

TEMODAL CAPSULES

S-CCDS-MK7365-MTL-062021b

TEMODAL® Capsules

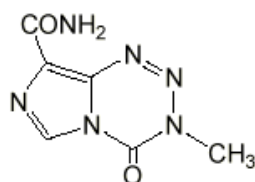
Brand of temozolomide

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 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:



Temozolomide

The material is a white to light tan/light pink powder with a molecular formula of C₆H₆N₆O₂ 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-methyltriazene-1-yl) imidazole-4-carboxamide (MTIC) at neutral and alkaline pH values, with hydrolysis taking place even faster at alkaline pH.

Each capsule contains either 20 mg or 100 mg of temozolomide. The inactive ingredients for TEMODAL 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.

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 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 SP logo, “100 mg” and two stripes.

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 O⁶ position of guanine with additional alkylation also occurring at the N⁷ position. Cytotoxic lesions that develop subsequently are thought to involve aberrant repair of the methyl adduct.

PRECLINICAL PHARMACOLOGY AND TOXICOLOGY: Single-dose toxicity of TEMODAL were conducted in mice, rats, and dogs. Estimated LD₅₀ doses by the oral route were moderately higher in the rat (approximately 1900 mg/m²) than in the mouse (approximately 1000 mg/m²). The minimum lethal dose in dogs was 600 mg/m². 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/m²), 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 + focal 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 adjuvant temozolomide ($150 - 200 \text{ mg/m}^2$) on day 1 -5 of every 28 -day cycle for 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 and adjuvant temozolomide to radiotherapy in the treatment of patients with newly diagnosed glioblastoma multiforme demonstrated a statistically significant improved overall survival compared with radiotherapy alone. (Figure 1).

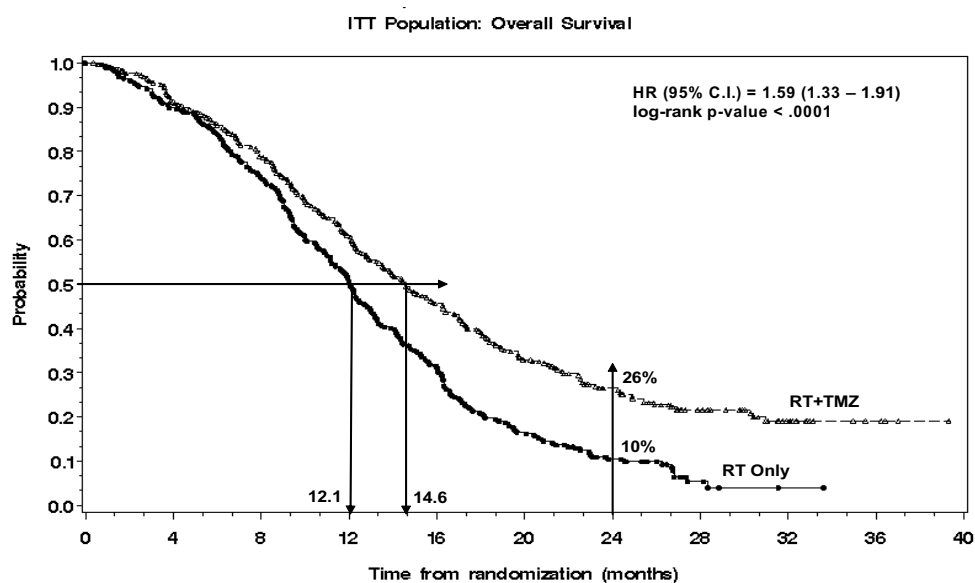


Figure 1 Kaplan-Meier Curves for Overall Survival (Intent To Treat) ITT Population

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 non-randomised 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 then as adjuvant 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:

Concomitant phase

TEMODAL is administered orally at 75 mg/m² 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 $\geq 1.5 \times 10^9/L$ thrombocyte count $\geq 100 \times 10^9/L$ common toxicity criteria (CTC) non-hematological toxicity $\leq$ Grade 1 (except for alopecia, nausea and vomiting). During treatment a complete blood count should be obtained weekly. 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 $<1.5 \times 10^9/L$	$<0.5 \times 10^9/L$
Thrombocyte Count	≥ 10 and $<100 \times 10^9/L$	$<10 \times 10^9/L$
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 $\geq 1.5 \times 10^9/L$; thrombocyte count $\geq 100 \times 10^9/L$; CTC non-hematological toxicity $\leq$ 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/m² once daily for 5 days followed by 23 days without treatment. At the start of Cycle 2, the dose is escalated to 200 mg/m² if the CTC non-hematologic toxicity for Cycle 1 is Grade ≤2 (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is ≥ 1.5 x 10⁹/L, and the thrombocyte count is ≥ 100 x 10⁹/L. If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles. The dose remains at 200 mg/m² per day for the first 5 days of each subsequent cycle except if toxicity occurs. 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/m²/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	$<1.0 \times 10^9/\text{L}$	See footnote b
Thrombocyte Count	$<50 \times 10^9/\text{L}$	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 $<100 \text{ mg}/\text{m}^2$ 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: In patients previously untreated with chemotherapy, TEMODAL is administered orally at a dose of $200 \text{ mg}/\text{m}^2$ once daily for 5 days per 28-day cycle. In patients previously treated with chemotherapy, the initial dose is $150 \text{ mg}/\text{m}^2$ once daily, to be increased in the second cycle to $200 \text{ mg}/\text{m}^2$ daily providing the absolute neutrophil count (ANC) is $\geq 1.5 \times 10^9/\text{L}$ and the thrombocyte count is $\geq 100 \times 10^9/\text{L}$ on Day 1 of the next cycle. Dose modification for TEMODAL should be based on toxicities according to nadir ANC or platelet counts.

Pediatric patient with recurrent or progressive glioma: In patients 3 years of age or older, TEMODAL is administered orally at a dose of $200 \text{ mg}/\text{m}^2$ once daily for 5 days per 28-day cycle. Pediatric patients previously treated with chemotherapy should receive an initial dose of $150 \text{ mg}/\text{m}^2$ once daily for 5 days, with escalation to $200 \text{ mg}/\text{m}^2$ 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.

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: 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, H₂-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:

Newly diagnosed patients with glioblastoma multiforme

Table 4 provides treatment emergent adverse events, in (causality not determined during clinical trials) 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: Uncommon:	Candidiasis oral, herpes simplex, infection, pharyngitis, wound infection	Candidiasis oral, infection Herpes simplex, herpes zoster, influenza-like symptoms

Blood and the lymphatic system disorders Common: Uncommon:	Leukopenia, lymphopenia, neutropenia, thrombocytopenia Anemia, febrile neutropenia	Anemia, febrile neutropenia, leukopenia, thrombocytopenia Lymphopenia, petechiae
Endocrine disorders Uncommon:	Cushingoid	Cushingoid
Metabolism and nutrition disorders Very Common: Common: Uncommon:	Anorexia Hyperglycemia, weight decreased Hypokalemia, alkaline phosphatase increased, weight increased	Anorexia Weight decreased Hyperglycemia, weight increased
Psychiatric disorders Common: Uncommon:	Anxiety, emotional lability, insomnia Agitation, apathy, behavior disorder, depression, hallucination	Anxiety, depression, emotional lability, insomnia Hallucination, amnesia
Nervous system disorders Very Common: Common: Uncommon:	Headache Dizziness, aphasia, balance impaired, concentration impaired, confusion, consciousness decreased, convulsions, memory impairment, neuropathy, paresthesia, somnolence, speech disorder, tremor	Headache, convulsions Dizziness, aphasia, balance impaired, concentration impaired, confusion, dysphasia, hemiparesis, memory impairment, neurological disorder (NOS), neuropathy, peripheral neuropathy, paresthesia, somnolence, speech disorder, tremor

	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: Uncommon:	Vision blurred Eye pain, hemianopia, vision disorder, visual acuity reduced, visual field defect	Vision blurred, diplopia, visual field defect Eye pain, eyes dry, visual acuity reduced
Ear and labyrinth disorders Common: Uncommon:	Hearing impairment Earache, hyperacusis, tinnitus, otitis media	Hearing impairment, tinnitus Deafness, earache, vertigo
Cardiac disorders Uncommon:	Palpitation	
Vascular disorders Common: Uncommon:	Edema, oedema leg, hemorrhage Hypertension, cerebral hemorrhage	Edema leg, hemorrhage, deep venous thrombosis 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: Uncommon	Micturition frequency, urinary incontinence 	Urinary incontinence Dysuria
Reproductive system and breast disorders Uncommon:	Impotence	

		Amenorrhea, breast pain, menorrhagia, vaginal haemorrhage, 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 discolouration, 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 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.

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.

Adult 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 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%. Severe myelosuppression, predominantly thrombocytopenia, was the dose-limiting AE, and occurred in 9% of all patients. Anemia, neutropenia, leukopenia, lymphopenia and pancytopenia were reported. Myelosuppression was usually predictable and most often occurred in the first few cycles, with platelet and neutrophil nadir occurring late in the cycle (usually between days 21 to 28) and recovery was rapid (usually within 1-2 weeks). No evidence of cumulative myelosuppression was observed.

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.

In a population pharmacokinetics 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/ μ L), 12% versus 5%, and thrombocytopenia (<20,000 cells/ μ L), 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 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 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 also been observed. Prolonged pancytopenia, which may result in aplastic anemia has been reported, and in some cases has resulted in 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).

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

TEMODAL must not be used by breastfeeding women (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 temozolomide,
- 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.

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) $> 1.5 \times 10^9/\text{L}$ and platelets $> 100 \times 10^9/\text{L}$. 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 $1.5 \times 10^9/\text{L}$ and platelet count exceeds $100 \times 10^9/\text{L}$. If the ANC falls to $<1.0 \times 10^9/\text{L}$ or the platelet count is $<50 \times 10^9/\text{L}$ during any cycle, the next cycle should be reduced by 50 mg/m². The lowest recommended dose is 100 mg/m². (See DOSAGE AND ADMINISTRATION for full dosing information for recurrent or progressive malignant glioma and newly diagnosed glioblastoma multiforme.)

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 to these patients.

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.

Use in Children

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: In preclinical studies in rats and rabbits administered 150 mg/m² teratogenicity and/or fetal toxicity were demonstrated. There have been no studies in pregnant women. TEMODAL could be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while they are receiving TEMODAL therapy. If using this drug during pregnancy must be considered, or if the patient becomes pregnant while taking TEMODAL, the patient should be apprised of the potential hazard to the fetus. It is not known whether TEMODAL is excreted in human milk, therefore a decision should be taken whether to discontinue nursing or to discontinue TEMODAL therapy. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with TEMODAL and for at least 6 months after the final dose.

Use in Men

Effective contraception should also be used by male patients taking TEMODAL. Temozolomide can have genotoxic effects. Because of potential risk of genotoxic effects on sperm, advise male patients with female partners of reproductive potential to use condoms during treatment with TEMODAL and for at least 3 months after the final dose.

Advise male patients not to donate semen during treatment with TEMODAL and for at least 3 months after the final dose. Men being treated with temozolomide are advised not to father a child and to seek advice on cryoconservation of spermatozoa prior to treatment because of the possibility of irreversible impairment in fertility 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.

INCOMPATIBILITIES: None known.

HOW SUPPLIED:

Bottle presentation

TEMODAL Capsules are packaged in amber glass bottles with child-resistant closure. Each bottle contains 5 capsules of TEMODAL Capsules 20 mg or 100 mg.

Sachet presentation

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

Not all pack sizes may be marketed.

STORAGE: Store below 30° C.

Keep this medication out of the reach of children.

Further information can be obtained from the doctor or pharmacist.

Shelf-life information can be found on the immediate and outer labels of the product.

Manufactured by:

Orion Pharma, Turku, Finland.

Repacked by:
Organon Heist bv, Belgium.

Product Registration Holder:
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