SCHEDULING STATUS **APPROVED PACKAGE INSERT**

S4

PROPRIETARY NAME AND DOSAGE FORM

TEMODAL® 5 mg Capsules
TEMODAL® 20 mg Capsules
TEMODAL® 100 mg Capsules
TEMODAL® 140 mg Capsules
TEMODAL® 180 mg Capsules
TEMODAL® 250 mg Capsules

COMPOSITION

Each TEMODAL Capsule contains 5 mg, 20 mg, 100, 140 mg, 180 mg or 250 mg temozolomide.

Inactive ingredients:

Capsules: Colloidal silicon dioxide, lactose, sodium starch glycolate, stearic acid and tartaric acid.

TEMODAL Capsules contain lactose.

PHARMACOLOGICAL CLASSIFICATION

A.26 Cytostatic Agents

PHARMACOLOGICAL ACTION

Temozolomide is an imidazotetrazene alkylating agent with antitumour 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.

Pharmacokinetic properties:

Pre-clinical data suggest that temozolomide crosses the blood-brain barrier rapidly and is present in the cerebrospinal fluid. CSF-levels are 20 to 40 % of plasma levels. After oral administration to adult patients, temozolomide is absorbed with peak concentrations reached as early as 20 minutes post-dose (mean times between 0,5 and 1,5 hours).

Plasma concentrations increase in a dose-related manner. Plasma clearance, volume of distribution and half-life are independent of dose. Temozolomide demonstrates low protein binding (10 to 20 %). After oral administration of ^{14}C -labelled temozolomide, mean faecal excretion of ^{14}C over 7 days post-dose was 0,8 %. Following oral administration, approximately 5 to 10 % of the dose is recovered unchanged in the urine over 24 hours, and the remainder excreted as 4-amino-5-imidazole-carboxamide hydrochloride (AIC) or unidentified polar metabolites.

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

INDICATIONS

TEMODAL is indicated for the treatment of adult patients with newly diagnosed glioblastoma multiforme after debulking surgery concomitantly with radiotherapy and then as adjuvant treatment.

TEMODAL is indicated in the treatment of patients with recurrent malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma.

TEMODAL is also indicated in the treatment of patients with advanced metastatic malignant melanoma.

CONTRA-INDICATIONS

TEMODAL is contra-indicated in patients who have a history of hypersensitivity reaction to its components or to dacarbazine (DTIC).

TEMODAL is contra-indicated for use during pregnancy (See **"PREGNANCY AND LACTATION"**).

TEMODAL is contra-indicated in patients with severe myelosuppression.

WARNINGS

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, they are to continue the prophylaxis until recovery of lymphopenia to grade ≤ 1.

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 TEMODAL.

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

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 foetal toxicity were demonstrated. TEMODAL therefore should not be administered to pregnant women. If use during pregnancy must be considered, the patient should be apprised of the potential risks to the foetus. Women of childbearing potential should be advised to avoid pregnancy while they are receiving TEMODAL and during the 6 months after discontinuation of TEMODAL therapy.

It is not known whether TEMODAL is excreted in human milk and therefore should not be used by women who are breastfeeding their babies.

Male Patients: Effective contraception should also be used by male patients who are taking TEMODAL. TEMODAL can have genotoxic effects. Therefore, men being treated with

TEMODAL 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 TEMODAL.

DOSAGE AND DIRECTIONS FOR USE

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 (adjuvant phase).

Concomitant phase

TEMODAL is administered orally at a dose of 75 mg/m^2 daily for 42 days concomitant with focal radiotherapy (60 Gy administered in 30 fractions). No dose reductions will be made, but delay or discontinuation of TEMODAL 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/litre, thrombocyte count ≥ 100 x 10^9/litre, Common Toxicity Criteria (CTC) non-haematological toxicity ≤ Grade 1 (except for alopecia, nausea and vomiting).

During treatment a complete blood count should be obtained weekly. TEMODAL administration should be interrupted or discontinued during concomitant phase according to the haematological and non-haematological 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/litre	< 0,5 x 10^9/litre
Thrombocyte Count	≥ 10 and < 100 x 10^9/litre	< 10 x 10^9/litre
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 are met: absolute neutrophil count ≥ 1,5 x 10^9/litre; thrombocyte count ≥ 100 x 10^9/litre; CTC non-hematological toxicity ≤ Grade 1 (except for alopecia, nausea, vomiting)		

TMZ = TEMODAL CTC = Common Toxicity Criteria

Adjuvant (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 (adjuvant/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-haematological toxicity for Cycle I is Grade ≤ 2 (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is ≥ 1,5 x 10^9/litre, and the thrombocyte count is ≥ 100 x 10^9/litre. 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 adjuvant/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 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 to 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/litre	See footnote b
Thrombocyte Count	< 50 x 10^9/litre	See footnote b
CTC Non-haematological 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 level -1 (100 mg/m^2) still results in unacceptable toxicity
- the same Grade 3 non-haematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction

TMZ = TEMODAL CTC = Common Toxicity Criteria

Adult patients 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 $\geq$ 1,5 x 10^9/litre and the thrombocyte count is $\geq$ 100 x 10^9/litre on Day 1 of the next cycle. Dose modification for TEMODAL should be based on toxicities according to nadir ANC or platelet counts.

Paediatric patients recurrent or progressive glioma: In patients 3 years of age and older previously untreated with chemotherapy, TEMODAL is administered orally at a dose of 200 mg/m^2 once daily for the first 5 days per 28-day cycle. Paediatric 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 haematological toxicity.

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

Prior to dosing the following laboratory parameters must be met: ANC $\geq$ 1,5 x 10^9/litre and platelet count $\geq$ 100 x 10^9/litre. 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/litre and platelet count exceeds 100 x 10^9/litre. If the ANC falls to < 1,0 x 10^9/litre or the platelet count is < 50 x 10^9/litre 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.

TEMODAL Capsules should be administered in the fasting state, at least 1 hour before a meal.

Anti-emetic 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.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

SIDE EFFECTS

Clinical Trial Experience in Patients Treated with TEMODAL Capsules

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 and < 1/10), Uncommon (≥ 1/1 000 and < 1/100), CIOMS III

Body System	**TMZ + Concomitant Radiotherapy** n=288*	**TMZ Adjuvant Therapy** n=224
Infections and Infestations		
Common:	Oral candidiasis, *Herpes simplex*, infection, pharyngitis, wound infection	Oral candidiasis, infection
Uncommon:		*Herpes simplex, Herpes zoster*, influenza-like symptoms
Blood and the lymphatic system disorders		
Common:	Leukopenia, lymphopenia, neutropenia, thrombocytopenia	Anaemia, febrile neutropenia, leukopenia, thrombocytopenia
Uncommon:	Anaemia, febrile neutropenia	Lymphopenia, petechiae
Endocrine disorders		
Uncommon:	Cushingoid	Cushingoid

Table 4. TEMODAL (TMZ) and Radiotherapy: Treatment-Emergent Events during Concomitant and Adjuvant Treatment Very Common (≥ 1/10), Common (≥ 1/100 and < 1/10), Uncommon (≥ 1/1 000 and < 1/100), CIOMS III		
Metabolism and nutrition disorders		
Very Common:	Anorexia	Anorexia
Common:	Hyperglycaemia, weight decreased	Weight decreased
Uncommon:	Hypokalaemia, alkaline phosphatase increased, weight increased	Hyperglycaemia, 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, impaired balance, impaired concentration, confusion, decreased consciousness, convulsions, memory impairment, neuropathy, paraesthesia, somnolence, speech disorder, tremor	Dizziness, aphasia, impaired balance, impaired concentration, confusion, dysphasia, hemiparesis, memory impairment, neurological disorder (NOS), neuropathy, peripheral neuropathy, paraesthesia, somnolence, speech disorder, tremor
Uncommon:	Ataxia, impaired cognition, dysphasia, extrapyramidal disorder, abnormal gait, hemiparesis, hyperesthesia,	Ataxia, abnormal coordination, abnormal gait, hemiplegia, hyperaesthesia, sensory disturbance

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

Very Common (≥ 1/10), Common (≥ 1/100 and < 1/10), Uncommon (≥ 1/1 000 and < 1/100), CIOMS III

	hypoaesthesia, neurological disorder (NOS), peripheral neuropathy, status epilepticus	
Eye disorders		
Common:	Vision blurred	Vision blurred, diplopia, visual field defect
Uncommon:	Eye pain, hemianopia, vision disorder, reduced visual acuity, visual field defect	Eye pain, eyes dry, reduced visual acuity
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:	Oedema, leg oedema, haemorrhage	Leg oedema, haemorrhage, deep venous thrombosis
Uncommon:	Hypertension, cerebral haemorrhage	Oedema, peripheral oedema, pulmonary embolism
Respiratory, thoracic and mediastinal disorders		
Common:	Coughing, dyspnoea	Coughing, dyspnoea
Uncommon:	Pneumonia, upper respiratory infection, nasal congestion	Pneumonia, sinusitis, upper respiratory infection, bronchitis
Gastrointestinal disorders		
Very Common:	Constipation, nausea, vomiting	Constipation, nausea, vomiting

Table 4. TEMODAL (TMZ) and Radiotherapy: Treatment-Emergent Events during Concomitant and Adjuvant Treatment Very Common (≥ 1/10), Common (≥ 1/100 and < 1/10), Uncommon (≥ 1/1 000 and < 1/100), CIOMS III		
Common: Uncommon:	Abdominal pain, diarrhoea, dyspepsia, dysphagia, stomatitis	Diarrhoea, dyspepsia, dysphagia, dry mouth, stomatitis Abdominal distension, faecal incontinence, gastrointestinal disorder (NOS), gastroenteritis, haemorrhoids
Skin and subcutaneous tissue disorders Very Common: Common: Uncommon:	 Alopecia, rash Dermatitis, dry skin, erythema, pruritus Photosensitivity reaction, abnormal pigmentation, skin exfoliation	 Alopecia, rash Dry skin, pruritus Erythema, abnormal pigmentation, increased sweating
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:	 Frequent micturition, urinary incontinence 	 Urinary incontinence Dysuria
Reproductive system and breast disorders Uncommon:	 Impotence	 Amenorrhoea, breast pain,

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

Very Common (≥ 1/10), Common (≥ 1/100 and < 1/10), Uncommon (≥ 1/1 000 and < 1/100), CIOMS III

		menorrhagia, vaginal haemorrhage, vaginitis
General disorders and administration site conditions		
Very Common:	Fatigue	Fatigue
Common:	Fever, pain, allergic reaction, radiation injury, facial oedema, 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 oedema, taste perversion
Investigation		
Common:	ALT increased	ALT increased
Uncommon:	Gamma GT increased, hepatic enzymes increased, AST 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.

Patients with recurrent anaplastic astrocytoma, glioblastoma multiforme or malignant melanoma:

Table 5: Frequency of adverse drug reactions reported in clinical trials or spontaneously, classified according to body system:

Table 5: Adverse Effects in patients with recurrent anaplastic astrocytoma, glioblastoma multiforme or malignant melanoma Very Common (≥ 10 %), Common (≥ 1 % and < 10 %)	
Neurological Very common: Common:	 Fatigue, headache Somnolence, asthenia, dizziness, paresthesia
Gastrointestinal Very common: Common:	 Nausea, vomiting, constipation, anorexia Diarrhoea, abdominal pain, dyspepsia, taste perversion
Haematological Very Common: Common:	 Thrombocytopenia, neutropenia Anaemia, leucopenia
Dermatological Common:	 Rash, alopecia, pruritus, petechiae
Respiratory Common:	 Dyspnoea
General Common:	 Fever, pain, malaise, weight decrease, rigors

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 (Grade 3) nausea and vomiting was 4 %.

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 hospitalisation 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 28), and recovery was usually within 1 to 2 weeks. No evidence of cumulative myelosuppression was observed.

Pancytopenia, leukopenia and anaemia have also been reported. Lymphopenia has also been reported very commonly.

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/µL), 12 % versus 5 %, and thrombocytopenia (<20 000 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 versus 4 % of male subjects and Grade 4 thrombocytopenia in 8 % of female versus 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 versus 0 % of male subjects and Grade 4 thrombocytopenia in 1 % of female versus 0 % of male subjects in the first cycle of therapy.

Post-Marketing Experience with TEMODAL

During the marketing of TEMODAL allergic reactions including anaphylaxis have been reported Cases of erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome have also been observed. There have been reported cases of hepatotoxicity including elevations of liver enzymes, hyperbilirubinaemia, cholestasis and hepatitis.

Cases of opportunistic infections including *Pneumocystis carinii* pneumonia (PCP) have been reported. Cases of herpes simplex encephalitis, including cases of fatal outcomes, have also been reported. Cases of interstitial pneumonitis/pneumonitis and pulmonary fibrosis have been reported.

Cases of myelodysplatic syndrome (MDS) and secondary malignancies, including myeloid leukaemia have been reported in patients treated with regimens that included TEMODAL.

Prolonged pancytopenia, which may result in aplastic anaemia have been reported.

SPECIAL PRECAUTIONS

There may be a higher occurrence of PCP when TEMODAL is administered during a longer dosing regimen. However, all patients receiving TEMODAL, particularly patients receiving steroids should be observed closely for the development of PCP regardless of the regimen.

Anti-emetic 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.

Laboratory parameters: Prior to dosing the following laboratory parameters must be met: ANC $\geq$ 1,5 x 10^9/L and platelet count $\geq$ 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 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.

Use in patients with hepatic or renal dysfunction: The pharmacokinetics of TEMODAL was 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 TEMODAL, 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 with use of TEMODAL in children under the age of 18 years.

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

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucosegalactose malabsorption should not take TEMODAL Capsules.

Effects on ability to drive or use machines: No studies on the effects on the ability to drive and use machines have been performed. The ability to drive and use machines may be impaired in patients treated with TEMODAL due to fatigue and somnolence.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

See **"SIDE EFFECTS AND SPECIAL PRECAUTIONS"**.

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 haematological 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, haematologic evaluation is needed. Supportive measures should be provided as necessary.

IDENTIFICATION

TEMODAL 5 mg Capsules: No. 3 capsule with opaque green cap and opaque white body containing a white to light pink, light tan powder. The cap is imprinted in black ink with "TEMODAL", the body is imprinted in black ink with 2 stripes, "5 mg" and the SP logo.

TEMODAL 20 mg Capsules: No. 2 capsule with yellow cap and opaque white body containing a white to light pink, light tan powder. The cap is imprinted in black ink with "TEMODAL", the body is imprinted in black ink with 2 stripes, "20 mg" and the SP logo.

TEMODAL 100 mg Capsules: No. 1 capsule with opaque pink cap and opaque white body containing a white to light pink, light tan powder. The cap is imprinted in black ink with "TEMODAL", the body is imprinted in black ink with 2 stripes, "100 mg" and the SP logo.

TEMODAL 140 mg Capsules: No. 0 capsule with blue cap and opaque white body containing a white to light pink, light tan powder. The cap is imprinted in black ink with “TEMODAL”, the body is imprinted in black ink with 2 stripes, “140 mg” and the SP logo

TEMODAL 180 mg Capsules: No. 0 capsule with opaque orange cap and opaque white body containing a white to light pink, light tan powder. The cap is imprinted in black ink with “TEMODAL”, the body is imprinted in black ink with 2 stripes, “180 mg” and the SP logo

TEMODAL 250 mg Capsules: No. 0 capsule with opaque white cap and opaque white body containing a white to light pink, light tan powder. The cap is imprinted in black ink with “TEMODAL”, the body is imprinted in black ink with 2 stripes, “250 mg” and the SP logo.

PRESENTATION

TEMODAL Capsules are packaged in sachets with a child-resistant tear notch in packs of 5 capsules.

STORAGE INSTRUCTIONS

Keep at or below 30 °C. Do not refrigerate. Protect from moisture.
Keep out of reach of children.

REGISTRATION NUMBERS

TEMODAL 5 mg Capsules: 32/26/0721
TEMODAL 20 mg Capsules: 32/26/0722
TEMODAL 100 mg Capsules: 32/26/0723
TEMODAL 140 mg Capsules: 42/26/0961
TEMODAL 180 mg Capsules: 42/26/0962
TEMODAL 250 mg Capsules: 32/26/0724

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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