMACIST:

Dispense enclosed Patient Package Insert to each patient.

PHARMACIST INFORMATION SHEET

IMPORTANT DISPENSING INFORMATION

For every patient, TEMODAR must be dispensed in a separate vial or in its original glass bottle making sure each container lists the strength per capsule and that patients take the appropriate number of capsules from each bottle or vial.

Please see the dispensing instructions below for more information.

What is TEMODAR?

TEMODAR[®] (temozolomide) is an oral alkylating agent for the treatment of newly diagnosed glioblastoma multiforme and refractory anaplastic astrocytoma.

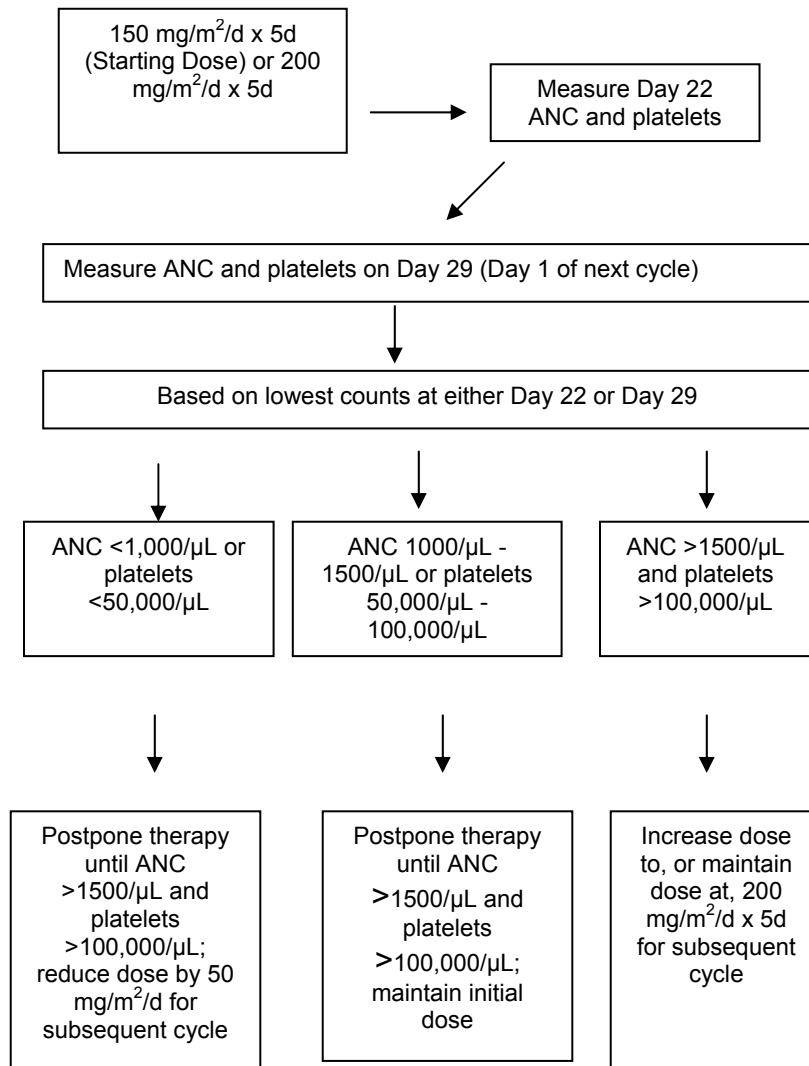
How is TEMODAR dosed?

The daily dose of TEMODAR Capsules for a given patient is calculated by the physician, based on the patient's body surface area (BSA). The resulting dose is then rounded off to the nearest 5 mg. An example of the dosing may be as follows: the initial daily dose of TEMODAR in milligrams is the BSA multiplied by mg/m²/day, (a patient with a BSA of 1.84 is 1.84 x 75 mg = 138, or 140 mg/day). The dose for subsequent cycles may be adjusted according to nadir neutrophil and platelet counts in the previous cycle and at the time of initiating the next cycle.

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

Dosage of TEMODAR must be adjusted according to nadir neutrophil and platelet counts in the previous cycle and neutrophil and platelet counts at the time of initiating the next cycle. The initial dose is 150 mg/m² orally once daily for 5 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 $\geq 1.5 \times 10^9/L$ (1500/ μ L) and both the nadir and Day 29, Day 1 of next cycle platelet counts are $\geq 100 \times 10^9/L$ (100,000/ μ L), the TEMODAR dose may be increased to 200 mg/m²/day for 5 consecutive days per 28-day treatment cycle. During treatment, a complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above $1.5 \times 10^9/L$ (1500/ μ L) and the platelet count exceeds $100 \times 10^9/L$ (100,000/ μ L). The next cycle of TEMODAR should not be started until the ANC and platelet count exceed these levels. If the ANC falls to $< 1.0 \times 10^9/L$ (1000/ μ L) or the platelet count is $< 50 \times 10^9/L$ (50,000/ μ L) during any cycle, the next cycle should be reduced by 50 mg/m², but not below 100 mg/m², the lowest recommended dose (see **Table 1** below).

TABLE 1:
Dosing Modification Table for Refractory Anaplastic Astrocytoma



What is the TEMODAR Capsules treatment regimen?

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

Newly Diagnosed Concomitant Phase Treatment Schedule

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

TABLE 2: Temozolomide Dosing Interruption or Discontinuation During Concomitant Radiotherapy and Temozolomide

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

TMZ = temozolomide; CTC = Common Toxicity Criteria.

Maintenance Phase Treatment Schedule

Four weeks after completing the TEMODAR + RT phase, TEMODAR is administered for an additional 6 cycles of maintenance treatment. Dosage in Cycle 1 (maintenance) is 150 mg/m² once daily for 5 days followed by 23 days without treatment. At the start of Cycle 2, the dose is escalated to 200 mg/m², if the CTC nonhematologic toxicity for Cycle 1 is Grade ≤ 2 (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is $\geq 1.5 \times 10^9/L$, and the platelet count is $\geq 100 \times 10^9/L$. If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles. The dose remains at 200 mg/m² per day for the first 5 days of each subsequent cycle except if toxicity occurs.

During treatment a complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above $1.5 \times 10^9/L$ ($1500/\mu L$) and the platelet count exceeds $100 \times 10^9/L$ ($100,000/\mu L$). 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 3 and 4.

TABLE 3: Temozolomide Dose Levels for Maintenance Treatment

Dose Level	Dose (mg/m ² /day)	Remarks
-1	100	Reduction for prior toxicity
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2-6 in absence of toxicity

TABLE 4: Temozolomide Dose Reduction or Discontinuation During Maintenance Treatment

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

* TMZ dose levels are listed in Table 3.

† TMZ is to be discontinued if dose reduction to $<100 \text{ mg/m}^2$ 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.

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. 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. Noncumulative 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, alopecia, anorexia, and headache.

How is TEMODAR supplied?

TEMODAR Capsules are available in 5-mg, 20-mg, 100-mg, 140-mg, 180-mg, and 250-mg strengths. The capsules contain a white capsule body with a color cap, and the colors vary based on the dosage strength.

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

The 5-mg, 20-mg, 100-mg, 140-mg, and 180-mg capsule strengths are available in 5-count and 14-count packages. The 250-mg capsule strength is available in a 5-count package.

How is TEMODAR dispensed?

Each strength of TEMODAR must be dispensed in a separate vial or in its original glass bottle (one strength per one container). Follow the instructions below: Based on the dose prescribed, determine the number of each strength of TEMODAR capsules needed for the full 42- or 5-day cycle as prescribed by the physician. For example, in a 5-day cycle, 275 mg/day would be dispensed as five 250-mg capsules, five 20-mg capsules and five 5-mg capsules. Label each container with the appropriate number of capsules to be taken each day. Dispense to the patient, making sure each container lists the strength (mg) per capsule and that he or she understands to take the appropriate number of capsules of TEMODAR from each bottle or vial to equal the total daily dose prescribed by the physician.

How can TEMODAR be ordered? TEMODAR can be ordered from your wholesaler. It is important to understand if TEMODAR is being used as part of a 42-day regimen or as part of a 5-day course. Remember to order enough TEMODAR for the appropriate cycle.

For example:

- a 5-day course of 360 mg/day would require the following to be ordered:

two 5-count packages of 180-mg capsules.

- a 42-day course of 140 mg/day would require the following to be ordered: three 14-count packages of 140-mg capsules.

For examples of other dosing regimens, please refer to the full **Prescribing Information (Table 6)**.

TEMODAR Product	NDC Number
5-mg capsules (5 count)	0085-3004-02
5-mg capsules (14 count)	0085-3004-01
20-mg capsules (5 count)	0085-1519-02
20-mg capsules (14 count)	0085-1519-01
100-mg capsules (5 count)	0085-1366-02
100-mg capsules (14 count)	0085-1366-01
140-mg capsules (5 count)	0085-1425-01
140-mg capsules (14 count)	0085-1425-02
180-mg capsules (5 count)	0085-1430-01
180-mg capsules (14 count)	0085-1430-02
250-mg capsules (5 count)	0085-1417-01

TEMODAR Capsules

Manufactured by: Schering Corporation, a subsidiary of



MERCK & CO., INC.

Whitehouse Station, NJ 08889, USA

U.S. Patent No. 5,260,291.

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PHARMACIST INFORMATION SHEET

What is TEMODAR? [See Full Prescribing Information, Indications and Usage (1)].

TEMODAR[®] (temozolomide) is an alkylating drug for the treatment of adult patients with newly diagnosed glioblastoma multiforme and refractory anaplastic astrocytoma.

How is TEMODAR dosed? [See Full Prescribing Information, Recommended Dosing and Dose Modification Guidelines (2.1)].

The daily dose of TEMODAR for a given patient is calculated by the physician, based on the patient's body surface area (BSA) [see **Table 5** in the Full Prescribing Information, Recommended Dosing and Dose Modification Guidelines (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. 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.

Dosing for Patients with Refractory Anaplastic Astrocytoma [See Full Prescribing Information, Recommended Dosing and Dose Modification Guidelines, Patients with Refractory Anaplastic Astrocytoma (2.1)].

Dosage of TEMODAR must be adjusted according to nadir neutrophil and platelet counts in the previous cycle and neutrophil and platelet counts at the time of initiating the next cycle. The initial dose is 150 mg/m² orally once daily for 5 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 $\geq 1.5 \times 10^9/L$ (1500/ μ L) and both the nadir and Day 29, Day 1 of next cycle platelet counts are $\geq 100 \times 10^9/L$ (100,000/ μ L), the TEMODAR dose may be increased to 200 mg/m²/day for 5 consecutive days per 28-day treatment cycle. During treatment, a complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above $1.5 \times 10^9/L$ (1500/ μ L) and the platelet count exceeds $100 \times 10^9/L$ (100,000/ μ L). The next cycle of TEMODAR should not be started until the ANC and platelet count exceed these levels. If the ANC falls to $< 1.0 \times 10^9/L$ (1000/ μ L) or the platelet count is $< 50 \times 10^9/L$ (50,000/ μ L) during any cycle, the next cycle should be reduced by 50 mg/m², but not below 100 mg/m², the lowest recommended dose [see **Table 4** in the Full Prescribing Information, Recommended Dosing and Dose Modification Guidelines (2.1)].

Patients should continue to receive TEMODAR until their physician determines that their disease has progressed, or until unacceptable side effects or toxicities occur. Physicians may alter the treatment regimen for a given patient.

Dosing for Patients with Newly Diagnosed Glioblastoma Multiforme [See Full Prescribing Information, Recommended Dosing and Dose Modification Guidelines, Patients with Newly Diagnosed High Grade Glioma (2.1)].

Concomitant Phase Treatment Schedule

TEMODAR is administered at 75 mg/m² daily for 42 days concomitant with focal radiotherapy (60 Gy administered in 30 fractions), followed by maintenance TEMODAR for 6 cycles. No dose reductions are recommended; however, dose interruptions may occur based on patient tolerance. The TEMODAR dose can be continued throughout the 42-day concomitant period up to 49 days if all of the following conditions are met: absolute neutrophil count $\geq 1.5 \times 10^9/L$, platelet count $\geq 100 \times 10^9/L$, common toxicity criteria (CTC) non-hematological toxicity \leq Grade 1 (except for alopecia, nausea, and vomiting). During treatment a complete blood count should be obtained weekly. Temozolomide dosing should be interrupted or discontinued during concomitant phase according to the hematological and non-hematological toxicity criteria as noted in **Table 1** of the Full Prescribing Information under 2.1 Recommended Dosing and Dose Modification Guidelines. PCP prophylaxis is required during the concomitant administration of TEMODAR and radiotherapy and should be continued in patients who develop lymphocytopenia until recovery from lymphocytopenia (CTC Grade ≤ 1).

Maintenance Phase Treatment Schedule

Four weeks after completing the TEMODAR + RT phase, TEMODAR is administered for an additional 6 cycles of maintenance treatment. Dosage in Cycle 1 (maintenance) is 150 mg/m² once daily for 5 days followed by 23 days without treatment. At the start of Cycle 2, the dose can be escalated to 200 mg/m², if the CTC non-hematologic toxicity for Cycle 1 is Grade ≤ 2 (except for alopecia, nausea, and vomiting), absolute neutrophil count (ANC) is $\geq 1.5 \times 10^9/L$, and the platelet count is $\geq 100 \times 10^9/L$. If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles. The dose remains at 200 mg/m² per day for the first 5 days of each subsequent cycle except if toxicity occurs.

During treatment a complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above $1.5 \times 10^9/L$ (1500/ μL) and the platelet count exceeds $100 \times 10^9/L$ (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** in the Full Prescribing Information under 2.1 Recommended Dosing and Dose Modification Guidelines.

How is TEMODAR for Injection prepared? [See Full Prescribing Information, Preparation and Administration, TEMODAR for Injection (2.2)].

Care should be exercised in the handling and preparation of TEMODAR. Vials should not be opened. If vials 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 of the vial. Procedures for proper handling and disposal of anticancer drugs should be considered.¹⁻⁴ Several guidelines on this subject have been published.

1. TEMODAR for Injection vials should be stored refrigerated at 2°-8°C (36°-46°F).
2. Bring the vial to room temperature prior to reconstitution with Sterile Water for Injection.
3. Using aseptic technique, reconstitute each vial with 41 mL Sterile Water for Injection. The resulting solution will contain 2.5 mg/mL temozolomide.
4. Vial should be gently swirled and not shaken. Inspect vials, and any vial containing visible particulate matter should not be used. Do not further dilute the reconstituted solution. Upon reconstitution, store at room temperature for up to 14 hours, including infusion time.
5. Using aseptic technique, withdraw up to 40 mL from each vial to make up the total dose and transfer into an empty 250 mL infusion bag.
6. Attach the pump tubing to the bag, purge the tubing and then cap.

How is TEMODAR for Injection administered? [See Full Prescribing Information, Preparation and Administration, TEMODAR for Injection (2.2)].

TEMODAR for Injection is administered as an intravenous infusion over 90 minutes. Bioequivalence has been established only when TEMODAR for Injection was given over 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.

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.

What should the patient avoid during treatment with TEMODAR? [See Full Prescribing Information, Use in Specific Populations, Pregnancy (8.1) and Nursing Mothers (8.3)].

There are no dietary restrictions for patients taking TEMODAR. 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. It is not known whether TEMODAR

is excreted into breast 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 the drug to the mother from TEMODAR.

What are the side effects of TEMODAR? [See Full Prescribing Information, Adverse Reactions (6)].

Nausea and vomiting are the most common side effects associated with TEMODAR. Noncumulative 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, alopecia, anorexia, headache, and bruising, as well as pain, irritation, itching, warmth, swelling, and redness at the site of infusion.

How is TEMODAR supplied? [See Full Prescribing Information, How Supplied/Storage and Handling (16)].

TEMODAR for Injection is supplied in single-use glass vials containing 100 mg temozolomide. TEMODAR is also available as capsules in 5-mg, 20-mg, 100-mg, 140-mg, 180-mg, and 250-mg strengths.

1. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999.
2. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm.* 2006; 63:1172-1193.
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.

TEMODAR for Injection

Manufactured by: Baxter Oncology GmbH, Halle/Westfalen, Germany
Distributed by: Schering Corporation, a subsidiary of



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