S-CCDS-MK7365-MTL-062021

TEMODAL® Capsules

Brand of temozolomide

This insert contains basic prescribing information only. For more comprehensive information, a Professional Brochure is available to physicians on request.

FOR ORAL ADMINISTRATION

DESCRIPTION: TEMODAL Capsule 5 mg is an opaque green cap with white opaque body; its cap is imprinted in black ink with “TEMODAL”, while the body is imprinted in black ink with an SP logo, “5 mg” and two stripes. TEMODAL Capsule 20 mg is a yellow cap with white opaque body; its cap is imprinted in black ink with “TEMODAL”, while the body is imprinted in black ink with an SP logo, “20 mg” and two stripes. TEMODAL Capsule 100 mg is a pink opaque cap and white, opaque body; its cap is imprinted in black ink with “TEMODAL”, while the body is imprinted in black ink with an SP logo, “100 mg” and two stripes. TEMODAL Capsule 250 mg is a white opaque cap and body; its cap is imprinted in black ink with “TEMODAL”, while the body is imprinted in black ink with an SP logo, “250 mg” and two stripes.

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.

PRECLINICAL PHARMACOLOGY AND TOXICOLOGY: Single-dose toxicity studies of TEMODAL were conducted in mice, rats, and dogs. Estimated LD_{50} doses by the oral route were moderately higher in the rat (approximately 1900 mg/m^2) than in the mouse (approximately 1000 mg/m^2). The minimum lethal dose in dogs was 600 mg/m^2. In the single-dose studies, clinical signs of toxicity and death were generally delayed, reflecting a delayed toxicity to tissues that normally proliferate more rapidly resulting in general deterioration of organ function; toxicity is consistent with that expected of an alkylating agent.

TEMODAL is rapidly absorbed following oral administration and is rapidly eliminated in the urine. Systemic exposure at the therapeutic dose level in humans is similar to that of the rat and dog. Single-cycle (5-day dosing, 23 days nontreatment) three- and six-cycle toxicity studies were conducted in rats and dogs. In multiple-cycle studies, the primary targets of toxicity included the bone marrow, lymphoreticular system, testes and gastrointestinal tract. TEMODAL is more toxic to the rat and dog than to humans, as the therapeutic dose regimen (200 mg/m^2), which has been well-tolerated in humans, approximates the minimum lethal dose following multiple doses in both rats and dogs. Dose-related

reductions in leukocytes and platelets appear to be sensitive indicators of toxicity in both rats and dogs. During intervals when dosing is discontinued, significant evidence of recovery from most hematologic, biochemical and histopathologic changes occurs. Neoplasms observed in the six-cycle rat study included mammary carcinoma, keratoacanthoma of the skin, basal cell adenoma and a variety of mesenchymal neoplasms. No tumors or preneoplastic changes were observed in the dog studies. Considering that TEMODAL is a prodrug of the alkylating agent MTIC, its tumorigenic potential is not unexpected and has been observed with other alkylating agents, including those producing MTIC. The overall oncogenic potential of TEMODAL in rats appears to be species specific and not significantly different from other chemotherapeutic drugs.

Results of the Ames/Salmonella and HPBL tests showed a positive mutagenicity response. TEMODAL also produced chromosome aberrations in a human peripheral lymphocyte assay.

CLINICAL PHARMACOLOGY: Preclinical data suggest that TEMODAL crosses the blood-brain barrier rapidly and is present in the cerebrospinal fluid. After oral administration to adult patients, TEMODAL is absorbed rapidly with peak concentrations reached as early as 20 minutes post-dose, (mean times between 0.5 and 1.5 hours). Plasma clearance, volume of distribution and half-life are independent of dose. TEMODAL demonstrates low protein binding (10% to 20%), and thus is not expected to interact with highly protein bound agents. After oral administration of ^{14}C labeled TEMODAL, mean fecal excretion, of ^{14}C over 7 days post-dose was 0.8% indicating complete absorption. Following oral administration approximately 5% to 10% of the dose is recovered unchanged in the urine over 24 hours, and the remainder excreted as AIC (4-amino-5-imidazole-carboxamide hydrochloride) or unidentified polar metabolites.

Analysis of population based pharmacokinetics of TEMODAL revealed that plasma TEMODAL clearance was independent of age, renal function, or tobacco use.

Pediatric patients had a higher AUC than adult patients; however, the maximum tolerated dose (MTD) was 1000 mg/m^2 per cycle both in children and in adults.

CLINICAL EFFICACY:

Newly diagnosed glioblastoma multiforme

Five hundred and seventy-three patients were randomised to receive either temozolomide + Radiotherapy (RT) (n=287) or RT alone (n=286). Patients in the temozolomide + RT arm received concomitant temozolomide (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 monotherapy temozolomide (150 - 200 mg/m^2) on days 1 - 5 of every 28 -day cycle for up to 6 cycles, starting 4 weeks after the end of RT. Patients in the control arm received RT only. *Pneumocystis carinii* pneumonia (PCP) prophylaxis was

required during RT and combined temozolomide therapy, and was to continue until recovery of lymphopenia to Grade <1.

Temozolomide was administered as salvage therapy in the follow-up phase in 161 patients of the 282 (57%) in the RT alone arm, and 62 patients of the 277 (22%) in the temozolomide + RT arm.

The hazard ratio (HR) for overall survival was 1.59 (95% CI for HR=1.33 - 1.91) with a log-rank p <0.0001 in favor of the temozolomide arm. The estimated probability of surviving 2 years or more (26% vs 10%) is higher for the RT + temozolomide arm. The addition of concomitant temozolomide to radiotherapy, followed by temozolomide monotherapy in the treatment of patients with newly diagnosed glioblastoma multiforme demonstrated a statistically significant improved overall survival compared with radiotherapy alone. (Figure 1)

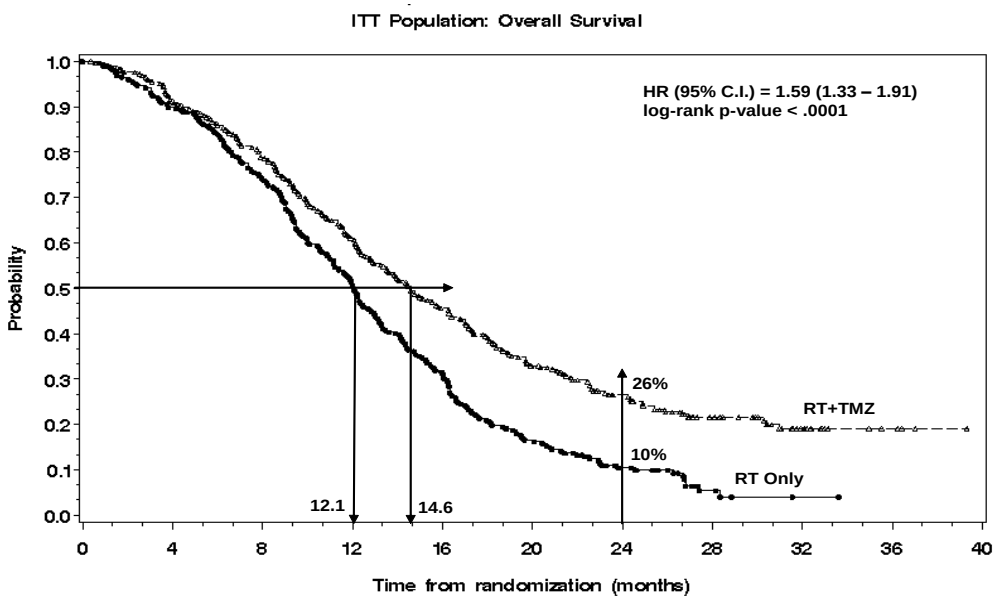

Figure 1 Kaplan-Meier Curves for Overall Survival (Intent To Treat) ITT Population

Malignant glioma showing recurrence or progression after standard therapy

Data on clinical efficacy in-patients with glioblastoma multiforme (Karnofsky performance status [KPS] ≥ 70), progressive or recurrent after surgery and radiotherapy, were based on two clinical trials. One was a non-comparative trial in 138 patients (29% received prior chemotherapy), and the other was a randomised reference controlled trial of temozolomide and procarbazine in a total of 225 patients (67% received prior treatment with nitrosourea based chemotherapy.) In both trials, the primary endpoint was progression-free survival (PFS) defined by MRI scans or neurological worsening. In the non-comparative trial, the PFS at 6 months was 19%, the median progression-free survival was 2.1 months, and the median overall survival, 5.4 months. The objective response rate based on MRI scans was 8%.

In the randomised trial, the 6 month PFS was significantly greater for temozolomide than for procarbazine (21% vs 8%, respectively – chi-square p = 0.008) with median PFS of 2.89 and 1.88 months respectively (log rank p = 0.0063). The median survival was 7.34 and 5.66 months for temozolomide and procarbazine, respectively (log rank p = 0.33). At 6 months the fraction of surviving patients was significantly higher in the temozolomide arm (60%) compared with the procarbazine arm (44%) (chi-square p = 0.019). In patients with prior chemotherapy a benefit was indicated in those with a KPS of 80 or better.

Data on time to worsening of neurologic status favoured temozolomide over procarbazine as did data on time to worsening of performance status (KPS remaining above 60 or a decrease by at least 30 points). The median times to progression in these endpoints ranged from 0.7 to 2.1 months longer for temozolomide than for procarbazine (log rank p = < 0.01 to 0.03).

Anaplastic Astrocytoma

In a multicenter, global, prospective phase II trial evaluating the safety and efficacy of oral temozolomide in the treatment of patients with anaplastic astrocytoma (AA) at first relapse, the 6-month progression-free survival was 46%. The median progression-free survival was 5.4 months. Median overall survival was 14.6 months. Response rate, based on the central reviewer assessment, was 35% (13 CR and 43 PR) for the intent-to-treat population. Including 43 sustained disease responses, the response rate was 61%. The 6-month event-free survival for the ITT population was 44% with a median event-free survival of 4.6 months, which was similar to the results for the progression-free survival. For the eligible histology population, the efficacy results were similar. Achieving a radiologic objective response or maintaining progression-free status was strongly associated with maintained or improved quality of life.

INDICATIONS AND USAGE:

TEMODAL Capsules are indicated for the treatment of patients with:

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

DOSAGE AND ADMINISTRATION:

Adult patients with newly diagnosed glioblastoma multiforme

TEMODAL is administered in combination with focal radiotherapy (concomitant phase) followed by up to 6 cycles of temozolomide monotherapy.

Concomitant phase

TEMODAL is administered orally at 75 mg/m^2 daily for 42 days concomitant with focal radiotherapy (60 Gy administered in 30 fractions). No dose reductions are recommended, but delay or discontinuation of temozolomide administration will be decided weekly according to haematological and non-haematological toxicity criteria. 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.

Monotherapy Phase

Four weeks after completing the TEMODAL + Radiotherapy phase, TEMODAL is administered for up to 6 cycles of monotherapy treatment. Dosage in Cycle 1 (monotherapy) 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. Once escalated, 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 and discontinuations during the monotherapy 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 Monotherapy 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 Monotherapy 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.

Adult with recurrent or progressive glioma: 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: 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. Antiemetic therapy may be administered prior to or following administration of TEMODAL. If vomiting occurs after the dose is administered, a second dose should not be administered that day.

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 WITH ORAL TEMODAL (see also PRECAUTIONS): 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 temozolomide.

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

ADVERSE EFFECTS:
Clinical trial experience in patients treated with TEMODAL capsules

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

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

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

CIOMS III

Body System	TMZ +Concomitant Radiotherapy	TMZ monotherapy therapy

	n= 288*	n=224
Infections and Infestations		
Common:	Candidiasis oral, herpes simplex, infection, pharyngitis, wound infection	Candidiasis oral, infection
Uncommon:		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 nutrition disorders		
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,	Dizziness, aphasia, balance impaired, concentration impaired, confusion,

	consciousness decreased, convulsions, memory impairment, neuropathy, paresthesia, somnolence, speech disorder, tremor	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: Uncommon:	Coughing, dyspnea Pneumonia, upper respiratory infection, nasal congestion	Coughing, dyspnea Pneumonia, sinusitis, upper respiratory infection, bronchitis
Gastrointestinal disorders Very Common: Common: Uncommon:	 Constipation, nausea, vomiting Abdominal pain, diarrhoea, dyspepsia, dysphagia, stomatitis	 Constipation, nausea, vomiting Diarrhoea, dyspepsia, dysphagia, mouth dry, stomatitis Abdominal distension, fecal incontinence, gastrointestinal disorder (NOS), gastroenteritis, hemorrhoids
Skin and subcutaneous tissue disorders Very Common: Common: Uncommon:	 Alopecia, rash Dermatitis, dry skin, erythema, pruritus Photosensitivity reaction, pigmentation abnormal, skin exfoliation	 Alopecia, rash Dry skin, pruritus Erythema, pigmentation abnormal, sweating increased
Musculoskeletal and connective tissue disorders Common: Uncommon:	 Arthralgia, muscle weakness Back pain, musculoskeletal pain, myalgia, myopathy	 Arthralgia, musculoskeletal pain, myalgia, muscle weakness 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: Common: Uncommon:	Fatigue Fever, pain, allergic reaction, radiation injury, face edema, taste perversion Flushing, hot flushes, asthenia, condition aggravated, rigors, tongue discoloration, parosmia, thirst	Fatigue Fever, pain, allergic reaction, radiation injury, taste perversion Asthenia, condition aggravated, pain, rigors, tooth disorder, face edema, taste perversion
Investigation Common: Uncommon:	SGPT increased Gamma GT increased, hepatic enzymes increased, SGOT increased	SGPT 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 monotherapy 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: In clinical trials, the most frequently occurring undesirable effects were gastrointestinal disturbances, specifically nausea (43%) and vomiting (36%). These effects were usually CTC 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%.

Table 5: Treatment related undesirable effects: Recurrent or progressive malignant glioma

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

(CIOMS III)

Infections and infestations	
Rare:	Opportunistic infections, including *Pneumocystis carinii* pneumonia (PCP)
Blood and lymphatic system disorders	
Very common:	Thrombocytopenia, neutropenia or lymphopenia (Grade 3-4)
Uncommon:	Pancytopenia, leukopenia, anaemia (Grade 3-4)
Metabolism and nutrition disorders	
Very common:	Anorexia
Common:	Weight decrease
Nervous system disorders	
Very common:	Headache
Common:	Somnolence, dizziness, paresthesia
Respiratory, thoracic and mediastinal disorders	
Common:	Dyspnoea
Gastrointestinal disorders	
Very common:	Nausea, vomiting, constipation
Common:	Diarrhoea, abdominal pain, dyspepsia
Skin and subcutaneous tissue disorders	
Common:	Rash, alopecia, pruritus
Very rare:	Urticaria, exanthema, erythroderma, erythema multiforme
General disorders and administration site conditions	
Very common:	Fatigue
Common:	Fever, asthenia, pain, rigors, malaise, taste perversion
Rare:	Allergic reactions, including anaphylaxis, angioedema

Laboratory results: Grade 3 or 4 thrombocytopenia and neutropenia occurred in 19% and 17% respectively, of patients treated for glioma. This led to hospitalization and/or discontinuation of TEMODAL

in 8% and 4%, respectively, of patients with glioma. 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.

In a population pharmacokinetic analysis of clinical trial experience there were 101 female and 169 male subjects for whom nadir neutrophil counts were available and 110 female and 174 male subjects for whom nadir platelet counts were available. There were higher rates of Grade 4 neutropenia (ANC<500 cells/µl), 12% versus 5%, and thrombocytopenia (<20000 cells/µl), 9% versus 3%, in women vs men in the first cycle of therapy. In a 400-subject recurrent glioma data set, Grade 4 neutropenia occurred in 8% of female vs 4% of male subjects and Grade 4 thrombocytopenia in 8% of female vs 3% of male subjects in the first cycle of therapy. In a study of 288 subjects with newly diagnosed glioblastoma multiforme, Grade 4 neutropenia occurred in 3% of female vs 0% of male subjects and Grade 4 thrombocytopenia in 1% of female vs 0% of male subjects in the first cycle of therapy.

Post-marketing experience with TEMODAL

During the marketing of TEMODAL, cases of erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome and allergic reactions, including anaphylaxis, have been reported very rarely. There have been reported cases of hepatotoxicity including elevations of liver enzymes, hyperbilirubinemia, cholestasis and hepatitis. Hepatic injury, including fatal hepatic failure, has been reported very rarely (see WARNINGS/PRECAUTIONS).

Rare cases of opportunistic infections including *Pneumocystis carinii* pneumonia (PCP) and both primary and reactivated cytomegalovirus (CMV) infection have been reported. Cases of reactivation of hepatitis B infections, including some cases with fatal outcomes, have also been reported (see WARNINGS/PRECAUTIONS). Cases of herpes simplex encephalitis, including cases with fatal outcomes, have also been reported. Cases of interstitial pneumonitis/pneumonitis and pulmonary fibrosis have been reported very rarely. 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, and in some cases has resulted in a fatal outcome. Diabetes insipidus has also been reported.

CONTRAINDICATIONS: TEMODAL is contraindicated in patients who have a history of hypersensitivity reaction to its components or to dacarbazine (DTIC) since both drugs are metabolized to MTIC.

TEMODAL is contraindicated for use during pregnancy or breast feeding (see USAGE DURING PREGNANCY AND LACTATION).

TEMODAL is contraindicated in patients with severe myelosuppression.

WARNINGS/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) regardless of lymphocyte count. If lymphopenia occurs, prophylaxis until recovery of lymphopenia to at least Grade 1. 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 temozolomide.
- anti-emetic prophylaxis is strongly recommended during the monotherapy 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.

Laboratory parameters for dose modification in recurrent or progressive malignant glioma: Patients treated with TEMODAL 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 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 should 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 by 50 mg/m^2. The lowest recommended dose is 100 mg/m^2 (See Dosage and Administration for full dosing information for recurrent or progressive malignant glioma and newly diagnosed glioblastoma multiforme).

All patients

Use in patients with hepatic or renal dysfunction: -- Renal function as determined by the estimated creatinine clearance did not affect clearance of TEMODAL. The pharmacokinetics of temozolomide were comparable in patients with normal hepatic function and in those with mild or moderate hepatic dysfunction (Childs-Pugh Class I - II). The pharmacokinetics are not well defined in patients with severe

hepatic dysfunction. Based on the pharmacokinetic properties of temozolomide, dose reductions are not required in patients with mild to moderate hepatic impairment.

Hepatic injury, including fatal hepatic failure, has been reported very rarely in patients treated with temozolomide. Baseline liver function tests should be performed prior to treatment initiation. If abnormal, physicians should assess the benefit/risk prior to initiating temozolomide including the potential for fatal hepatic failure. For patients on a 42 day treatment cycle liver function tests should be repeated midway during this cycle. For all patients, liver function tests should be checked after each treatment cycle. For patients with significant liver function abnormalities, physicians should assess the benefit/risk of continuing treatment. Liver toxicity may occur several weeks or more after the last treatment with temozolomide.

Additionally, hepatitis due to hepatitis B virus (HBV) reactivation, in some cases resulting in death, has been reported. Patients should be screened for HBV infection before treatment initiation. Patients with evidence of prior HBV infection should be monitored for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following treatment with TEMODAL. Therapy should be discontinued for patients with evidence of active hepatitis B infection.

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.

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

Usage during pregnancy and lactation -- There are no studies in pregnant women. In preclinical studies in rats and rabbits administered 150 mg/m^2, 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.

The effect on the testes in both rats and dogs suggest a strong possibility for additional reproductive effects including infertility and possibly delayed offspring effects resulting in genetic damage to germ cells (a mutation in the germ cells that could be transmitted to the progeny may be possible). Considering that multiple cycles studies indicated testicular toxicity, effective contraception should be used by both male and female patients who are taking TEMODAL.

Considering that temozolomide is readily converted to MTIC, its tumorigenic potential is not unexpected. This is consistent with what has been observed with other alkylating agents, including those producing MTIC. The overall oncogenic potential of temozolomide in rats appears to be species specific and not significantly different from other cytotoxic drugs. TEMODAL capsules must not be opened or chewed, but should be swallowed whole with a glass of water. If a capsule becomes damaged, avoid contact of the powder contents with skin or mucous membranes. In case of powder contact, the hands should be washed.

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 3 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. Advise male patients not to donate semen during treatment with TEMODAL and for at least 3 months after the final dose.

OVERDOSAGE INFORMATION: Doses of 500, 750, 1,000, and 1,250 mg/m^2 (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.

INCOMPATIBILITIES: None known.

HOW SUPPLIED:

Sachet presentation
Each sachet contains 1 hard capsule.
Each carton contains 5 hard capsules, individually sealed in sachets.

STORAGE: Store below 30°C.
Keep this medication out of the reach of children.
Further information can be obtained from the doctor or pharmacist.

PRODUCT OWNER:
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