CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 21029

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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number:NDA 21029

Trade Name: TEMODAR Capsules

Generic Name: (temozolomide)

Sponsor:Schering Corporation

Approval Date: August 11, 1999

Indication: Provides for the use of TEMODAR (temozolomide) Capsules for the treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients as first relapse who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 21029

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-029

AUG 1 1 1999

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Attention: Joseph F. Lamendola, Ph.D.
Vice President, U.S. Regulatory Affairs

Dear Dr. Lamendola:

Please refer to your new drug application (NDA) dated August 12, 1998, received August 13, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TEMODAR (temozolomide) Capsules.

We acknowledge receipt of your submissions dated February 11 and 22, April 23, May 19 and 24, July 19, and August 2 and 4, 1999. Your submission of June 25, 1999 constituted a complete response to our February 12, 1999 action letter.

This new drug application provides for the use of TEMODAR (temozolomide) Capsules for the treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients at first relapse who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine.

We have completed the review of this application, as amended, according to the regulations for accelerated approval, and have concluded that adequate information has been presented to approve TEMODAR (temozolomide) Capsules for use as recommended in the enclosed labeling text. Accordingly, the application is approved under 21 CFR Subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced accelerated approval regulations.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert and text for the Pharmacist information sheet) and the draft copy of the immediate container and carton labels submitted on August 4, 1999. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for

approved NDA 21-029." Approval of this submission by FDA is not required before the labeling is used.

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your post marketing study (Subpart H Phase 4 commitments) specified in your submission dated June 24, 1999 and additional requirements that you committed to on July 19 and August 2, 1999. These commitments, along with any completion dates agreed upon, are listed below.

Schering will conduct a study according to the following protocol:

"A phase I/III randomized study of radiation therapy and temozolomide versus radiation therapy and BCNU versus radiation therapy and temozolomide and BCNU for anaplastic astrocytoma". The statistical analysis plan for this study will be performed according to your submission dated July 19, 1999.

In addition, as agreed upon in your letter dated August 2, 1999, you will provide the Phase I/II safety data to support the dosing schedule in the combination arm of the trial and agree that initiation of the combination arm will be contingent on FDA approval to proceed. Furthermore, you committed to completing the two monotherapy arms of the trial in the event that the combination arm is stopped for any reason.

Final study reports should be submitted to this NDA as a supplemental application. For administrative purposes, all submissions relating to this Phase 4 commitment must be clearly designated "Subpart H Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until December 2, 2000. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you

should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity [NOTE: You should still submit a pediatric drug development plan.] and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Patrick Guinn, Project Manager, at (301) 594-5767.

Sincerely,

/S/

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21029

APPROVABLE LETTER

NDA 21-029

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Attention: Joseph F. Lamendola, Ph.D.
Vice President, U.S. Regulatory Affairs

FEB 12 1999

Dear Dr. Lamendola:

Please refer to your new drug application (NDA) dated August 12, 1998, received August 13, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for temozolomide capsules.

We acknowledge receipt of your submissions dated September 18; October 2 and 30; November 6 and 18; and December 10 and 22, 1998.

We also refer to your submission dated February 4, 1999. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

This new drug application provides for the use of temozolomide capsules for the treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients at first relapse with disease progression on a nitrosourea and procarbazine containing drug regimen.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

> Provide us with a proposal for a new Trademark name. The use of the Tradename TEMODAL was determined to be still unacceptable by the review team and the Nomenclature Committee because erroneous substitution of TEMODAL for tramadol could result in life-threatening or lethal toxicities.

In addition, it will be necessary for you to submit draft labeling revised as recommended in the enclosed labeling text.

If additional information relating to the safety or effectiveness of this drug becomes available,

revision of the labeling may be required.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Oncologic Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with this Division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Patrick Guinn, Project Manager, at (301) 594-5767.

Sincerely,

/S/ 2/12/99

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

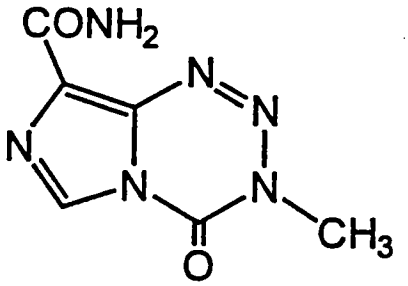
APPLICATION NUMBER: NDA 21029

FINAL PRINTED LABELING

TEMODAR (temozolomide)
CAPSULES

DESCRIPTION

TEMODAR Capsules for oral administration contain 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:



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 can be administered orally. The prodrug, temozolomide, is rapidly hydrolysed 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.

Each capsule contains 5 mg, 20 mg, 100 mg, or 250 mg of temozolomide. The inactive ingredients for TEMODAR CAPSULES are lactose anhydrous, colloidal silicon dioxide, sodium starch glycolate, tartaric acid, and stearic acid. Gelatin capsule shells contain titanium dioxide. The capsules are imprinted with pharmaceutical ink.
TEMODAR 5 mg: green imprint contains pharmaceutical grade shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, ammonium hydroxide, titanium dioxide, yellow iron oxide and FD&C Blue #2 aluminum lake.
TEMODAR 20 mg: brown imprint also contains pharmaceutical grade shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, purified water, ammonium hydroxide, potassium hydroxide, titanium dioxide, black iron oxide, yellow iron oxide, brown iron oxide, and red iron oxide.
TEMODAR 100 mg: blue imprint contains pharmaceutical glaze (modified) in an ethanol/shellac mixture, isopropyl alcohol, n-butyl alcohol, propylene glycol, titanium dioxide, and FD & C Blue #2 aluminium lake.
TEMODAR 250 mg: black, imprint contains pharmaceutical grade shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, purified water, ammonium hydroxide, potassium hydroxide, and black iron oxide.

CLINICAL PHARMACOLOGY

Mechanism of Action: Temozolomide is not directly active but undergoes rapid non-enzymatic conversion at physiologic pH to the reactive compound 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.

Pharmacokinetics: Temozolomide is rapidly and completely absorbed after oral administration; peak plasma concentrations occur in 1 hour. Food reduces the rate and extent of temozolomide absorption. Mean peak plasma concentration and AUC decreased by 32 % and 9 %, respectively, and Tmax increased 2-fold (from 1.1 to 2.25 hours) when temozolomide was administered after a modified high fat breakfast. Temozolomide is rapidly eliminated with a mean elimination half-life of 1.8 hours and exhibits linear kinetics over the therapeutic dosing range. 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, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (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. 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 as 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.

Special Populations:

Age: Population pharmacokinetic analysis indicates that age (range 19-78 years) has no influence on the pharmacokinetics of temozolomide. 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 in the first cycle of therapy than patients under 70 years of age. (See Precautions). In the entire safety database, however, there did not appear to be a higher incidence in patients 70 years of age or older. (See Adverse Reactions).

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

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

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

Creatinine Clearance: Population pharmacokinetic analysis indicates that creatinine clearance over the range of 36-130 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. TEMODAR has not been studied in patients on dialysis.

Hepatically Impaired Patients: In a pharmacokinetic study, the pharmacokinetics of temozolomide in patients with mild to moderate hepatic impairment (Child's-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.

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

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

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

Population analysis failed to demonstrate any influence of coadministered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H_2-receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.

Clinical Studies: 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 was 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 ≥1.5 x 10^9/L (1,500/μL) and the nadir and day 29, Day 1 of next cycle, platelet count was >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 of 16 to 114 weeks) and the median duration of complete responses was 64 weeks (range of 52 to 114 weeks). In this population, progression-free survival at 6 months was 45% (95% confidence interval 31-58%) and progression-free survival at 12 months was 29% (95% confidence interval 16-42%). Median progression-free survival was 4.4 months. Overall survival at 6 months was 74% (95% confidence interval 62-86%) and 12 month overall survival was 65% (95% confidence interval 52-78%). Median overall survival was 15.9 months.

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS

Patients treated with TEMODAR may experience myelosuppression. Prior to dosing patients must have an absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L and a platelet count $\geq 100 \times 10^9$/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 1.5×10^9/L and platelet count exceeds 100×10^9/L. In the clinical trials, if the ANC fell to $<1.0 \times 10^9$/L or the platelet count was $<50 \times 10^9$/L during any cycle, the next cycle was reduced by 50 mg/m^2, but not below 100 mg/m^2. Patients who do not tolerate 100 mg/m^2 should not receive TEMODAR. Geriatric patients and women have been shown in clinical trials to have a higher risk of developing myelosuppression. Myelosuppression generally occurred late in the treatment cycle. 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. Neutrophil and platelet counts returned to normal, on average, within 14 days of nadir counts (**see Precautions**).

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

respectively) caused numerous malformations of the external organs, soft tissues and skeleton in both species. Doses of 150 mg/m^2/day in rats and rabbits also caused embryolethality 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 the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with TEMODAR.

PRECAUTIONS

Information for Patients: In clinical trials, the most frequently occurring adverse effects were nausea and vomiting. These were usually either self-limiting or readily controlled with standard anti-emetic 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.

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

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

Geriatrics: 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. Caution should be exercised when treating elderly patients.
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=.31 and 2/10; 20%, p=.09, respectively) in the first cycle of therapy than patients under 70 years of age. (See Adverse Reactions).

Laboratory Tests: A complete blood count should be obtained on day 22 (21 days after the first dose). 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.

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

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

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

Pregnancy Category D. See Warnings Section.

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 from TEMODAR, patients receiving TEMODAR should discontinue nursing.

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

ADVERSE REACTIONS

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

Myelosuppression occurred late in the treatment cycle and returned to normal, on average, within 14 days of nadir counts. The median nadirs occurred at 26 days for platelets [range 21-40 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. (See Warnings). Less than 10% of patients required hospitalization, blood transfusion or discontinuation of therapy due to myelosuppression.

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

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

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.

OVERDOSAGE

Doses of 500, 750, 1,000 and 1,250 mg/m^2 (total dose per cycle over five days) have been evaluated clinically in patients. Dose-limiting toxicity was hematologic and was reported at 1,000 mg/m^2 and at 1,250 mg/m^2. Up to 1,000 mg/m^2 has been taken as a single dose, with only the expected effects of neutropenia and thrombocytopenia resulting. In the event of an overdose, hematologic evaluation is needed. Supportive measures should be provided as necessary.

DOSAGE AND ADMINISTRATION

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 x 10^9/L (1,500/μL) and both the nadir and day 29, Day 1 of next cycle platelet counts are $\geq$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 (1,500/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 <1.0 x 10^9/L (1,000/μL) or the platelet count is <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 3). **(See Warnings).**

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. For TEMODAR dosage calculations based on body surface area (BSA), see table 4. For suggested capsule combinations based on daily dose, see table 5.

Table 3 Dosing Modification

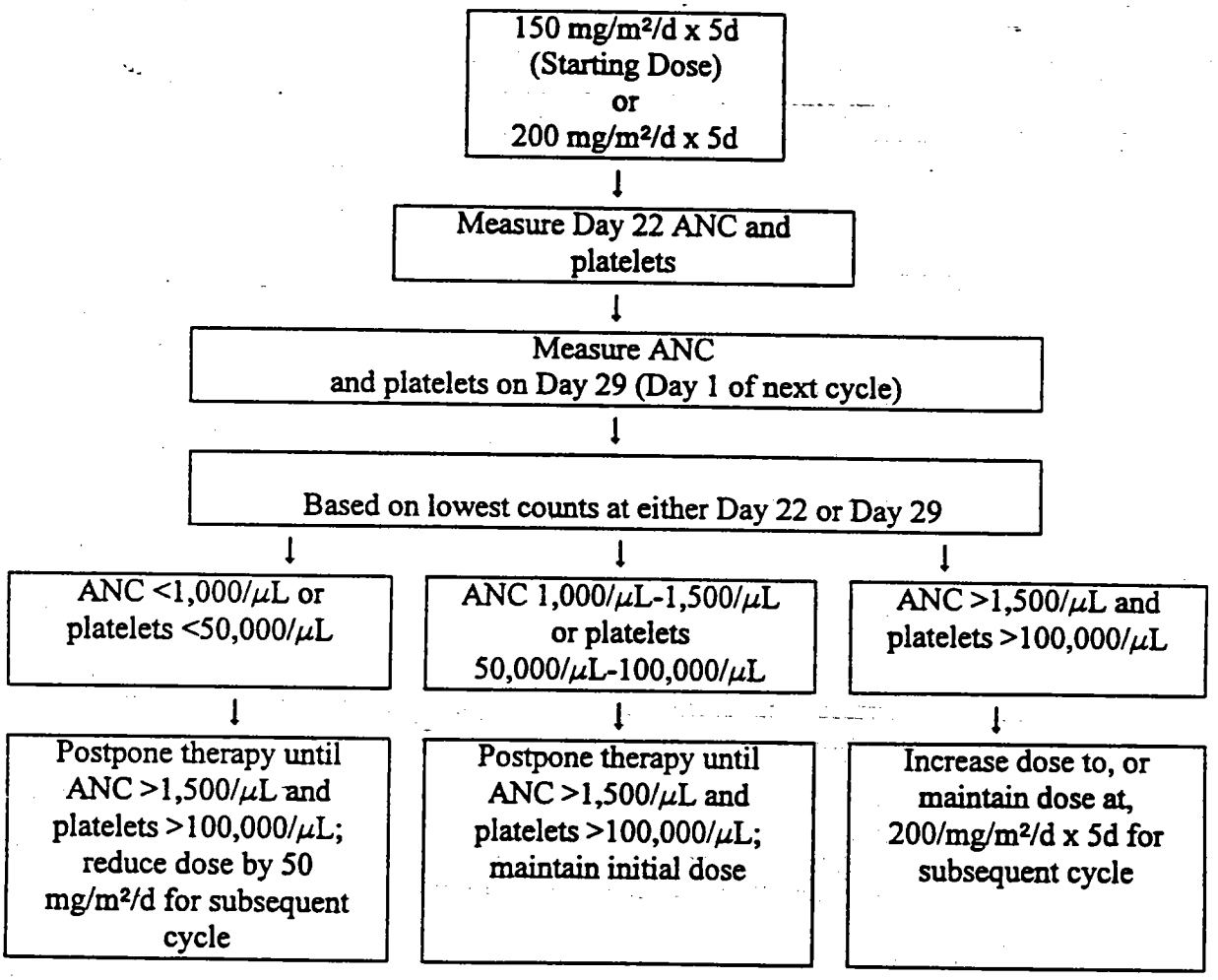


Table 4. Daily Dose Calculations by Body Surface Area (BSA) for 5 consecutive days per 28 day treatment cycle for the initial chemotherapy cycle (150 mg/m^2) and for subsequent chemotherapy cycles (200 mg/m^2) for patients whose nadir and day of dosing (Day 29, Day 1 of next cycle) absolute neutrophil count (ANC) is >1.5 x 10^9/L (1,500/μL) and whose nadir and day 29, Day 1 of next cycle platelet count is >100 x 10^9/L (100,000/μL).

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

Table 5. Suggested Capsule Combinations Based on Daily Dose

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

In the clinical trial, TEMODAR was administered under both fasting and non-fasting conditions; however, absorption is affected by food (see CLINICAL PHARMACOLOGY) and consistency of administration with respect to food is recommended. There are no dietary restrictions with temozolomide. To reduce nausea and vomiting, temozolomide 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.

Handling and Disposal: Temozolomide causes the rapid appearance of malignant tumors in rats. 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. Procedures for proper handling and disposal of anticancer drugs should be considered[1-7]. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

How Supplied:

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

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

5 count – NDC# 0085-1248-01

20 count – NDC# 0085-1248-02

TEMODAR (temozolomide) Capsules 20 mg: 5 and 20 capsule bottles.
5 count – NDC# 0085-1244-01
20 count – NDC# 0085-1244-02

TEMODAR (temozolomide) Capsules 100 mg: 5 and 20 capsule bottles.
5 count – NDC# 0085-1259-01
20 count – NDC# 0085-1259-02

TEMODAR (temozolomide) Capsules 250 mg: 5 and 20 capsule bottles.
5 count – NDC# 0085-1252-01
20 count – NDC# 0085-1252-02

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

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs, NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing office, Washington, DC 20402.

2. AMA Council Report, Guidelines for Handling Parenteral Antineoplastics. JAMA, 1985; 2.53(11):1590-1592.

3. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.

4. Clinical Oncological Society of Australia, Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Australia, 1983; 1:426-428.

5. Jones RB, et al: Safe Handling Of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. CA - A Cancer Journal for Clinicians, 1983; (Sept/Oct) 258-263.

6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J. Hosp Pharm, 1990; 47:1033--1049.

7. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines), Am J Health-Syst Pharm, 1996; 53:1669-1685.

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.

TE0014/22420801

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.

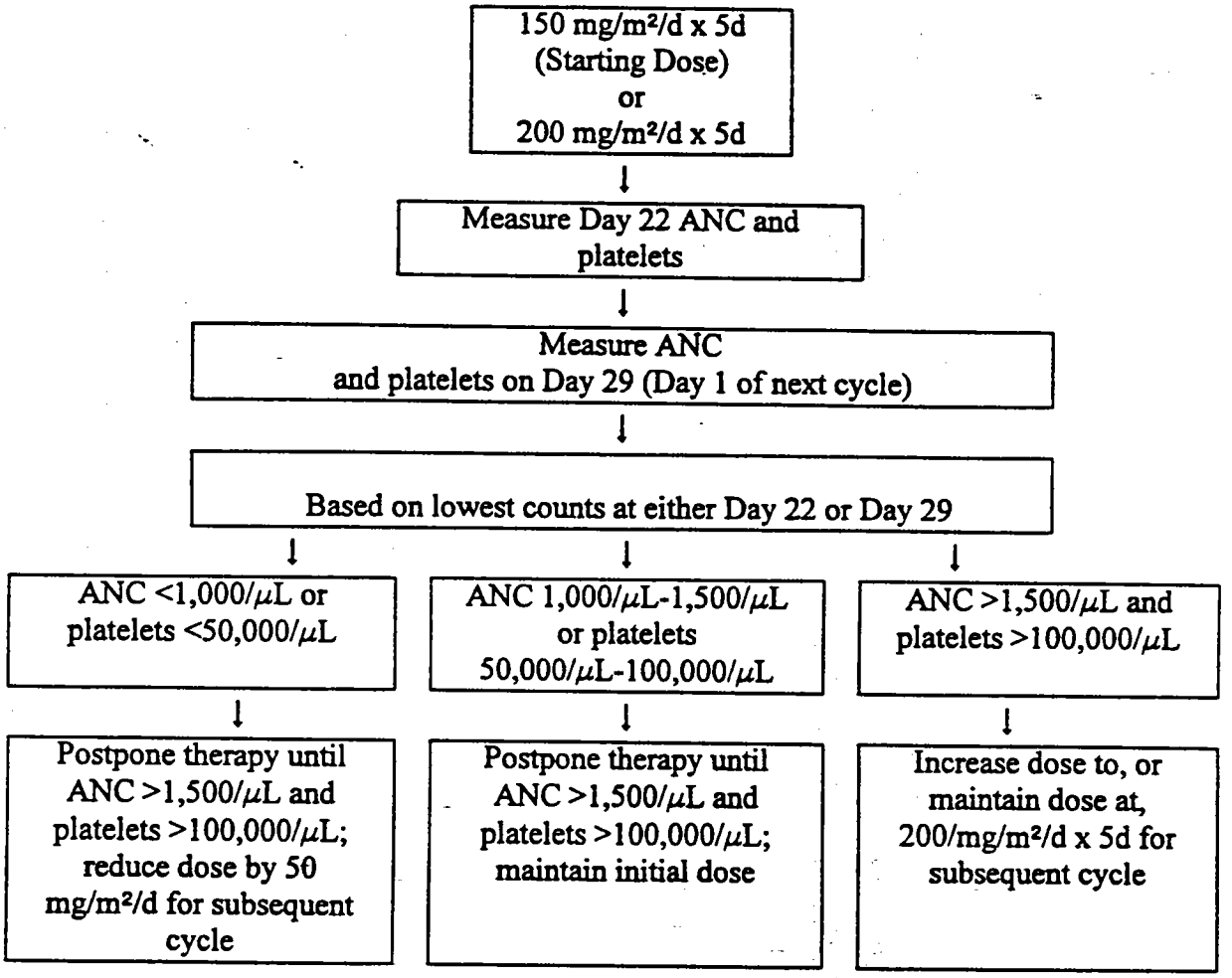
What is TEMODAR?
TEMODAR (temozolomide) is an oral alkylating agent for the treatment of refractory-anaplastic astrocytoma.

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 mg/m^2/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 x 150 = 276, or 275 mg/day. The dose for subsequent cycles may be adjusted according to nadir neutrophil and platelet counts in the previous cycle and at the time of initiating the next cycle.

How might the dose of TEMODAR be modified?

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 x 10^9/L (1,500/μL) and both the nadir and day 29, Day 1 of next cycle platelet counts are $\geq$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 (1,500/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 <1.0 x 10^9/L (1,000/μL) or the platelet count is <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 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

Strength	Color
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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