TEMODAL* Capsules

BRAND OF TEMOZOLOMIDE

For oral administration

DESCRIPTION: Each TEMODAL Capsule contains 5 mg (SECA), 20 mg (YRMA), 100 mg (LHKA), or 250 mg (IWHA) temozolomide. Inactive ingredients: lactose anhydrous, sodium starch glycolate, colloidal silicon dioxide, tartaric acid, and stearic acid.

ACTIONS: TEMODAL is an imidazotetrazine alkylating agent with antitumor activity. It undergoes rapid chemical conversion in the systemic circulation at physiologic pH to the active compound, MTIC (monomethyl triazeno imidazole carboxamide). The cytotoxicity of MTIC is thought to be due primarily to alkylation at the O^6 position of guanine with additional alkylation also occurring at the N^7 position. Cytotoxic lesions that develop subsequently are thought to involve aberrant repair of the methyl adduct.

INDICATIONS AND USAGE:

TEMODAL Capsules are indicated for the treatment of patients with:

- newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as adjuvant treatment.
- malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy.

TEMODAL Capsules are also indicated as first line treatment for patients with advanced metastatic malignant melanoma.

DOSAGE AND ADMINISTRATION:

Adult patients with newly diagnosed glioblastoma multiforme;

Concomitant phase

TEMODAL is administered orally at 75 mg/m^2 daily for 42 days concomitant with radiotherapy (60 Gy administered in 30 fractions) followed by adjuvant TEMODAL for 6 cycles. No dose reductions are recommended; however, dose interruptions may occur based on patient tolerance. The TEMODAL 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 ≥ 1.5 x 10^9/L thrombocyte count ≥ 100 x 10^9/L common toxicity criteria (CTC) non-hematological toxicity ≤ Grade 1 (except for alopecia, nausea and vomiting). During treatment a complete blood count should be obtained weekly. TEMODAL dosing should be interrupted or discontinued during concomitant phase according to the hematological and non-hematological toxicity criteria as noted in **Table 1** .

Table 1. TEMODAL Dosing Interruption or Discontinuation During Concomitant Radiotherapy and TEMODAL

Toxicity	TMZ Interruption[a]	TMZ Discontinuation
Absolute Neutrophil Count	≥ 0.5 and < 1.5 x 10^9/L	< 0.5 x 10^9/L
Thrombocyte Count	≥ 10 and < 100 x 10^9/L	< 10 x 10^9/L
CTC Non-hematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 2	CTC Grade 3 or 4

a: Treatment with concomitant TMZ could be continued when all of the following conditions were met: absolute neutrophil count ≥ 1.5 x 10^9/L; thrombocyte count ≥ 100 x 10^9/L; CTC non-hematological toxicity ≤ Grade 1 (except for alopecia, nausea, vomiting).

TMZ = TEMODAL; CTC = Common Toxicity Criteria.

Adjuvant Phase

Four weeks after completing the TEMODAL + Radiotherapy phase, TEMODAL is administered for an additional 6 cycles of adjuvant treatment. Dosage in Cycle 1 (adjuvant) is 150 mg/m^2 once daily for 5 days followed by 23 days without treatment. At the start of Cycle 2, the dose is escalated to 200 mg/m^2 if the CTC non-hematologic toxicity for Cycle 1 is Grade ≤ 2 (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is ≥ 1.5 x 10^9/L, and the thrombocyte count is ≥ 100 x 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/m^2 per day for the first 5 days of each subsequent cycle except if toxicity occurs. Dose reductions during the adjuvant 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 TEMODAL). The TEMODAL dose should be reduced or discontinued according to **Table 3**.

Table 2 TEMODAL Dose Levels for Adjuvant 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 3 TEMODAL Dose Reduction or Discontinuation During Adjuvant Treatment

Toxicity	Reduce TMZ by 1 Dose Level[a]	Discontinue TMZ
Absolute Neutrophil Count	< 1.0 x 10^9/L	See footnote b
Thrombocyte Count	< 50 x 10^9/L	See footnote b
CTC Non-hematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4[b]

a: TMZ dose levels are listed in **Table 2**

b: TMZ is to be discontinued if dose reduction to < 100 mg/m^2 is required or if the same Grade 3 non-hematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction.

TMZ = TEMODAL; CTC = Common Toxicity Criteria.

Adults with recurrent or progressive glioma or malignant melanoma

In patients previously untreated with chemotherapy, TEMODAL is administered orally at a dose of 200 mg/m^2 once daily for 5 days per 28-day cycle. In patients previously treated with chemotherapy, the initial dose is 150 mg/m^2 once daily, to be increased in the second cycle to 200 mg/m^2 daily providing the absolute neutrophil count (ANC) is ≥ 1.5 x 10^9/L and the thrombocyte count is ≥ 100 x 10^9/L on Day 1 of the next cycle. Dose modification for TEMODAL should be based on toxicities according to nadir ANC or platelet counts.

Pediatric patients with recurrent or progressive glioma: In patients 3 years of age or older, TEMODAL is administered orally at a dose of 200 mg/m^2 once daily for 5 days per 28-day cycle. Pediatric patients previously treated with chemotherapy should receive an initial dose of 150 mg/m^2 once daily for 5 days, with escalation to 200 mg/m^2 once daily for 5 days at the next cycle if there is no toxicity.

Therapy can be continued until disease progression for a maximum of 2 years.

Laboratory parameters for dose modification in recurrent or progressive malignant glioma, or malignant melanoma – Prior to dosing, the following laboratory parameters must be met: absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L and platelets ≥ 100 x 10^9/L. A complete blood count must be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until ANC is above 1.5 x 10^9/L and platelet count exceeds 100 x 10^9/L. If the ANC falls to < 1.0 x 10^9/L or the platelet count is < 50 x 10^9/L during any cycle, the next cycle should be reduced one dose level. Dose levels include 100 mg/m^2, 150 mg/m^2, and 200 mg/m^2. The lowest recommended dose is 100 mg/m^2.

All Patients

TEMODAL should be administered in the fasting state, at least one hour before a meal.

TEMODAL Capsules must not be opened or chewed, but are to be swallowed whole with a glass of water. If a capsule becomes damaged, avoid contact of the powder contents with skin or mucous membrane.

DRUG INTERACTIONS: Administration of TEMODAL with ranitidine or with food did not result in clinically significant alterations in the extent of absorption of TEMODAL. Co-administration of dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H_2 receptor antagonists, or phenobarbital did not alter the clearance of TEMODAL. Co-administration with valproic acid was associated with a small but statistically significant decrease in clearance of temozolamide.

Use of TEMODAL in combination with other myelosuppressive agents may increase the likelihood of myelosuppression.

ADVERSE EFFECTS

Adult patients with newly diagnosed glioblastoma muliforme

Table 4 provides treatment emergent adverse events, (causality not determined during clinical trials) in patients with newly diagnosed glioblastoma multiforme during the concomitant and adjuvant phases of treatment.

Table 4: TEMODAL (TMZ) and Radiotherapy: Treatment-Emergent Events During Concomitant and Adjuvant Treatment

Very Common (> 1/10); Common (> 1/100, < 1/10); Uncommon (> 1/1,000, < 1/100)

CIOMS III

Body System	**TMZ + Concomitant Radiotherapy** n = 288*	**TMZ Adjuvant Therapy** n = 224
Infections and Infestations		
Common:		Candidiasis oral, infection
Uncommon:	Candidiasis oral, herpes simplex, infection, pharyngitis, wound infection	Herpes simplex, herpes zoster, influenza-like symptoms
Blood and the lymphatic system disorders		
Common:	Leukopenia, lymphopenia, neutropenia, thrombocytopenia	Anemia, febrile neutropenia, leukopenia, thrombocytopenia
Uncommon:	Anemia, febrile neutropenia	Lymphopenia, petechiae
Endocrine disorders		
Uncommon:	Cushingoid	Cushingoid
Metabolism and nutritiondisorders		
Very Common:	Anorexia	Anorexia
Common:	Hyperglycemia, weight decreased	Weight decreased
Uncommon:	Hypokalemia, alkaline phosphatase increased, weight increased	Hyperglycemia, weight increased
Psychiatric disorders		
Common:	Anxiety, emotional lability, insomnia	Anxiety, depression, emotional lability, insomnia
Uncommon:	Agitation, apathy, behaviour disorder, depression, hallucination	Hallucination, amnesia
Nervous system disorders		
Very Common:	Headache	Headache, convulsions
Common:	Dizziness, aphasia, balance impaired, concentration impaired, confusion, consciousness decreased, convulsions, memory impairment, neuropathy, paresthesia, somnolence, speech disorder, tremor	Dizziness, aphasia, balance impaired, concentration impaired, confusion, dysphasia, hemiparesis, memory impairment, neurological disorder (NOS), neuropathy, peripheral neuropathy, paresthesia, somnolence, speech disorder, tremor
Uncommon:	Ataxia, cognition impaired, dysphasia, extrapyramidal disorder, gait abnormal, hemiparesis, hyperesthesia, hypoesthesia, neurological disorder (NOS), peripheral neuropathy, status epilepticus	Ataxia, coordination abnormal gait abnormal, hemiplegia, hyperesthesia, sensory disturbance

Eye disorders		
Common:	Vision blurred	Vision blurred, diplopia, visual field defect
Uncommon:	Eye pain, hemianopia , vision disorder, visual acuity reduced, visual field defect	Eye pain, eyes dry, visual acuity reduced
Ear and labyrinth disorders		
Common:	Hearing impairment	Hearing impairment, tinnitus
Uncommon:	Earache, hyperacusis, tinnitus, otitis media	Deafness, earache, vertigo
Cardiac disorders		
Uncommon:	Palpitation	
Vascular disorders		
Common:	Edema, edema leg, hemorrhage	Edema leg, hemorrhage, deep venous thrombosis
Uncommon:	Hypertension, cerebral hemorrhage	Edema, edema peripheral, embolism pulmonary
Respiratory, thoracic and mediastinal disorders		
Common:	Coughing, dyspnea	Coughing, dyspnea
Uncommon:	Pneumonia, upper respiratory infection, nasal congestion	Pneumonia, sinusitis, upper respiratory infection, bronchitis
Gastrointestinal disorders		
Very Common:	Constipation, nausea, vomiting	Constipation, nausea, vomiting
Common:	Abdominal pain, diarrhea, dyspepsia, dysphagia, stomatitis	Diarrhea, dyspepsia, dysphagia, mouth dry, stomatitis
Uncommon:		Abdominal distension, fecal incontinence, gastrointestinal disorder (NOS), gastroenteritis, hemorrhoids,
Skin and subcutaneous tissue disorders		
Very Common:	Alopecia, rash	Alopecia, rash
Common:	Dermatitis, dry skin, erythema, pruritus	Dry skin, pruritus
Uncommon:	Photosensitivity reaction, pigmentation abnormal, skin exfoliation	Erythema, pigmentation abnormal, sweating increased
Musculoskeletal and connective tissue disorders		
Common:	Arthralgia, muscle weakness	Arthralgia, musculoskeletal pain, myalgia, muscle weakness
Uncommon:	Back pain, musculoskeletal pain, myalgia, myopathy	Back pain, myopathy
Renal and urinary disorders		
Common:	Micturition frequency, urinary incontinence	Urinary incontinence
Uncommon:		Dysuria
Reproductive system and breast disorders		
Uncommon:	Impotence	Amenorrhea, breast pain, menorrhagia, vaginal hemorrhage, vaginitis
General disorders and administration site conditions		
Very Common:	Fatigue	Fatigue
Common:	Fever, pain, allergic reaction, radiation injury, face edema, taste perversion	Fever, pain, allergic reaction, radiation injury, taste perversion
Uncommon:	Flushing, hot flushes, asthenia condition aggravated, rigors tongue discoloration, parosmia, thirst	Asthenia, condition aggravated, pain, rigors, tooth disorder, face edema, taste perversion
Investigation		
Common:	SGPT increased	SGPT increased
Uncommon:	Gamma GT increased, hepatic enzymes increased, SGOT increased	

*A patient who was randomised to the RT arm only, received TEMODAL + RT.

Laboratory results: Myelosuppression, (neutropenia and thrombocytopenia), which are known dose limiting toxicities for most cytotoxic agents, including TEMODAL, were observed. When laboratory abnormalities and adverse events were combined across concomitant and adjuvant treatment phases, Grade 3 or Grade 4 neutrophil abnormalities including neutropenic events were observed in 8% of the patients. Grade 3 or Grade 4 thrombocyte abnormalities, including thrombocytopenic events were observed in 14% of the patients who received TEMODAL.

Adverse effects in patients with recurrent or progressive glioma or malignant melanoma: In clinical trials, the most frequently occurring undesirable effects were gastrointestinal disturbances, specifically nausea (43%) and vomiting (36%). These effects were usually Grade 1 or 2 (mild to moderate in severity) and were either self limiting or readily controlled with standard anti-emetic therapy. The incidence of severe nausea and vomiting was 4%.

Other adverse events reported frequently include fatigue (22%), constipation (17%) and headache (14%). Anorexia (11%), diarrhoea (8%), rash, fever, asthenia and somnolence (6% each) were also reported. Less common (2% to 5%) and in descending order of frequency, were abdominal pain, pain, dizziness, weight decrease, malaise, dyspnea, alopecia, rigors, pruritus, dyspepsia, taste perversion, paresthesia and petechiae.

Laboratory results: Grade 3 or 4 thrombocytopenia and neutropenia occurred in 19% and 17% respectively, of patients treated for glioma, and 20% and 22%, respectively of patients with metastatic melanoma. This led to hospitalization and/or discontinuation of TEMODAL in 8% and 4%, respectively, of patients with glioma, and 3% and 1.3%, respectively, of those with melanoma. Myelosuppression was predictable (usually within the first few cycles, with the nadir between Day 21 and Day 28), and recovery was rapid, usually within 1-2 weeks. No evidence of cumulative myelosuppression was observed. Pancytopenia, leukopenia, and anemia have also been reported. Lymphopenia has also been reported very commonly.

During the marketing of TEMODAL, cases of opportunistic infections including *Pneumocystis carinii* pneumonia (PCP) have been reported rarely. Very rarely, cases of erythema multiforme, and allergic reactions, including anaphylaxis, have been observed. Very rare cases of myelodysplastic syndrome (MDS) and secondary malignancies, including myeloid leukemia, have been reported in patients treated with regimens that included TEMODAL. Prolonged pancytopenia, which may result in aplastic anemia has been reported very rarely.

CONTRAINDICATIONS: TEMODAL is contraindicated in patients who have a history of hypersensitivity reaction to its components or to dacarbazine (DTIC).

TEMODAL is contraindicated for use during pregnancy (see Usage during pregnancy and lactation).

TEMODAL is contraindicated in patients with severe myelosuppression.

PRECAUTIONS: Patients who received concomitant TEMODAL and radiotherapy in a pilot trial for the prolonged 42 day schedule were shown to be at particular risk for developing *Pneumocystis carinii* pneumonia. Thus, prophylaxis against *Pneumocystis carinii* pneumonia is required for all patients receiving concomitant TEMODAL and radiotherapy for the 42 day regimen (with a maximum of 49 days)

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

Antiemetic therapy: Nausea and vomiting are very commonly associated with TEMODAL and guidelines are provided:

Patients with newly diagnosed glioblastoma multiforme:

– anti-emetic prophylaxis is recommended prior to the initial dose of concomitant TEMODAL

– anti-emetic prophylaxis is strongly recommended during the adjuvant phase.

Patients with recurrent or progressive glioma: Patients who have experienced severe (Grade 3 or 4) vomiting in previous treatment cycles may require anti-emetic therapy.

All patients

Use in patients with hepatic or renal dysfunction: – The pharmacokinetics of temozolomide were comparable in patients with normal hepatic function and in those with mild or moderate hepatic dysfunction. No data are available on the administration of TEMODAL in patients with severe hepatic dysfunction (Child's Class III) or with renal dysfunction. Based on the pharmacokinetic properties of temozolomide, it is unlikely that dose reductions are required in patients with severe hepatic or renal dysfunction. However, caution should be exercised when TEMODAL is administered in these patients.

Paediatric use – Glioblastoma multiforme: There is no clinical experience with use of TEMODAL in children under the age of 3 years. There is limited experience in children over the age of 3 years with glioma.

Melanoma: There is no clinical experience in patients under 18 years of age.

Use in elderly patients – Elderly patients (> 70 years of age) appear to be at increased risk of neutropenia and thrombocytopenia, compared with younger patients.

Keep this medication out of the reach of children.

USAGE DURING PREGNANCY AND LACTATION: There are no studies in pregnant women. In preclinical studies in rats and rabbits administered 150 mg/m², teratogenicity and/or fetal toxicity were demonstrated. TEMODAL, therefore, should not normally be administered to pregnant women. If use during pregnancy must be considered, the patient should be apprised of the potential risks to the fetus. Women of childbearing potential should be advised to avoid pregnancy while they are receiving TEMODAL and for the 6 months after discontinuation of TEMODAL therapy. It is not known whether TEMODAL is excreted in human milk; thus, TEMODAL should not be used by a nursing woman.

Male patients – Effective contraception should also be used by male patients taking TEMODAL. Temozolomide can have genotoxic effects. Therefore, men being treated with temozolomide are advised not to father a child during and up to 6 months after treatment and to seek advice on cryoconservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with temozolomide.

OVERDOSAGE INFORMATION: Doses of 500, 750, 1,000, and 1,250 mg/m² (total dose per cycle over 5 days) have been evaluated clinically in patients. Dose-limiting toxicity was hematological and was reported at any dose but is expected to be more severe at higher doses. An overdose of 2,000 mg per day for 5 days was taken by one patient and the adverse events reported were pancytopenia, pyrexia, multi-organ failure and death. There are reports of patients who have taken more than 5 days of treatment (up to 64 days) with adverse events reported including bone marrow suppression, with or without infection, in some cases severe and prolonged and resulting in death. In the event of an overdose, hematologic evaluation is needed. Supportive measures should be provided as necessary.

HOW SUPPLIED: Temodal (temozolomide) is available as 5, 20, 100, and 250 mg in boxes containing 5 capsules.

STORAGE: Store at 2° C to 30° C.

Manufactured by: Orion Corporation, Orion Pharma, Tengstrominkatu 6-8, Finland-2-360 Turku
Packaged & distributed by: Schering-Plough Labo N.V., Heist-op-den-Berg, Belgium
wholly owned subsidiary of Schering-Plough Corporation / U.S.A.