

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Temodal 5 mg hard capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 5 mg temozolomide.

### Excipient with known effect:

Each hard capsule contains 132.8 mg of anhydrous lactose.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Hard capsule (capsule).

The hard capsules have an opaque white body, an opaque green cap, and are imprinted with black ink. The cap is imprinted with "Temodal". The body is imprinted with "5 mg", the Schering-Plough logo and two stripes.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Temodal is indicated for the treatment of:

- adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment.
- children from the age of three years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy.

### 4.2 Posology and method of administration

Temodal should only be prescribed by physicians experienced in the oncological treatment of brain tumours.

Anti-emetic therapy may be administered (see section 4.4).

### Posology

#### 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 (TMZ) monotherapy (monotherapy phase).

#### *Concomitant phase*

TMZ is administered orally at a dose of 75 mg/m<sup>2</sup> daily for 42 days concomitant with focal radiotherapy (60 Gy administered in 30 fractions). No dose reductions are recommended, but delay or discontinuation of TMZ administration should be decided weekly according to haematological and non-haematological toxicity criteria. TMZ administration can be continued throughout the 42 day concomitant period (up to 49 days) if all of the following conditions are met:

- absolute neutrophil count (ANC)  $\geq 1.5 \times 10^9/l$
- thrombocyte count  $\geq 100 \times 10^9/l$
- common toxicity criteria (CTC) non-haematological toxicity  $\leq$  Grade 1 (except for alopecia, nausea and vomiting).

During treatment a complete blood count should be obtained weekly. TMZ administration should be temporarily interrupted or permanently discontinued during the concomitant phase according to the haematological and non-haematological toxicity criteria as noted in Table 1.

Toxicity	TMZ interruption <sup>a</sup>	TMZ discontinuation
Absolute neutrophil count	$\geq 0.5$ and $< 1.5 \times 10^9/l$	$< 0.5 \times 10^9/l$
Thrombocyte count	$\geq 10$ and $< 100 \times 10^9/l$	$< 10 \times 10^9/l$
CTC non-haematological toxicity (except for alopecia, nausea, vomiting)	CTC Grade 2	CTC Grade 3 or 4

a: Treatment with concomitant TMZ can be continued when all of the following conditions are met: absolute neutrophil count  $\geq 1.5 \times 10^9/l$ ; thrombocyte count  $\geq 100 \times 10^9/l$ ; CTC non-haematological toxicity  $\leq$  Grade 1 (except for alopecia, nausea, vomiting).

### *Monotherapy phase*

Four weeks after completing the TMZ + RT concomitant phase, TMZ is administered for up to 6 cycles of monotherapy treatment. Dose in Cycle 1 (monotherapy) is  $150 \text{ mg/m}^2$  once daily for 5 days followed by 23 days without treatment. At the start of Cycle 2, the dose is escalated to  $200 \text{ mg/m}^2$  if the CTC non-haematological toxicity for Cycle 1 is Grade  $\leq 2$  (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is  $\geq 1.5 \times 10^9/l$ , and the thrombocyte count is  $\geq 100 \times 10^9/l$ . If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles. Once escalated, the dose remains at  $200 \text{ mg/m}^2$  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 TMZ). The dose should be reduced or administration discontinued according to Table 3.

Dose level	TMZ dose ( $\text{mg/m}^2/\text{day}$ )	Remarks
-1	100	Reduction for prior toxicity
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2-6 in absence of toxicity

Toxicity	Reduce TMZ by 1 dose level <sup>a</sup>	Discontinue TMZ
Absolute neutrophil count	$< 1.0 \times 10^9/l$	See footnote b
Thrombocyte count	$< 50 \times 10^9/l$	See footnote b
CTC non-haematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4 <sup>b</sup>

a: TMZ dose levels are listed in Table 2.

b: TMZ is to be discontinued if:

- dose level -1 ( $100 \text{ mg/m}^2$ ) still results in unacceptable toxicity
- the same Grade 3 non-haematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction.

Adult and paediatric patients 3 years of age or older with recurrent or progressive malignant glioma:

A treatment cycle comprises 28 days. In patients previously untreated with chemotherapy, TMZ is administered orally at a dose of 200 mg/m<sup>2</sup> once daily for the first 5 days followed by a 23 day treatment interruption (total of 28 days). In patients previously treated with chemotherapy, the initial dose is 150 mg/m<sup>2</sup> once daily, to be increased in the second cycle to 200 mg/m<sup>2</sup> once daily, for 5 days if there is no haematological toxicity (see section 4.4)

Special populations

*Paediatric population*

In patients 3 years of age or older, TMZ is only to be used in recurrent or progressive malignant glioma. Experience in these children is very limited (see sections 4.4 and 5.1). The safety and efficacy of TMZ in children under the age of 3 years have not been established. No data are available.

*Patients with hepatic or renal impairment*

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

*Elderly patients*

Based on a population pharmacokinetic analysis in patients 19-78 years of age, clearance of TMZ is not affected by age. However, elderly patients (> 70 years of age) appear to be at increased risk of neutropenia and thrombocytopenia (see section 4.4).

Method of administration

Temodal hard capsules should be administered in the fasting state.

The capsules must be swallowed whole with a glass of water and must not be opened or chewed.

If vomiting occurs after the dose is administered, a second dose should not be administered that day.

**4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to dacarbazine (DTIC).

Severe myelosuppression (see section 4.4).

**4.4 Special warnings and precautions for use**

Opportunistic infections and reactivation of infections

Opportunistic infections (such as *Pneumocystis jirovecii* pneumonia) and reactivation of infections (such as HBV, CMV) have been observed during the treatment with TMZ (see section 4.8).

Meningoencephalitis herpetic

In post marketing cases, meningoencephalitis herpetic (including fatal cases) has been observed in patients receiving TMZ in combination with radiotherapy, including cases of concomitant steroids administration.

#### *Pneumocystis jirovecii* pneumonia

Patients who received concomitant TMZ and RT in a pilot trial for the prolonged 42-day schedule were shown to be at particular risk for developing *Pneumocystis jirovecii* pneumonia (PCP). Thus, prophylaxis against PCP is required for all patients receiving concomitant TMZ and RT 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  $\leq 1$ .

There may be a higher occurrence of PCP when TMZ is administered during a longer dosing regimen. However, all patients receiving TMZ, particularly patients receiving steroids, should be observed closely for the development of PCP, regardless of the regimen. Cases of fatal respiratory failure have been reported in patients using TMZ, in particular in combination with dexamethasone or other steroids.

#### HBV

Hepatitis due to hepatitis B virus (HBV) reactivation, in some cases resulting in death, has been reported. Experts in liver disease should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease). During treatment patients should be monitored and managed appropriately.

#### Hepatotoxicity

Hepatic injury, including fatal hepatic failure, has been reported in patients treated with TMZ (see section 4.8). 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.

#### Malignancies

Cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukaemia, have also been reported very rarely (see section 4.8).

#### Anti-emetic therapy

Nausea and vomiting are very commonly associated with TMZ.  
Anti-emetic therapy may be administered prior to or following administration of TMZ.

#### *Adult patients with newly-diagnosed glioblastoma multiforme*

Anti-emetic prophylaxis is recommended prior to the initial dose of concomitant phase and it is strongly recommended during the monotherapy phase.

#### *Patients with recurrent or progressive malignant glioma*

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

### Laboratory parameters

Patients treated with TMZ may experience myelosuppression, including prolonged pancytopenia, which may result in aplastic anaemia, which in some cases has resulted in a fatal outcome. In some cases, exposure to concomitant medicinal products associated with aplastic anaemia, including carbamazepine, phenytoin, and sulfamethoxazole/trimethoprim, complicates assessment. Prior to dosing, the following laboratory parameters must be met: ANC  $\geq 1.5 \times 10^9/l$  and platelet count  $\geq 100 \times 10^9/l$ . A complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until ANC  $> 1.5 \times 10^9/l$  and platelet count  $> 100 \times 10^9/l$ . If ANC falls to  $< 1.0 \times 10^9/l$  or the platelet count is  $< 50 \times 10^9/l$  during any cycle, the next cycle should be reduced one dose level (see section 4.2). Dose levels include  $100 \text{ mg/m}^2$ ,  $150 \text{ mg/m}^2$ , and  $200 \text{ mg/m}^2$ . The lowest recommended dose is  $100 \text{ mg/m}^2$ .

### Paediatric population

There is no clinical experience with use of TMZ in children under the age of 3 years. Experience in older children and adolescents is very limited (see sections 4.2 and 5.1).

### Elderly patients (> 70 years of age)

Elderly patients appear to be at increased risk of neutropenia and thrombocytopenia, compared with younger patients. Therefore, special care should be taken when TMZ is administered in elderly patients.

### Male patients

Men being treated with TMZ should be advised not to father a child up to 6 months after receiving the last dose and to seek advice on cryoconservation of sperm prior to treatment (see section 4.6).

### Lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## **4.5 Interaction with other medicinal products and other forms of interaction**

In a separate phase I study, administration of TMZ with ranitidine did not result in alterations in the extent of absorption of temozolomide or the exposure to its active metabolite monomethyl triazenoimidazole carboxamide (MTIC).

Administration of TMZ with food resulted in a 33 % decrease in  $C_{\text{max}}$  and a 9 % decrease in area under the curve (AUC).

As it cannot be excluded that the change in  $C_{\text{max}}$  is clinically significant, Temodal should be administered without food.

Based on an analysis of population pharmacokinetics in phase II trials, co-administration of dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron,  $H_2$  receptor antagonists, or phenobarbital did not alter the clearance of TMZ. Co-administration with valproic acid was associated with a small but statistically significant decrease in clearance of TMZ.

No studies have been conducted to determine the effect of TMZ on the metabolism or elimination of other medicinal products. However, since TMZ does not undergo hepatic metabolism and exhibits low protein binding, it is unlikely that it would affect the pharmacokinetics of other medicinal products (see section 5.2).

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

#### Paediatric population

Interaction studies have only been performed in adults.

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

There are no data in pregnant women. In preclinical studies in rats and rabbits receiving 150 mg/m<sup>2</sup> TMZ, teratogenicity and/or foetal toxicity were demonstrated (see section 5.3). Temodal should not be administered to pregnant women. If use during pregnancy must be considered, the patient should be apprised of the potential risk to the foetus.

#### Breast-feeding

It is not known whether TMZ is excreted in human milk; thus, breast-feeding should be discontinued while receiving treatment with TMZ.

#### Women of childbearing potential

Women of childbearing potential should be advised to use effective contraception to avoid pregnancy while they are receiving TMZ.

#### Male fertility

TMZ can have genotoxic effects. Therefore, men being treated with it should be advised not to father a child up to 6 months after receiving the last dose and to seek advice on cryoconservation of sperm prior to treatment, because of the possibility of irreversible infertility due to therapy with TMZ.

### **4.7 Effects on ability to drive and use machines**

TMZ has minor influence on the ability to drive and use machines due to fatigue and somnolence (see section 4.8).

### **4.8 Undesirable effects**

#### Clinical trial experience

In patients treated with TMZ, whether used in combination with RT or as monotherapy following RT for newly-diagnosed glioblastoma multiforme, or as monotherapy in patients with recurrent or progressive glioma, the reported very common adverse reactions were similar: nausea, vomiting, constipation, anorexia, headache and fatigue. Convulsions were reported very commonly in the newly-diagnosed glioblastoma multiforme patients receiving monotherapy, and rash was reported very commonly in newly-diagnosed glioblastoma multiforme patients receiving TMZ concurrent with RT and also as monotherapy, and commonly in recurrent glioma. Most haematologic adverse reactions were reported commonly or very commonly in both indications (Tables 4 and 5); the frequency of grade 3-4 laboratory findings is presented after each table.

In the tables undesirable effects are classified according to System Organ Class and frequency. Frequency groupings are defined according to the following convention: Very common ( $\geq 1/10$ ); Common ( $\geq 1/100$  to  $< 1/10$ ); Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); Very rare ( $< 1/10,000$ ). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Newly-diagnosed glioblastoma multiforme

Table 4 provides treatment-emergent adverse events in patients with newly-diagnosed glioblastoma multiforme during the concomitant and monotherapy phases of treatment.

<i>Table 4. Treatment-emergent events during concomitant and monotherapy treatment phases in patients with newly-diagnosed glioblastoma multiforme</i>		
System organ class	TMZ + concomitant RT n=288*	TMZ monotherapy n=224
Infections and infestations		
Common:	Infection, <i>Herpes simplex</i> , wound infection, pharyngitis, candidiasis oral	Infection, candidiasis oral
Uncommon:		<i>Herpes simplex</i> , herpes zoster, influenza-like symptoms
Blood and lymphatic system disorders		
Common:	Neutropenia, thrombocytopenia, lymphopenia, leukopenia	Febrile neutropenia, thrombocytopenia, anaemia, leukopenia
Uncommon:	Febrile neutropenia, anaemia	Lymphopenia, petechiae
Endocrine disorders		
Uncommon:	Cushingoid	Cushingoid
Metabolism and nutrition disorders		
Very common:	Anorexia	Anorexia
Common:	Hyperglycaemia, weight decreased	Weight decreased
Uncommon:	Hypokalemia, 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	Convulsions, headache
Common:	Convulsions, consciousness decreased, somnolence, aphasia, balance impaired, dizziness, confusion, memory impairment, concentration impaired, neuropathy, paresthesia, speech disorder, tremor	Hemiparesis, aphasia, balance impaired, somnolence, confusion, dizziness, memory impairment, concentration impaired, dysphasia, neurological disorder (NOS), neuropathy, peripheral neuropathy, paresthesia, speech disorder, tremor

<i>Table 4. Treatment-emergent events during concomitant and monotherapy treatment phases in patients with newly-diagnosed glioblastoma multiforme</i>		
System organ class	TMZ + concomitant RT n=288*	TMZ monotherapy n=224
Uncommon:	Status epilepticus, extrapyramidal disorder, hemiparesis, ataxia, cognition impaired, dysphasia, gait abnormal, hyperesthesia, hypoesthesia, neurological disorder (NOS), peripheral neuropathy	Hemiplegia, ataxia, coordination abnormal, gait abnormal, hyperesthesia, sensory disturbance
Eye disorders		
Common:	Vision blurred	Visual field defect, vision blurred, diplopia
Uncommon:	Hemianopia, visual acuity reduced, vision disorder, visual field defect, eye pain	Visual acuity reduced, eye pain, eyes dry
Ear and labyrinth disorders		
Common:	Hearing impairment	Hearing impairment, tinnitus
Uncommon:	Otitis media, tinnitus, hyperacusis, earache	Deafness, vertigo, earache
Cardiac disorders		
Uncommon:	Palpitation	
Vascular disorders		
Common:	Haemorrhage, oedema, oedema leg	Haemorrhage, deep venous thrombosis, oedema leg
Uncommon:	Cerebral haemorrhage, hypertension	Embolism pulmonary, oedema, oedema peripheral
Respiratory, thoracic and mediastinal disorders		
Common:	Dyspnoea, coughing	Dyspnoea, coughing
Uncommon:	Pneumonia, upper respiratory infection, nasal congestion	Pneumonia, sinusitis, upper respiratory infection, bronchitis
Gastrointestinal disorders		
Very common:	Constipation, nausea, vomiting	Constipation, nausea, vomiting
Common:	Stomatitis, diarrhoea, abdominal pain, dyspepsia, dysphagia	Stomatitis, diarrhoea, dyspepsia, dysphagia, mouth dry
Uncommon:		Abdominal distension, fecal incontinence, gastrointestinal disorder (NOS), gastroenteritis, haemorrhoids
Skin and subcutaneous tissue disorders		
Very common:	Rash, alopecia	Rash, alopecia
Common:	Dermatitis, dry skin, erythema, pruritus	Dry skin, pruritus

<i>Table 4. Treatment-emergent events during concomitant and monotherapy treatment phases in patients with newly-diagnosed glioblastoma multiforme</i>		
System organ class	TMZ + concomitant RT n=288*	TMZ monotherapy n=224
Uncommon:	Skin exfoliation, photosensitivity reaction, pigmentation abnormal	Erythema, pigmentation abnormal, sweating increased
Musculoskeletal and connective tissue disorders		
Common:	Muscle weakness, arthralgia	Muscle weakness, arthralgia, musculoskeletal pain, myalgia
Uncommon:	Myopathy, back pain, musculoskeletal pain, myalgia	Myopathy, back pain
Renal and urinary disorders		
Common:	Micturition frequency, urinary incontinence	Urinary incontinence
Uncommon:		Dysuria
Reproductive system and breast disorders		
Uncommon:	Impotence	Vaginal haemorrhage, menorrhagia, amenorrhea, vaginitis, breast pain
General disorders and administration site conditions		
Very common:	Fatigue	Fatigue
Common:	Allergic reaction, fever, radiation injury, face oedema, pain, taste perversion	Allergic reaction, fever, radiation injury, pain, taste perversion
Uncommon:	Asthenia, flushing, hot flushes, condition aggravated, rigors, tongue discolouration, parosmia, thirst	Asthenia, face oedema, pain, condition aggravated, rigors, tooth disorder
Investigations		
Common:	ALT increased	ALT increased
Uncommon:	Hepatic enzymes increased, Gamma GT increased, AST increased	

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

#### *Laboratory results*

Myelosuppression (neutropenia and thrombocytopenia), which is known dose-limiting toxicity for most cytotoxic agents, including TMZ, was 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 TMZ.

#### *Recurrent or progressive malignant glioma*

In clinical trials, the most frequently occurring treatment-related undesirable effects were gastrointestinal disorders, specifically nausea (43 %) and vomiting (36 %). These reactions were usually Grade 1 or 2 (0 – 5 episodes of vomiting in 24 hours) and were either self-limiting or readily controlled with standard anti-emetic therapy. The incidence of severe nausea and vomiting was 4 %.

Table 5 includes adverse reactions reported during clinical trials for recurrent or progressive malignant glioma and following the marketing of Temodal.

<i>Table 5. Adverse reactions in patients with recurrent or progressive malignant glioma</i>	
Infections and infestations	
Rare:	Opportunistic infections, including PCP
Blood and lymphatic system disorders	
Very common:	Neutropenia or lymphopenia (grade 3-4), thrombocytopenia (grade 3-4)
Uncommon:	Pancytopenia, anaemia (grade 3-4), leukopenia
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:	Vomiting, nausea, constipation
Common:	Diarrhoea, abdominal pain, dyspepsia
Skin and subcutaneous tissue disorders	
Common:	Rash, pruritus, alopecia
Very rare:	Erythema multiforme, erythroderma, urticaria, exanthema
General disorders and administration site conditions	
Very common:	Fatigue
Common:	Fever, asthenia, rigors, malaise, pain, taste perversion
Very 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 malignant glioma. This led to hospitalisation and/or discontinuation of TMZ in 8 % and 4 %, respectively. 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. The presence of thrombocytopenia may increase the risk of bleeding, and the presence of neutropenia or leukopenia may increase the risk of infection.

#### *Gender*

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 ( $ANC < 0.5 \times 10^9/l$ ), 12 % vs 5 %, and thrombocytopenia ( $< 20 \times 10^9/l$ ), 9 % vs 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.

### Paediatric population

Oral TMZ has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. Although the data is limited, tolerance in children is expected to be the same as in adults. The safety of TMZ in children under the age of 3 years has not been established.

### Post-Marketing Experience

The following additional serious adverse reactions have been identified during post-marketing exposure:

<i>Table 6. Summary of events reported with temozolomide in the post-marketing setting</i>	
<b>Infections and infestations*</b>	
Uncommon:	cytomegalovirus infection, infection reactivation such as cytomegalovirus, hepatitis B virus <sup>†</sup> , meningoencephalitis herpetic <sup>†</sup> , sepsis <sup>†</sup>
<b>Blood and lymphatic system disorders</b>	
Very rare:	prolonged pancytopenia, aplastic anaemia <sup>†</sup>
<b>Neoplasm benign, malignant and unspecified</b>	
Very rare:	myelodysplastic syndrome (MDS), secondary malignancies, including myeloid leukaemia
<b>Endocrine disorders*</b>	
Uncommon:	diabetes insipidus
<b>Respiratory, thoracic and mediastinal disorders</b>	
Very rare:	interstitial pneumonitis/pneumonitis, pulmonary fibrosis, respiratory failure <sup>†</sup>
<b>Hepatobiliary disorders*</b>	
Common:	liver enzymes elevations
Uncommon:	hyperbilirubinemia, cholestasis, hepatitis, hepatic injury, hepatic failure <sup>†</sup>
<b>Skin and subcutaneous tissue disorders</b>	
Very rare:	toxic epidermal necrolysis, Stevens-Johnson syndrome

<sup>†</sup> Including cases with fatal outcome

\* Frequencies estimated based on relevant clinical trials.

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system** listed in [Appendix V](#).

## **4.9 Overdose**

Doses of 500, 750, 1,000, and 1,250 mg/m<sup>2</sup> (total dose per cycle over 5 days) have been evaluated clinically in patients. Dose-limiting toxicity was haematological and was reported with any dose but is expected to be more severe at higher doses. An overdose of 10,000 mg (total dose in a single cycle,

over 5 days) was taken by one patient and the adverse reactions reported were pancytopenia, pyrexia, multi-organ failure and death. There are reports of patients who have taken the recommended dose for 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, haematological evaluation is needed. Supportive measures should be provided as necessary.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents - Other alkylating agents, ATC code: L01A X03

#### Mechanism of action

Temozolomide is a triazene, which undergoes rapid chemical conversion at physiologic pH to the active monomethyl triazenoimidazole carboxamide (MTIC). The cytotoxicity of MTIC is thought to be due primarily to alkylation at the O<sup>6</sup> position of guanine with additional alkylation also occurring at the N<sup>7</sup> position. Cytotoxic lesions that develop subsequently are thought to involve aberrant repair of the methyl adduct.

#### Clinical efficacy and safety

##### *Newly-diagnosed glioblastoma multiforme*

A total of 573 patients were randomised to receive either TMZ + RT (n=287) or RT alone (n=286). Patients in the TMZ + RT arm received concomitant TMZ (75 mg/m<sup>2</sup>) 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 TMZ (150 - 200 mg/m<sup>2</sup>) 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 jirovecii* pneumonia (PCP) prophylaxis was required during RT and combined TMZ therapy.

TMZ 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 TMZ + 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 favour of the TMZ arm. The estimated probability of surviving 2 years or more (26 % vs 10 %) is higher for the RT + TMZ arm. The addition of concomitant TMZ to RT, followed by TMZ monotherapy in the treatment of patients with newly-diagnosed glioblastoma multiforme demonstrated a statistically significant improvement in overall survival (OS) compared with RT alone (Figure 1).

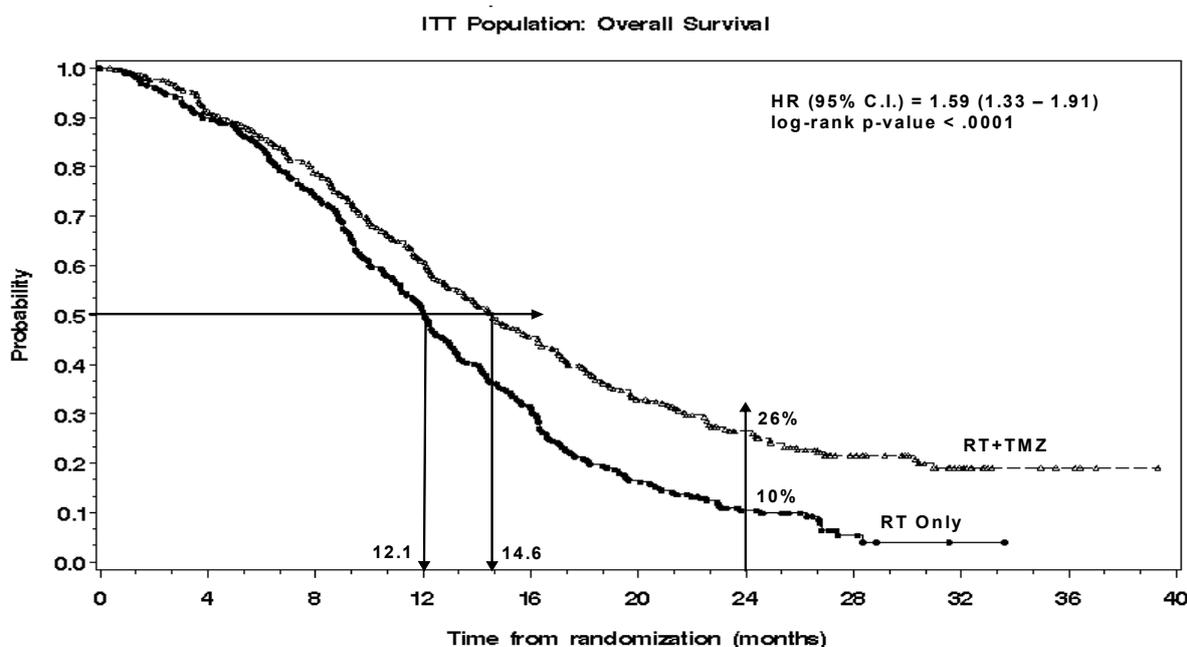


Figure 1 Kaplan-Meier curves for overall survival (intent-to-treat population)

The results from the trial were not consistent in the subgroup of patients with a poor performance status (WHO PS=2, n=70), where overall survival and time to progression were similar in both arms. However, no unacceptable risks appear to be present in this patient group.

#### Recurrent or progressive malignant glioma

Data on clinical efficacy in patients with glioblastoma multiforme (Karnofsky performance status [KPS]  $\geq 70$ ), progressive or recurrent after surgery and RT, were based on two clinical trials with oral TMZ. One was a non-comparative trial in 138 patients (29 % received prior chemotherapy), and the other was a randomised active-controlled trial of TMZ vs 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 (ORR) based on MRI scans was 8 %.

In the randomised active-controlled trial, the PFS at 6 months was significantly greater for TMZ 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 TMZ and procarbazine, respectively (log rank  $p = 0.33$ ). At 6 months, the fraction of surviving patients was significantly higher in the TMZ 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  $\geq 80$ .

Data on time to worsening of neurological status favoured TMZ over procarbazine as did data on time to worsening of performance status (decrease to a KPS of  $< 70$  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 TMZ than for procarbazine (log rank  $p = < 0.01$  to 0.03).

#### Recurrent anaplastic astrocytoma

In a multicentre, prospective phase II trial evaluating the safety and efficacy of oral TMZ in the treatment of patients with anaplastic astrocytoma at first relapse, the 6 month PFS was 46 %. The median PFS 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 (ITT)

n=162. In 43 patients stable disease was reported. 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 radiological objective response or maintaining progression-free status was strongly associated with maintained or improved quality of life.

### Paediatric population

Oral TMZ has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. Tolerance to TMZ is similar to adults.

## **5.2 Pharmacokinetic properties**

TMZ is spontaneously hydrolyzed at physiologic pH primarily to the active species, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC). MTIC is spontaneously hydrolyzed to 5-aminoimidazole-4-carboxamide (AIC), a known intermediate in purine and nucleic acid biosynthesis, and to methylhydrazine, which is believed to be the active alkylating species. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA mainly at the O<sup>6</sup> and N<sup>7</sup> positions of guanine. Relative to the AUC of TMZ, the exposure to MTIC and AIC is ~ 2.4 % and 23 %, respectively. *In vivo*, the t<sub>1/2</sub> of MTIC was similar to that of TMZ, 1.8 hr.

### Absorption

After oral administration to adult patients, TMZ is absorbed rapidly, with peak concentrations reached as early as 20 minutes post-administration (mean time between 0.5 and 1.5 hours). After oral administration of <sup>14</sup>C-labelled TMZ, mean faecal excretion of <sup>14</sup>C over 7 days post-dose was 0.8 % indicating complete absorption.

### Distribution

TMZ demonstrates low protein binding (10 % to 20 %), and thus it is not expected to interact with highly protein-bound substances.

PET studies in humans and preclinical data suggest that TMZ crosses the blood-brain barrier rapidly and is present in the CSF. CSF penetration was confirmed in one patient; CSF exposure based on AUC of TMZ was approximately 30 % of that in plasma, which is consistent with animal data.

### Elimination

The half-life (t<sub>1/2</sub>) in plasma is approximately 1.8 hours. The major route of <sup>14</sup>C elimination is renal. Following oral administration, approximately 5 % to 10 % of the dose is recovered unchanged in the urine over 24 hours, and the remainder excreted as temozolomide acid, 5-aminoimidazole-4-carboxamide (AIC) or unidentified polar metabolites.

Plasma concentrations increase in a dose-related manner. Plasma clearance, volume of distribution and half-life are independent of dose.

### Special populations

Analysis of population-based pharmacokinetics of TMZ revealed that plasma TMZ clearance was independent of age, renal function or tobacco use. In a separate pharmacokinetic study, plasma pharmacokinetic profiles in patients with mild to moderate hepatic impairment were similar to those observed in patients with normal hepatic function.

Paediatric patients had a higher AUC than adult patients; however, the maximum tolerated dose (MTD) was 1,000 mg/m<sup>2</sup> per cycle both in children and in adults.

### **5.3 Preclinical safety data**

Single-cycle (5-day dosing, 23 days non-treatment), 3- and 6-cycle toxicity studies were conducted in rats and dogs. The primary targets of toxicity included the bone marrow, lymphoreticular system, testes, the gastrointestinal tract and, at higher doses, which were lethal to 60 % to 100 % of rats and dogs tested, degeneration of the retina occurred. Most of the toxicity showed evidence of reversibility, except for adverse events on the male reproductive system and retinal degeneration. However, because the doses implicated in retinal degeneration were in the lethal dose range, and no comparable effect has been observed in clinical studies, this finding was not considered to have clinical relevance.

TMZ is an embryotoxic, teratogenic and genotoxic alkylating agent. TMZ is more toxic to the rat and dog than to humans, and the clinical dose approximates the minimum lethal dose in rats and dogs. Dose-related reductions in leukocytes and platelets appear to be sensitive indicators of toxicity. A variety of neoplasms, including mammary carcinomas, keratocanthoma of the skin and basal cell adenoma were observed in the 6-cycle rat study while no tumours or pre-neoplastic changes were evident in dog studies. Rats appear to be particularly sensitive to oncogenic effects of TMZ, with the occurrence of first tumours within 3 months of initiating dosing. This latency period is very short even for an alkylating agent.

Results of the Ames/salmonella and Human Peripheral Blood Lymphocyte (HPBL) chromosome aberration tests showed a positive mutagenicity response.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Capsule content:

anhydrous lactose,  
colloidal anhydrous silica,  
sodium starch glycolate type A,  
tartaric acid,  
stearic acid.

#### Capsule shell:

gelatin,  
titanium dioxide (E 171),  
sodium laurilsulfate,  
yellow iron oxide (E 172),  
indigo carmine (E 132),

#### Printing ink:

shellac,  
propylene glycol,  
purified water,  
ammonium hydroxide,  
potassium hydroxide,  
black iron oxide (E 172).

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years

### **6.4 Special precautions for storage**

#### Bottle presentation

Do not store above 30 °C.  
Store in the original bottle in order to protect from moisture.  
Keep the bottle tightly closed.

#### Sachet presentation

Do not store above 30 °C.

### **6.5 Nature and contents of container**

#### Bottle presentation

Type I amber glass bottles with polypropylene child-resistant closures containing 5 or 20 hard capsules.  
The carton contains one bottle.

#### Sachet presentation

Sachets are composed of linear low density polyethylene (innermost layer), aluminium and polyethylene terephthalate.  
Each sachet contains 1 hard capsule and is dispensed in a cardboard carton.  
The carton contains 5 or 20 hard capsules, individually sealed in sachets.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal and other handling**

Capsules should not be opened. If a capsule becomes damaged, contact of the powder contents with skin or mucous membrane must be avoided. If Temodal comes into contact with skin or mucosa, it should be washed immediately and thoroughly with soap and water.

Patients should be advised to keep capsules out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN Haarlem  
The Netherlands

**8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/98/096/001

EU/1/98/096/002

EU/1/98/096/024

EU/1/98/096/025

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 26 January 1999

Date of latest renewal: 26 January 2009

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## 1. NAME OF THE MEDICINAL PRODUCT

Temodal 20 mg hard capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 20 mg temozolomide.

### Excipient with known effect:

Each hard capsule contains 182.2 mg of anhydrous lactose.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Hard capsule (capsule).

The hard capsules have an opaque white body, an opaque yellow cap, and are imprinted with black ink. The cap is imprinted with "Temodal". The body is imprinted with "20 mg", the Schering-Plough logo and two stripes.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Temodal is indicated for the treatment of:

- adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment.
- children from the age of three years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy.

### 4.2 Posology and method of administration

Temodal should only be prescribed by physicians experienced in the oncological treatment of brain tumours.

Anti-emetic therapy may be administered (see section 4.4).

### Posology

#### 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 (TMZ) monotherapy (monotherapy phase).

#### *Concomitant phase*

TMZ is administered orally at a dose of 75 mg/m<sup>2</sup> daily for 42 days concomitant with focal radiotherapy (60 Gy administered in 30 fractions). No dose reductions are recommended, but delay or discontinuation of TMZ administration should be decided weekly according to haematological and non-haematological toxicity criteria. TMZ administration can be continued throughout the 42 day concomitant period (up to 49 days) if all of the following conditions are met:

- absolute neutrophil count (ANC)  $\geq 1.5 \times 10^9/l$
- thrombocyte count  $\geq 100 \times 10^9/l$
- common toxicity criteria (CTC) non-haematological toxicity  $\leq$  Grade 1 (except for alopecia, nausea and vomiting).

During treatment a complete blood count should be obtained weekly. TMZ administration should be temporarily interrupted or permanently discontinued during the concomitant phase according to the haematological and non-haematological toxicity criteria as noted in Table 1.

Toxicity	TMZ interruption <sup>a</sup>	TMZ discontinuation
Absolute neutrophil count	$\geq 0.5$ and $< 1.5 \times 10^9/l$	$< 0.5 \times 10^9/l$
Thrombocyte count	$\geq 10$ and $< 100 \times 10^9/l$	$< 10 \times 10^9/l$
CTC non-haematological toxicity (except for alopecia, nausea, vomiting)	CTC Grade 2	CTC Grade 3 or 4

a: Treatment with concomitant TMZ can be continued when all of the following conditions are met: absolute neutrophil count  $\geq 1.5 \times 10^9/l$ ; thrombocyte count  $\geq 100 \times 10^9/l$ ; CTC non-haematological toxicity  $\leq$  Grade 1 (except for alopecia, nausea, vomiting).

### *Monotherapy phase*

Four weeks after completing the TMZ + RT concomitant phase, TMZ is administered for up to 6 cycles of monotherapy treatment. Dose in Cycle 1 (monotherapy) is  $150 \text{ mg/m}^2$  once daily for 5 days followed by 23 days without treatment. At the start of Cycle 2, the dose is escalated to  $200 \text{ mg/m}^2$  if the CTC non-haematological toxicity for Cycle 1 is Grade  $\leq 2$  (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is  $\geq 1.5 \times 10^9/l$ , and the thrombocyte count is  $\geq 100 \times 10^9/l$ . If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles. Once escalated, the dose remains at  $200 \text{ mg/m}^2$  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 TMZ). The dose should be reduced or administration discontinued according to Table 3.

Dose level	TMZ dose (mg/m <sup>2</sup> /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

Toxicity	Reduce TMZ by 1 dose level <sup>a</sup>	Discontinue TMZ
Absolute neutrophil count	$< 1.0 \times 10^9/l$	See footnote b
Thrombocyte count	$< 50 \times 10^9/l$	See footnote b
CTC non-haematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4 <sup>b</sup>

a: TMZ dose levels are listed in Table 2.

b: TMZ is to be discontinued if:

- dose level -1 ( $100 \text{ mg/m}^2$ ) still results in unacceptable toxicity
- the same Grade 3 non-haematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction.

Adult and paediatric patients 3 years of age or older with recurrent or progressive malignant glioma:

A treatment cycle comprises 28 days. In patients previously untreated with chemotherapy, TMZ is administered orally at a dose of 200 mg/m<sup>2</sup> once daily for the first 5 days followed by a 23 day treatment interruption (total of 28 days). In patients previously treated with chemotherapy, the initial dose is 150 mg/m<sup>2</sup> once daily, to be increased in the second cycle to 200 mg/m<sup>2</sup> once daily, for 5 days if there is no haematological toxicity (see section 4.4)

Special populations

*Paediatric population*

In patients 3 years of age or older, TMZ is only to be used in recurrent or progressive malignant glioma. Experience in these children is very limited (see sections 4.4 and 5.1). The safety and efficacy of TMZ in children under the age of 3 years have not been established. No data are available.

*Patients with hepatic or renal impairment*

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

*Elderly patients*

Based on a population pharmacokinetic analysis in patients 19-78 years of age, clearance of TMZ is not affected by age. However, elderly patients (> 70 years of age) appear to be at increased risk of neutropenia and thrombocytopenia (see section 4.4).

Method of administration

Temodal hard capsules should be administered in the fasting state.

The capsules must be swallowed whole with a glass of water and must not be opened or chewed.

If vomiting occurs after the dose is administered, a second dose should not be administered that day.

**4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to dacarbazine (DTIC).

Severe myelosuppression (see section 4.4).

**4.4 Special warnings and precautions for use**

Opportunistic infections and reactivation of infections

Opportunistic infections (such as *Pneumocystis jirovecii* pneumonia) and reactivation of infections (such as HBV, CMV) have been observed during the treatment with TMZ (see section 4.8).

Meningoencephalitis herpetic

In post marketing cases, meningoencephalitis herpetic (including fatal cases) has been observed in patients receiving TMZ in combination with radiotherapy, including cases of concomitant steroids administration.

#### *Pneumocystis jirovecii pneumonia*

Patients who received concomitant TMZ and RT in a pilot trial for the prolonged 42-day schedule were shown to be at particular risk for developing *Pneumocystis jirovecii* pneumonia (PCP). Thus, prophylaxis against PCP is required for all patients receiving concomitant TMZ and RT 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  $\leq 1$ .

There may be a higher occurrence of PCP when TMZ is administered during a longer dosing regimen. However, all patients receiving TMZ, particularly patients receiving steroids, should be observed closely for the development of PCP, regardless of the regimen. Cases of fatal respiratory failure have been reported in patients using TMZ, in particular in combination with dexamethasone or other steroids.

#### HBV

Hepatitis due to hepatitis B virus (HBV) reactivation, in some cases resulting in death, has been reported. Experts in liver disease should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease). During treatment patients should be monitored and managed appropriately.

#### Hepatotoxicity

Hepatic injury, including fatal hepatic failure, has been reported in patients treated with TMZ (see section 4.8). 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.

#### Malignancies

Cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukaemia, have also been reported very rarely (see section 4.8).

#### Anti-emetic therapy

Nausea and vomiting are very commonly associated with TMZ.  
Anti-emetic therapy may be administered prior to or following administration of TMZ.

#### *Adult patients with newly-diagnosed glioblastoma multiforme*

Anti-emetic prophylaxis is recommended prior to the initial dose of concomitant phase and it is strongly recommended during the monotherapy phase.

#### *Patients with recurrent or progressive malignant glioma*

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

### Laboratory parameters

Patients treated with TMZ may experience myelosuppression, including prolonged pancytopenia, which may result in aplastic anaemia, which in some cases has resulted in a fatal outcome. In some cases, exposure to concomitant medicinal products associated with aplastic anaemia, including carbamazepine, phenytoin, and sulfamethoxazole/trimethoprim, complicates assessment. Prior to dosing, the following laboratory parameters must be met: ANC  $\geq 1.5 \times 10^9/l$  and platelet count  $\geq 100 \times 10^9/l$ . A complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until ANC  $> 1.5 \times 10^9/l$  and platelet count  $> 100 \times 10^9/l$ . If ANC falls to  $< 1.0 \times 10^9/l$  or the platelet count is  $< 50 \times 10^9/l$  during any cycle, the next cycle should be reduced one dose level (see section 4.2). Dose levels include  $100 \text{ mg/m}^2$ ,  $150 \text{ mg/m}^2$ , and  $200 \text{ mg/m}^2$ . The lowest recommended dose is  $100 \text{ mg/m}^2$ .

### Paediatric population

There is no clinical experience with use of TMZ in children under the age of 3 years. Experience in older children and adolescents is very limited (see sections 4.2 and 5.1).

### Elderly patients (> 70 years of age)

Elderly patients appear to be at increased risk of neutropenia and thrombocytopenia, compared with younger patients. Therefore, special care should be taken when TMZ is administered in elderly patients.

### Male patients

Men being treated with TMZ should be advised not to father a child up to 6 months after receiving the last dose and to seek advice on cryoconservation of sperm prior to treatment (see section 4.6).

### Lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## **4.5 Interaction with other medicinal products and other forms of interaction**

In a separate phase I study, administration of TMZ with ranitidine did not result in alterations in the extent of absorption of temozolomide or the exposure to its active metabolite monomethyl triazenoimidazole carboxamide (MTIC).

Administration of TMZ with food resulted in a 33 % decrease in  $C_{\text{max}}$  and a 9 % decrease in area under the curve (AUC).

As it cannot be excluded that the change in  $C_{\text{max}}$  is clinically significant, Temodal should be administered without food.

Based on an analysis of population pharmacokinetics in phase II trials, co-administration of dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron,  $H_2$  receptor antagonists, or phenobarbital did not alter the clearance of TMZ. Co-administration with valproic acid was associated with a small but statistically significant decrease in clearance of TMZ.

No studies have been conducted to determine the effect of TMZ on the metabolism or elimination of other medicinal products. However, since TMZ does not undergo hepatic metabolism and exhibits low protein binding, it is unlikely that it would affect the pharmacokinetics of other medicinal products (see section 5.2).

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

#### Paediatric population

Interaction studies have only been performed in adults.

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

There are no data in pregnant women. In preclinical studies in rats and rabbits receiving 150 mg/m<sup>2</sup> TMZ, teratogenicity and/or foetal toxicity were demonstrated (see section 5.3). Temodal should not be administered to pregnant women. If use during pregnancy must be considered, the patient should be apprised of the potential risk to the foetus.

#### Breast-feeding

It is not known whether TMZ is excreted in human milk; thus, breast-feeding should be discontinued while receiving treatment with TMZ.

#### Women of childbearing potential

Women of childbearing potential should be advised to use effective contraception to avoid pregnancy while they are receiving TMZ.

#### Male fertility

TMZ can have genotoxic effects. Therefore, men being treated with it should be advised not to father a child up to 6 months after receiving the last dose and to seek advice on cryoconservation of sperm prior to treatment, because of the possibility of irreversible infertility due to therapy with TMZ.

### **4.7 Effects on ability to drive and use machines**

TMZ has minor influence on the ability to drive and use machines due to fatigue and somnolence (see section 4.8).

### **4.8 Undesirable effects**

#### Clinical trial experience

In patients treated with TMZ, whether used in combination with RT or as monotherapy following RT for newly-diagnosed glioblastoma multiforme, or as monotherapy in patients with recurrent or progressive glioma, the reported very common adverse reactions were similar: nausea, vomiting, constipation, anorexia, headache and fatigue. Convulsions were reported very commonly in the newly-diagnosed glioblastoma multiforme patients receiving monotherapy, and rash was reported very commonly in newly-diagnosed glioblastoma multiforme patients receiving TMZ concurrent with RT and also as monotherapy, and commonly in recurrent glioma. Most haematologic adverse reactions were reported commonly or very commonly in both indications (Tables 4 and 5); the frequency of grade 3-4 laboratory findings is presented after each table.

In the tables undesirable effects are classified according to System Organ Class and frequency. Frequency groupings are defined according to the following convention: Very common ( $\geq 1/10$ ); Common ( $\geq 1/100$  to  $< 1/10$ ); Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); Very rare ( $< 1/10,000$ ). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Newly-diagnosed glioblastoma multiforme

Table 4 provides treatment-emergent adverse events in patients with newly-diagnosed glioblastoma multiforme during the concomitant and monotherapy phases of treatment.

<i>Table 4. Treatment-emergent events during concomitant and monotherapy treatment phases in patients with newly-diagnosed glioblastoma multiforme</i>		
System organ class	TMZ + concomitant RT n=288*	TMZ monotherapy n=224
Infections and infestations		
Common:	Infection, <i>Herpes simplex</i> , wound infection, pharyngitis, candidiasis oral	Infection, candidiasis oral
Uncommon:		<i>Herpes simplex</i> , herpes zoster, influenza-like symptoms
Blood and lymphatic system disorders		
Common:	Neutropenia, thrombocytopenia, lymphopenia, leukopenia	Febrile neutropenia, thrombocytopenia, anaemia, leukopenia
Uncommon:	Febrile neutropenia, anaemia	Lymphopenia, petechiae
Endocrine disorders		
Uncommon:	Cushingoid	Cushingoid
Metabolism and nutrition disorders		
Very common:	Anorexia	Anorexia
Common:	Hyperglycaemia, weight decreased	Weight decreased
Uncommon:	Hypokalemia, 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	Convulsions, headache
Common:	Convulsions, consciousness decreased, somnolence, aphasia, balance impaired, dizziness, confusion, memory impairment, concentration impaired, neuropathy, paresthesia, speech disorder, tremor	Hemiparesis, aphasia, balance impaired, somnolence, confusion, dizziness, memory impairment, concentration impaired, dysphasia, neurological disorder (NOS), neuropathy, peripheral neuropathy, paresthesia, speech disorder, tremor
Uncommon:	Status epilepticus, extrapyramidal disorder, hemiparesis, ataxia, cognition impaired, dysphasia, gait abnormal, hyperesthesia, hypoesthesia, neurological disorder (NOS), peripheral neuropathy	Hemiplegia, ataxia, coordination abnormal, gait abnormal, hyperesthesia, sensory disturbance

<i>Table 4. Treatment-emergent events during concomitant and monotherapy treatment phases in patients with newly-diagnosed glioblastoma multiforme</i>		
System organ class	TMZ + concomitant RT n=288*	TMZ monotherapy n=224
Eye disorders		
Common:	Vision blurred	Visual field defect, vision blurred, diplopia
Uncommon:	Hemianopia, visual acuity reduced, vision disorder, visual field defect, eye pain	Visual acuity reduced, eye pain, eyes dry
Ear and labyrinth disorders		
Common:	Hearing impairment	Hearing impairment, tinnitus
Uncommon:	Otitis media, tinnitus, hyperacusis, earache	Deafness, vertigo, earache
Cardiac disorders		
Uncommon:	Palpitation	
Vascular disorders		
Common:	Haemorrhage, oedema, oedema leg	Haemorrhage, deep venous thrombosis, oedema leg
Uncommon:	Cerebral haemorrhage, hypertension	Embolism pulmonary, oedema, oedema peripheral
Respiratory, thoracic and mediastinal disorders		
Common:	Dyspnoea, coughing	Dyspnoea, coughing
Uncommon:	Pneumonia, upper respiratory infection, nasal congestion	Pneumonia, sinusitis, upper respiratory infection, bronchitis
Gastrointestinal disorders		
Very common:	Constipation, nausea, vomiting	Constipation, nausea, vomiting
Common:	Stomatitis, diarrhoea, abdominal pain, dyspepsia, dysphagia	Stomatitis, diarrhoea, dyspepsia, dysphagia, mouth dry
Uncommon:		Abdominal distension, fecal incontinence, gastrointestinal disorder (NOS), gastroenteritis, haemorrhoids
Skin and subcutaneous tissue disorders		
Very common:	Rash, alopecia	Rash, alopecia
Common:	Dermatitis, dry skin, erythema, pruritus	Dry skin, pruritus
Uncommon:	Skin exfoliation, photosensitivity reaction, pigmentation abnormal	Erythema, pigmentation abnormal, sweating increased

<i>Table 4. Treatment-emergent events during concomitant and monotherapy treatment phases in patients with newly-diagnosed glioblastoma multiforme</i>		
System organ class	TMZ + concomitant RT n=288*	TMZ monotherapy n=224
Musculoskeletal and connective tissue disorders		
Common:	Muscle weakness, arthralgia	Muscle weakness, arthralgia, musculoskeletal pain, myalgia
Uncommon:	Myopathy, back pain, musculoskeletal pain, myalgia	Myopathy, back pain
Renal and urinary disorders		
Common:	Micturition frequency, urinary incontinence	Urinary incontinence
Uncommon:		Dysuria
Reproductive system and breast disorders		
Uncommon:	Impotence	Vaginal haemorrhage, menorrhagia, amenorrhoea, vaginitis, breast pain
General disorders and administration site conditions		
Very common:	Fatigue	Fatigue
Common:	Allergic reaction, fever, radiation injury, face oedema, pain, taste perversion	Allergic reaction, fever, radiation injury, pain, taste perversion
Uncommon:	Asthenia, flushing, hot flushes, condition aggravated, rigors, tongue discolouration, parosmia, thirst	Asthenia, face oedema, pain, condition aggravated, rigors, tooth disorder
Investigations		
Common:	ALT increased	ALT increased
Uncommon:	Hepatic enzymes increased, Gamma GT increased, AST increased	

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

#### *Laboratory results*

Myelosuppression (neutropenia and thrombocytopenia), which is known dose-limiting toxicity for most cytotoxic agents, including TMZ, was 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 TMZ.

#### *Recurrent or progressive malignant glioma*

In clinical trials, the most frequently occurring treatment-related undesirable effects were gastrointestinal disorders, specifically nausea (43 %) and vomiting (36 %). These reactions were usually Grade 1 or 2 (0 – 5 episodes of vomiting in 24 hours) and were either self-limiting or readily controlled with standard anti-emetic therapy. The incidence of severe nausea and vomiting was 4 %.

Table 5 includes adverse reactions reported during clinical trials for recurrent or progressive malignant glioma and following the marketing of Temodal.

<i>Table 5. Adverse reactions in patients with recurrent or progressive malignant glioma</i>	
Infections and infestations	
Rare:	Opportunistic infections, including PCP
Blood and lymphatic system disorders	
Very common:	Neutropenia or lymphopenia (grade 3-4), thrombocytopenia (grade 3-4)
Uncommon:	Pancytopenia, anaemia (grade 3-4), leukopenia
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:	Vomiting, nausea, constipation
Common:	Diarrhoea, abdominal pain, dyspepsia
Skin and subcutaneous tissue disorders	
Common:	Rash, pruritus, alopecia
Very rare:	Erythema multiforme, erythroderma, urticaria, exanthema
General disorders and administration site conditions	
Very common:	Fatigue
Common:	Fever, asthenia, rigors, malaise, pain, taste perversion
Very 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 malignant glioma. This led to hospitalisation and/or discontinuation of TMZ in 8 % and 4 %, respectively. 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. The presence of thrombocytopenia may increase the risk of bleeding, and the presence of neutropenia or leukopenia may increase the risk of infection.

### *Gender*

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 ( $ANC < 0.5 \times 10^9/l$ ), 12 % vs 5 %, and thrombocytopenia ( $< 20 \times 10^9/l$ ), 9 % vs 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.

### Paediatric population

Oral TMZ has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. Although the data is limited, tolerance in children is expected to be the same as in adults. The safety of TMZ in children under the age of 3 years has not been established.

### Post-Marketing Experience

The following additional serious adverse reactions have been identified during post-marketing exposure:

<i>Table 6. Summary of events reported with temozolomide in the post-marketing setting</i>	
<b>Infections and infestations*</b>	
Uncommon:	cytomegalovirus infection, infection reactivation such as cytomegalovirus, hepatitis B virus <sup>†</sup> , meningoencephalitis herpetic <sup>†</sup> , sepsis <sup>†</sup>
<b>Blood and lymphatic system disorders</b>	
Very rare:	prolonged pancytopenia, aplastic anaemia <sup>†</sup>
<b>Neoplasm benign, malignant and unspecified</b>	
Very rare:	myelodysplastic syndrome (MDS), secondary malignancies, including myeloid leukaemia
<b>Endocrine disorders*</b>	
Uncommon:	diabetes insipidus
<b>Respiratory, thoracic and mediastinal disorders</b>	
Very rare:	interstitial pneumonitis/pneumonitis, pulmonary fibrosis, respiratory failure <sup>†</sup>
<b>Hepatobiliary disorders*</b>	
Common:	liver enzymes elevations
Uncommon:	hyperbilirubinemia, cholestasis, hepatitis, hepatic injury, hepatic failure <sup>†</sup>
<b>Skin and subcutaneous tissue disorders</b>	
Very rare:	toxic epidermal necrolysis, Stevens-Johnson syndrome

<sup>†</sup> Including cases with fatal outcome

\* Frequencies estimated based on relevant clinical trials.

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

## **4.9 Overdose**

Doses of 500, 750, 1,000, and 1,250 mg/m<sup>2</sup> (total dose per cycle over 5 days) have been evaluated clinically in patients. Dose-limiting toxicity was haematological and was reported with any dose but is expected to be more severe at higher doses. An overdose of 10,000 mg (total dose in a single cycle, over 5 days) was taken by one patient and the adverse reactions reported were pancytopenia, pyrexia,

multi-organ failure and death. There are reports of patients who have taken the recommended dose for 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, haematological evaluation is needed. Supportive measures should be provided as necessary.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents - Other alkylating agents, ATC code: L01A X03

#### Mechanism of action

Temozolomide is a triazene, which undergoes rapid chemical conversion at physiologic pH to the active monomethyl triazenoimidazole carboxamide (MTIC). The cytotoxicity of MTIC is thought to be due primarily to alkylation at the O<sup>6</sup> position of guanine with additional alkylation also occurring at the N<sup>7</sup> position. Cytotoxic lesions that develop subsequently are thought to involve aberrant repair of the methyl adduct.

#### Clinical efficacy and safety

##### *Newly-diagnosed glioblastoma multiforme*

A total of 573 patients were randomised to receive either TMZ + RT (n=287) or RT alone (n=286). Patients in the TMZ + RT arm received concomitant TMZ (75 mg/m<sup>2</sup>) 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 TMZ (150 - 200 mg/m<sup>2</sup>) 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 jirovecii* pneumonia (PCP) prophylaxis was required during RT and combined TMZ therapy.

TMZ 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 TMZ + 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 favour of the TMZ arm. The estimated probability of surviving 2 years or more (26 % vs 10 %) is higher for the RT + TMZ arm. The addition of concomitant TMZ to RT, followed by TMZ monotherapy in the treatment of patients with newly-diagnosed glioblastoma multiforme demonstrated a statistically significant improvement in overall survival (OS) compared with RT alone (Figure 1).

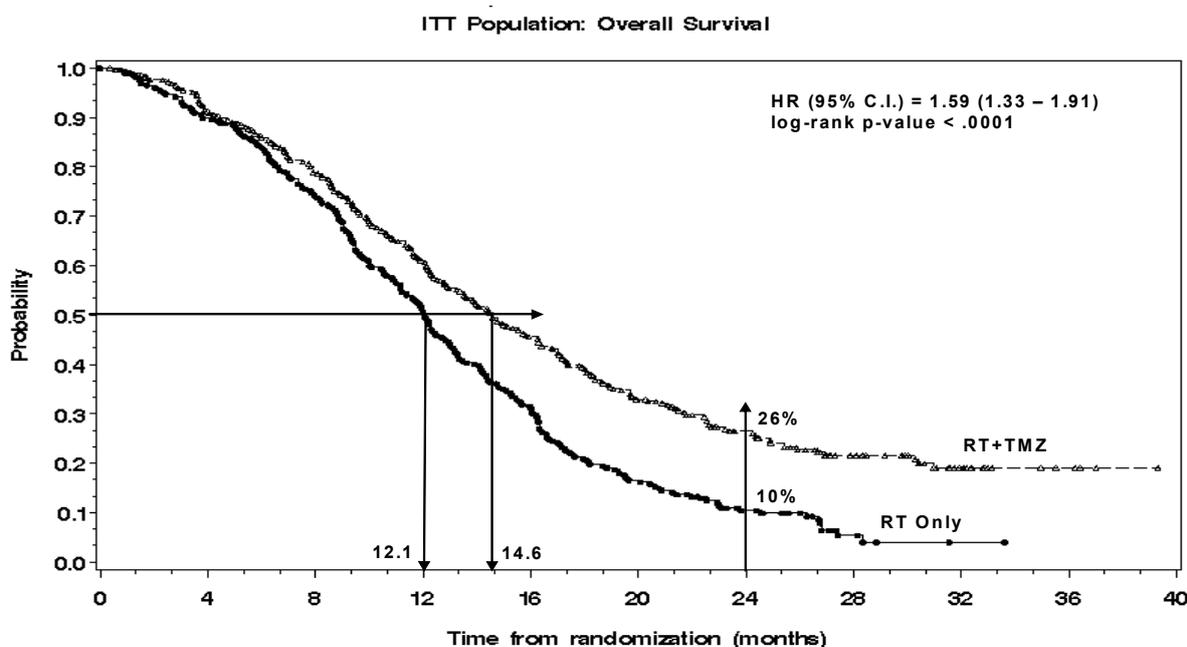


Figure 1 Kaplan-Meier curves for overall survival (intent-to-treat population)

The results from the trial were not consistent in the subgroup of patients with a poor performance status (WHO PS=2, n=70), where overall survival and time to progression were similar in both arms. However, no unacceptable risks appear to be present in this patient group.

#### Recurrent or progressive malignant glioma

Data on clinical efficacy in patients with glioblastoma multiforme (Karnofsky performance status [KPS]  $\geq 70$ ), progressive or recurrent after surgery and RT, were based on two clinical trials with oral TMZ. One was a non-comparative trial in 138 patients (29 % received prior chemotherapy), and the other was a randomised active-controlled trial of TMZ vs 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 (ORR) based on MRI scans was 8 %.

In the randomised active-controlled trial, the PFS at 6 months was significantly greater for TMZ 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 TMZ and procarbazine, respectively (log rank  $p = 0.33$ ). At 6 months, the fraction of surviving patients was significantly higher in the TMZ 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  $\geq 80$ .

Data on time to worsening of neurological status favoured TMZ over procarbazine as did data on time to worsening of performance status (decrease to a KPS of  $< 70$  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 TMZ than for procarbazine (log rank  $p = < 0.01$  to 0.03).

#### Recurrent anaplastic astrocytoma

In a multicentre, prospective phase II trial evaluating the safety and efficacy of oral TMZ in the treatment of patients with anaplastic astrocytoma at first relapse, the 6 month PFS was 46 %. The median PFS 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 (ITT)

n=162. In 43 patients stable disease was reported. 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 radiological objective response or maintaining progression-free status was strongly associated with maintained or improved quality of life.

### Paediatric population

Oral TMZ has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. Tolerance to TMZ is similar to adults.

## **5.2 Pharmacokinetic properties**

TMZ is spontaneously hydrolyzed at physiologic pH primarily to the active species, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC). MTIC is spontaneously hydrolyzed to 5-aminoimidazole-4-carboxamide (AIC), a known intermediate in purine and nucleic acid biosynthesis, and to methylhydrazine, which is believed to be the active alkylating species. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA mainly at the O<sup>6</sup> and N<sup>7</sup> positions of guanine. Relative to the AUC of TMZ, the exposure to MTIC and AIC is ~ 2.4 % and 23 %, respectively. *In vivo*, the t<sub>1/2</sub> of MTIC was similar to that of TMZ, 1.8 hr.

### Absorption

After oral administration to adult patients, TMZ is absorbed rapidly, with peak concentrations reached as early as 20 minutes post-administration (mean time between 0.5 and 1.5 hours). After oral administration of <sup>14</sup>C-labelled TMZ, mean faecal excretion of <sup>14</sup>C over 7 days post-dose was 0.8 % indicating complete absorption.

### Distribution

TMZ demonstrates low protein binding (10 % to 20 %), and thus it is not expected to interact with highly protein-bound substances.

PET studies in humans and preclinical data suggest that TMZ crosses the blood-brain barrier rapidly and is present in the CSF. CSF penetration was confirmed in one patient; CSF exposure based on AUC of TMZ was approximately 30 % of that in plasma, which is consistent with animal data.

### Elimination

The half-life (t<sub>1/2</sub>) in plasma is approximately 1.8 hours. The major route of <sup>14</sup>C elimination is renal. Following oral administration, approximately 5 % to 10 % of the dose is recovered unchanged in the urine over 24 hours, and the remainder excreted as temozolomide acid, 5-aminoimidazole-4-carboxamide (AIC) or unidentified polar metabolites.

Plasma concentrations increase in a dose-related manner. Plasma clearance, volume of distribution and half-life are independent of dose.

### Special populations

Analysis of population-based pharmacokinetics of TMZ revealed that plasma TMZ clearance was independent of age, renal function or tobacco use. In a separate pharmacokinetic study, plasma pharmacokinetic profiles in patients with mild to moderate hepatic impairment were similar to those observed in patients with normal hepatic function.

Paediatric patients had a higher AUC than adult patients; however, the maximum tolerated dose (MTD) was 1,000 mg/m<sup>2</sup> per cycle both in children and in adults.

### **5.3 Preclinical safety data**

Single-cycle (5-day dosing, 23 days non-treatment), 3- and 6-cycle toxicity studies were conducted in rats and dogs. The primary targets of toxicity included the bone marrow, lymphoreticular system, testes, the gastrointestinal tract and, at higher doses, which were lethal to 60 % to 100 % of rats and dogs tested, degeneration of the retina occurred. Most of the toxicity showed evidence of reversibility, except for adverse events on the male reproductive system and retinal degeneration. However, because the doses implicated in retinal degeneration were in the lethal dose range, and no comparable effect has been observed in clinical studies, this finding was not considered to have clinical relevance.

TMZ is an embryotoxic, teratogenic and genotoxic alkylating agent. TMZ is more toxic to the rat and dog than to humans, and the clinical dose approximates the minimum lethal dose in rats and dogs. Dose-related reductions in leukocytes and platelets appear to be sensitive indicators of toxicity. A variety of neoplasms, including mammary carcinomas, keratocanthoma of the skin and basal cell adenoma were observed in the 6-cycle rat study while no tumours or pre-neoplastic changes were evident in dog studies. Rats appear to be particularly sensitive to oncogenic effects of TMZ, with the occurrence of first tumours within 3 months of initiating dosing. This latency period is very short even for an alkylating agent.

Results of the Ames/salmonella and Human Peripheral Blood Lymphocyte (HPBL) chromosome aberration tests showed a positive mutagenicity response.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Capsule content:

anhydrous lactose,  
colloidal anhydrous silica,  
sodium starch glycolate type A,  
tartaric acid,  
stearic acid.

#### Capsule shell:

gelatin,  
titanium dioxide (E 171),  
sodium lauril sulfate,  
yellow iron oxide (E 172)

#### Printing ink:

shellac,  
propylene glycol,  
purified water,  
ammonium hydroxide,  
potassium hydroxide,  
black iron oxide (E 172).

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years

### **6.4 Special precautions for storage**

#### Bottle presentation

Do not store above 30 °C.  
Store in the original bottle in order to protect from moisture.  
Keep the bottle tightly closed.

#### Sachet presentation

Do not store above 30 °C.

### **6.5 Nature and contents of container**

#### Bottle presentation

Type I amber glass bottles with polypropylene child-resistant closures containing 5 or 20 hard capsules.  
The carton contains one bottle.

#### Sachet presentation

Sachets are composed of linear low density polyethylene (innermost layer), aluminium and polyethylene terephthalate.  
Each sachet contains 1 hard capsule and is dispensed in a cardboard carton.  
The carton contains 5 or 20 hard capsules, individually sealed in sachets.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal and other handling**

Capsules should not be opened. If a capsule becomes damaged, contact of the powder contents with skin or mucous membrane must be avoided. If Temodal comes into contact with skin or mucosa, it should be washed immediately and thoroughly with soap and water.

Patients should be advised to keep capsules out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN Haarlem  
The Netherlands

**8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/98/096/003

EU/1/98/096/004

EU/1/98/096/013

EU/1/98/096/014

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 26 January 1999

Date of latest renewal: 26 January 2009

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## 1. NAME OF THE MEDICINAL PRODUCT

Temodal 100 mg hard capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 100 mg temozolomide.

### Excipient with known effect:

Each hard capsule contains 175.7 mg of anhydrous lactose.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Hard capsule (capsule).

The hard capsules have an opaque white body, an opaque pink cap, and are imprinted with black ink. The cap is imprinted with "Temodal". The body is imprinted with "100 mg", the Schering-Plough logo and two stripes.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Temodal is indicated for the treatment of:

- adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment.
- children from the age of three years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy.

### 4.2 Posology and method of administration

Temodal should only be prescribed by physicians experienced in the oncological treatment of brain tumours.

Anti-emetic therapy may be administered (see section 4.4).

### Posology

#### 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 (TMZ) monotherapy (monotherapy phase).

#### *Concomitant phase*

TMZ is administered orally at a dose of 75 mg/m<sup>2</sup> daily for 42 days concomitant with focal radiotherapy (60 Gy administered in 30 fractions). No dose reductions are recommended, but delay or discontinuation of TMZ administration should be decided weekly according to haematological and non-haematological toxicity criteria. TMZ administration can be continued throughout the 42 day concomitant period (up to 49 days) if all of the following conditions are met:

- absolute neutrophil count (ANC)  $\geq 1.5 \times 10^9/l$
- thrombocyte count  $\geq 100 \times 10^9/l$
- common toxicity criteria (CTC) non-haematological toxicity  $\leq$  Grade 1 (except for alopecia, nausea and vomiting).

During treatment a complete blood count should be obtained weekly. TMZ administration should be temporarily interrupted or permanently discontinued during the concomitant phase according to the haematological and non-haematological toxicity criteria as noted in Table 1.

Toxicity	TMZ interruption <sup>a</sup>	TMZ discontinuation
Absolute neutrophil count	$\geq 0.5$ and $< 1.5 \times 10^9/l$	$< 0.5 \times 10^9/l$
Thrombocyte count	$\geq 10$ and $< 100 \times 10^9/l$	$< 10 \times 10^9/l$
CTC non-haematological toxicity (except for alopecia, nausea, vomiting)	CTC Grade 2	CTC Grade 3 or 4

a: Treatment with concomitant TMZ can be continued when all of the following conditions are met: absolute neutrophil count  $\geq 1.5 \times 10^9/l$ ; thrombocyte count  $\geq 100 \times 10^9/l$ ; CTC non-haematological toxicity  $\leq$  Grade 1 (except for alopecia, nausea, vomiting).

### *Monotherapy phase*

Four weeks after completing the TMZ + RT concomitant phase, TMZ is administered for up to 6 cycles of monotherapy treatment. Dose in Cycle 1 (monotherapy) is  $150 \text{ mg/m}^2$  once daily for 5 days followed by 23 days without treatment. At the start of Cycle 2, the dose is escalated to  $200 \text{ mg/m}^2$  if the CTC non-haematological toxicity for Cycle 1 is Grade  $\leq 2$  (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is  $\geq 1.5 \times 10^9/l$ , and the thrombocyte count is  $\geq 100 \times 10^9/l$ . If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles. Once escalated, the dose remains at  $200 \text{ mg/m}^2$  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 TMZ). The dose should be reduced or administration discontinued according to Table 3.

Dose level	TMZ dose ( $\text{mg/m}^2/\text{day}$ )	Remarks
-1	100	Reduction for prior toxicity
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2-6 in absence of toxicity

Toxicity	Reduce TMZ by 1 dose level <sup>a</sup>	Discontinue TMZ
Absolute neutrophil count	$< 1.0 \times 10^9/l$	See footnote b
Thrombocyte count	$< 50 \times 10^9/l$	See footnote b
CTC non-haematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4 <sup>b</sup>

a: TMZ dose levels are listed in Table 2.

b: TMZ is to be discontinued if:

- dose level -1 ( $100 \text{ mg/m}^2$ ) still results in unacceptable toxicity
- the same Grade 3 non-haematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction.

Adult and paediatric patients 3 years of age or older with recurrent or progressive malignant glioma:

A treatment cycle comprises 28 days. In patients previously untreated with chemotherapy, TMZ is administered orally at a dose of 200 mg/m<sup>2</sup> once daily for the first 5 days followed by a 23 day treatment interruption (total of 28 days). In patients previously treated with chemotherapy, the initial dose is 150 mg/m<sup>2</sup> once daily, to be increased in the second cycle to 200 mg/m<sup>2</sup> once daily, for 5 days if there is no haematological toxicity (see section 4.4)

Special populations

*Paediatric population*

In patients 3 years of age or older, TMZ is only to be used in recurrent or progressive malignant glioma. Experience in these children is very limited (see sections 4.4 and 5.1). The safety and efficacy of TMZ in children under the age of 3 years have not been established. No data are available.

*Patients with hepatic or renal impairment*

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

*Elderly patients*

Based on a population pharmacokinetic analysis in patients 19-78 years of age, clearance of TMZ is not affected by age. However, elderly patients (> 70 years of age) appear to be at increased risk of neutropenia and thrombocytopenia (see section 4.4).

Method of administration

Temodal hard capsules should be administered in the fasting state.

The capsules must be swallowed whole with a glass of water and must not be opened or chewed.

If vomiting occurs after the dose is administered, a second dose should not be administered that day.

**4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to dacarbazine (DTIC).

Severe myelosuppression (see section 4.4).

**4.4 Special warnings and precautions for use**

Opportunistic infections and reactivation of infections

Opportunistic infections (such as *Pneumocystis jirovecii* pneumonia) and reactivation of infections (such as HBV, CMV) have been observed during the treatment with TMZ (see section 4.8).

Meningoencephalitis herpetic

In post marketing cases, meningoencephalitis herpetic (including fatal cases) has been observed in patients receiving TMZ in combination with radiotherapy, including cases of concomitant steroids administration.

#### *Pneumocystis jirovecii* pneumonia

Patients who received concomitant TMZ and RT in a pilot trial for the prolonged 42-day schedule were shown to be at particular risk for developing *Pneumocystis jirovecii* pneumonia (PCP). Thus, prophylaxis against PCP is required for all patients receiving concomitant TMZ and RT 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  $\leq 1$ .

There may be a higher occurrence of PCP when TMZ is administered during a longer dosing regimen. However, all patients receiving TMZ, particularly patients receiving steroids, should be observed closely for the development of PCP, regardless of the regimen. Cases of fatal respiratory failure have been reported in patients using TMZ, in particular in combination with dexamethasone or other steroids.

#### HBV

Hepatitis due to hepatitis B virus (HBV) reactivation, in some cases resulting in death, has been reported. Experts in liver disease should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease). During treatment patients should be monitored and managed appropriately.

#### Hepatotoxicity

Hepatic injury, including fatal hepatic failure, has been reported in patients treated with TMZ (see section 4.8). 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.

#### Malignancies

Cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukaemia, have also been reported very rarely (see section 4.8).

#### Anti-emetic therapy

Nausea and vomiting are very commonly associated with TMZ. Anti-emetic therapy may be administered prior to or following administration of TMZ.

#### *Adult patients with newly-diagnosed glioblastoma multiforme*

Anti-emetic prophylaxis is recommended prior to the initial dose of concomitant phase and it is strongly recommended during the monotherapy phase.

#### *Patients with recurrent or progressive malignant glioma*

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

### Laboratory parameters

Patients treated with TMZ may experience myelosuppression, including prolonged pancytopenia, which may result in aplastic anaemia, which in some cases has resulted in a fatal outcome. In some cases, exposure to concomitant medicinal products associated with aplastic anaemia, including carbamazepine, phenytoin, and sulfamethoxazole/trimethoprim, complicates assessment. Prior to dosing, the following laboratory parameters must be met: ANC  $\geq 1.5 \times 10^9/l$  and platelet count  $\geq 100 \times 10^9/l$ . A complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until ANC  $> 1.5 \times 10^9/l$  and platelet count  $> 100 \times 10^9/l$ . If ANC falls to  $< 1.0 \times 10^9/l$  or the platelet count is  $< 50 \times 10^9/l$  during any cycle, the next cycle should be reduced one dose level (see section 4.2). Dose levels include  $100 \text{ mg/m}^2$ ,  $150 \text{ mg/m}^2$ , and  $200 \text{ mg/m}^2$ . The lowest recommended dose is  $100 \text{ mg/m}^2$ .

### Paediatric population

There is no clinical experience with use of TMZ in children under the age of 3 years. Experience in older children and adolescents is very limited (see sections 4.2 and 5.1).

### Elderly patients (> 70 years of age)

Elderly patients appear to be at increased risk of neutropenia and thrombocytopenia, compared with younger patients. Therefore, special care should be taken when TMZ is administered in elderly patients.

### Male patients

Men being treated with TMZ should be advised not to father a child up to 6 months after receiving the last dose and to seek advice on cryoconservation of sperm prior to treatment (see section 4.6).

### Lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## **4.5 Interaction with other medicinal products and other forms of interaction**

In a separate phase I study, administration of TMZ with ranitidine did not result in alterations in the extent of absorption of temozolomide or the exposure to its active metabolite monomethyl triazenoimidazole carboxamide (MTIC).

Administration of TMZ with food resulted in a 33 % decrease in  $C_{\text{max}}$  and a 9 % decrease in area under the curve (AUC).

As it cannot be excluded that the change in  $C_{\text{max}}$  is clinically significant, Temodal should be administered without food.

Based on an analysis of population pharmacokinetics in phase II trials, co-administration of dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron,  $H_2$  receptor antagonists, or phenobarbital did not alter the clearance of TMZ. Co-administration with valproic acid was associated with a small but statistically significant decrease in clearance of TMZ.

No studies have been conducted to determine the effect of TMZ on the metabolism or elimination of other medicinal products. However, since TMZ does not undergo hepatic metabolism and exhibits low protein binding, it is unlikely that it would affect the pharmacokinetics of other medicinal products (see section 5.2).

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

#### Paediatric population

Interaction studies have only been performed in adults.

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

There are no data in pregnant women. In preclinical studies in rats and rabbits receiving 150 mg/m<sup>2</sup> TMZ, teratogenicity and/or foetal toxicity were demonstrated (see section 5.3). Temodal should not be administered to pregnant women. If use during pregnancy must be considered, the patient should be apprised of the potential risk to the foetus.

#### Breast-feeding

It is not known whether TMZ is excreted in human milk; thus, breast-feeding should be discontinued while receiving treatment with TMZ.

#### Women of childbearing potential

Women of childbearing potential should be advised to use effective contraception to avoid pregnancy while they are receiving TMZ.

#### Male fertility

TMZ can have genotoxic effects. Therefore, men being treated with it should be advised not to father a child up to 6 months after receiving the last dose and to seek advice on cryoconservation of sperm prior to treatment, because of the possibility of irreversible infertility due to therapy with TMZ.

### **4.7 Effects on ability to drive and use machines**

TMZ has minor influence on the ability to drive and use machines due to fatigue and somnolence (see section 4.8).

### **4.8 Undesirable effects**

#### Clinical trial experience

In patients treated with TMZ, whether used in combination with RT or as monotherapy following RT for newly-diagnosed glioblastoma multiforme, or as monotherapy in patients with recurrent or progressive glioma, the reported very common adverse reactions were similar: nausea, vomiting, constipation, anorexia, headache and fatigue. Convulsions were reported very commonly in the newly-diagnosed glioblastoma multiforme patients receiving monotherapy, and rash was reported very commonly in newly-diagnosed glioblastoma multiforme patients receiving TMZ concurrent with RT and also as monotherapy, and commonly in recurrent glioma. Most haematologic adverse reactions were reported commonly or very commonly in both indications (Tables 4 and 5); the frequency of grade 3-4 laboratory findings is presented after each table.

In the tables undesirable effects are classified according to System Organ Class and frequency. Frequency groupings are defined according to the following convention: Very common ( $\geq 1/10$ ); Common ( $\geq 1/100$  to  $< 1/10$ ); Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); Very rare ( $< 1/10,000$ ). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Newly-diagnosed glioblastoma multiforme

Table 4 provides treatment-emergent adverse events in patients with newly-diagnosed glioblastoma multiforme during the concomitant and monotherapy phases of treatment.

<i>Table 4. Treatment-emergent events during concomitant and monotherapy treatment phases in patients with newly-diagnosed glioblastoma multiforme</i>		
System organ class	TMZ + concomitant RT n=288*	TMZ monotherapy n=224
Infections and infestations		
Common:	Infection, <i>Herpes simplex</i> , wound infection, pharyngitis, candidiasis oral	Infection, candidiasis oral
Uncommon:		<i>Herpes simplex</i> , herpes zoster, influenza-like symptoms
Blood and lymphatic system disorders		
Common:	Neutropenia, thrombocytopenia, lymphopenia, leukopenia	Febrile neutropenia, thrombocytopenia, anaemia, leukopenia
Uncommon:	Febrile neutropenia, anaemia	Lymphopenia, petechiae
Endocrine disorders		
Uncommon:	Cushingoid	Cushingoid
Metabolism and nutrition disorders		
Very common:	Anorexia	Anorexia
Common:	Hyperglycaemia, weight decreased	Weight decreased
Uncommon:	Hypokalemia, 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	Convulsions, headache
Common:	Convulsions, consciousness decreased, somnolence, aphasia, balance impaired, dizziness, confusion, memory impairment, concentration impaired, neuropathy, paresthesia, speech disorder, tremor	Hemiparesis, aphasia, balance impaired, somnolence, confusion, dizziness, memory impairment, concentration impaired, dysphasia, neurological disorder (NOS), neuropathy, peripheral neuropathy, paresthesia, speech disorder, tremor
Uncommon:	Status epilepticus, extrapyramidal disorder, hemiparesis, ataxia, cognition impaired, dysphasia, gait abnormal, hyperesthesia, hypoesthesia, neurological disorder (NOS), peripheral neuropathy	Hemiplegia, ataxia, coordination abnormal, gait abnormal, hyperesthesia, sensory disturbance
Eye disorders		

<i>Table 4. Treatment-emergent events during concomitant and monotherapy treatment phases in patients with newly-diagnosed glioblastoma multiforme</i>		
System organ class	TMZ + concomitant RT n=288*	TMZ monotherapy n=224
Common:	Vision blurred	Visual field defect, vision blurred, diplopia
Uncommon:	Hemianopia, visual acuity reduced, vision disorder, visual field defect, eye pain	Visual acuity reduced, eye pain, eyes dry
Ear and labyrinth disorders		
Common:	Hearing impairment	Hearing impairment, tinnitus
Uncommon:	Otitis media, tinnitus, hyperacusis, earache	Deafness, vertigo, earache
Cardiac disorders		
Uncommon:	Palpitation	
Vascular disorders		
Common:	Haemorrhage, oedema, oedema leg	Haemorrhage, deep venous thrombosis, oedema leg
Uncommon:	Cerebral haemorrhage, hypertension	Embolism pulmonary, oedema, oedema peripheral
Respiratory, thoracic and mediastinal disorders		
Common:	Dyspnoea, coughing	Dyspnoea, coughing
Uncommon:	Pneumonia, upper respiratory infection, nasal congestion	Pneumonia, sinusitis, upper respiratory infection, bronchitis
Gastrointestinal disorders		
Very common:	Constipation, nausea, vomiting	Constipation, nausea, vomiting
Common:	Stomatitis, diarrhoea, abdominal pain, dyspepsia, dysphagia	Stomatitis, diarrhoea, dyspepsia, dysphagia, mouth dry
Uncommon:		Abdominal distension, fecal incontinence, gastrointestinal disorder (NOS), gastroenteritis, haemorrhoids
Skin and subcutaneous tissue disorders		
Very common:	Rash, alopecia	Rash, alopecia
Common:	Dermatitis, dry skin, erythema, pruritus	Dry skin, pruritus
Uncommon:	Skin exfoliation, photosensitivity reaction, pigmentation abnormal	Erythema, pigmentation abnormal, sweating increased
Musculoskeletal and connective tissue disorders		
Common:	Muscle weakness, arthralgia	Muscle weakness, arthralgia, musculoskeletal pain, myalgia

<i>Table 4. Treatment-emergent events during concomitant and monotherapy treatment phases in patients with newly-diagnosed glioblastoma multiforme</i>		
System organ class	TMZ + concomitant RT n=288*	TMZ monotherapy n=224
Uncommon:	Myopathy, back pain, musculoskeletal pain, myalgia	Myopathy, back pain
Renal and urinary disorders		
Common:	Micturition frequency, urinary incontinence	Urinary incontinence
Uncommon:		Dysuria
Reproductive system and breast disorders		
Uncommon:	Impotence	Vaginal haemorrhage, menorrhagia, amenorrhea, vaginitis, breast pain
General disorders and administration site conditions		
Very common:	Fatigue	Fatigue
Common:	Allergic reaction, fever, radiation injury, face oedema, pain, taste perversion	Allergic reaction, fever, radiation injury, pain, taste perversion
Uncommon:	Asthenia, flushing, hot flushes, condition aggravated, rigors, tongue discolouration, parosmia, thirst	Asthenia, face oedema, pain, condition aggravated, rigors, tooth disorder
Investigations		
Common:	ALT increased	ALT increased
Uncommon:	Hepatic enzymes increased, Gamma GT increased, AST increased	

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

### *Laboratory results*

Myelosuppression (neutropenia and thrombocytopenia), which is known dose-limiting toxicity for most cytotoxic agents, including TMZ, was 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 TMZ.

### *Recurrent or progressive malignant glioma*

In clinical trials, the most frequently occurring treatment-related undesirable effects were gastrointestinal disorders, specifically nausea (43 %) and vomiting (36 %). These reactions were usually Grade 1 or 2 (0 – 5 episodes of vomiting in 24 hours) and were either self-limiting or readily controlled with standard anti-emetic therapy. The incidence of severe nausea and vomiting was 4 %.

Table 5 includes adverse reactions reported during clinical trials for recurrent or progressive malignant glioma and following the marketing of Temodal.

<i>Table 5. Adverse reactions in patients with recurrent or progressive malignant glioma</i>	
Infections and infestations	
Rare:	Opportunistic infections, including PCP
Blood and lymphatic system disorders	
Very common:	Neutropenia or lymphopenia (grade 3-4), thrombocytopenia (grade 3-4)
Uncommon:	Pancytopenia, anaemia (grade 3-4), leukopenia
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:	Vomiting, nausea, constipation
Common:	Diarrhoea, abdominal pain, dyspepsia
Skin and subcutaneous tissue disorders	
Common:	Rash, pruritus, alopecia
Very rare:	Erythema multiforme, erythroderma, urticaria, exanthema
General disorders and administration site conditions	
Very common:	Fatigue
Common:	Fever, asthenia, rigors, malaise, pain, taste perversion
Very 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 malignant glioma. This led to hospitalisation and/or discontinuation of TMZ in 8 % and 4 %, respectively. 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. The presence of thrombocytopenia may increase the risk of bleeding, and the presence of neutropenia or leukopenia may increase the risk of infection.

### *Gender*

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 ( $ANC < 0.5 \times 10^9/l$ ), 12 % vs 5 %, and thrombocytopenia ( $< 20 \times 10^9/l$ ), 9 % vs 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.

### Paediatric population

Oral TMZ has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. Although the data is limited, tolerance in children is expected to be the same as in adults. The safety of TMZ in children under the age of 3 years has not been established.

### Post-Marketing Experience

The following additional serious adverse reactions have been identified during post-marketing exposure:

<i>Table 6. Summary of events reported with temozolomide in the post-marketing setting</i>	
<b>Infections and infestations*</b>	
Uncommon:	cytomegalovirus infection, infection reactivation such as cytomegalovirus, hepatitis B virus <sup>†</sup> , meningoencephalitis herpetic <sup>†</sup> , sepsis <sup>†</sup>
<b>Blood and lymphatic system disorders</b>	
Very rare:	prolonged pancytopenia, aplastic anaemia <sup>†</sup>
<b>Neoplasm benign, malignant and unspecified</b>	
Very rare:	myelodysplastic syndrome (MDS), secondary malignancies, including myeloid leukaemia
<b>Endocrine disorders*</b>	
Uncommon:	diabetes insipidus
<b>Respiratory, thoracic and mediastinal disorders</b>	
Very rare:	interstitial pneumonitis/pneumonitis, pulmonary fibrosis, respiratory failure <sup>†</sup>
<b>Hepatobiliary disorders*</b>	
Common:	liver enzymes elevations
Uncommon:	hyperbilirubinemia, cholestasis, hepatitis, hepatic injury, hepatic failure <sup>†</sup>
<b>Skin and subcutaneous tissue disorders</b>	
Very rare:	toxic epidermal necrolysis, Stevens-Johnson syndrome

<sup>†</sup> Including cases with fatal outcome

\* Frequencies estimated based on relevant clinical trials.

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

## **4.9 Overdose**

Doses of 500, 750, 1,000, and 1,250 mg/m<sup>2</sup> (total dose per cycle over 5 days) have been evaluated clinically in patients. Dose-limiting toxicity was haematological and was reported with any dose but is expected to be more severe at higher doses. An overdose of 10,000 mg (total dose in a single cycle, over 5 days) was taken by one patient and the adverse reactions reported were pancytopenia, pyrexia,

multi-organ failure and death. There are reports of patients who have taken the recommended dose for 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, haematological evaluation is needed. Supportive measures should be provided as necessary.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents - Other alkylating agents, ATC code: L01A X03

#### Mechanism of action

Temozolomide is a triazene, which undergoes rapid chemical conversion at physiologic pH to the active monomethyl triazenoimidazole carboxamide (MTIC). The cytotoxicity of MTIC is thought to be due primarily to alkylation at the O<sup>6</sup> position of guanine with additional alkylation also occurring at the N<sup>7</sup> position. Cytotoxic lesions that develop subsequently are thought to involve aberrant repair of the methyl adduct.

#### Clinical efficacy and safety

##### *Newly-diagnosed glioblastoma multiforme*

A total of 573 patients were randomised to receive either TMZ + RT (n=287) or RT alone (n=286). Patients in the TMZ + RT arm received concomitant TMZ (75 mg/m<sup>2</sup>) 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 TMZ (150 - 200 mg/m<sup>2</sup>) 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 jirovecii* pneumonia (PCP) prophylaxis was required during RT and combined TMZ therapy.

TMZ 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 TMZ + 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 favour of the TMZ arm. The estimated probability of surviving 2 years or more (26 % vs 10 %) is higher for the RT + TMZ arm. The addition of concomitant TMZ to RT, followed by TMZ monotherapy in the treatment of patients with newly-diagnosed glioblastoma multiforme demonstrated a statistically significant improvement in overall survival (OS) compared with RT alone (Figure 1).

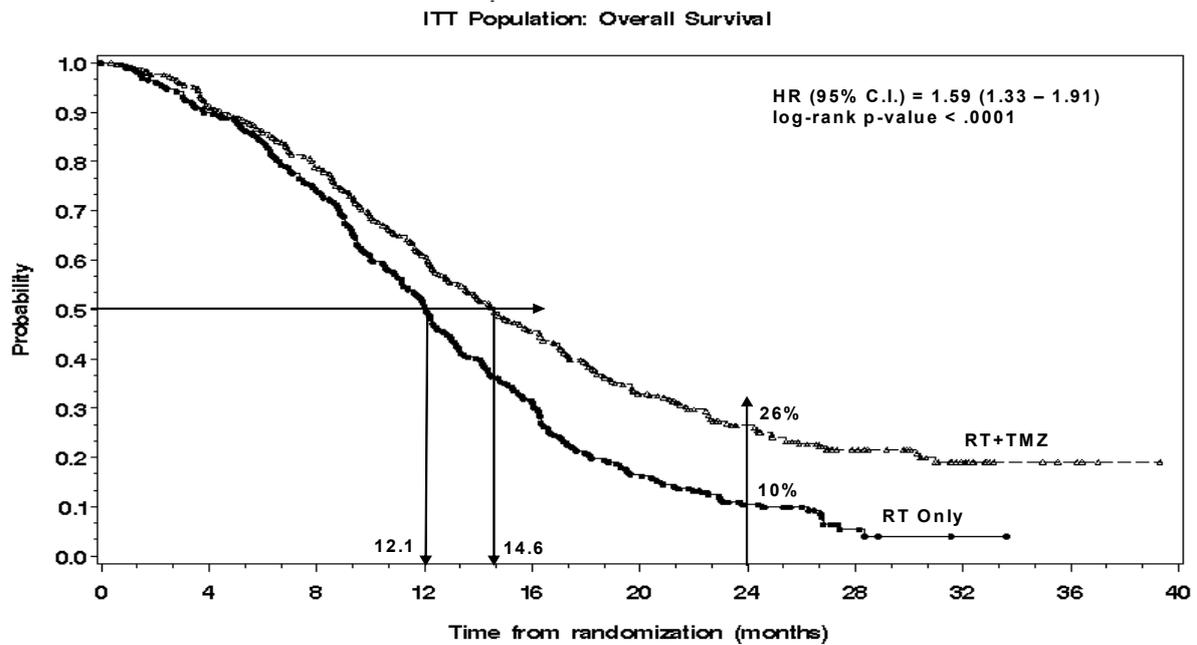


Figure 1 Kaplan-Meier curves for overall survival (intent-to-treat population)

The results from the trial were not consistent in the subgroup of patients with a poor performance status (WHO PS=2, n=70), where overall survival and time to progression were similar in both arms. However, no unacceptable risks appear to be present in this patient group.

#### Recurrent or progressive malignant glioma

Data on clinical efficacy in patients with glioblastoma multiforme (Karnofsky performance status [KPS]  $\geq 70$ ), progressive or recurrent after surgery and RT, were based on two clinical trials with oral TMZ. One was a non-comparative trial in 138 patients (29 % received prior chemotherapy), and the other was a randomised active-controlled trial of TMZ vs 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 (ORR) based on MRI scans was 8 %.

In the randomised active-controlled trial, the PFS at 6 months was significantly greater for TMZ 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 TMZ and procarbazine, respectively (log rank  $p = 0.33$ ). At 6 months, the fraction of surviving patients was significantly higher in the TMZ 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  $\geq 80$ .

Data on time to worsening of neurological status favoured TMZ over procarbazine as did data on time to worsening of performance status (decrease to a KPS of  $< 70$  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 TMZ than for procarbazine (log rank  $p = < 0.01$  to 0.03).

#### Recurrent anaplastic astrocytoma

In a multicentre, prospective phase II trial evaluating the safety and efficacy of oral TMZ in the treatment of patients with anaplastic astrocytoma at first relapse, the 6 month PFS was 46 %. The median PFS 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 (ITT) n=162. In 43 patients stable disease was reported. 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 radiological objective response or maintaining progression-free status was strongly associated with maintained or improved quality of life.

### Paediatric population

Oral TMZ has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. Tolerance to TMZ is similar to adults.

## **5.2 Pharmacokinetic properties**

TMZ is spontaneously hydrolyzed at physiologic pH primarily to the active species, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC). MTIC is spontaneously hydrolyzed to 5-aminoimidazole-4-carboxamide (AIC), a known intermediate in purine and nucleic acid biosynthesis, and to methylhydrazine, which is believed to be the active alkylating species. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA mainly at the O<sup>6</sup> and N<sup>7</sup> positions of guanine. Relative to the AUC of TMZ, the exposure to MTIC and AIC is ~ 2.4 % and 23 %, respectively. *In vivo*, the t<sub>1/2</sub> of MTIC was similar to that of TMZ, 1.8 hr.

### Absorption

After oral administration to adult patients, TMZ is absorbed rapidly, with peak concentrations reached as early as 20 minutes post-administration (mean time between 0.5 and 1.5 hours). After oral administration of <sup>14</sup>C-labelled TMZ, mean faecal excretion of <sup>14</sup>C over 7 days post-dose was 0.8 % indicating complete absorption.

### Distribution

TMZ demonstrates low protein binding (10 % to 20 %), and thus it is not expected to interact with highly protein-bound substances.

PET studies in humans and preclinical data suggest that TMZ crosses the blood-brain barrier rapidly and is present in the CSF. CSF penetration was confirmed in one patient; CSF exposure based on AUC of TMZ was approximately 30 % of that in plasma, which is consistent with animal data.

### Elimination

The half-life (t<sub>1/2</sub>) in plasma is approximately 1.8 hours. The major route of <sup>14</sup>C elimination is renal. Following oral administration, approximately 5 % to 10 % of the dose is recovered unchanged in the urine over 24 hours, and the remainder excreted as temozolomide acid, 5-aminoimidazole-4-carboxamide (AIC) or unidentified polar metabolites.

Plasma concentrations increase in a dose-related manner. Plasma clearance, volume of distribution and half-life are independent of dose.

### Special populations

Analysis of population-based pharmacokinetics of TMZ revealed that plasma TMZ clearance was independent of age, renal function or tobacco use. In a separate pharmacokinetic study, plasma pharmacokinetic profiles in patients with mild to moderate hepatic impairment were similar to those observed in patients with normal hepatic function.

Paediatric patients had a higher AUC than adult patients; however, the maximum tolerated dose (MTD) was 1,000 mg/m<sup>2</sup> per cycle both in children and in adults.

### **5.3 Preclinical safety data**

Single-cycle (5-day dosing, 23 days non-treatment), 3- and 6-cycle toxicity studies were conducted in rats and dogs. The primary targets of toxicity included the bone marrow, lymphoreticular system, testes, the gastrointestinal tract and, at higher doses, which were lethal to 60 % to 100 % of rats and dogs tested, degeneration of the retina occurred. Most of the toxicity showed evidence of reversibility, except for adverse events on the male reproductive system and retinal degeneration. However, because the doses implicated in retinal degeneration were in the lethal dose range, and no comparable effect has been observed in clinical studies, this finding was not considered to have clinical relevance.

TMZ is an embryotoxic, teratogenic and genotoxic alkylating agent. TMZ is more toxic to the rat and dog than to humans, and the clinical dose approximates the minimum lethal dose in rats and dogs. Dose-related reductions in leukocytes and platelets appear to be sensitive indicators of toxicity. A variety of neoplasms, including mammary carcinomas, keratocanthoma of the skin and basal cell adenoma were observed in the 6-cycle rat study while no tumours or pre-neoplastic changes were evident in dog studies. Rats appear to be particularly sensitive to oncogenic effects of TMZ, with the occurrence of first tumours within 3 months of initiating dosing. This latency period is very short even for an alkylating agent.

Results of the Ames/salmonella and Human Peripheral Blood Lymphocyte (HPBL) chromosome aberration tests showed a positive mutagenicity response.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Capsule content:

anhydrous lactose,  
colloidal anhydrous silica,  
sodium starch glycolate type A,  
tartaric acid,  
stearic acid.

#### Capsule shell:

gelatin,  
titanium dioxide (E 171),  
sodium lauril sulfate,  
red iron oxide (E172).

#### Printing ink:

shellac,  
propylene glycol,  
purified water,  
ammonium hydroxide,  
potassium hydroxide,  
black iron oxide (E 172).

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years

### **6.4 Special precautions for storage**

#### Bottle presentation

Do not store above 30 °C.  
Store in the original bottle in order to protect from moisture.  
Keep the bottle tightly closed.

#### Sachet presentation

Do not store above 30 °C.

### **6.5 Nature and contents of container**

#### Bottle presentation

Type I amber glass bottles with polypropylene child-resistant closures containing 5 or 20 hard capsules.  
The carton contains one bottle.

#### Sachet presentation

Sachets are composed of linear low density polyethylene (innermost layer), aluminium and polyethylene terephthalate.  
Each sachet contains 1 hard capsule and is dispensed in a cardboard carton.  
The carton contains 5 or 20 hard capsules, individually sealed in sachets.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal and other handling**

Capsules should not be opened. If a capsule becomes damaged, contact of the powder contents with skin or mucous membrane must be avoided. If Temodal comes into contact with skin or mucosa, it should be washed immediately and thoroughly with soap and water.

Patients should be advised to keep capsules out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN Haarlem  
The Netherlands

**8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/98/096/005

EU/1/98/096/006

EU/1/98/096/015

EU/1/98/096/016

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 26 January 1999

Date of latest renewal: 26 January 2009

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## 1. NAME OF THE MEDICINAL PRODUCT

Temodal 140 mg hard capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 140 mg temozolomide.

### Excipient with known effect:

Each hard capsule contains 246 mg of anhydrous lactose.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Hard capsule (capsule).

The hard capsules have an opaque white body, a blue cap, and are imprinted with black ink. The cap is imprinted with "Temodal". The body is imprinted with "140 mg", the Schering-Plough logo and two stripes.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Temodal is indicated for the treatment of:

- adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment.
- children from the age of three years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy.

### 4.2 Posology and method of administration

Temodal should only be prescribed by physicians experienced in the oncological treatment of brain tumours.

Anti-emetic therapy may be administered (see section 4.4).

### Posology

#### 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 (TMZ) monotherapy (monotherapy phase).

#### *Concomitant phase*

TMZ is administered orally at a dose of 75 mg/m<sup>2</sup> daily for 42 days concomitant with focal radiotherapy (60 Gy administered in 30 fractions). No dose reductions are recommended, but delay or discontinuation of TMZ administration should be decided weekly according to haematological and non-haematological toxicity criteria. TMZ administration can be continued throughout the 42 day concomitant period (up to 49 days) if all of the following conditions are met:

- absolute neutrophil count (ANC)  $\geq 1.5 \times 10^9/l$
- thrombocyte count  $\geq 100 \times 10^9/l$
- common toxicity criteria (CTC) non-haematological toxicity  $\leq$  Grade 1 (except for alopecia, nausea and vomiting).

During treatment a complete blood count should be obtained weekly. TMZ administration should be temporarily interrupted or permanently discontinued during the concomitant phase according to the haematological and non-haematological toxicity criteria as noted in Table 1.

Toxicity	TMZ interruption <sup>a</sup>	TMZ discontinuation
Absolute neutrophil count	$\geq 0.5$ and $< 1.5 \times 10^9/l$	$< 0.5 \times 10^9/l$
Thrombocyte count	$\geq 10$ and $< 100 \times 10^9/l$	$< 10 \times 10^9/l$
CTC non-haematological toxicity (except for alopecia, nausea, vomiting)	CTC Grade 2	CTC Grade 3 or 4

a: Treatment with concomitant TMZ can be continued when all of the following conditions are met: absolute neutrophil count  $\geq 1.5 \times 10^9/l$ ; thrombocyte count  $\geq 100 \times 10^9/l$ ; CTC non-haematological toxicity  $\leq$  Grade 1 (except for alopecia, nausea, vomiting).

### *Monotherapy phase*

Four weeks after completing the TMZ + RT concomitant phase, TMZ is administered for up to 6 cycles of monotherapy treatment. Dose in Cycle 1 (monotherapy) is  $150 \text{ mg/m}^2$  once daily for 5 days followed by 23 days without treatment. At the start of Cycle 2, the dose is escalated to  $200 \text{ mg/m}^2$  if the CTC non-haematological toxicity for Cycle 1 is Grade  $\leq 2$  (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is  $\geq 1.5 \times 10^9/l$ , and the thrombocyte count is  $\geq 100 \times 10^9/l$ . If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles. Once escalated, the dose remains at  $200 \text{ mg/m}^2$  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 TMZ). The dose should be reduced or administration discontinued according to Table 3.

Dose level	TMZ dose ( $\text{mg/m}^2/\text{day}$ )	Remarks
-1	100	Reduction for prior toxicity
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2-6 in absence of toxicity

Toxicity	Reduce TMZ by 1 dose level <sup>a</sup>	Discontinue TMZ
Absolute neutrophil count	$< 1.0 \times 10^9/l$	See footnote b
Thrombocyte count	$< 50 \times 10^9/l$	See footnote b
CTC non-haematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4 <sup>b</sup>

a: TMZ dose levels are listed in Table 2.

b: TMZ is to be discontinued if:

- dose level -1 ( $100 \text{ mg/m}^2$ ) still results in unacceptable toxicity
- the same Grade 3 non-haematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction.

Adult and paediatric patients 3 years of age or older with recurrent or progressive malignant glioma:

A treatment cycle comprises 28 days. In patients previously untreated with chemotherapy, TMZ is administered orally at a dose of 200 mg/m<sup>2</sup> once daily for the first 5 days followed by a 23 day treatment interruption (total of 28 days). In patients previously treated with chemotherapy, the initial dose is 150 mg/m<sup>2</sup> once daily, to be increased in the second cycle to 200 mg/m<sup>2</sup> once daily, for 5 days if there is no haematological toxicity (see section 4.4)

Special populations

*Paediatric population*

In patients 3 years of age or older, TMZ is only to be used in recurrent or progressive malignant glioma. Experience in these children is very limited (see sections 4.4 and 5.1). The safety and efficacy of TMZ in children under the age of 3 years have not been established. No data are available.

*Patients with hepatic or renal impairment*

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

*Elderly patients*

Based on a population pharmacokinetic analysis in patients 19-78 years of age, clearance of TMZ is not affected by age. However, elderly patients (> 70 years of age) appear to be at increased risk of neutropenia and thrombocytopenia (see section 4.4).

Method of administration

Temodal hard capsules should be administered in the fasting state.

The capsules must be swallowed whole with a glass of water and must not be opened or chewed.

If vomiting occurs after the dose is administered, a second dose should not be administered that day.

**4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to dacarbazine (DTIC).

Severe myelosuppression (see section 4.4).

**4.4 Special warnings and precautions for use**

Opportunistic infections and reactivation of infections

Opportunistic infections (such as *Pneumocystis jirovecii* pneumonia) and reactivation of infections (such as HBV, CMV) have been observed during the treatment with TMZ (see section 4.8).

Meningoencephalitis herpetic

In post marketing cases, meningoencephalitis herpetic (including fatal cases) has been observed in patients receiving TMZ in combination with radiotherapy, including cases of concomitant steroids administration.

#### *Pneumocystis jirovecii* pneumonia

Patients who received concomitant TMZ and RT in a pilot trial for the prolonged 42-day schedule were shown to be at particular risk for developing *Pneumocystis jirovecii* pneumonia (PCP). Thus, prophylaxis against PCP is required for all patients receiving concomitant TMZ and RT 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  $\leq 1$ .

There may be a higher occurrence of PCP when TMZ is administered during a longer dosing regimen. However, all patients receiving TMZ, particularly patients receiving steroids, should be observed closely for the development of PCP, regardless of the regimen. Cases of fatal respiratory failure have been reported in patients using TMZ, in particular in combination with dexamethasone or other steroids.

#### HBV

Hepatitis due to hepatitis B virus (HBV) reactivation, in some cases resulting in death, has been reported. Experts in liver disease should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease). During treatment patients should be monitored and managed appropriately.

#### Hepatotoxicity

Hepatic injury, including fatal hepatic failure, has been reported in patients treated with TMZ (see section 4.8). 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.

#### Malignancies

Cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukaemia, have also been reported very rarely (see section 4.8).

#### Anti-emetic therapy

Nausea and vomiting are very commonly associated with TMZ.  
Anti-emetic therapy may be administered prior to or following administration of TMZ.

#### *Adult patients with newly-diagnosed glioblastoma multiforme*

Anti-emetic prophylaxis is recommended prior to the initial dose of concomitant phase and it is strongly recommended during the monotherapy phase.

#### *Patients with recurrent or progressive malignant glioma*

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

### Laboratory parameters

Patients treated with TMZ may experience myelosuppression, including prolonged pancytopenia, which may result in aplastic anaemia, which in some cases has resulted in a fatal outcome. In some cases, exposure to concomitant medicinal products associated with aplastic anaemia, including carbamazepine, phenytoin, and sulfamethoxazole/trimethoprim, complicates assessment. Prior to dosing, the following laboratory parameters must be met: ANC  $\geq 1.5 \times 10^9/l$  and platelet count  $\geq 100 \times 10^9/l$ . A complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until ANC  $> 1.5 \times 10^9/l$  and platelet count  $> 100 \times 10^9/l$ . If ANC falls to  $< 1.0 \times 10^9/l$  or the platelet count is  $< 50 \times 10^9/l$  during any cycle, the next cycle should be reduced one dose level (see section 4.2). Dose levels include  $100 \text{ mg/m}^2$ ,  $150 \text{ mg/m}^2$ , and  $200 \text{ mg/m}^2$ . The lowest recommended dose is  $100 \text{ mg/m}^2$ .

### Paediatric population

There is no clinical experience with use of TMZ in children under the age of 3 years. Experience in older children and adolescents is very limited (see sections 4.2 and 5.1).

### Elderly patients (> 70 years of age)

Elderly patients appear to be at increased risk of neutropenia and thrombocytopenia, compared with younger patients. Therefore, special care should be taken when TMZ is administered in elderly patients.

### Male patients

Men being treated with TMZ should be advised not to father a child up to 6 months after receiving the last dose and to seek advice on cryoconservation of sperm prior to treatment (see section 4.6).

### Lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## **4.5 Interaction with other medicinal products and other forms of interaction**

In a separate phase I study, administration of TMZ with ranitidine did not result in alterations in the extent of absorption of temozolomide or the exposure to its active metabolite monomethyl triazenoimidazole carboxamide (MTIC).

Administration of TMZ with food resulted in a 33 % decrease in  $C_{\text{max}}$  and a 9 % decrease in area under the curve (AUC).

As it cannot be excluded that the change in  $C_{\text{max}}$  is clinically significant, Temodal should be administered without food.

Based on an analysis of population pharmacokinetics in phase II trials, co-administration of dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron,  $H_2$  receptor antagonists, or phenobarbital did not alter the clearance of TMZ. Co-administration with valproic acid was associated with a small but statistically significant decrease in clearance of TMZ.

No studies have been conducted to determine the effect of TMZ on the metabolism or elimination of other medicinal products. However, since TMZ does not undergo hepatic metabolism and exhibits low protein binding, it is unlikely that it would affect the pharmacokinetics of other medicinal products (see section 5.2).

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

#### Paediatric population

Interaction studies have only been performed in adults.

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

There are no data in pregnant women. In preclinical studies in rats and rabbits receiving 150 mg/m<sup>2</sup> TMZ, teratogenicity and/or foetal toxicity were demonstrated (see section 5.3). Temodal should not be administered to pregnant women. If use during pregnancy must be considered, the patient should be apprised of the potential risk to the foetus.

#### Breast-feeding

It is not known whether TMZ is excreted in human milk; thus, breast-feeding should be discontinued while receiving treatment with TMZ.

#### Women of childbearing potential

Women of childbearing potential should be advised to use effective contraception to avoid pregnancy while they are receiving TMZ.

#### Male fertility

TMZ can have genotoxic effects. Therefore, men being treated with it should be advised not to father a child up to 6 months after receiving the last dose and to seek advice on cryoconservation of sperm prior to treatment, because of the possibility of irreversible infertility due to therapy with TMZ.

### **4.7 Effects on ability to drive and use machines**

TMZ has minor influence on the ability to drive and use machines due to fatigue and somnolence (see section 4.8).

### **4.8 Undesirable effects**

#### Clinical trial experience

In patients treated with TMZ, whether used in combination with RT or as monotherapy following RT for newly-diagnosed glioblastoma multiforme, or as monotherapy in patients with recurrent or progressive glioma, the reported very common adverse reactions were similar: nausea, vomiting, constipation, anorexia, headache and fatigue. Convulsions were reported very commonly in the newly-diagnosed glioblastoma multiforme patients receiving monotherapy, and rash was reported very commonly in newly-diagnosed glioblastoma multiforme patients receiving TMZ concurrent with RT and also as monotherapy, and commonly in recurrent glioma. Most haematologic adverse reactions were reported commonly or very commonly in both indications (Tables 4 and 5); the frequency of grade 3-4 laboratory findings is presented after each table.

In the tables undesirable effects are classified according to System Organ Class and frequency. Frequency groupings are defined according to the following convention: Very common ( $\geq 1/10$ ); Common ( $\geq 1/100$  to  $< 1/10$ ); Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); Very rare ( $< 1/10,000$ ). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Newly-diagnosed glioblastoma multiforme

Table 4 provides treatment-emergent adverse events in patients with newly-diagnosed glioblastoma multiforme during the concomitant and monotherapy phases of treatment.

<i>Table 4. Treatment-emergent events during concomitant and monotherapy treatment phases in patients with newly-diagnosed glioblastoma multiforme</i>		
System organ class	TMZ + concomitant RT n=288*	TMZ monotherapy n=224
Infections and infestations		
Common:	Infection, <i>Herpes simplex</i> , wound infection, pharyngitis, candidiasis oral	Infection, candidiasis oral
Uncommon:		<i>Herpes simplex</i> , herpes zoster, influenza-like symptoms
Blood and lymphatic system disorders		
Common:	Neutropenia, thrombocytopenia, lymphopenia, leukopenia	Febrile neutropenia, thrombocytopenia, anaemia, leukopenia
Uncommon:	Febrile neutropenia, anaemia	Lymphopenia, petechiae
Endocrine disorders		
Uncommon:	Cushingoid	Cushingoid
Metabolism and nutrition disorders		
Very common:	Anorexia	Anorexia
Common:	Hyperglycaemia, weight decreased	Weight decreased
Uncommon:	Hypokalemia, 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	Convulsions, headache
Common:	Convulsions, consciousness decreased, somnolence, aphasia, balance impaired, dizziness, confusion, memory impairment, concentration impaired, neuropathy, paresthesia, speech disorder, tremor	Hemiparesis, aphasia, balance impaired, somnolence, confusion, dizziness, memory impairment, concentration impaired, dysphasia, neurological disorder (NOS), neuropathy, peripheral neuropathy, paresthesia, speech disorder, tremor
Uncommon:	Status epilepticus, extrapyramidal disorder, hemiparesis, ataxia, cognition impaired, dysphasia, gait abnormal, hyperesthesia, hypoesthesia, neurological disorder (NOS), peripheral neuropathy	Hemiplegia, ataxia, coordination abnormal, gait abnormal, hyperesthesia, sensory disturbance
Eye disorders		

<i>Table 4. Treatment-emergent events during concomitant and monotherapy treatment phases in patients with newly-diagnosed glioblastoma multiforme</i>		
System organ class	TMZ + concomitant RT n=288*	TMZ monotherapy n=224
Common:	Vision blurred	Visual field defect, vision blurred, diplopia
Uncommon:	Hemianopia, visual acuity reduced, vision disorder, visual field defect, eye pain	Visual acuity reduced, eye pain, eyes dry
Ear and labyrinth disorders		
Common:	Hearing impairment	Hearing impairment, tinnitus
Uncommon:	Otitis media, tinnitus, hyperacusis, earache	Deafness, vertigo, earache
Cardiac disorders		
Uncommon:	Palpitation	
Vascular disorders		
Common:	Haemorrhage, oedema, oedema leg	Haemorrhage, deep venous thrombosis, oedema leg
Uncommon:	Cerebral haemorrhage, hypertension	Embolism pulmonary, oedema, oedema peripheral
Respiratory, thoracic and mediastinal disorders		
Common:	Dyspnoea, coughing	Dyspnoea, coughing
Uncommon:	Pneumonia, upper respiratory infection, nasal congestion	Pneumonia, sinusitis, upper respiratory infection, bronchitis
Gastrointestinal disorders		
Very common:	Constipation, nausea, vomiting	Constipation, nausea, vomiting
Common:	Stomatitis, diarrhoea, abdominal pain, dyspepsia, dysphagia	Stomatitis, diarrhoea, dyspepsia, dysphagia, mouth dry
Uncommon:		Abdominal distension, fecal incontinence, gastrointestinal disorder (NOS), gastroenteritis, haemorrhoids
Skin and subcutaneous tissue disorders		
Very common:	Rash, alopecia	Rash, alopecia
Common:	Dermatitis, dry skin, erythema, pruritus	Dry skin, pruritus
Uncommon:	Skin exfoliation, photosensitivity reaction, pigmentation abnormal	Erythema, pigmentation abnormal, sweating increased
Musculoskeletal and connective tissue disorders		

<i>Table 4. Treatment-emergent events during concomitant and monotherapy treatment phases in patients with newly-diagnosed glioblastoma multiforme</i>		
System organ class	TMZ + concomitant RT n=288*	TMZ monotherapy n=224
Common:	Muscle weakness, arthralgia	Muscle weakness, arthralgia, musculoskeletal pain, myalgia
Uncommon:	Myopathy, back pain, musculoskeletal pain, myalgia	Myopathy, back pain
Renal and urinary disorders		
Common:	Micturition frequency, urinary incontinence	Urinary incontinence
Uncommon:		Dysuria
Reproductive system and breast disorders		
Uncommon:	Impotence	Vaginal haemorrhage, menorrhagia, amenorrhoea, vaginitis, breast pain
General disorders and administration site conditions		
Very common:	Fatigue	Fatigue
Common:	Allergic reaction, fever, radiation injury, face oedema, pain, taste perversion	Allergic reaction, fever, radiation injury, pain, taste perversion
Uncommon:	Asthenia, flushing, hot flushes, condition aggravated, rigors, tongue discolouration, parosmia, thirst	Asthenia, face oedema, pain, condition aggravated, rigors, tooth disorder
Investigations		
Common:	ALT increased	ALT increased
Uncommon:	Hepatic enzymes increased, Gamma GT increased, AST increased	

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

### *Laboratory results*

Myelosuppression (neutropenia and thrombocytopenia), which is known dose-limiting toxicity for most cytotoxic agents, including TMZ, was 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 TMZ.

### *Recurrent or progressive malignant glioma*

In clinical trials, the most frequently occurring treatment-related undesirable effects were gastrointestinal disorders, specifically nausea (43 %) and vomiting (36 %). These reactions were usually Grade 1 or 2 (0 – 5 episodes of vomiting in 24 hours) and were either self-limiting or readily controlled with standard anti-emetic therapy. The incidence of severe nausea and vomiting was 4 %.

Table 5 includes adverse reactions reported during clinical trials for recurrent or progressive malignant glioma and following the marketing of Temodal.

<i>Table 5. Adverse reactions in patients with recurrent or progressive malignant glioma</i>	
Infections and infestations	
Rare:	Opportunistic infections, including PCP
Blood and lymphatic system disorders	
Very common:	Neutropenia or lymphopenia (grade 3-4), thrombocytopenia (grade 3-4)
Uncommon:	Pancytopenia, anaemia (grade 3-4), leukopenia
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:	Vomiting, nausea, constipation
Common:	Diarrhoea, abdominal pain, dyspepsia
Skin and subcutaneous tissue disorders	
Common:	Rash, pruritus, alopecia
Very rare:	Erythema multiforme, erythroderma, urticaria, exanthema
General disorders and administration site conditions	
Very common:	Fatigue
Common:	Fever, asthenia, rigors, malaise, pain, taste perversion
Very 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 malignant glioma. This led to hospitalisation and/or discontinuation of TMZ in 8 % and 4 %, respectively. 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. The presence of thrombocytopenia may increase the risk of bleeding, and the presence of neutropenia or leukopenia may increase the risk of infection.

### *Gender*

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 < 0.5 x 10<sup>9</sup>/l), 12 % vs 5 %, and thrombocytopenia (< 20 x 10<sup>9</sup>/l), 9 % vs 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.

### Paediatric population

Oral TMZ has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. Although the data is limited, tolerance in children is expected to be the same as in adults. The safety of TMZ in children under the age of 3 years has not been established.

### Post-Marketing Experience

The following additional serious adverse reactions have been identified during post-marketing exposure:

<i>Table 6. Summary of events reported with temozolomide in the post-marketing setting</i>	
<b>Infections and infestations*</b>	
Uncommon:	cytomegalovirus infection, infection reactivation such as cytomegalovirus, hepatitis B virus <sup>†</sup> , meningoencephalitis herpetic <sup>†</sup> , sepsis <sup>†</sup>
<b>Blood and lymphatic system disorders</b>	
Very rare:	prolonged pancytopenia, aplastic anaemia <sup>†</sup>
<b>Neoplasm benign, malignant and unspecified</b>	
Very rare:	myelodysplastic syndrome (MDS), secondary malignancies, including myeloid leukaemia
<b>Endocrine disorders*</b>	
Uncommon:	diabetes insipidus
<b>Respiratory, thoracic and mediastinal disorders</b>	
Very rare:	interstitial pneumonitis/pneumonitis, pulmonary fibrosis, respiratory failure <sup>†</sup>
<b>Hepatobiliary disorders*</b>	
Common:	liver enzymes elevations
Uncommon:	hyperbilirubinemia, cholestasis, hepatitis, hepatic injury, hepatic failure <sup>†</sup>
<b>Skin and subcutaneous tissue disorders</b>	
Very rare:	toxic epidermal necrolysis, Stevens-Johnson syndrome

<sup>†</sup> Including cases with fatal outcome

\* Frequencies estimated based on relevant clinical trials.

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

## **4.9 Overdose**

Doses of 500, 750, 1,000, and 1,250 mg/m<sup>2</sup> (total dose per cycle over 5 days) have been evaluated clinically in patients. Dose-limiting toxicity was haematological and was reported with any dose but is expected to be more severe at higher doses. An overdose of 10,000 mg (total dose in a single cycle, over 5 days) was taken by one patient and the adverse reactions reported were pancytopenia, pyrexia,

multi-organ failure and death. There are reports of patients who have taken the recommended dose for 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, haematological evaluation is needed. Supportive measures should be provided as necessary.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents - Other alkylating agents, ATC code: L01A X03

#### Mechanism of action

Temozolomide is a triazene, which undergoes rapid chemical conversion at physiologic pH to the active monomethyl triazenoimidazole carboxamide (MTIC). The cytotoxicity of MTIC is thought to be due primarily to alkylation at the O<sup>6</sup> position of guanine with additional alkylation also occurring at the N<sup>7</sup> position. Cytotoxic lesions that develop subsequently are thought to involve aberrant repair of the methyl adduct.

#### Clinical efficacy and safety

##### *Newly-diagnosed glioblastoma multiforme*

A total of 573 patients were randomised to receive either TMZ + RT (n=287) or RT alone (n=286). Patients in the TMZ + RT arm received concomitant TMZ (75 mg/m<sup>2</sup>) 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 TMZ (150 - 200 mg/m<sup>2</sup>) 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 jirovecii* pneumonia (PCP) prophylaxis was required during RT and combined TMZ therapy.

TMZ 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 TMZ + 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 favour of the TMZ arm. The estimated probability of surviving 2 years or more (26 % vs 10 %) is higher for the RT + TMZ arm. The addition of concomitant TMZ to RT, followed by TMZ monotherapy in the treatment of patients with newly-diagnosed glioblastoma multiforme demonstrated a statistically significant improvement in overall survival (OS) compared with RT alone (Figure 1).

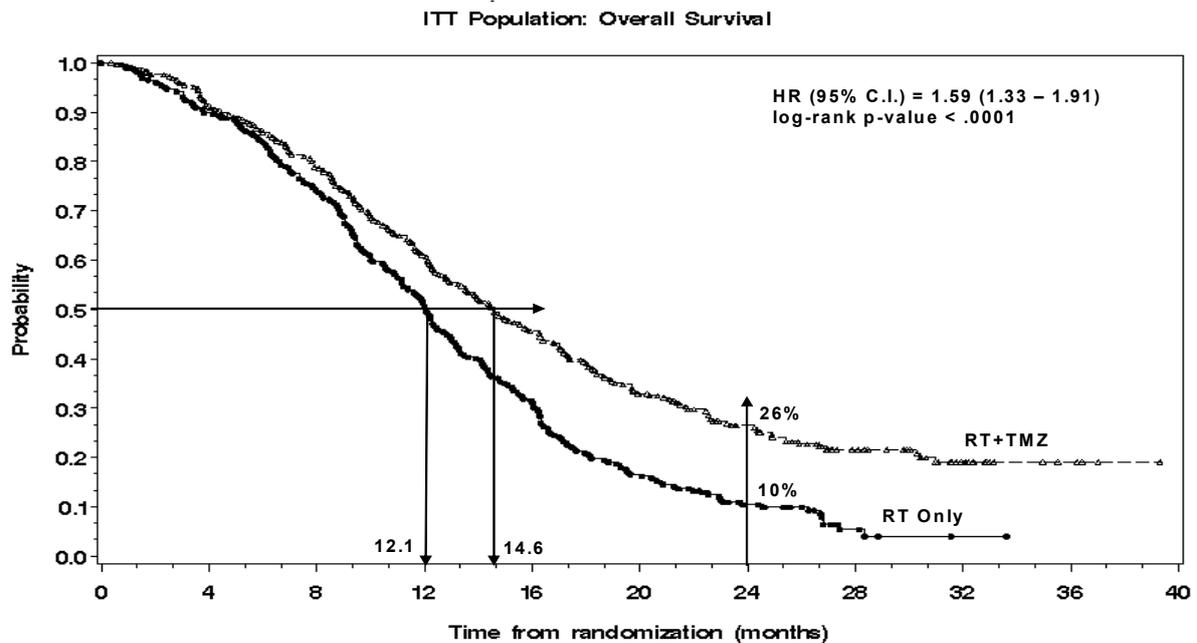


Figure 1 Kaplan-Meier curves for overall survival (intent-to-treat population)

The results from the trial were not consistent in the subgroup of patients with a poor performance status (WHO PS=2, n=70), where overall survival and time to progression were similar in both arms. However, no unacceptable risks appear to be present in this patient group.

#### Recurrent or progressive malignant glioma

Data on clinical efficacy in patients with glioblastoma multiforme (Karnofsky performance status [KPS]  $\geq 70$ ), progressive or recurrent after surgery and RT, were based on two clinical trials with oral TMZ. One was a non-comparative trial in 138 patients (29 % received prior chemotherapy), and the other was a randomised active-controlled trial of TMZ vs 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 (ORR) based on MRI scans was 8 %.

In the randomised active-controlled trial, the PFS at 6 months was significantly greater for TMZ 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 TMZ and procarbazine, respectively (log rank  $p = 0.33$ ). At 6 months, the fraction of surviving patients was significantly higher in the TMZ 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  $\geq 80$ .

Data on time to worsening of neurological status favoured TMZ over procarbazine as did data on time to worsening of performance status (decrease to a KPS of  $< 70$  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 TMZ than for procarbazine (log rank  $p = < 0.01$  to 0.03).

#### Recurrent anaplastic astrocytoma

In a multicentre, prospective phase II trial evaluating the safety and efficacy of oral TMZ in the treatment of patients with anaplastic astrocytoma at first relapse, the 6 month PFS was 46 %. The median PFS 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 (ITT) n=162. In 43 patients stable disease was reported. 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 radiological objective response or maintaining progression-free status was strongly associated with maintained or improved quality of life.

### Paediatric population

Oral TMZ has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. Tolerance to TMZ is similar to adults.

## **5.2 Pharmacokinetic properties**

TMZ is spontaneously hydrolyzed at physiologic pH primarily to the active species, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC). MTIC is spontaneously hydrolyzed to 5-aminoimidazole-4-carboxamide (AIC), a known intermediate in purine and nucleic acid biosynthesis, and to methylhydrazine, which is believed to be the active alkylating species. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA mainly at the O<sup>6</sup> and N<sup>7</sup> positions of guanine. Relative to the AUC of TMZ, the exposure to MTIC and AIC is ~ 2.4 % and 23 %, respectively. *In vivo*, the t<sub>1/2</sub> of MTIC was similar to that of TMZ, 1.8 hr.

### Absorption

After oral administration to adult patients, TMZ is absorbed rapidly, with peak concentrations reached as early as 20 minutes post-administration (mean time between 0.5 and 1.5 hours). After oral administration of <sup>14</sup>C-labelled TMZ, mean faecal excretion of <sup>14</sup>C over 7 days post-dose was 0.8 % indicating complete absorption.

### Distribution

TMZ demonstrates low protein binding (10 % to 20 %), and thus it is not expected to interact with highly protein-bound substances.

PET studies in humans and preclinical data suggest that TMZ crosses the blood-brain barrier rapidly and is present in the CSF. CSF penetration was confirmed in one patient; CSF exposure based on AUC of TMZ was approximately 30 % of that in plasma, which is consistent with animal data.

### Elimination

The half-life (t<sub>1/2</sub>) in plasma is approximately 1.8 hours. The major route of <sup>14</sup>C elimination is renal. Following oral administration, approximately 5 % to 10 % of the dose is recovered unchanged in the urine over 24 hours, and the remainder excreted as temozolomide acid, 5-aminoimidazole-4-carboxamide (AIC) or unidentified polar metabolites.

Plasma concentrations increase in a dose-related manner. Plasma clearance, volume of distribution and half-life are independent of dose.

### Special populations

Analysis of population-based pharmacokinetics of TMZ revealed that plasma TMZ clearance was independent of age, renal function or tobacco use. In a separate pharmacokinetic study, plasma pharmacokinetic profiles in patients with mild to moderate hepatic impairment were similar to those observed in patients with normal hepatic function.

Paediatric patients had a higher AUC than adult patients; however, the maximum tolerated dose (MTD) was 1,000 mg/m<sup>2</sup> per cycle both in children and in adults.

### **5.3 Preclinical safety data**

Single-cycle (5-day dosing, 23 days non-treatment), 3- and 6-cycle toxicity studies were conducted in rats and dogs. The primary targets of toxicity included the bone marrow, lymphoreticular system, testes, the gastrointestinal tract and, at higher doses, which were lethal to 60 % to 100 % of rats and dogs tested, degeneration of the retina occurred. Most of the toxicity showed evidence of reversibility, except for adverse events on the male reproductive system and retinal degeneration. However, because the doses implicated in retinal degeneration were in the lethal dose range, and no comparable effect has been observed in clinical studies, this finding was not considered to have clinical relevance.

TMZ is an embryotoxic, teratogenic and genotoxic alkylating agent. TMZ is more toxic to the rat and dog than to humans, and the clinical dose approximates the minimum lethal dose in rats and dogs. Dose-related reductions in leukocytes and platelets appear to be sensitive indicators of toxicity. A variety of neoplasms, including mammary carcinomas, keratocanthoma of the skin and basal cell adenoma were observed in the 6-cycle rat study while no tumours or pre-neoplastic changes were evident in dog studies. Rats appear to be particularly sensitive to oncogenic effects of TMZ, with the occurrence of first tumours within 3 months of initiating dosing. This latency period is very short even for an alkylating agent.

Results of the Ames/salmonella and Human Peripheral Blood Lymphocyte (HPBL) chromosome aberration tests showed a positive mutagenicity response.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Capsule content:

anhydrous lactose,  
colloidal anhydrous silica,  
sodium starch glycolate type A,  
tartaric acid,  
stearic acid.

#### Capsule shell:

gelatin,  
titanium dioxide (E 171),  
sodium lauril sulfate ,  
indigo carmine (E 132),

#### Printing ink:

shellac,  
propylene glycol,  
purified water,  
ammonium hydroxide,  
potassium hydroxide,  
black iron oxide (E 172).

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years

### **6.4 Special precautions for storage**

#### Bottle presentation

Do not store above 30 °C.  
Store in the original bottle in order to protect from moisture.  
Keep the bottle tightly closed.

#### Sachet presentation

Do not store above 30 °C.

### **6.5 Nature and contents of container**

#### Bottle presentation

Type I amber glass bottles with polypropylene child-resistant closures containing 5 or 20 hard capsules.  
The carton contains one bottle.

#### Sachet presentation

Sachets are composed of linear low density polyethylene (innermost layer), aluminium and polyethylene terephthalate.  
Each sachet contains 1 hard capsule and is dispensed in a cardboard carton.  
The carton contains 5 or 20 hard capsules, individually sealed in sachets.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal and other handling**

Capsules should not be opened. If a capsule becomes damaged, contact of the powder contents with skin or mucous membrane must be avoided. If Temodal comes into contact with skin or mucosa, it should be washed immediately and thoroughly with soap and water.

Patients should be advised to keep capsules out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN Haarlem  
The Netherlands

**8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/98/096/009

EU/1/98/096/010

EU/1/98/096/017

EU/1/98/096/018

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 26 January 1999

Date of latest renewal: 26 January 2009

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## 1. NAME OF THE MEDICINAL PRODUCT

Temodal 180 mg hard capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 180 mg temozolomide.

### Excipient with known effect:

Each hard capsule contains 316.3 mg of anhydrous lactose.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Hard capsule (capsule).

The hard capsules have an opaque white body, an opaque orange cap, and are imprinted with black ink. The cap is imprinted with "Temodal". The body is imprinted with "180 mg", the Schering-Plough logo and two stripes.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Temodal is indicated for the treatment of:

- adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment.
- children from the age of three years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy.

### 4.2 Posology and method of administration

Temodal should only be prescribed by physicians experienced in the oncological treatment of brain tumours.

Anti-emetic therapy may be administered (see section 4.4).

### Posology

#### 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 (TMZ) monotherapy (monotherapy phase).

#### *Concomitant phase*

TMZ is administered orally at a dose of 75 mg/m<sup>2</sup> daily for 42 days concomitant with focal radiotherapy (60 Gy administered in 30 fractions). No dose reductions are recommended, but delay or discontinuation of TMZ administration should be decided weekly according to haematological and non-haematological toxicity criteria. TMZ administration can be continued throughout the 42 day concomitant period (up to 49 days) if all of the following conditions are met:

- absolute neutrophil count (ANC)  $\geq 1.5 \times 10^9/l$
- thrombocyte count  $\geq 100 \times 10^9/l$
- common toxicity criteria (CTC) non-haematological toxicity  $\leq$  Grade 1 (except for alopecia, nausea and vomiting).

During treatment a complete blood count should be obtained weekly. TMZ administration should be temporarily interrupted or permanently discontinued during the concomitant phase according to the haematological and non-haematological toxicity criteria as noted in Table 1.

Toxicity	TMZ interruption <sup>a</sup>	TMZ discontinuation
Absolute neutrophil count	$\geq 0.5$ and $< 1.5 \times 10^9/l$	$< 0.5 \times 10^9/l$
Thrombocyte count	$\geq 10$ and $< 100 \times 10^9/l$	$< 10 \times 10^9/l$
CTC non-haematological toxicity (except for alopecia, nausea, vomiting)	CTC Grade 2	CTC Grade 3 or 4

a: Treatment with concomitant TMZ can be continued when all of the following conditions are met: absolute neutrophil count  $\geq 1.5 \times 10^9/l$ ; thrombocyte count  $\geq 100 \times 10^9/l$ ; CTC non-haematological toxicity  $\leq$  Grade 1 (except for alopecia, nausea, vomiting).

### *Monotherapy phase*

Four weeks after completing the TMZ + RT concomitant phase, TMZ is administered for up to 6 cycles of monotherapy treatment. Dose in Cycle 1 (monotherapy) is  $150 \text{ mg/m}^2$  once daily for 5 days followed by 23 days without treatment. At the start of Cycle 2, the dose is escalated to  $200 \text{ mg/m}^2$  if the CTC non-haematological toxicity for Cycle 1 is Grade  $\leq 2$  (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is  $\geq 1.5 \times 10^9/l$ , and the thrombocyte count is  $\geq 100 \times 10^9/l$ . If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles. Once escalated, the dose remains at  $200 \text{ mg/m}^2$  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 TMZ). The dose should be reduced or administration discontinued according to Table 3.

Dose level	TMZ dose ( $\text{mg/m}^2/\text{day}$ )	Remarks
-1	100	Reduction for prior toxicity
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2-6 in absence of toxicity

Toxicity	Reduce TMZ by 1 dose level <sup>a</sup>	Discontinue TMZ
Absolute neutrophil count	$< 1.0 \times 10^9/l$	See footnote b
Thrombocyte count	$< 50 \times 10^9/l$	See footnote b
CTC non-haematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4 <sup>b</sup>

a: TMZ dose levels are listed in Table 2.

b: TMZ is to be discontinued if:

- dose level -1 ( $100 \text{ mg/m}^2$ ) still results in unacceptable toxicity
- the same Grade 3 non-haematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction.

Adult and paediatric patients 3 years of age or older with recurrent or progressive malignant glioma:

A treatment cycle comprises 28 days. In patients previously untreated with chemotherapy, TMZ is administered orally at a dose of 200 mg/m<sup>2</sup> once daily for the first 5 days followed by a 23 day treatment interruption (total of 28 days). In patients previously treated with chemotherapy, the initial dose is 150 mg/m<sup>2</sup> once daily, to be increased in the second cycle to 200 mg/m<sup>2</sup> once daily, for 5 days if there is no haematological toxicity (see section 4.4)

Special populations

*Paediatric population*

In patients 3 years of age or older, TMZ is only to be used in recurrent or progressive malignant glioma. Experience in these children is very limited (see sections 4.4 and 5.1). The safety and efficacy of TMZ in children under the age of 3 years have not been established. No data are available.

*Patients with hepatic or renal impairment*

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

*Elderly patients*

Based on a population pharmacokinetic analysis in patients 19-78 years of age, clearance of TMZ is not affected by age. However, elderly patients (> 70 years of age) appear to be at increased risk of neutropenia and thrombocytopenia (see section 4.4).

Method of administration

Temodal hard capsules should be administered in the fasting state.

The capsules must be swallowed whole with a glass of water and must not be opened or chewed.

If vomiting occurs after the dose is administered, a second dose should not be administered that day.

**4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to dacarbazine (DTIC).

Severe myelosuppression (see section 4.4).

**4.4 Special warnings and precautions for use**

Opportunistic infections and reactivation of infections

Opportunistic infections (such as *Pneumocystis jirovecii* pneumonia) and reactivation of infections (such as HBV, CMV) have been observed during the treatment with TMZ (see section 4.8).

Meningoencephalitis herpetic

In post marketing cases, meningoencephalitis herpetic (including fatal cases) has been observed in patients receiving TMZ in combination with radiotherapy, including cases of concomitant steroids administration.

#### *Pneumocystis jirovecii* pneumonia

Patients who received concomitant TMZ and RT in a pilot trial for the prolonged 42-day schedule were shown to be at particular risk for developing *Pneumocystis jirovecii* pneumonia (PCP). Thus, prophylaxis against PCP is required for all patients receiving concomitant TMZ and RT 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  $\leq 1$ .

There may be a higher occurrence of PCP when TMZ is administered during a longer dosing regimen. However, all patients receiving TMZ, particularly patients receiving steroids, should be observed closely for the development of PCP, regardless of the regimen. Cases of fatal respiratory failure have been reported in patients using TMZ, in particular in combination with dexamethasone or other steroids.

#### HBV

Hepatitis due to hepatitis B virus (HBV) reactivation, in some cases resulting in death, has been reported. Experts in liver disease should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease). During treatment patients should be monitored and managed appropriately.

#### Hepatotoxicity

Hepatic injury, including fatal hepatic failure, has been reported in patients treated with TMZ (see section 4.8). 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.

#### Malignancies

Cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukaemia, have also been reported very rarely (see section 4.8).

#### Anti-emetic therapy

Nausea and vomiting are very commonly associated with TMZ.  
Anti-emetic therapy may be administered prior to or following administration of TMZ.

#### *Adult patients with newly-diagnosed glioblastoma multiforme*

Anti-emetic prophylaxis is recommended prior to the initial dose of concomitant phase and it is strongly recommended during the monotherapy phase.

#### *Patients with recurrent or progressive malignant glioma*

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

### Laboratory parameters

Patients treated with TMZ may experience myelosuppression, including prolonged pancytopenia, which may result in aplastic anaemia, which in some cases has resulted in a fatal outcome. In some cases, exposure to concomitant medicinal products associated with aplastic anaemia, including carbamazepine, phenytoin, and sulfamethoxazole/trimethoprim, complicates assessment. Prior to dosing, the following laboratory parameters must be met: ANC  $\geq 1.5 \times 10^9/l$  and platelet count  $\geq 100 \times 10^9/l$ . A complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until ANC  $> 1.5 \times 10^9/l$  and platelet count  $> 100 \times 10^9/l$ . If ANC falls to  $< 1.0 \times 10^9/l$  or the platelet count is  $< 50 \times 10^9/l$  during any cycle, the next cycle should be reduced one dose level (see section 4.2). Dose levels include  $100 \text{ mg/m}^2$ ,  $150 \text{ mg/m}^2$ , and  $200 \text{ mg/m}^2$ . The lowest recommended dose is  $100 \text{ mg/m}^2$ .

### Paediatric population

There is no clinical experience with use of TMZ in children under the age of 3 years. Experience in older children and adolescents is very limited (see sections 4.2 and 5.1).

### Elderly patients (> 70 years of age)

Elderly patients appear to be at increased risk of neutropenia and thrombocytopenia, compared with younger patients. Therefore, special care should be taken when TMZ is administered in elderly patients.

### Male patients

Men being treated with TMZ should be advised not to father a child up to 6 months after receiving the last dose and to seek advice on cryoconservation of sperm prior to treatment (see section 4.6).

### Lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## **4.5 Interaction with other medicinal products and other forms of interaction**

In a separate phase I study, administration of TMZ with ranitidine did not result in alterations in the extent of absorption of temozolomide or the exposure to its active metabolite monomethyl triazenoimidazole carboxamide (MTIC).

Administration of TMZ with food resulted in a 33 % decrease in  $C_{\text{max}}$  and a 9 % decrease in area under the curve (AUC).

As it cannot be excluded that the change in  $C_{\text{max}}$  is clinically significant, Temodal should be administered without food.

Based on an analysis of population pharmacokinetics in phase II trials, co-administration of dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron,  $H_2$  receptor antagonists, or phenobarbital did not alter the clearance of TMZ. Co-administration with valproic acid was associated with a small but statistically significant decrease in clearance of TMZ.

No studies have been conducted to determine the effect of TMZ on the metabolism or elimination of other medicinal products. However, since TMZ does not undergo hepatic metabolism and exhibits low protein binding, it is unlikely that it would affect the pharmacokinetics of other medicinal products (see section 5.2).

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

#### Paediatric population

Interaction studies have only been performed in adults.

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

There are no data in pregnant women. In preclinical studies in rats and rabbits receiving 150 mg/m<sup>2</sup> TMZ, teratogenicity and/or foetal toxicity were demonstrated (see section 5.3). Temodal should not be administered to pregnant women. If use during pregnancy must be considered, the patient should be apprised of the potential risk to the foetus.

#### Breast-feeding

It is not known whether TMZ is excreted in human milk; thus, breast-feeding should be discontinued while receiving treatment with TMZ.

#### Women of childbearing potential

Women of childbearing potential should be advised to use effective contraception to avoid pregnancy while they are receiving TMZ.

#### Male fertility

TMZ can have genotoxic effects. Therefore, men being treated with it should be advised not to father a child up to 6 months after receiving the last dose and to seek advice on cryoconservation of sperm prior to treatment, because of the possibility of irreversible infertility due to therapy with TMZ.

### **4.7 Effects on ability to drive and use machines**

TMZ has minor influence on the ability to drive and use machines due to fatigue and somnolence (see section 4.8).

### **4.8 Undesirable effects**

#### Clinical trial experience

In patients treated with TMZ, whether used in combination with RT or as monotherapy following RT for newly-diagnosed glioblastoma multiforme, or as monotherapy in patients with recurrent or progressive glioma, the reported very common adverse reactions were similar: nausea, vomiting, constipation, anorexia, headache and fatigue. Convulsions were reported very commonly in the newly-diagnosed glioblastoma multiforme patients receiving monotherapy, and rash was reported very commonly in newly-diagnosed glioblastoma multiforme patients receiving TMZ concurrent with RT and also as monotherapy, and commonly in recurrent glioma. Most haematologic adverse reactions were reported commonly or very commonly in both indications (Tables 4 and 5); the frequency of grade 3-4 laboratory findings is presented after each table.

In the tables undesirable effects are classified according to System Organ Class and frequency. Frequency groupings are defined according to the following convention: Very common ( $\geq 1/10$ ); Common ( $\geq 1/100$  to  $< 1/10$ ); Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); Very rare ( $< 1/10,000$ ). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Newly-diagnosed glioblastoma multiforme

Table 4 provides treatment-emergent adverse events in patients with newly-diagnosed glioblastoma multiforme during the concomitant and monotherapy phases of treatment.

<i>Table 4. Treatment-emergent events during concomitant and monotherapy treatment phases in patients with newly-diagnosed glioblastoma multiforme</i>		
System organ class	TMZ + concomitant RT n=288*	TMZ monotherapy n=224
Infections and infestations		
Common:	Infection, <i>Herpes simplex</i> , wound infection, pharyngitis, candidiasis oral	Infection, candidiasis oral
Uncommon:		<i>Herpes simplex</i> , herpes zoster, influenza-like symptoms
Blood and lymphatic system disorders		
Common:	Neutropenia, thrombocytopenia, lymphopenia, leukopenia	Febrile neutropenia, thrombocytopenia, anaemia, leukopenia
Uncommon:	Febrile neutropenia, anaemia	Lymphopenia, petechiae
Endocrine disorders		
Uncommon:	Cushingoid	Cushingoid
Metabolism and nutrition disorders		
Very common:	Anorexia	Anorexia
Common:	Hyperglycaemia, weight decreased	Weight decreased
Uncommon:	Hypokalemia, 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	Convulsions, headache
Common:	Convulsions, consciousness decreased, somnolence, aphasia, balance impaired, dizziness, confusion, memory impairment, concentration impaired, neuropathy, paresthesia, speech disorder, tremor	Hemiparesis, aphasia, balance impaired, somnolence, confusion, dizziness, memory impairment, concentration impaired, dysphasia, neurological disorder (NOS), neuropathy, peripheral neuropathy, paresthesia, speech disorder, tremor
Uncommon:	Status epilepticus, extrapyramidal disorder, hemiparesis, ataxia, cognition impaired, dysphasia, gait abnormal, hyperesthesia, hypoesthesia, neurological disorder (NOS), peripheral neuropathy	Hemiplegia, ataxia, coordination abnormal, gait abnormal, hyperesthesia, sensory disturbance
Eye disorders		

*Table 4. Treatment-emergent events during concomitant and monotherapy treatment phases in patients with newly-diagnosed glioblastoma multiforme*

System organ class	TMZ + concomitant RT n=288*	TMZ monotherapy n=224
Common:	Vision blurred	Visual field defect, vision blurred, diplopia
Uncommon:	Hemianopia, visual acuity reduced, vision disorder, visual field defect, eye pain	Visual acuity reduced, eye pain, eyes dry
Ear and labyrinth disorders		
Common:	Hearing impairment	Hearing impairment, tinnitus
Uncommon:	Otitis media, tinnitus, hyperacusis, earache	Deafness, vertigo, earache
Cardiac disorders		
Uncommon:	Palpitation	
Vascular disorders		
Common:	Haemorrhage, oedema, oedema leg	Haemorrhage, deep venous thrombosis, oedema leg
Uncommon:	Cerebral haemorrhage, hypertension	Embolism pulmonary, oedema, oedema peripheral
Respiratory, thoracic and mediastinal disorders		
Common:	Dyspnoea, coughing	Dyspnoea, coughing
Uncommon:	Pneumonia, upper respiratory infection, nasal congestion	Pneumonia, sinusitis, upper respiratory infection, bronchitis
Gastrointestinal disorders		
Very common:	Constipation, nausea, vomiting	Constipation, nausea, vomiting
Common:	Stomatitis, diarrhoea, abdominal pain, dyspepsia, dysphagia	Stomatitis, diarrhoea, dyspepsia, dysphagia, mouth dry
Uncommon:		Abdominal distension, fecal incontinence, gastrointestinal disorder (NOS), gastroenteritis, haemorrhoids
Skin and subcutaneous tissue disorders		
Very common:	Rash, alopecia	Rash, alopecia
Common:	Dermatitis, dry skin, erythema, pruritus	Dry skin, pruritus
Uncommon:	Skin exfoliation, photosensitivity reaction, pigmentation abnormal	Erythema, pigmentation abnormal, sweating increased
Musculoskeletal and connective tissue disorders		
Common:	Muscle weakness, arthralgia	Muscle weakness, arthralgia, musculoskeletal pain, myalgia

<i>Table 4. Treatment-emergent events during concomitant and monotherapy treatment phases in patients with newly-diagnosed glioblastoma multiforme</i>		
System organ class	TMZ + concomitant RT n=288*	TMZ monotherapy n=224
Uncommon:	Myopathy, back pain, musculoskeletal pain, myalgia	Myopathy, back pain
Renal and urinary disorders		
Common:	Micturition frequency, urinary incontinence	Urinary incontinence
Uncommon:		Dysuria
Reproductive system and breast disorders		
Uncommon:	Impotence	Vaginal haemorrhage, menorrhagia, amenorrhea, vaginitis, breast pain
General disorders and administration site conditions		
Very common:	Fatigue	Fatigue
Common:	Allergic reaction, fever, radiation injury, face oedema, pain, taste perversion	Allergic reaction, fever, radiation injury, pain, taste perversion
Uncommon:	Asthenia, flushing, hot flushes, condition aggravated, rigors, tongue discolouration, parosmia, thirst	Asthenia, face oedema, pain, condition aggravated, rigors, tooth disorder
Investigations		
Common:	ALT increased	ALT increased
Uncommon:	Hepatic enzymes increased, Gamma GT increased, AST increased	

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

### *Laboratory results*

Myelosuppression (neutropenia and thrombocytopenia), which is known dose-limiting toxicity for most cytotoxic agents, including TMZ, was 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 TMZ.

### *Recurrent or progressive malignant glioma*

In clinical trials, the most frequently occurring treatment-related undesirable effects were gastrointestinal disorders, specifically nausea (43 %) and vomiting (36 %). These reactions were usually Grade 1 or 2 (0 – 5 episodes of vomiting in 24 hours) and were either self-limiting or readily controlled with standard anti-emetic therapy. The incidence of severe nausea and vomiting was 4 %.

Table 5 includes adverse reactions reported during clinical trials for recurrent or progressive malignant glioma and following the marketing of Temodal.

<i>Table 5. Adverse reactions in patients with recurrent or progressive malignant glioma</i>	
Infections and infestations	
Rare:	Opportunistic infections, including PCP
Blood and lymphatic system disorders	
Very common:	Neutropenia or lymphopenia (grade 3-4), thrombocytopenia (grade 3-4)
Uncommon:	Pancytopenia, anaemia (grade 3-4), leukopenia
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:	Vomiting, nausea, constipation
Common:	Diarrhoea, abdominal pain, dyspepsia
Skin and subcutaneous tissue disorders	
Common:	Rash, pruritus, alopecia
Very rare:	Erythema multiforme, erythroderma, urticaria, exanthema
General disorders and administration site conditions	
Very common:	Fatigue
Common:	Fever, asthenia, rigors, malaise, pain, taste perversion
Very 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 malignant glioma. This led to hospitalisation and/or discontinuation of TMZ in 8 % and 4 %, respectively. 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. The presence of thrombocytopenia may increase the risk of bleeding, and the presence of neutropenia or leukopenia may increase the risk of infection.

### *Gender*

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 ( $ANC < 0.5 \times 10^9/l$ ), 12 % vs 5 %, and thrombocytopenia ( $< 20 \times 10^9/l$ ), 9 % vs 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.

### Paediatric population

Oral TMZ has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. Although the data is limited, tolerance in children is expected to be the same as in adults. The safety of TMZ in children under the age of 3 years has not been established.

### Post-Marketing Experience

The following additional serious adverse reactions have been identified during post-marketing exposure:

<i>Table 6. Summary of events reported with temozolomide in the post-marketing setting</i>	
<b>Infections and infestations*</b>	
Uncommon:	cytomegalovirus infection, infection reactivation such as cytomegalovirus, hepatitis B virus <sup>†</sup> , meningoencephalitis herpetic <sup>†</sup> , sepsis <sup>†</sup>
<b>Blood and lymphatic system disorders</b>	
Very rare:	prolonged pancytopenia, aplastic anaemia <sup>†</sup>
<b>Neoplasm benign, malignant and unspecified</b>	
Very rare:	myelodysplastic syndrome (MDS), secondary malignancies, including myeloid leukaemia
<b>Endocrine disorders*</b>	
Uncommon:	diabetes insipidus
<b>Respiratory, thoracic and mediastinal disorders</b>	
Very rare:	interstitial pneumonitis/pneumonitis, pulmonary fibrosis, respiratory failure <sup>†</sup>
<b>Hepatobiliary disorders*</b>	
Common:	liver enzymes elevations
Uncommon:	hyperbilirubinemia, cholestasis, hepatitis, hepatic injury, hepatic failure <sup>†</sup>
<b>Skin and subcutaneous tissue disorders</b>	
Very rare:	toxic epidermal necrolysis, Stevens-Johnson syndrome

<sup>†</sup> Including cases with fatal outcome

\* Frequencies estimated based on relevant clinical trials.

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

## **4.9 Overdose**

Doses of 500, 750, 1,000, and 1,250 mg/m<sup>2</sup> (total dose per cycle over 5 days) have been evaluated clinically in patients. Dose-limiting toxicity was haematological and was reported with any dose but is expected to be more severe at higher doses. An overdose of 10,000 mg (total dose in a single cycle, over 5 days) was taken by one patient and the adverse reactions reported were pancytopenia, pyrexia,

multi-organ failure and death. There are reports of patients who have taken the recommended dose for 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, haematological evaluation is needed. Supportive measures should be provided as necessary.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents - Other alkylating agents, ATC code: L01A X03

#### Mechanism of action

Temozolomide is a triazene, which undergoes rapid chemical conversion at physiologic pH to the active monomethyl triazenoimidazole carboxamide (MTIC). The cytotoxicity of MTIC is thought to be due primarily to alkylation at the O<sup>6</sup> position of guanine with additional alkylation also occurring at the N<sup>7</sup> position. Cytotoxic lesions that develop subsequently are thought to involve aberrant repair of the methyl adduct.

#### Clinical efficacy and safety

##### *Newly-diagnosed glioblastoma multiforme*

A total of 573 patients were randomised to receive either TMZ + RT (n=287) or RT alone (n=286). Patients in the TMZ + RT arm received concomitant TMZ (75 mg/m<sup>2</sup>) 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 TMZ (150 - 200 mg/m<sup>2</sup>) 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 jirovecii* pneumonia (PCP) prophylaxis was required during RT and combined TMZ therapy.

TMZ 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 TMZ + 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 favour of the TMZ arm. The estimated probability of surviving 2 years or more (26 % vs 10 %) is higher for the RT + TMZ arm. The addition of concomitant TMZ to RT, followed by TMZ monotherapy in the treatment of patients with newly-diagnosed glioblastoma multiforme demonstrated a statistically significant improvement in overall survival (OS) compared with RT alone (Figure 1).

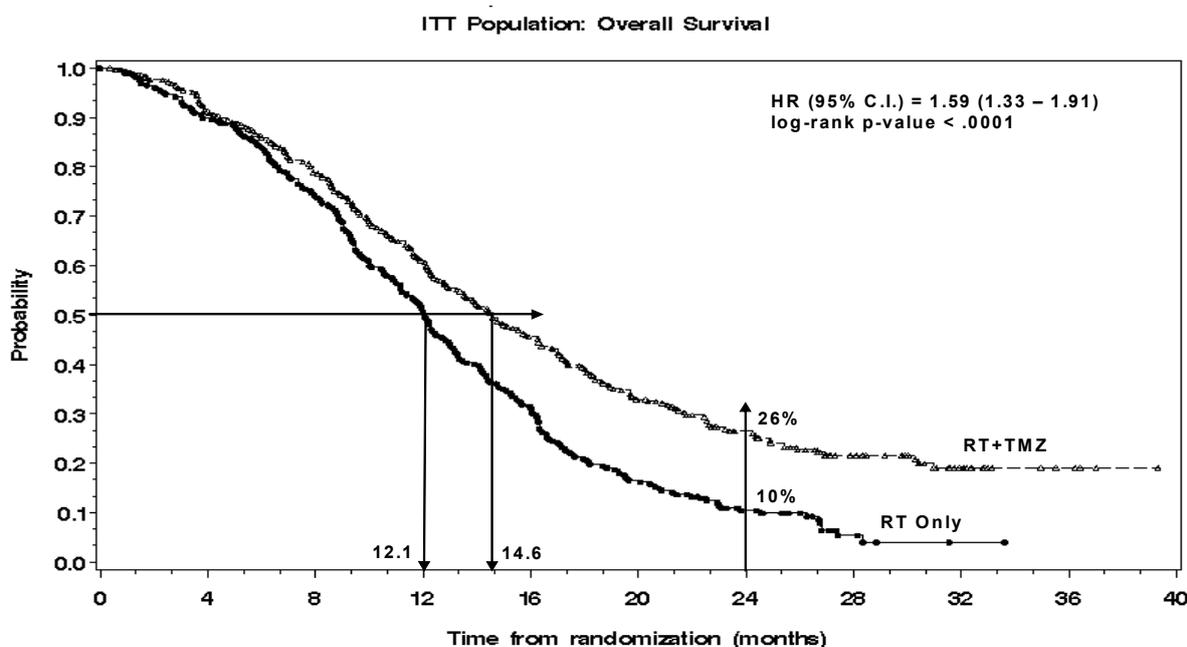


Figure 1 Kaplan-Meier curves for overall survival (intent-to-treat population)

The results from the trial were not consistent in the subgroup of patients with a poor performance status (WHO PS=2, n=70), where overall survival and time to progression were similar in both arms. However, no unacceptable risks appear to be present in this patient group.

#### Recurrent or progressive malignant glioma

Data on clinical efficacy in patients with glioblastoma multiforme (Karnofsky performance status [KPS]  $\geq 70$ ), progressive or recurrent after surgery and RT, were based on two clinical trials with oral TMZ. One was a non-comparative trial in 138 patients (29 % received prior chemotherapy), and the other was a randomised active-controlled trial of TMZ vs 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 (ORR) based on MRI scans was 8 %.

In the randomised active-controlled trial, the PFS at 6 months was significantly greater for TMZ 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 TMZ and procarbazine, respectively (log rank  $p = 0.33$ ). At 6 months, the fraction of surviving patients was significantly higher in the TMZ 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  $\geq 80$ .

Data on time to worsening of neurological status favoured TMZ over procarbazine as did data on time to worsening of performance status (decrease to a KPS of  $< 70$  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 TMZ than for procarbazine (log rank  $p = < 0.01$  to 0.03).

#### Recurrent anaplastic astrocytoma

In a multicentre, prospective phase II trial evaluating the safety and efficacy of oral TMZ in the treatment of patients with anaplastic astrocytoma at first relapse, the 6 month PFS was 46 %. The median PFS 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 (ITT)

n=162. In 43 patients stable disease was reported. 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 radiological objective response or maintaining progression-free status was strongly associated with maintained or improved quality of life.

### Paediatric population

Oral TMZ has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. Tolerance to TMZ is similar to adults.

## **5.2 Pharmacokinetic properties**

TMZ is spontaneously hydrolyzed at physiologic pH primarily to the active species, 3-methyl-(triazene-1-yl)imidazole-4-carboxamide (MTIC). MTIC is spontaneously hydrolyzed to 5-aminoimidazole-4-carboxamide (AIC), a known intermediate in purine and nucleic acid biosynthesis, and to methylhydrazine, which is believed to be the active alkylating species. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA mainly at the O<sup>6</sup> and N<sup>7</sup> positions of guanine. Relative to the AUC of TMZ, the exposure to MTIC and AIC is ~ 2.4 % and 23 %, respectively. *In vivo*, the t<sub>1/2</sub> of MTIC was similar to that of TMZ, 1.8 hr.

### Absorption

After oral administration to adult patients, TMZ is absorbed rapidly, with peak concentrations reached as early as 20 minutes post-administration (mean time between 0.5 and 1.5 hours). After oral administration of <sup>14</sup>C-labelled TMZ, mean faecal excretion of <sup>14</sup>C over 7 days post-dose was 0.8 % indicating complete absorption.

### Distribution

TMZ demonstrates low protein binding (10 % to 20 %), and thus it is not expected to interact with highly protein-bound substances.

PET studies in humans and preclinical data suggest that TMZ crosses the blood-brain barrier rapidly and is present in the CSF. CSF penetration was confirmed in one patient; CSF exposure based on AUC of TMZ was approximately 30 % of that in plasma, which is consistent with animal data.

### Elimination

The half-life (t<sub>1/2</sub>) in plasma is approximately 1.8 hours. The major route of <sup>14</sup>C elimination is renal. Following oral administration, approximately 5 % to 10 % of the dose is recovered unchanged in the urine over 24 hours, and the remainder excreted as temozolomide acid, 5-aminoimidazole-4-carboxamide (AIC) or unidentified polar metabolites.

Plasma concentrations increase in a dose-related manner. Plasma clearance, volume of distribution and half-life are independent of dose.

### Special populations

Analysis of population-based pharmacokinetics of TMZ revealed that plasma TMZ clearance was independent of age, renal function or tobacco use. In a separate pharmacokinetic study, plasma pharmacokinetic profiles in patients with mild to moderate hepatic impairment were similar to those observed in patients with normal hepatic function.

Paediatric patients had a higher AUC than adult patients; however, the maximum tolerated dose (MTD) was 1,000 mg/m<sup>2</sup> per cycle both in children and in adults.

### **5.3 Preclinical safety data**

Single-cycle (5-day dosing, 23 days non-treatment), 3- and 6-cycle toxicity studies were conducted in rats and dogs. The primary targets of toxicity included the bone marrow, lymphoreticular system, testes, the gastrointestinal tract and, at higher doses, which were lethal to 60 % to 100 % of rats and dogs tested, degeneration of the retina occurred. Most of the toxicity showed evidence of reversibility, except for adverse events on the male reproductive system and retinal degeneration. However, because the doses implicated in retinal degeneration were in the lethal dose range, and no comparable effect has been observed in clinical studies, this finding was not considered to have clinical relevance.

TMZ is an embryotoxic, teratogenic and genotoxic alkylating agent. TMZ is more toxic to the rat and dog than to humans, and the clinical dose approximates the minimum lethal dose in rats and dogs. Dose-related reductions in leukocytes and platelets appear to be sensitive indicators of toxicity. A variety of neoplasms, including mammary carcinomas, keratocanthoma of the skin and basal cell adenoma were observed in the 6-cycle rat study while no tumours or pre-neoplastic changes were evident in dog studies. Rats appear to be particularly sensitive to oncogenic effects of TMZ, with the occurrence of first tumours within 3 months of initiating dosing. This latency period is very short even for an alkylating agent.

Results of the Ames/salmonella and Human Peripheral Blood Lymphocyte (HPBL) chromosome aberration tests showed a positive mutagenicity response.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Capsule content:

anhydrous lactose,  
colloidal anhydrous silica,  
sodium starch glycolate type A,  
tartaric acid,  
stearic acid.

#### Capsule shell:

gelatin,  
titanium dioxide (E 171),  
sodium lauril sulfate,  
yellow iron oxide (E 172),  
red iron oxide (E 172)

#### Printing ink:

shellac,  
propylene glycol,  
purified water,  
ammonium hydroxide,  
potassium hydroxide,  
black iron oxide (E 172).

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years

### **6.4 Special precautions for storage**

#### Bottle presentation

Do not store above 30 °C.  
Store in the original bottle in order to protect from moisture.  
Keep the bottle tightly closed.

#### Sachet presentation

Do not store above 30 °C.

### **6.5 Nature and contents of container**

#### Bottle presentation

Type I amber glass bottles with polypropylene child-resistant closures containing 5 or 20 hard capsules.  
The carton contains one bottle.

#### Sachet presentation

Sachets are composed of linear low density polyethylene (innermost layer), aluminium and polyethylene terephthalate.  
Each sachet contains 1 hard capsule and is dispensed in a cardboard carton.  
The carton contains 5 or 20 hard capsules, individually sealed in sachets.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal and other handling**

Capsules should not be opened. If a capsule becomes damaged, contact of the powder contents with skin or mucous membrane must be avoided. If Temodal comes into contact with skin or mucosa, it should be washed immediately and thoroughly with soap and water.

Patients should be advised to keep capsules out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN Haarlem  
The Netherlands

**8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/98/096/011

EU/1/98/096/012

EU/1/98/096/019

EU/1/98/096/020

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 26 January 1999

Date of latest renewal: 26 January 2009

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## 1. NAME OF THE MEDICINAL PRODUCT

Temodal 250 mg hard capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 250 mg temozolomide.

### Excipient with known effect:

Each hard capsule contains 154.3 mg of anhydrous lactose.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Hard capsule (capsule).

The hard capsules have an opaque white body and cap, and are imprinted with black ink. The cap is imprinted with "Temodal". The body is imprinted with "250 mg", the Schering-Plough logo and two stripes.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Temodal is indicated for the treatment of:

- adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment.
- children from the age of three years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy.

### 4.2 Posology and method of administration

Temodal should only be prescribed by physicians experienced in the oncological treatment of brain tumours.

Anti-emetic therapy may be administered (see section 4.4).

### Posology

#### 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 (TMZ) monotherapy (monotherapy phase).

#### *Concomitant phase*

TMZ is administered orally at a dose of 75 mg/m<sup>2</sup> daily for 42 days concomitant with focal radiotherapy (60 Gy administered in 30 fractions). No dose reductions are recommended, but delay or discontinuation of TMZ administration should be decided weekly according to haematological and non-haematological toxicity criteria. TMZ administration can be continued throughout the 42 day concomitant period (up to 49 days) if all of the following conditions are met:

- absolute neutrophil count (ANC)  $\geq 1.5 \times 10^9/l$
- thrombocyte count  $\geq 100 \times 10^9/l$
- common toxicity criteria (CTC) non-haematological toxicity  $\leq$  Grade 1 (except for alopecia, nausea and vomiting).

During treatment a complete blood count should be obtained weekly. TMZ administration should be temporarily interrupted or permanently discontinued during the concomitant phase according to the haematological and non-haematological toxicity criteria as noted in Table 1.

Toxicity	TMZ interruption <sup>a</sup>	TMZ discontinuation
Absolute neutrophil count	$\geq 0.5$ and $< 1.5 \times 10^9/l$	$< 0.5 \times 10^9/l$
Thrombocyte count	$\geq 10$ and $< 100 \times 10^9/l$	$< 10 \times 10^9/l$
CTC non-haematological toxicity (except for alopecia, nausea, vomiting)	CTC Grade 2	CTC Grade 3 or 4

a: Treatment with concomitant TMZ can be continued when all of the following conditions are met: absolute neutrophil count  $\geq 1.5 \times 10^9/l$ ; thrombocyte count  $\geq 100 \times 10^9/l$ ; CTC non-haematological toxicity  $\leq$  Grade 1 (except for alopecia, nausea, vomiting).

### *Monotherapy phase*

Four weeks after completing the TMZ + RT concomitant phase, TMZ is administered for up to 6 cycles of monotherapy treatment. Dose in Cycle 1 (monotherapy) is  $150 \text{ mg/m}^2$  once daily for 5 days followed by 23 days without treatment. At the start of Cycle 2, the dose is escalated to  $200 \text{ mg/m}^2$  if the CTC non-haematological toxicity for Cycle 1 is Grade  $\leq 2$  (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is  $\geq 1.5 \times 10^9/l$ , and the thrombocyte count is  $\geq 100 \times 10^9/l$ . If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles. Once escalated, the dose remains at  $200 \text{ mg/m}^2$  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 TMZ). The dose should be reduced or administration discontinued according to Table 3.

Dose level	TMZ dose (mg/m <sup>2</sup> /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

Toxicity	Reduce TMZ by 1 dose level <sup>a</sup>	Discontinue TMZ
Absolute neutrophil count	$< 1.0 \times 10^9/l$	See footnote b
Thrombocyte count	$< 50 \times 10^9/l$	See footnote b
CTC non-haematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4 <sup>b</sup>

a: TMZ dose levels are listed in Table 2.

b: TMZ is to be discontinued if:

- dose level -1 ( $100 \text{ mg/m}^2$ ) still results in unacceptable toxicity
- the same Grade 3 non-haematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction.

Adult and paediatric patients 3 years of age or older with recurrent or progressive malignant glioma:

A treatment cycle comprises 28 days. In patients previously untreated with chemotherapy, TMZ is administered orally at a dose of 200 mg/m<sup>2</sup> once daily for the first 5 days followed by a 23 day treatment interruption (total of 28 days). In patients previously treated with chemotherapy, the initial dose is 150 mg/m<sup>2</sup> once daily, to be increased in the second cycle to 200 mg/m<sup>2</sup> once daily, for 5 days if there is no haematological toxicity (see section 4.4)

Special populations

*Paediatric population*

In patients 3 years of age or older, TMZ is only to be used in recurrent or progressive malignant glioma. Experience in these children is very limited (see sections 4.4 and 5.1). The safety and efficacy of TMZ in children under the age of 3 years have not been established. No data are available.

*Patients with hepatic or renal impairment*

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

*Elderly patients*

Based on a population pharmacokinetic analysis in patients 19-78 years of age, clearance of TMZ is not affected by age. However, elderly patients (> 70 years of age) appear to be at increased risk of neutropenia and thrombocytopenia (see section 4.4).

Method of administration

Temodal hard capsules should be administered in the fasting state.

The capsules must be swallowed whole with a glass of water and must not be opened or chewed.

If vomiting occurs after the dose is administered, a second dose should not be administered that day.

**4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to dacarbazine (DTIC).

Severe myelosuppression (see section 4.4).

**4.4 Special warnings and precautions for use**

Opportunistic infections and reactivation of infections

Opportunistic infections (such as *Pneumocystis jirovecii* pneumonia) and reactivation of infections (such as HBV, CMV) have been observed during the treatment with TMZ (see section 4.8).

Meningoencephalitis herpetic

In post marketing cases, meningoencephalitis herpetic (including fatal cases) has been observed in patients receiving TMZ in combination with radiotherapy, including cases of concomitant steroids administration.

#### *Pneumocystis jirovecii* pneumonia

Patients who received concomitant TMZ and RT in a pilot trial for the prolonged 42-day schedule were shown to be at particular risk for developing *Pneumocystis jirovecii* pneumonia (PCP). Thus, prophylaxis against PCP is required for all patients receiving concomitant TMZ and RT 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  $\leq 1$ .

There may be a higher occurrence of PCP when TMZ is administered during a longer dosing regimen. However, all patients receiving TMZ, particularly patients receiving steroids, should be observed closely for the development of PCP, regardless of the regimen. Cases of fatal respiratory failure have been reported in patients using TMZ, in particular in combination with dexamethasone or other steroids.

#### HBV

Hepatitis due to hepatitis B virus (HBV) reactivation, in some cases resulting in death, has been reported. Experts in liver disease should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease). During treatment patients should be monitored and managed appropriately.

#### Hepatotoxicity

Hepatic injury, including fatal hepatic failure, has been reported in patients treated with TMZ (see section 4.8). 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.

#### Malignancies

Cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukaemia, have also been reported very rarely (see section 4.8).

#### Anti-emetic therapy

Nausea and vomiting are very commonly associated with TMZ. Anti-emetic therapy may be administered prior to or following administration of TMZ.

#### *Adult patients with newly-diagnosed glioblastoma multiforme*

Anti-emetic prophylaxis is recommended prior to the initial dose of concomitant phase and it is strongly recommended during the monotherapy phase.

#### *Patients with recurrent or progressive malignant glioma*

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

### Laboratory parameters

Patients treated with TMZ may experience myelosuppression, including prolonged pancytopenia, which may result in aplastic anaemia, which in some cases has resulted in a fatal outcome. In some cases, exposure to concomitant medicinal products associated with aplastic anaemia, including carbamazepine, phenytoin, and sulfamethoxazole/trimethoprim, complicates assessment. Prior to dosing, the following laboratory parameters must be met: ANC  $\geq 1.5 \times 10^9/l$  and platelet count  $\geq 100 \times 10^9/l$ . A complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until ANC  $> 1.5 \times 10^9/l$  and platelet count  $> 100 \times 10^9/l$ . If ANC falls to  $< 1.0 \times 10^9/l$  or the platelet count is  $< 50 \times 10^9/l$  during any cycle, the next cycle should be reduced one dose level (see section 4.2). Dose levels include  $100 \text{ mg/m}^2$ ,  $150 \text{ mg/m}^2$ , and  $200 \text{ mg/m}^2$ . The lowest recommended dose is  $100 \text{ mg/m}^2$ .

### Paediatric population

There is no clinical experience with use of TMZ in children under the age of 3 years. Experience in older children and adolescents is very limited (see sections 4.2 and 5.1).

### Elderly patients (> 70 years of age)

Elderly patients appear to be at increased risk of neutropenia and thrombocytopenia, compared with younger patients. Therefore, special care should be taken when TMZ is administered in elderly patients.

### Male patients

Men being treated with TMZ should be advised not to father a child up to 6 months after receiving the last dose and to seek advice on cryoconservation of sperm prior to treatment (see section 4.6).

### Lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## **4.5 Interaction with other medicinal products and other forms of interaction**

In a separate phase I study, administration of TMZ with ranitidine did not result in alterations in the extent of absorption of temozolomide or the exposure to its active metabolite monomethyl triazenoimidazole carboxamide (MTIC).

Administration of TMZ with food resulted in a 33 % decrease in  $C_{\text{max}}$  and a 9 % decrease in area under the curve (AUC).

As it cannot be excluded that the change in  $C_{\text{max}}$  is clinically significant, Temodal should be administered without food.

Based on an analysis of population pharmacokinetics in phase II trials, co-administration of dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron,  $H_2$  receptor antagonists, or phenobarbital did not alter the clearance of TMZ. Co-administration with valproic acid was associated with a small but statistically significant decrease in clearance of TMZ.

No studies have been conducted to determine the effect of TMZ on the metabolism or elimination of other medicinal products. However, since TMZ does not undergo hepatic metabolism and exhibits low protein binding, it is unlikely that it would affect the pharmacokinetics of other medicinal products (see section 5.2).

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

#### Paediatric population

Interaction studies have only been performed in adults.

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

There are no data in pregnant women. In preclinical studies in rats and rabbits receiving 150 mg/m<sup>2</sup> TMZ, teratogenicity and/or foetal toxicity were demonstrated (see section 5.3). Temodal should not be administered to pregnant women. If use during pregnancy must be considered, the patient should be apprised of the potential risk to the foetus.

#### Breast-feeding

It is not known whether TMZ is excreted in human milk; thus, breast-feeding should be discontinued while receiving treatment with TMZ.

#### Women of childbearing potential

Women of childbearing potential should be advised to use effective contraception to avoid pregnancy while they are receiving TMZ.

#### Male fertility

TMZ can have genotoxic effects. Therefore, men being treated with it should be advised not to father a child up to 6 months after receiving the last dose and to seek advice on cryoconservation of sperm prior to treatment, because of the possibility of irreversible infertility due to therapy with TMZ.

### **4.7 Effects on ability to drive and use machines**

TMZ has minor influence on the ability to drive and use machines due to fatigue and somnolence (see section 4.8).

### **4.8 Undesirable effects**

#### Clinical trial experience

In patients treated with TMZ, whether used in combination with RT or as monotherapy following RT for newly-diagnosed glioblastoma multiforme, or as monotherapy in patients with recurrent or progressive glioma, the reported very common adverse reactions were similar: nausea, vomiting, constipation, anorexia, headache and fatigue. Convulsions were reported very commonly in the newly-diagnosed glioblastoma multiforme patients receiving monotherapy, and rash was reported very commonly in newly-diagnosed glioblastoma multiforme patients receiving TMZ concurrent with RT and also as monotherapy, and commonly in recurrent glioma. Most haematologic adverse reactions were reported commonly or very commonly in both indications (Tables 4 and 5); the frequency of grade 3-4 laboratory findings is presented after each table.

In the tables undesirable effects are classified according to System Organ Class and frequency. Frequency groupings are defined according to the following convention: Very common ( $\geq 1/10$ ); Common ( $\geq 1/100$  to  $< 1/10$ ); Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); Very rare ( $< 1/10,000$ ). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Newly-diagnosed glioblastoma multiforme

Table 4 provides treatment-emergent adverse events in patients with newly-diagnosed glioblastoma multiforme during the concomitant and monotherapy phases of treatment.

<i>Table 4. Treatment-emergent events during concomitant and monotherapy treatment phases in patients with newly-diagnosed glioblastoma multiforme</i>		
System organ class	TMZ + concomitant RT n=288*	TMZ monotherapy n=224
Infections and infestations		
Common:	Infection, <i>Herpes simplex</i> , wound infection, pharyngitis, candidiasis oral	Infection, candidiasis oral
Uncommon:		<i>Herpes simplex</i> , herpes zoster, influenza-like symptoms
Blood and lymphatic system disorders		
Common:	Neutropenia, thrombocytopenia, lymphopenia, leukopenia	Febrile neutropenia, thrombocytopenia, anaemia, leukopenia
Uncommon:	Febrile neutropenia, anaemia	Lymphopenia, petechiae
Endocrine disorders		
Uncommon:	Cushingoid	Cushingoid
Metabolism and nutrition disorders		
Very common:	Anorexia	Anorexia
Common:	Hyperglycaemia, weight decreased	Weight decreased
Uncommon:	Hypokalemia, 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	Convulsions, headache
Common:	Convulsions, consciousness decreased, somnolence, aphasia, balance impaired, dizziness, confusion, memory impairment, concentration impaired, neuropathy, paresthesia, speech disorder, tremor	Hemiparesis, aphasia, balance impaired, somnolence, confusion, dizziness, memory impairment, concentration impaired, dysphasia, neurological disorder (NOS), neuropathy, peripheral neuropathy, paresthesia, speech disorder, tremor
Uncommon:	Status epilepticus, extrapyramidal disorder, hemiparesis, ataxia, cognition impaired, dysphasia, gait abnormal, hyperesthesia, hypoesthesia, neurological disorder (NOS), peripheral neuropathy	Hemiplegia, ataxia, coordination abnormal, gait abnormal, hyperesthesia, sensory disturbance
Eye disorders		

<i>Table 4. Treatment-emergent events during concomitant and monotherapy treatment phases in patients with newly-diagnosed glioblastoma multiforme</i>		
System organ class	TMZ + concomitant RT n=288*	TMZ monotherapy n=224
Common:	Vision blurred	Visual field defect, vision blurred, diplopia
Uncommon:	Hemianopia, visual acuity reduced, vision disorder, visual field defect, eye pain	Visual acuity reduced, eye pain, eyes dry
Ear and labyrinth disorders		
Common:	Hearing impairment	Hearing impairment, tinnitus
Uncommon:	Otitis media, tinnitus, hyperacusis, earache	Deafness, vertigo, earache
Cardiac disorders		
Uncommon:	Palpitation	
Vascular disorders		
Common:	Haemorrhage, oedema, oedema leg	Haemorrhage, deep venous thrombosis, oedema leg
Uncommon:	Cerebral haemorrhage, hypertension	Embolism pulmonary, oedema, oedema peripheral
Respiratory, thoracic and mediastinal disorders		
Common:	Dyspnoea, coughing	Dyspnoea, coughing
Uncommon:	Pneumonia, upper respiratory infection, nasal congestion	Pneumonia, sinusitis, upper respiratory infection, bronchitis
Gastrointestinal disorders		
Very common:	Constipation, nausea, vomiting	Constipation, nausea, vomiting
Common:	Stomatitis, diarrhoea, abdominal pain, dyspepsia, dysphagia	Stomatitis, diarrhoea, dyspepsia, dysphagia, mouth dry
Uncommon:		Abdominal distension, fecal incontinence, gastrointestinal disorder (NOS), gastroenteritis, haemorrhoids
Skin and subcutaneous tissue disorders		
Very common:	Rash, alopecia	Rash, alopecia
Common:	Dermatitis, dry skin, erythema, pruritus	Dry skin, pruritus
Uncommon:	Skin exfoliation, photosensitivity reaction, pigmentation abnormal	Erythema, pigmentation abnormal, sweating increased
Musculoskeletal and connective tissue disorders		
Common:	Muscle weakness, arthralgia	Muscle weakness, arthralgia, musculoskeletal pain, myalgia

<i>Table 4. Treatment-emergent events during concomitant and monotherapy treatment phases in patients with newly-diagnosed glioblastoma multiforme</i>		
System organ class	TMZ + concomitant RT n=288*	TMZ monotherapy n=224
Uncommon:	Myopathy, back pain, musculoskeletal pain, myalgia	Myopathy, back pain
Renal and urinary disorders		
Common:	Micturition frequency, urinary incontinence	Urinary incontinence
Uncommon:		Dysuria
Reproductive system and breast disorders		
Uncommon:	Impotence	Vaginal haemorrhage, menorrhagia, amenorrhea, vaginitis, breast pain
General disorders and administration site conditions		
Very common:	Fatigue	Fatigue
Common:	Allergic reaction, fever, radiation injury, face oedema, pain, taste perversion	Allergic reaction, fever, radiation injury, pain, taste perversion
Uncommon:	Asthenia, flushing, hot flushes, condition aggravated, rigors, tongue discolouration, parosmia, thirst	Asthenia, face oedema, pain, condition aggravated, rigors, tooth disorder
Investigations		
Common:	ALT increased	ALT increased
Uncommon:	Hepatic enzymes increased, Gamma GT increased, AST increased	

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

### *Laboratory results*

Myelosuppression (neutropenia and thrombocytopenia), which is known dose-limiting toxicity for most cytotoxic agents, including TMZ, was 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 TMZ.

### *Recurrent or progressive malignant glioma*

In clinical trials, the most frequently occurring treatment-related undesirable effects were gastrointestinal disorders, specifically nausea (43 %) and vomiting (36 %). These reactions were usually Grade 1 or 2 (0 – 5 episodes of vomiting in 24 hours) and were either self-limiting or readily controlled with standard anti-emetic therapy. The incidence of severe nausea and vomiting was 4 %.

Table 5 includes adverse reactions reported during clinical trials for recurrent or progressive malignant glioma and following the marketing of Temodal.

<i>Table 5. Adverse reactions in patients with recurrent or progressive malignant glioma</i>	
Infections and infestations	
Rare:	Opportunistic infections, including PCP
Blood and lymphatic system disorders	
Very common:	Neutropenia or lymphopenia (grade 3-4), thrombocytopenia (grade 3-4)
Uncommon:	Pancytopenia, anaemia (grade 3-4), leukopenia
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:	Vomiting, nausea, constipation
Common:	Diarrhoea, abdominal pain, dyspepsia
Skin and subcutaneous tissue disorders	
Common:	Rash, pruritus, alopecia
Very rare:	Erythema multiforme, erythroderma, urticaria, exanthema
General disorders and administration site conditions	
Very common:	Fatigue
Common:	Fever, asthenia, rigors, malaise, pain, taste perversion
Very 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 malignant glioma. This led to hospitalisation and/or discontinuation of TMZ in 8 % and 4 %, respectively. 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. The presence of thrombocytopenia may increase the risk of bleeding, and the presence of neutropenia or leukopenia may increase the risk of infection.

### *Gender*

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 ( $ANC < 0.5 \times 10^9/l$ ), 12 % vs 5 %, and thrombocytopenia ( $< 20 \times 10^9/l$ ), 9 % vs 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.

### Paediatric population

Oral TMZ has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. Although the data is limited, tolerance in children is expected to be the same as in adults. The safety of TMZ in children under the age of 3 years has not been established.

### Post-Marketing Experience

The following additional serious adverse reactions have been identified during post-marketing exposure:

<i>Table 6. Summary of events reported with temozolomide in the post-marketing setting</i>	
<b>Infections and infestations*</b>	
Uncommon:	cytomegalovirus infection, infection reactivation such as cytomegalovirus, hepatitis B virus <sup>†</sup> , meningoencephalitis herpetic <sup>†</sup> , sepsis <sup>†</sup>
<b>Blood and lymphatic system disorders</b>	
Very rare:	prolonged pancytopenia, aplastic anaemia <sup>†</sup>
<b>Neoplasm benign, malignant and unspecified</b>	
Very rare:	myelodysplastic syndrome (MDS), secondary malignancies, including myeloid leukaemia
<b>Endocrine disorders*</b>	
Uncommon:	diabetes insipidus
<b>Respiratory, thoracic and mediastinal disorders</b>	
Very rare:	interstitial pneumonitis/pneumonitis, pulmonary fibrosis, respiratory failure <sup>†</sup>
<b>Hepatobiliary disorders*</b>	
Common:	liver enzymes elevations
Uncommon:	hyperbilirubinemia, cholestasis, hepatitis, hepatic injury, hepatic failure <sup>†</sup>
<b>Skin and subcutaneous tissue disorders</b>	
Very rare:	toxic epidermal necrolysis, Stevens-Johnson syndrome

<sup>†</sup> Including cases with fatal outcome

\* Frequencies estimated based on relevant clinical trials.

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

## **4.9 Overdose**

Doses of 500, 750, 1,000, and 1,250 mg/m<sup>2</sup> (total dose per cycle over 5 days) have been evaluated clinically in patients. Dose-limiting toxicity was haematological and was reported with any dose but is expected to be more severe at higher doses. An overdose of 10,000 mg (total dose in a single cycle, over 5 days) was taken by one patient and the adverse reactions reported were pancytopenia, pyrexia,

multi-organ failure and death. There are reports of patients who have taken the recommended dose for 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, haematological evaluation is needed. Supportive measures should be provided as necessary.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents - Other alkylating agents, ATC code: L01A X03

#### Mechanism of action

Temozolomide is a triazene, which undergoes rapid chemical conversion at physiologic pH to the active monomethyl triazenoimidazole carboxamide (MTIC). The cytotoxicity of MTIC is thought to be due primarily to alkylation at the O<sup>6</sup> position of guanine with additional alkylation also occurring at the N<sup>7</sup> position. Cytotoxic lesions that develop subsequently are thought to involve aberrant repair of the methyl adduct.

#### Clinical efficacy and safety

##### *Newly-diagnosed glioblastoma multiforme*

A total of 573 patients were randomised to receive either TMZ + RT (n=287) or RT alone (n=286). Patients in the TMZ + RT arm received concomitant TMZ (75 mg/m<sup>2</sup>) 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 TMZ (150 - 200 mg/m<sup>2</sup>) 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 jirovecii* pneumonia (PCP) prophylaxis was required during RT and combined TMZ therapy.

TMZ 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 TMZ + 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 favour of the TMZ arm. The estimated probability of surviving 2 years or more (26 % vs 10 %) is higher for the RT + TMZ arm. The addition of concomitant TMZ to RT, followed by TMZ monotherapy in the treatment of patients with newly-diagnosed glioblastoma multiforme demonstrated a statistically significant improvement in overall survival (OS) compared with RT alone (Figure 1).

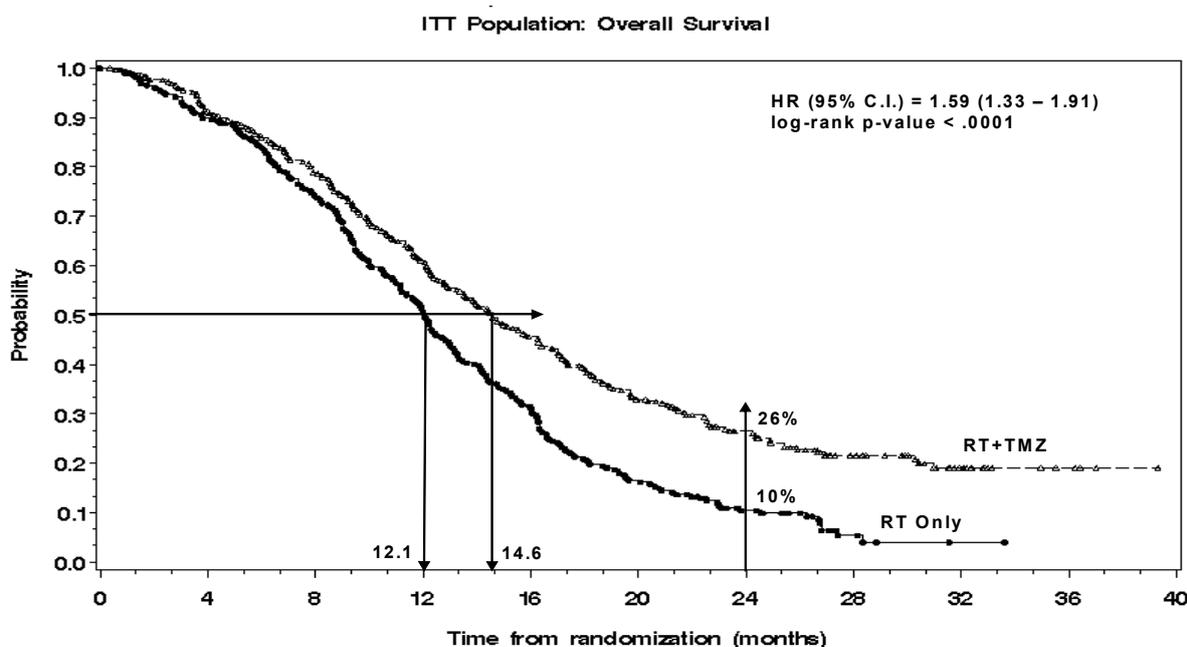


Figure 1 Kaplan-Meier curves for overall survival (intent-to-treat population)

The results from the trial were not consistent in the subgroup of patients with a poor performance status (WHO PS=2, n=70), where overall survival and time to progression were similar in both arms. However, no unacceptable risks appear to be present in this patient group.

#### Recurrent or progressive malignant glioma

Data on clinical efficacy in patients with glioblastoma multiforme (Karnofsky performance status [KPS]  $\geq 70$ ), progressive or recurrent after surgery and RT, were based on two clinical trials with oral TMZ. One was a non-comparative trial in 138 patients (29 % received prior chemotherapy), and the other was a randomised active-controlled trial of TMZ vs 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 (ORR) based on MRI scans was 8 %.

In the randomised active-controlled trial, the PFS at 6 months was significantly greater for TMZ 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 TMZ and procarbazine, respectively (log rank  $p = 0.33$ ). At 6 months, the fraction of surviving patients was significantly higher in the TMZ 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  $\geq 80$ .

Data on time to worsening of neurological status favoured TMZ over procarbazine as did data on time to worsening of performance status (decrease to a KPS of  $< 70$  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 TMZ than for procarbazine (log rank  $p = < 0.01$  to 0.03).

#### Recurrent anaplastic astrocytoma

In a multicentre, prospective phase II trial evaluating the safety and efficacy of oral TMZ in the treatment of patients with anaplastic astrocytoma at first relapse, the 6 month PFS was 46 %. The median PFS 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 (ITT)

n=162. In 43 patients stable disease was reported. 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 radiological objective response or maintaining progression-free status was strongly associated with maintained or improved quality of life.

### Paediatric population

Oral TMZ has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. Tolerance to TMZ is similar to adults.

## **5.2 Pharmacokinetic properties**

TMZ is spontaneously hydrolyzed at physiologic pH primarily to the active species, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC). MTIC is spontaneously hydrolyzed to 5-aminoimidazole-4-carboxamide (AIC), a known intermediate in purine and nucleic acid biosynthesis, and to methylhydrazine, which is believed to be the active alkylating species. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA mainly at the O<sup>6</sup> and N<sup>7</sup> positions of guanine. Relative to the AUC of TMZ, the exposure to MTIC and AIC is ~ 2.4 % and 23 %, respectively. *In vivo*, the t<sub>1/2</sub> of MTIC was similar to that of TMZ, 1.8 hr.

### Absorption

After oral administration to adult patients, TMZ is absorbed rapidly, with peak concentrations reached as early as 20 minutes post-administration (mean time between 0.5 and 1.5 hours). After oral administration of <sup>14</sup>C-labelled TMZ, mean faecal excretion of <sup>14</sup>C over 7 days post-dose was 0.8 % indicating complete absorption.

### Distribution

TMZ demonstrates low protein binding (10 % to 20 %), and thus it is not expected to interact with highly protein-bound substances.

PET studies in humans and preclinical data suggest that TMZ crosses the blood-brain barrier rapidly and is present in the CSF. CSF penetration was confirmed in one patient; CSF exposure based on AUC of TMZ was approximately 30 % of that in plasma, which is consistent with animal data.

### Elimination

The half-life (t<sub>1/2</sub>) in plasma is approximately 1.8 hours. The major route of <sup>14</sup>C elimination is renal. Following oral administration, approximately 5 % to 10 % of the dose is recovered unchanged in the urine over 24 hours, and the remainder excreted as temozolomide acid, 5-aminoimidazole-4-carboxamide (AIC) or unidentified polar metabolites.

Plasma concentrations increase in a dose-related manner. Plasma clearance, volume of distribution and half-life are independent of dose.

### Special populations

Analysis of population-based pharmacokinetics of TMZ revealed that plasma TMZ clearance was independent of age, renal function or tobacco use. In a separate pharmacokinetic study, plasma pharmacokinetic profiles in patients with mild to moderate hepatic impairment were similar to those observed in patients with normal hepatic function.

Paediatric patients had a higher AUC than adult patients; however, the maximum tolerated dose (MTD) was 1,000 mg/m<sup>2</sup> per cycle both in children and in adults.

### **5.3 Preclinical safety data**

Single-cycle (5-day dosing, 23 days non-treatment), 3- and 6-cycle toxicity studies were conducted in rats and dogs. The primary targets of toxicity included the bone marrow, lymphoreticular system, testes, the gastrointestinal tract and, at higher doses, which were lethal to 60 % to 100 % of rats and dogs tested, degeneration of the retina occurred. Most of the toxicity showed evidence of reversibility, except for adverse events on the male reproductive system and retinal degeneration. However, because the doses implicated in retinal degeneration were in the lethal dose range, and no comparable effect has been observed in clinical studies, this finding was not considered to have clinical relevance.

TMZ is an embryotoxic, teratogenic and genotoxic alkylating agent. TMZ is more toxic to the rat and dog than to humans, and the clinical dose approximates the minimum lethal dose in rats and dogs. Dose-related reductions in leukocytes and platelets appear to be sensitive indicators of toxicity. A variety of neoplasms, including mammary carcinomas, keratocanthoma of the skin and basal cell adenoma were observed in the 6-cycle rat study while no tumours or pre-neoplastic changes were evident in dog studies. Rats appear to be particularly sensitive to oncogenic effects of TMZ, with the occurrence of first tumours within 3 months of initiating dosing. This latency period is very short even for an alkylating agent.

Results of the Ames/salmonella and Human Peripheral Blood Lymphocyte (HPBL) chromosome aberration tests showed a positive mutagenicity response.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Capsule content:

anhydrous lactose,  
colloidal anhydrous silica,  
sodium starch glycolate type A,  
tartaric acid,  
stearic acid.

#### Capsule shell:

gelatin,  
titanium dioxide (E 171),  
sodium lauril sulfate

#### Printing ink:

shellac,  
propylene glycol,  
purified water,  
ammonium hydroxide,  
potassium hydroxide,  
black iron oxide (E 172).

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years

### **6.4 Special precautions for storage**

#### Bottle presentation

Do not store above 30 °C.  
Store in the original bottle in order to protect from moisture.  
Keep the bottle tightly closed.

#### Sachet presentation

Do not store above 30 °C.

### **6.5 Nature and contents of container**

#### Bottle presentation

Type I amber glass bottles with polypropylene child-resistant closures containing 5 or 20 hard capsules.  
The carton contains one bottle.

#### Sachet presentation

Sachets are composed of linear low density polyethylene (innermost layer), aluminium and polyethylene terephthalate.  
Each sachet contains 1 hard capsule and is dispensed in a cardboard carton.  
The carton contains 5 or 20 hard capsules, individually sealed in sachets.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal and other handling**

Capsules should not be opened. If a capsule becomes damaged, contact of the powder contents with skin or mucous membrane must be avoided. If Temodal comes into contact with skin or mucosa, it should be washed immediately and thoroughly with soap and water.

Patients should be advised to keep capsules out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN Haarlem  
The Netherlands

**8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/98/096/007

EU/1/98/096/008

EU/1/98/096/021

EU/1/98/096/022

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 26 January 1999

Date of latest renewal: 26 January 2009

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## 1. NAME OF THE MEDICINAL PRODUCT

Temodal 2.5 mg/ml powder for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg of temozolomide.

After reconstitution, 1 ml solution for infusion contains 2.5 mg temozolomide.

### Excipient with known effect:

Each vial contains 2.4 mmol sodium.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder for solution for infusion.

White powder.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Temodal is indicated for the treatment of:

- adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment.
- children from the age of three years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy.

### 4.2 Posology and method of administration

Temodal should only be prescribed by physicians experienced in the oncological treatment of brain tumours.

Anti-emetic therapy may be administered (see section 4.4).

### Posology

#### 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 (TMZ) monotherapy (monotherapy phase).

#### *Concomitant phase*

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

TMZ administration can be continued throughout the 42 day concomitant period (up to 49 days) if all of the following conditions are met:

- absolute neutrophil count (ANC)  $\geq 1.5 \times 10^9/l$
- thrombocyte count  $\geq 100 \times 10^9/l$
- common toxicity criteria (CTC) non-haematological toxicity  $\leq$  Grade 1 (except for alopecia, nausea and vomiting).

During treatment a complete blood count should be obtained weekly. TMZ administration should be temporarily interrupted or permanently discontinued during the concomitant phase according to the haematological and non-haematological toxicity criteria as noted in Table 1.

Toxicity	TMZ interruption <sup>a</sup>	TMZ discontinuation
Absolute neutrophil count	$\geq 0.5$ and $< 1.5 \times 10^9/l$	$< 0.5 \times 10^9/l$
Thrombocyte count	$\geq 10$ and $< 100 \times 10^9/l$	$< 10 \times 10^9/l$
CTC non-haematological toxicity (except for alopecia, nausea, vomiting)	CTC Grade 2	CTC Grade 3 or 4

a: Treatment with concomitant TMZ can be continued when all of the following conditions are met: absolute neutrophil count  $\geq 1.5 \times 10^9/l$ ; thrombocyte count  $\geq 100 \times 10^9/l$ ; CTC non-haematological toxicity  $\leq$  Grade 1 (except for alopecia, nausea, vomiting).

### *Monotherapy phase*

Four weeks after completing the TMZ + RT concomitant phase, TMZ is administered for up to 6 cycles of monotherapy treatment. Dose in Cycle 1 (monotherapy) is 150 mg/m<sup>2</sup> 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<sup>2</sup> if the CTC non-haematological toxicity for Cycle 1 is Grade  $\leq 2$  (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is  $\geq 1.5 \times 10^9/l$ , and the thrombocyte count is  $\geq 100 \times 10^9/l$ . 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<sup>2</sup> 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 TMZ). The dose should be reduced or administration discontinued according to Table 3.

Dose level	TMZ dose (mg/m <sup>2</sup> /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

Toxicity	Reduce TMZ by 1 dose level <sup>a</sup>	Discontinue TMZ
Absolute neutrophil count	$< 1.0 \times 10^9/l$	See footnote b
Thrombocyte count	$< 50 \times 10^9/l$	See footnote b
CTC non-haematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4 <sup>b</sup>

a: TMZ dose levels are listed in Table 2.

b: TMZ is to be discontinued if:

- dose level -1 (100 mg/m<sup>2</sup>) still results in unacceptable toxicity
- the same Grade 3 non-haematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction.

Adult and paediatric patients 3 years of age or older with recurrent or progressive malignant glioma:

A treatment cycle comprises 28 days. In patients previously untreated with chemotherapy, TMZ is administered at a dose of 200 mg/m<sup>2</sup> once daily for the first 5 days followed by a 23 day treatment interruption (total of 28 days). In patients previously treated with chemotherapy, the initial dose is 150 mg/m<sup>2</sup> once daily, to be increased in the second cycle to 200 mg/m<sup>2</sup> once daily, for 5 days if there is no haematological toxicity (see section 4.4)

Special populations

*Paediatric population*

In patients 3 years of age or older, TMZ is only to be used in recurrent or progressive malignant glioma. Experience in these children is very limited (see sections 4.4 and 5.1). The safety and efficacy of TMZ in children under the age of 3 years have not been established. No data are available.

*Patients with hepatic or renal impairment*

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

*Elderly patients*

Based on a population pharmacokinetic analysis in patients 19-78 years of age, clearance of TMZ is not affected by age. However, elderly patients (> 70 years of age) appear to be at increased risk of neutropenia and thrombocytopenia (see section 4.4).

Method of administration

Temodal 2.5 mg/ml powder for solution for infusion must be administered **only by intravenous infusion**. It **must not** be given by other routes of administration, such as the intrathecal, intramuscular, or subcutaneous route. Temodal 2.5 mg/ml powder for solution for infusion may be administered in the same IV line with 0.9% Sodium Chloride injection. It is incompatible with dextrose solutions.

The appropriate dose of TMZ should be infused intravenously using a pump over a period of 90 minutes.

As with other similar chemotherapeutic agents, caution is recommended to avoid extravasation. Local injection site adverse reactions, which were mostly mild and short-lived were reported in patients receiving Temodal 2.5 mg/ml powder for solution for infusion. Preclinical studies did not show permanent tissue damage (see sections 4.8 and 5.3).

Temodal is also available as a hard capsule formulation (oral use). Temodal 2.5 mg/ml powder for solution for infusion, given as an intravenous infusion over 90 minutes, is bioequivalent to the hard capsule formulation (see section 5.2).

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to dacarbazine (DTIC).

Severe myelosuppression (see section 4.4).

#### **4.4 Special warnings and precautions for use**

##### Opportunistic infections and reactivation of infections

Opportunistic infections (such as *Pneumocystis jirovecii* pneumonia) and reactivation of infections (such as HBV, CMV) have been observed during the treatment with TMZ (see section 4.8).

##### Meningoencephalitis herpetic

In post marketing cases, meningoencephalitis herpetic (including fatal cases) has been observed in patients receiving TMZ in combination with radiotherapy, including cases of concomitant steroids administration.

##### *Pneumocystis jirovecii* pneumonia

Patients who received concomitant TMZ and RT in a pilot trial for the prolonged 42-day schedule were shown to be at particular risk for developing *Pneumocystis jirovecii* pneumonia (PCP). Thus, prophylaxis against PCP is required for all patients receiving concomitant TMZ and RT 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  $\leq 1$ .

There may be a higher occurrence of PCP when TMZ is administered during a longer dosing regimen. However, all patients receiving TMZ, particularly patients receiving steroids, should be observed closely for the development of PCP, regardless of the regimen. Cases of fatal respiratory failure have been reported in patients using TMZ, in particular in combination with dexamethasone or other steroids.

##### HBV

Hepatitis due to hepatitis B virus (HBV) reactivation, in some cases resulting in death, has been reported. Experts in liver disease should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease). During treatment patients should be monitored and managed appropriately.

##### Hepatotoxicity

Hepatic injury, including fatal hepatic failure, has been reported in patients treated with TMZ (see section 4.8). 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.

##### Malignancies

Cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukaemia, have also been reported very rarely (see section 4.8).

##### Anti-emetic therapy

Nausea and vomiting are very commonly associated with TMZ.

Anti-emetic therapy may be administered prior to or following administration of TMZ.

#### Adult patients with newly-diagnosed glioblastoma multiforme

Anti-emetic prophylaxis is recommended prior to the initial dose of concomitant phase and it is strongly recommended during the monotherapy phase.

#### Patients with recurrent or progressive malignant glioma

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

#### Laboratory parameters

Patients treated with TMZ may experience myelosuppression, including prolonged pancytopenia, which may result in aplastic anaemia, which in some cases has resulted in a fatal outcome. In some cases, exposure to concomitant medicinal products associated with aplastic anaemia, including carbamazepine, phenytoin, and sulfamethoxazole/trimethoprim, complicates assessment. Prior to dosing, the following laboratory parameters must be met: ANC  $\geq 1.5 \times 10^9/l$  and platelet count  $\geq 100 \times 10^9/l$ . A complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until ANC  $> 1.5 \times 10^9/l$  and platelet count  $> 100 \times 10^9/l$ . If ANC falls to  $< 1.0 \times 10^9/l$  or the platelet count is  $< 50 \times 10^9/l$  during any cycle, the next cycle should be reduced one dose level (see section 4.2). Dose levels include  $100 \text{ mg/m}^2$ ,  $150 \text{ mg/m}^2$ , and  $200 \text{ mg/m}^2$ . The lowest recommended dose is  $100 \text{ mg/m}^2$ .

#### Paediatric population

There is no clinical experience with use of TMZ in children under the age of 3 years. Experience in older children and adolescents is very limited (see sections 4.2 and 5.1).

#### Elderly patients (> 70 years of age)

Elderly patients appear to be at increased risk of neutropenia and thrombocytopenia, compared with younger patients. Therefore, special care should be taken when TMZ is administered in elderly patients.

#### Male patients

Men being treated with TMZ should be advised not to father a child up to 6 months after receiving the last dose and to seek advice on cryoconservation of sperm prior to treatment (see section 4.6).

#### Sodium

This medicinal product contains 2.4 mmol sodium per vial. This should be taken into consideration by patients on a controlled sodium diet.

### **4.5 Interaction with other medicinal products and other forms of interaction**

In a separate phase I study, administration of TMZ with ranitidine did not result in alterations in the extent of absorption of temozolomide or the exposure to its active metabolite monomethyl triazenoimidazole carboxamide (MTIC).

Based on an analysis of population pharmacokinetics in phase II trials, co-administration of dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron,  $H_2$  receptor antagonists, or phenobarbital did not alter the clearance of TMZ. Co-administration with valproic acid was associated with a small but statistically significant decrease in clearance of TMZ.

No studies have been conducted to determine the effect of TMZ on the metabolism or elimination of other medicinal products. However, since TMZ does not undergo hepatic metabolism and exhibits low protein binding, it is unlikely that it would affect the pharmacokinetics of other medicinal products (see section 5.2).

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

#### Paediatric population

Interaction studies have only been performed in adults.

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

There are no data in pregnant women. In preclinical studies in rats and rabbits receiving 150 mg/m<sup>2</sup> TMZ, teratogenicity and/or foetal toxicity were demonstrated (see section 5.3).

Temodal should not be administered to pregnant women. If use during pregnancy must be considered, the patient should be apprised of the potential risk to the foetus.

#### Breast-feeding

It is not known whether TMZ is excreted in human milk; thus, breast-feeding should be discontinued while receiving treatment with TMZ.

#### Women of childbearing potential

Women of childbearing potential should be advised to use effective contraception to avoid pregnancy while they are receiving TMZ.

#### Male fertility

TMZ can have genotoxic effects. Therefore, men being treated with it should be advised not to father a child up to 6 months after receiving the last dose and to seek advice on cryoconservation of sperm prior to treatment, because of the possibility of irreversible infertility due to therapy with TMZ.

### **4.7 Effects on ability to drive and use machines**

TMZ has minor influence on the ability to drive and use machines due to fatigue and somnolence (see section 4.8).

### **4.8 Undesirable effects**

#### Clinical trial experience with hard capsules

In patients treated with TMZ, whether used in combination with RT or as monotherapy following RT for newly-diagnosed glioblastoma multiforme, or as monotherapy in patients with recurrent or progressive glioma, the reported very common adverse reactions were similar: nausea, vomiting, constipation, anorexia, headache and fatigue. Convulsions were reported very commonly in the newly-diagnosed glioblastoma multiforme patients receiving monotherapy, and rash was reported very commonly in newly-diagnosed glioblastoma multiforme patients receiving TMZ concurrent with RT and also as monotherapy, and commonly in recurrent glioma. Most haematological adverse reactions were reported commonly or very commonly in both indications (Tables 4 and 5); the frequency of grade 3-4 laboratory findings is presented after each table.

In the tables undesirable effects are classified according to System Organ Class and frequency. Frequency groupings are defined according to the following convention: Very common ( $\geq 1/10$ ); Common ( $\geq 1/100$  to  $< 1/10$ ); Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); Very rare ( $< 1/10,000$ ). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Newly-diagnosed glioblastoma multiforme

Table 4 provides treatment-emergent adverse events in patients with newly-diagnosed glioblastoma multiforme during the concomitant and monotherapy phases of treatment.

<i>Table 4. Treatment-emergent events during concomitant and monotherapy treatment phases in patients with newly-diagnosed glioblastoma multiforme</i>		
System organ class	TMZ + concomitant RT n=288*	TMZ monotherapy n=224
Infections and infestations		
Common:	Infection, <i>Herpes simplex</i> , wound infection, pharyngitis, candidiasis oral	Infection, candidiasis oral
Uncommon:		<i>Herpes simplex</i> , herpes zoster, influenza-like symptoms
Blood and lymphatic system disorders		
Common:	Neutropenia, thrombocytopenia, lymphopenia, leukopenia	Febrile neutropenia, thrombocytopenia, anaemia, leukopenia
Uncommon:	Febrile neutropenia, anaemia	Lymphopenia, petechiae
Endocrine disorders		
Uncommon:	Cushingoid	Cushingoid
Metabolism and nutrition disorders		
Very common:	Anorexia	Anorexia
Common:	Hyperglycaemia, weight decreased	Weight decreased
Uncommon:	Hypokalemia, 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	Convulsions, headache
Common:	Convulsions, consciousness decreased, somnolence, aphasia, balance impaired, dizziness, confusion, memory impairment, concentration impaired, neuropathy, paresthesia, speech disorder, tremor	Hemiparesis, aphasia, balance impaired, somnolence, confusion, dizziness, memory impairment, concentration impaired, dysphasia, neurological disorder (NOS), neuropathy, peripheral neuropathy, paresthesia, speech disorder, tremor

<i>Table 4. Treatment-emergent events during concomitant and monotherapy treatment phases in patients with newly-diagnosed glioblastoma multiforme</i>		
System organ class	TMZ + concomitant RT n=288*	TMZ monotherapy n=224
Uncommon:	Status epilepticus, extrapyramidal disorder, hemiparesis, ataxia, cognition impaired, dysphasia, gait abnormal, hyperesthesia, hypoesthesia, neurological disorder (NOS), peripheral neuropathy	Hemiplegia, ataxia, coordination abnormal, gait abnormal, hyperesthesia, sensory disturbance
Eye disorders		
Common:	Vision blurred	Visual field defect, vision blurred, diplopia
Uncommon:	Hemianopia, visual acuity reduced, vision disorder, visual field defect, eye pain	Visual acuity reduced, eye pain, eyes dry
Ear and labyrinth disorders		
Common:	Hearing impairment	Hearing impairment, tinnitus
Uncommon:	Otitis media, tinnitus, hyperacusis, earache	Deafness, vertigo, earache
Cardiac disorders		
Uncommon:	Palpitation	
Vascular disorders		
Common:	Haemorrhage, oedema, oedema leg	Haemorrhage, deep venous thrombosis, oedema leg
Uncommon:	Cerebral haemorrhage, hypertension	Embolism pulmonary, oedema, oedema peripheral
Respiratory, thoracic and mediastinal disorders		
Common:	Dyspnoea, coughing	Dyspnoea, coughing
Uncommon:	Pneumonia, upper respiratory infection, nasal congestion	Pneumonia, sinusitis, upper respiratory infection, bronchitis
Gastrointestinal disorders		
Very common:	Constipation, nausea, vomiting	Constipation, nausea, vomiting
Common:	Stomatitis, diarrhoea, abdominal pain, dyspepsia, dysphagia	Stomatitis, diarrhoea, dyspepsia, dysphagia, mouth dry
Uncommon:		Abdominal distension, fecal incontinence, gastrointestinal disorder (NOS), gastroenteritis, haemorrhoids
Skin and subcutaneous tissue disorders		
Very common:	Rash, alopecia	Rash, alopecia
Common:	Dermatitis, dry skin, erythema, pruritus	Dry skin, pruritus

<i>Table 4. Treatment-emergent events during concomitant and monotherapy treatment phases in patients with newly-diagnosed glioblastoma multiforme</i>		
System organ class	TMZ + concomitant RT n=288*	TMZ monotherapy n=224
Uncommon:	Skin exfoliation, photosensitivity reaction, pigmentation abnormal	Erythema, pigmentation abnormal, sweating increased
Musculoskeletal and connective tissue disorders		
Common:	Muscle weakness, arthralgia	Muscle weakness, arthralgia, musculoskeletal pain, myalgia
Uncommon:	Myopathy, back pain, musculoskeletal pain, myalgia	Myopathy, back pain
Renal and urinary disorders		
Common:	Micturition frequency, urinary incontinence	Urinary incontinence
Uncommon:		Dysuria
Reproductive system and breast disorders		
Uncommon:	Impotence	Vaginal haemorrhage, menorrhagia, amenorrhea, vaginitis, breast pain
General disorders and administration site conditions		
Very common:	Fatigue	Fatigue
Common:	Allergic reaction, fever, radiation injury, face oedema, pain, taste perversion	Allergic reaction, fever, radiation injury, pain, taste perversion
Uncommon:	Asthenia, flushing, hot flushes, condition aggravated, rigors, tongue discolouration, parosmia, thirst	Asthenia, face oedema, pain, condition aggravated, rigors, tooth disorder
Investigations		
Common:	ALT increased	ALT increased
Uncommon:	Hepatic enzymes increased, Gamma GT increased, AST increased	

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

### *Laboratory results*

Myelosuppression (neutropenia and thrombocytopenia), which is known dose-limiting toxicity for most cytotoxic agents, including TMZ, was 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 TMZ.

### Recurrent or progressive malignant glioma

In clinical trials, the most frequently occurring treatment-related undesirable effects were gastrointestinal disorders, specifically nausea (43 %) and vomiting (36 %). These reactions were usually Grade 1 or 2 (0 – 5 episodes of vomiting in 24 hours) and were either self-limiting or readily controlled with standard anti-emetic therapy. The incidence of severe nausea and vomiting was 4 %.

Table 5 includes adverse reactions reported during clinical trials for recurrent or progressive malignant glioma and following the marketing of Temodal.

Infections and infestations	
Rare:	Opportunistic infections, including PCP
Blood and lymphatic system disorders	
Very common:	Neutropenia or lymphopenia (grade 3-4), thrombocytopenia (grade 3-4)
Uncommon:	Pancytopenia, anaemia (grade 3-4), leukopenia
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:	Vomiting, nausea, constipation
Common:	Diarrhoea, abdominal pain, dyspepsia
Skin and subcutaneous tissue disorders	
Common:	Rash, pruritus, alopecia
Very rare:	Erythema multiforme, erythroderma, urticaria, exanthema
General disorders and administration site conditions	
Very common:	Fatigue
Common:	Fever, asthenia, rigors, malaise, pain, taste perversion
Very 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 malignant glioma. This led to hospitalisation and/or discontinuation of TMZ in 8 % and 4 %, respectively. 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. The presence of thrombocytopenia may increase the risk of bleeding, and the presence of neutropenia or leukopenia may increase the risk of infection.

## Gender

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 ( $ANC < 0.5 \times 10^9/l$ ), 12 % vs 5 %, and thrombocytopenia ( $< 20 \times 10^9/l$ ), 9 % vs 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.

## Paediatric population

Oral TMZ has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. Although the data is limited, tolerance in children is expected to be the same as in adults. The safety of TMZ in children under the age of 3 years has not been established.

## Clinical trial experience with IV

Temodal 2.5 mg/ml powder for solution for infusion delivers equivalent TMZ dose and exposure to both TMZ and its active metabolite MTIC as the corresponding Temodal hard capsules (see section 5.2). Adverse reactions reported during the two studies with the intravenous formulation (n=35) but not in studies using hard capsules, were infusion site reactions: pain, irritation, pruritus, warmth, swelling, and erythema, as well as haematoma.

## Post-Marketing Experience

The following additional serious adverse reactions have been identified during post-marketing exposure:

<b>Infections and infestations*</b>	
Uncommon:	cytomegalovirus infection, infection reactivation such as cytomegalovirus, hepatitis B virus <sup>†</sup> , meningococcal meningitis <sup>†</sup> , sepsis <sup>†</sup>
<b>Blood and lymphatic system disorders</b>	
Very rare:	prolonged pancytopenia, aplastic anaemia <sup>†</sup>
<b>Neoplasm benign, malignant and unspecified</b>	
Very rare:	myelodysplastic syndrome (MDS), secondary malignancies, including myeloid leukaemia
<b>Endocrine disorders*</b>	
Uncommon:	diabetes insipidus
<b>Respiratory, thoracic and mediastinal disorders</b>	
Very rare:	interstitial pneumonitis/pneumonitis, pulmonary fibrosis, respiratory failure <sup>†</sup>
<b>Hepatobiliary disorders*</b>	
Common:	liver enzymes elevations

<i>Table 6. Summary of events reported with temozolomide in the post-marketing setting</i>	
Uncommon:	hyperbilirubinemia, cholestasis, hepatitis, hepatic injury, hepatic failure <sup>†</sup>
<b>Skin and subcutaneous tissue disorders</b>	
Very rare:	toxic epidermal necrolysis, Stevens-Johnson syndrome

<sup>†</sup> Including cases with fatal outcome

\* Frequencies estimated based on relevant clinical trials.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system listed in [Appendix V](#)**.

## 4.9 Overdose

Doses of 500, 750, 1,000, and 1,250 mg/m<sup>2</sup> (total dose per cycle over 5 days) have been evaluated clinically in patients. Dose-limiting toxicity was haematological and was reported with any dose but is expected to be more severe at higher doses. An overdose of 10,000 mg (total dose in a single cycle, over 5 days) was taken by one patient and the adverse reactions reported were pancytopenia, pyrexia, multi-organ failure and death. There are reports of patients who have taken the recommended dose for 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, haematological evaluation is needed. Supportive measures should be provided as necessary.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents - Other alkylating agents, ATC code: L01A X03

#### Mechanism of action

Temozolomide is a triazene, which undergoes rapid chemical conversion at physiologic pH to the active monomethyl triazenoimidazole carboxamide (MTIC). The cytotoxicity of MTIC is thought to be due primarily to alkylation at the O<sup>6</sup> position of guanine with additional alkylation also occurring at the N<sup>7</sup> position. Cytotoxic lesions that develop subsequently are thought to involve aberrant repair of the methyl adduct.

#### Clinical efficacy and safety

##### *Newly-diagnosed glioblastoma multiforme*

A total of 573 patients were randomised to receive either TMZ + RT (n=287) or RT alone (n=286). Patients in the TMZ + RT arm received concomitant TMZ (75 mg/m<sup>2</sup>) 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 TMZ (150 - 200 mg/m<sup>2</sup>) 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 jirovecii* pneumonia (PCP) prophylaxis was required during RT and combined TMZ therapy.

TMZ 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 TMZ + 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 favour of the TMZ arm. The estimated probability of surviving 2 years or more (26 % vs 10 %) is higher for the RT + TMZ arm. The addition of concomitant TMZ to RT, followed by TMZ monotherapy in the treatment of patients with newly-diagnosed glioblastoma multiforme demonstrated a statistically significant improvement in overall survival (OS) compared with RT alone (Figure 1).

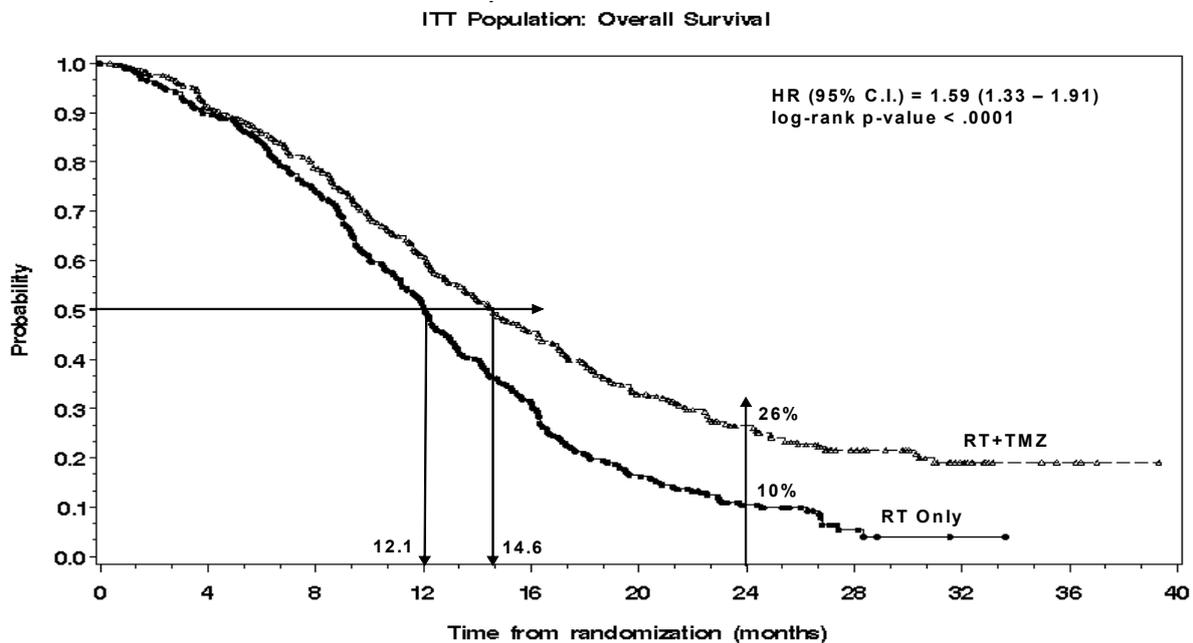


Figure 1 Kaplan-Meier curves for overall survival (Intent to treat population)

The results from the trial were not consistent in the subgroup of patients with a poor performance status (WHO PS=2, n=70), where overall survival and time to progression were similar in both arms. However, no unacceptable risks appear to be present in this patient group.

#### Recurrent or progressive malignant glioma

Data on clinical efficacy in patients with glioblastoma multiforme (Karnofsky performance status [KPS]  $\geq 70$ ), progressive or recurrent after surgery and RT, were based on two clinical trials with oral TMZ. One was a non-comparative trial in 138 patients (29 % received prior chemotherapy), and the other was a randomised active-controlled trial of TMZ vs 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 (ORR) based on MRI scans was 8 %.

In the randomised active-controlled trial, the PFS at 6 months was significantly greater for TMZ 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 TMZ and procarbazine, respectively (log rank  $p = 0.33$ ). At 6 months, the fraction of surviving patients was significantly higher in the TMZ 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  $\geq 80$ .

Data on time to worsening of neurological status favoured TMZ over procarbazine as did data on time to worsening of performance status (decrease to a KPS of  $< 70$  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 TMZ than for procarbazine (log rank  $p = < 0.01$  to  $0.03$ ).

### *Recurrent anaplastic astrocytoma*

In a multicentre, prospective phase II trial evaluating the safety and efficacy of oral TMZ in the treatment of patients with anaplastic astrocytoma at first relapse, the 6 month PFS was 46 %. The median PFS 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 (ITT)  $n=162$ . In 43 patients stable disease was reported. 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 radiological objective response or maintaining progression-free status was strongly associated with maintained or improved quality of life.

### Paediatric population

Oral TMZ has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. Tolerance to TMZ is similar to adults.

## **5.2 Pharmacokinetic properties**

TMZ is spontaneously hydrolyzed at physiologic pH primarily to the active species, 3- methyl(triazene-1-yl)imidazole-4-carboxamide (MTIC). MTIC is spontaneously hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC), a known intermediate in purine and nucleic acid biosynthesis, and to methylhydrazine, which is believed to be the active alkylating species. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA mainly at the O<sup>6</sup> and N<sup>7</sup> positions of guanine. Relative to the AUC of TMZ, the exposure to MTIC and AIC is ~ 2.4 % and 23 %, respectively. *In vivo*, the  $t_{1/2}$  of MTIC was similar to that of TMZ, 1.8 hr.

In an open-label, two-way crossover bioequivalence study of the pharmacokinetics of oral and intravenous TMZ in patients with primary CNS malignancies, Temodal 2.5 mg/ml powder for solution for infusion administered over 90 minutes was found to be bioequivalent for  $C_{max}$  and AUC of TMZ and MTIC as compared to Temodal hard capsules, following administration of 150 mg/m<sup>2</sup> dose. Mean  $C_{max}$  values for TMZ and MTIC were 7.4 µg/ml and 320 ng/ml, respectively, following 90 minute intravenous infusion. Mean AUC (0 → ∞) values for TMZ and MTIC were 25 µg•h/ml and 1,004 ng•h/ml, respectively.

### Absorption

After oral administration to adult patients, TMZ is absorbed rapidly, with peak concentrations reached as early as 20 minutes post-administration (mean time between 0.5 and 1.5 hours). After oral administration of <sup>14</sup>C-labelled TMZ, mean faecal excretion of <sup>14</sup>C over 7 days post-dose was 0.8 % indicating complete absorption.

### Distribution

TMZ demonstrates low protein binding (10 % to 20 %), and thus it is not expected to interact with highly protein-bound substances.

PET studies in humans and preclinical data suggest that TMZ crosses the blood-brain barrier rapidly and is present in the CSF. CSF penetration was confirmed in one patient; CSF exposure based on AUC of TMZ was approximately 30 % of that in plasma, which is consistent with animal data.

## Elimination

The half-life ( $t_{1/2}$ ) in plasma is approximately 1.8 hours. The major route of  $^{14}\text{C}$  elimination is renal. Following oral administration, approximately 5 % to 10 % of the dose is recovered unchanged in the urine over 24 hours, and the remainder excreted as temozolomide acid, 5-aminoimidazole-4-carboxamide (AIC) or unidentified polar metabolites.

Plasma concentrations increase in a dose-related manner. Plasma clearance, volume of distribution and half-life are independent of dose.

## Special populations

Analysis of population-based pharmacokinetics of TMZ revealed that plasma TMZ clearance was independent of age, renal function or tobacco use. In a separate pharmacokinetic study, plasma pharmacokinetic profiles in patients with mild to moderate hepatic impairment were similar to those observed in patients with normal hepatic function.

Paediatric patients had a higher AUC than adult patients; however, the maximum tolerated dose (MTD) was  $1,000 \text{ mg/m}^2$  per cycle both in children and in adults.

### **5.3 Preclinical safety data**

Single-cycle (5-day dosing, 23 days non-treatment), 3- and 6-cycle toxicity studies were conducted in rats and dogs. The primary targets of toxicity included the bone marrow, lymphoreticular system, testes, the gastrointestinal tract and, at higher doses, which were lethal to 60 % to 100 % of rats and dogs tested, degeneration of the retina occurred. Most of the toxicity showed evidence of reversibility, except for adverse events on the male reproductive system and retinal degeneration. However, because the doses implicated in retinal degeneration were in the lethal dose range, and no comparable effect has been observed in clinical studies, this finding was not considered to have clinical relevance.

TMZ is an embryotoxic, teratogenic and genotoxic alkylating agent. TMZ is more toxic to the rat and dog than to humans, and the clinical dose approximates the minimum lethal dose in rats and dogs. Dose-related reductions in leukocytes and platelets appear to be sensitive indicators of toxicity. A variety of neoplasms, including mammary carcinomas, keratocanthoma of the skin and basal cell adenoma were observed in the 6-cycle rat study while no tumours or pre-neoplastic changes were evident in dog studies. Rats appear to be particularly sensitive to oncogenic effects of TMZ, with the occurrence of first tumours within 3 months of initiating dosing. This latency period is very short even for an alkylating agent.

Results of the Ames/salmonella and Human Peripheral Blood Lymphocyte (HPBL) chromosome aberration tests showed a positive mutagenicity response.

The intravenous formulation produced local irritation at the site of injection in both rabbits and rats. The irritation was transient and not associated with lasting tissue damage.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Mannitol (E421)

Threonine

Polysorbate 80

Sodium citrate (for pH adjustment)

Hydrochloric acid concentrated (for pH adjustment)

## **6.2 Incompatibilities**

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

## **6.3 Shelf life**

Unopened vial: 4 years

Reconstituted solution: after reconstitution the chemical and physical in-use stability has been demonstrated for 14 hours at 25°C, including infusion time.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

## **6.4 Special precautions for storage**

Store in a refrigerator (2 °C – 8 °C).

For storage conditions of the reconstituted medicinal product, see section 6.3.

## **6.5 Nature and contents of container**

Clear type I glass vial sealed with bromobutyl rubber stopper and aluminium overseal with peach-coloured flip-off bonnet. Each vial contains 100 mg TMZ.

Temodal 2.5 mg/ml is supplied as a pack of 1 vial.

## **6.6 Special precautions for disposal and other handling**

Caution must be exercised in handling Temodal 2.5 mg/ml powder for solution for infusion. The use of gloves and aseptic technique is required. If Temodal 2.5 mg/ml comes into contact with skin or mucosa, it should be washed immediately and thoroughly with soap and water.

Each vial must be reconstituted with 41 ml sterilised water for injections. The resulting solution contains 2.5 mg/ml TMZ. The vials should be gently swirled and not shaken. The solution should be inspected and any vial containing visible particulate matter should not be used. A volume up to 40 ml reconstituted solution should be withdrawn, according to the total prescribed dose and transferred into an empty 250 ml infusion bag (PVC or polyolefin). The pump tubing should be attached to the bag, the tubing purged and then capped. Temodal 2.5 mg/ml must be administered by intravenous infusion **only** over a period of 90 minutes.

Temodal 2.5 mg/ml powder for solution for infusion may be administered in the same IV line with 0.9% Sodium Chloride injection. It is incompatible with dextrose solutions.

In the absence of additional data, this medicinal product must not be mixed with other medicinal products or infused simultaneously through the same intravenous line.

This medicinal product is for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**7. MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN Haarlem  
The Netherlands

**8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/98/096/023

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 26 January 1999

Date of latest renewal: 26 January 2009

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## **ANNEX II**

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## **A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer responsible for batch release

SP Labo N.V.  
Industriepark 30  
2220 Heist op den Berg  
Belgium

## **B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

## **C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

## **D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON CONTAINING 1 BOTTLE OF 5 OR 20 HARD CAPSULES OF TEMODAL 5 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Temodal 5 mg hard capsules  
temozolomide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each hard capsule contains 5 mg temozolomide.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

5 hard capsules  
20 hard capsules

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**Cytotoxic**

Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30 °C.  
Store in the original bottle in order to protect from moisture.  
Keep the bottle tightly closed.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN Haarlem  
The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/98/096/001 (5 hard capsules)  
EU/1/98/096/002 (20 hard capsules)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Temodal 5 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:

NN:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON CONTAINING 1 BOTTLE OF 5 OR 20 HARD CAPSULES OF TEMODAL 20 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Temodal 20 mg hard capsules  
temozolomide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each hard capsule contains 20 mg temozolomide.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

5 hard capsules  
20 hard capsules

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**Cytotoxic**

Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30 °C.  
Store in the original bottle in order to protect from moisture.  
Keep the bottle tightly closed.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN Haarlem  
The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/98/096/003 (5 hard capsules)  
EU/1/98/096/004 (20 hard capsules)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Temodal 20 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:

NN:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON CONTAINING 1 BOTTLE OF 5 OR 20 HARD CAPSULES OF TEMODAL 100 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Temodal 100 mg hard capsules  
temozolomide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each hard capsule contains 100 mg temozolomide.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

5 hard capsules  
20 hard capsules

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**Cytotoxic**

Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30 °C.  
Store in the original bottle in order to protect from moisture.  
Keep the bottle tightly closed.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN Haarlem  
The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/98/096/005 (5 hard capsules)  
EU/1/98/096/006 (20 hard capsules)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Temodal 100 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:

NN:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON CONTAINING 1 BOTTLE OF 5 OR 20 HARD CAPSULES OF TEMODAL 140 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Temodal 140 mg hard capsules  
temozolomide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each hard capsule contains 140 mg temozolomide.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

5 hard capsules  
20 hard capsules

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the enclosed package leaflet before use.  
Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental -ingestion can be lethal for children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**Cytotoxic**

Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30 °C.  
Store in the original bottle in order to protect from moisture.  
Keep the bottle tightly closed.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN Haarlem  
The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/98/096/009 (5 hard capsules)  
EU/1/98/096/010 (20 hard capsules)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Temodal 140 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:

NN:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON CONTAINING 1 BOTTLE OF 5 OR 20 HARD CAPSULES OF TEMODAL 180 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Temodal 180 mg hard capsules  
temozolomide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each hard capsule contains 180 mg temozolomide.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

5 hard capsules  
20 hard capsules

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the enclosed package leaflet before use.  
Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental -ingestion can be lethal for children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**Cytotoxic**

Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30 °C.  
Store in the original bottle in order to protect from moisture.  
Keep the bottle tightly closed.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN Haarlem  
The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/98/096/011 (5 hard capsules)  
EU/1/98/096/012 (20 hard capsules)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Temodal 180 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:

NN:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON CONTAINING 1 BOTTLE OF 5 OR 20 HARD CAPSULES OF TEMODAL 250 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Temodal 250 mg hard capsules  
temozolomide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each hard capsule contains 250 mg temozolomide.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

5 hard capsules  
20 hard capsules

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**Cytotoxic**

Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30 °C.  
Store in the original bottle in order to protect from moisture.  
Keep the bottle tightly closed.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN Haarlem  
The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/98/096/007 (5 hard capsules)  
EU/1/98/096/008 (20 hard capsules)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Temodal 250 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:

NN:

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS  
LABEL FOR BOTTLES CONTAINING 5 OR 20 HARD CAPSULES OF TEMODAL 5 mg**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Temodal 5 mg hard capsules  
temozolomide  
Oral use

**2. METHOD OF ADMINISTRATION**

Read the package leaflet before use.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

5 hard capsules  
20 hard capsules

**6. OTHER**

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS  
LABEL FOR BOTTLES CONTAINING 5 OR 20 HARD CAPSULES OF TEMODAL 20 mg**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Temodal 20 mg hard capsules  
temozolomide  
Oral use

**2. METHOD OF ADMINISTRATION**

Read the package leaflet before use.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

5 hard capsules  
20 hard capsules

**6. OTHER**

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**  
**LABEL FOR BOTTLES CONTAINING 5 OR 20 HARD CAPSULES OF TEMODAL 100 mg**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Temodal 100 mg hard capsules  
temozolomide  
Oral use

**2. METHOD OF ADMINISTRATION**

Read the package leaflet before use.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

5 hard capsules  
20 hard capsules

**6. OTHER**

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**  
**LABEL FOR BOTTLES CONTAINING 5 OR 20 HARD CAPSULES OF TEMODAL 140 mg**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Temodal 140 mg hard capsules  
temozolomide  
Oral use

**2. METHOD OF ADMINISTRATION**

Read the package leaflet before use.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

5 hard capsules  
20 hard capsules

**6. OTHER**

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**  
**LABEL FOR BOTTLES CONTAINING 5 OR 20 HARD CAPSULES OF TEMODAL 180 mg**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Temodal 180 mg hard capsules  
temozolomide  
Oral use

**2. METHOD OF ADMINISTRATION**

Read the package leaflet before use.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

5 hard capsules  
20 hard capsules

**6. OTHER**

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**  
**LABEL FOR BOTTLES CONTAINING 5 OR 20 HARD CAPSULES OF TEMODAL 250 mg**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Temodal 250 mg hard capsules  
temozolomide  
Oral use

**2. METHOD OF ADMINISTRATION**

Read the package leaflet before use.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

5 hard capsules  
20 hard capsules

**6. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON CONTAINING 5 OR 20 HARD CAPSULES OF TEMODAL 5 mg INDIVIDUALLY SEALED IN SACHETS**

**1. NAME OF THE MEDICINAL PRODUCT**

Temodal 5 mg hard capsules  
temozolomide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each hard capsule contains 5 mg temozolomide.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

5 hard capsules in sachets  
20 hard capsules in sachets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**Cytotoxic**

Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30 °C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN Haarlem  
The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/98/096/024 (5 hard capsules)  
EU/1/98/096/025 (20 hard capsules)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Temodal 5 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON CONTAINING 5 OR 20 HARD CAPSULES OF TEMODAL 20 mg  
INDIVIDUALLY SEALED IN SACHETS**

**1. NAME OF THE MEDICINAL PRODUCT**

Temodal 20 mg hard capsules  
temozolomide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each hard capsule contains 20 mg temozolomide.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

5 hard capsules in sachets  
20 hard capsules in sachets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT  
OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**Cytotoxic**

Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30 °C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN Haarlem  
The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/98/096/013 (5 hard capsules)  
EU/1/98/096/014 (20 hard capsules)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Temodal 20 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON CONTAINING 5 OR 20 HARD CAPSULES OF TEMODAL 100 mg  
INDIVIDUALLY SEALED IN SACHETS**

**1. NAME OF THE MEDICINAL PRODUCT**

Temodal 100 mg hard capsules  
temozolomide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each hard capsule contains 100 mg temozolomide.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

5 hard capsules in sachets  
20 hard capsules in sachets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT  
OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**Cytotoxic**

Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30 °C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN Haarlem  
The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/98/096/015 (5 hard capsules)  
EU/1/98/096/016 (20 hard capsules)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Temodal 100 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON CONTAINING 5 OR 20 HARD CAPSULES OF TEMODAL 140 mg  
INDIVIDUALLY SEALED IN SACHETS**

**1. NAME OF THE MEDICINAL PRODUCT**

Temodal 140 mg hard capsules  
temozolomide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each hard capsule contains 140 mg temozolomide.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

5 hard capsules in sachets  
20 hard capsules in sachets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the enclosed package leaflet before use.  
Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT  
OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**Cytotoxic**

Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30 °C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN Haarlem  
The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/98/096/017 (5 hard capsules)  
EU/1/98/096/018 (20 hard capsules)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Temodal 140 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON CONTAINING 5 OR 20 HARD CAPSULES OF TEMODAL 180 mg  
INDIVIDUALLY SEALED IN SACHETS**

**1. NAME OF THE MEDICINAL PRODUCT**

Temodal 180 mg hard capsules  
temozolomide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each hard capsule contains 180 mg temozolomide.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

5 hard capsules in sachets  
20 hard capsules in sachets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the enclosed package leaflet before use.  
Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT  
OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**Cytotoxic**

Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30 °C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN Haarlem  
The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/98/096/019 (5 hard capsules)  
EU/1/98/096/020 (20 hard capsules)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Temodal 180 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON CONTAINING 5 OR 20 HARD CAPSULES OF TEMODAL 250 mg  
INDIVIDUALLY SEALED IN SACHETS**

**1. NAME OF THE MEDICINAL PRODUCT**

Temodal 250 mg hard capsules  
temozolomide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each hard capsule contains 250 mg temozolomide.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

5 hard capsules in sachets  
20 hard capsules in sachets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the enclosed package leaflet before use.  
Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT  
OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**Cytotoxic**

Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30 °C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN Haarlem  
The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/98/096/021 (5 hard capsules)  
EU/1/98/096/022 (20 hard capsules)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Temodal 250 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**  
**SACHET CONTAINING 1 HARD CAPSULE OF TEMODAL 5 mg**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Temodal 5 mg capsules  
temozolomide  
Oral use

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

1 capsule

**6. OTHER**

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**  
**SACHET CONTAINING 1 HARD CAPSULE OF TEMODAL 20 mg**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Temodal 20 mg capsules  
temozolomide  
Oral use

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

1 capsule

**6. OTHER**

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**  
**SACHET CONTAINING 1 HARD CAPSULE OF TEMODAL 100 mg**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Temodal 100 mg capsules  
temozolomide  
Oral use

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

1 capsule

**6. OTHER**

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**  
**SACHET CONTAINING 1 HARD CAPSULE OF TEMODAL 140 mg**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Temodal 140 mg capsules  
temozolomide  
Oral use

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

1 capsule

**6. OTHER**

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**  
**SACHET CONTAINING 1 HARD CAPSULE OF TEMODAL 180 mg**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Temodal 180 mg capsules  
temozolomide  
Oral use

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

1 capsule

**6. OTHER**

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**  
**SACHET CONTAINING 1 HARD CAPSULE OF TEMODAL 250 mg**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Temodal 250 mg capsules  
temozolomide  
Oral use

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

1 capsule

**6. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Temodal 2.5 mg/ml powder for solution for infusion  
temozolomide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each vial contains 100 mg temozolomide.  
After reconstitution, 1 ml of solution for infusion contains 2.5 mg temozolomide.

**3. LIST OF EXCIPIENTS**

Excipients: mannitol (E421), threonine, polysorbate 80, sodium citrate and hydrochloric acid concentrated for pH adjustment.  
For sodium, see leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder for solution for infusion  
1 vial 100 mg

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Intravenous use only.  
For single use only.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**Cytotoxic**  
Avoid contact with skin, eyes or nose.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator.

After reconstitution, use the solution within 14 hours at 25 °C, including infusion time.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.

Waarderweg 39

2031 BN Haarlem

The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/98/096/023

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:

SN:

NN:

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**VIAL LABEL**

**1. NAME OF THE MEDICINAL PRODUCT**

Temodal 2.5 mg/ml powder for solution for infusion  
temozolomide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each vial contains 100 mg temozolomide.  
After reconstitution, 1 ml of solution for infusion contains 2.5 mg.

**3. LIST OF EXCIPIENTS**

Mannitol (E421), threonine, polysorbate 80, sodium citrate and hydrochloric acid.  
For sodium, see leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder for solution for infusion  
100 mg

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Intravenous use, single use only.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**Cytotoxic**  
Avoid contact with skin, eyes, nose.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator.

After reconstitution: 14 hours at 25 °C, including infusion time.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Dispose of in accordance with local requirements.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN Haarlem  
The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/98/096/023

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE**

**B. PACKAGE LEAFLET**

## Package Leaflet: Information for the user

**Temodal 5 mg hard capsules**  
**Temodal 20 mg hard capsules**  
**Temodal 100 mg hard capsules**  
**Temodal 140 mg hard capsules**  
**Temodal 180 mg hard capsules**  
**Temodal 250 mg hard capsules**  
temozolomide

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

### **What is in this leaflet**

1. What Temodal is and what it is used for
2. What you need to know before you take Temodal
3. How to take Temodal
4. Possible side effects
5. How to store Temodal
6. Contents of the pack and other information

### **1. What Temodal is and what it is used for**

Temodal contains a medicine called temozolomide. This medicine is an antitumour agent.

Temodal is used for the treatment of specific forms of brain tumours:

- in adults with newly-diagnosed glioblastoma multiforme. Temodal is first used together with radiotherapy (concomitant phase of treatment) and after that alone (monotherapy phase of treatment).
- in children 3 years and older and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma. Temodal is used in these tumours if they return or get worse after standard treatment.

### **2. What you need to know before you take Temodal**

#### **Do not take Temodal**

- if you are allergic to temozolomide or any of the other ingredients of this medicine (listed in section 6).
- if you have had an allergic reaction to dacarbazine (an anticancer medicine sometimes called DTIC). Signs of allergic reaction include feeling itchy, breathlessness or wheezing, swelling of the face, lips, tongue or throat.
- if certain kinds of blood cells are severely reduced (myelosuppression), such as your white blood cell count and platelet count. These blood cells are important for fighting infection and for proper blood clotting. Your doctor will check your blood to make sure you have enough of these cells before you begin treatment.

## Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Temodal,

- as you should be observed closely for the development of a serious form of chest infection called *Pneumocystis jirovecii* pneumonia (PCP). If you are a newly-diagnosed patient (glioblastoma multiforme) you may be receiving Temodal for 42 days in combination with radiotherapy. In this case, your doctor will also prescribe medicine to help you prevent this type of pneumonia (PCP).
- if you have ever had or might now have a hepatitis B infection. This is because Temodal could cause hepatitis B to become active again, which can be fatal in some cases. Patients will be carefully checked by their doctor for signs of this infection before treatment is started.
- if you have low counts of red blood cells (anaemia), white blood cells and platelets, or blood clotting problems before starting the treatment, or if you develop them during treatment. Your doctor may decide to reduce the dose, interrupt, stop or change your treatment. You may also need other treatments. In some cases, it may be necessary to stop treatment with Temodal. Your blood will be tested frequently during treatment to monitor the side effects of Temodal on your blood cells.
- as you may have a small risk of other changes in blood cells, including leukaemia.
- if you have nausea (feeling sick in your stomach) and/or vomiting which are very common side effects of Temodal (see section 4), your doctor may prescribe you a medicine (an anti-emetic) to help prevent vomiting.  
If you vomit frequently before or during treatment, ask your doctor about the best time to take Temodal until the vomiting is under control. If you vomit after taking your dose, do not take a second dose on the same day.
- if you develop fever or symptoms of an infection, contact your doctor immediately.
- if you are older than 70 years of age, you might be more prone to infections, bruising or bleeding.
- if you have liver or kidney problems, your dose of Temodal may need to be adjusted.

## Children and adolescents

Do not give this medicine to children under the age of 3 years because it has not been studied. There is limited information in patients over 3 years of age who have taken Temodal.

## Other medicines and Temodal

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

## Pregnancy, breast-feeding and fertility

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. This is because you must not be treated with Temodal during pregnancy unless clearly indicated by your doctor.

Effective contraceptive precautions must be taken by **both male and female patients** who are taking Temodal (see also “Male fertility” below).

You should stop breast-feeding while receiving treatment with Temodal.

## Male fertility

Temodal may cause permanent infertility. Male patients should use effective contraception and not father a child for up to 6 months after stopping treatment. It is recommended to seek advice on conservation of sperm prior to treatment.

## Driving and using machines

Temodal may make you feel tired or sleepy. In this case, do not drive or use any tools or machines or cycle until you see how this medicine affects you (see section 4).

### **Temodal contains lactose**

Temodal contains lactose (a kind of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

### **3. How to take Temodal**

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

#### Dosage and duration of treatment

Your doctor will work out your dose of Temodal. This is based on your size (height and weight) and if you have a recurrent tumour and have had chemotherapy treatment in the past.

You may be given other medicines (anti-emetics) to take before and/or after taking Temodal to prevent or control nausea and vomiting.

#### Patients with newly-diagnosed glioblastoma multiforme:

If you are a newly-diagnosed patient, treatment will occur in two phases:

- treatment together with radiotherapy (concomitant phase) first
- followed by treatment with only Temodal (monotherapy phase).

During the concomitant phase, your doctor will start Temodal at a dose of 75 mg/m<sup>2</sup> (usual dose). You will take this dose every day for 42 days (up to 49 days) in combination with radiotherapy. The Temodal dose may be delayed or stopped, depending on your blood counts and how you tolerate your medicine during the concomitant phase.

Once the radiotherapy is completed, you will interrupt treatment for 4 weeks. This will give your body a chance to recover.

Then, you will start the monotherapy phase.

During the monotherapy phase, the dose and way you take Temodal will be different. Your doctor will work out your exact dose. There may be up to 6 treatment periods (cycles). Each one lasts 28 days. You will take your new dose of Temodal alone once daily for the first 5 days (“dosing days”) of each cycle. The first dose will be 150 mg/m<sup>2</sup>. Then you will have 23 days without Temodal. This adds up to a 28-day treatment cycle.

After Day 28, the next cycle will begin. You will again take Temodal once daily for 5 days followed by 23 days without Temodal. The Temodal dose may be adjusted, delayed or stopped depending on your blood counts and how you tolerate your medicine during each treatment cycle.

#### Patients with tumours that have returned or worsened (malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma) taking Temodal only:

A treatment cycle with Temodal lasts 28 days.

You will take Temodal alone once daily for the first 5 days. This daily dose depends on whether or not you have received chemotherapy before.

If you have not been previously treated with chemotherapy, your first dose of Temodal will be 200 mg/m<sup>2</sup> once daily for the first 5 days. If you have been previously treated with chemotherapy, your first dose of Temodal will be 150 mg/m<sup>2</sup> once daily for the first 5 days.

Then, you will have 23 days without Temodal. This adds up to a 28-day treatment cycle.

After Day 28, the next cycle will begin. You will again receive Temodal once daily for 5 days, followed by 23 days without Temodal.

Before each new treatment cycle, your blood will be tested to see if the Temodal dose needs to be adjusted. Depending on your blood test results, your doctor may adjust your dose for the next cycle.

## How to take Temodal

Take your prescribed dose of Temodal once a day, preferably at the same time each day.

Take the capsules on an empty stomach; for example, at least one hour before you plan to eat breakfast. Swallow the capsule(s) whole with a glass of water. Do not open, crush or chew the capsules. If a capsule is damaged, avoid contact of the powder with your skin, eyes or nose. If you accidentally get some in your eyes or nose, flush the area with water.

Depending on the prescribed dose, you may have to take more than one capsule together, eventually with different strengths (content of active substance, in mg). The colour of the capsule cap is different for each strength (see in the table below).

Strength	Colour of the cap
Temodal <b>5 mg</b> hard capsules	green
Temodal <b>20 mg</b> hard capsules	yellow
Temodal <b>100 mg</b> hard capsules	pink
Temodal <b>140 mg</b> hard capsules	blue
Temodal <b>180 mg</b> hard capsules	orange
Temodal <b>250 mg</b> hard capsules	white

You should make sure you fully understand and remember the following:

- how many capsules you need to take every dosing day. Ask your doctor or pharmacist to write it down (including the colour).
- which days are your dosing days.

Review the dose with your doctor each time you start a new cycle, since it may be different from the last cycle.

Always take Temodal exactly as your doctor has told you. It is very important to check with your doctor or pharmacist if you are not sure. Errors in how you take this medicine may have serious health consequences.

### **If you take more Temodal than you should**

If you accidentally take more Temodal capsules than you were told to, contact your doctor, pharmacist or nurse immediately.

### **If you forget to take Temodal**

Take the missed dose as soon as possible during the same day. If a full day has gone by, check with your doctor. Do not take a double dose to make up for a forgotten dose, unless your doctor tells you to do so.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

## **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Contact your doctor **immediately** if you have any of the following:

- a severe allergic (hypersensitive) reaction (hives, wheezing or other breathing difficulty),
- uncontrolled bleeding,

- seizures (convulsions),
- fever,
- chills,
- severe headache that does not go away.

Temodal treatment can cause a reduction in certain kinds of blood cells. This may cause you to have increased bruising or bleeding, anaemia (a shortage of red blood cells), fever, and reduced resistance to infections. The reduction in blood cell counts is usually short-lived. In some cases, it may be prolonged and may lead to a very severe form of anaemia (aplastic anaemia). Your doctor will monitor your blood regularly for any changes, and will decide if any specific treatment is needed. In some cases, your Temodal dose will be reduced or treatment stopped.

#### Side effects from clinical studies:

##### *Temodal in combination treatment with radiotherapy in newly-diagnosed glioblastoma*

Patients receiving Temodal in combination with radiotherapy may experience different side effects than patients taking Temodal alone. The following side effects may occur, and may require medical attention.

**Very common (may affect more than 1 in 10 people):** loss of appetite, headache, constipation (difficulty passing stools), nausea (feeling sick in your stomach), vomiting, rash, hair loss, tiredness.

**Common (may affect up to 1 in 10 people):** oral infections, wound infection, reduced number of blood cells (neutropenia, thrombocytopenia, lymphopenia, leukopenia), increased sugar in the blood, loss of weight, change in mental status or alertness, anxiety/depression, sleepiness, difficulty speaking, impaired balance, dizziness, confusion, forgetfulness, difficulty concentrating, inability to fall asleep or stay asleep, tingling sensation, bruising, shaking, abnormal or blurry vision, double vision, hearing impairment, shortness of breath, cough, blood clot in the legs, fluid retention, swollen legs, diarrhoea, stomach or abdominal pain, heartburn, upset stomach, difficulty swallowing, dry mouth, skin irritation or redness, dry skin, itching, muscle weakness, painful joints, muscle aches and pains, frequent urination, difficulty with holding your urine, allergic reaction, fever, radiation injury, face swelling, pain, abnormal taste, abnormal liver function tests.

**Uncommon (may affect up to 1 in 100 people):** flu-like symptoms, red spots under the skin, low potassium level in the blood, weight gain, mood swings, hallucination and memory impairment, partial paralysis, impaired coordination, impaired sensations, partial loss of vision, dry or painful eyes, deafness, infection of the middle ear, ringing in the ears, earache, palpitations (when you can feel your heart beat), blood clot in the lung, high blood pressure, pneumonia, inflammation of your sinuses, bronchitis, a cold or the flu, swollen stomach, difficulty controlling your bowel movements, haemorrhoids, peeling skin, increased skin sensitivity to sunlight, change in skin colour, increased sweating, muscle damage, back pain, difficulty in urinating, vaginal bleeding, sexual impotence, absent or heavy menstrual periods, vaginal irritation, breast pain, hot flushes, shivering, discolouration of your tongue, change in your sense of smell, thirst, tooth disorder.

##### *Temodal monotherapy in recurrent or progressive glioma*

The following side effects may occur, and may require medical attention.

**Very common (may affect more than 1 in 10 people):** reduced number of blood cells (neutropenia or lymphopenia, thrombocytopenia), loss of appetite, headache, vomiting, nausea (feeling sick in your stomach), constipation (difficulty passing stools), tiredness.

**Common (may affect up to 1 in 10 people):** loss of weight, sleepiness, dizziness, tingling sensation, shortness of breath, diarrhoea, abdominal pain, upset stomach, rash, itching, hair loss, fever, weakness, shivering, feeling unwell, pain, change in taste.

**Uncommon (may affect up to 1 in 100 people):** reduced blood cell counts (pancytopenia, anaemia, leukopenia).

**Rare (may affect up to 1 in 1,000 people):** cough, infections including pneumonia.

**Very rare (may affect up to 1 in 10,000 people):** skin redness, urticaria (hives), skin eruption, allergic reactions.

Other side effects:

Cases of elevations of liver enzymes have been commonly reported. Cases of increased bilirubin, problems with bile flow (cholestasis), hepatitis and injury to the liver, including fatal liver failure, have been uncommonly reported.

Very rare cases of severe rash with skin swelling, including on the palms of the hands and soles of the feet, or painful reddening of the skin and/or blisters on the body or in the mouth have been observed. Tell your doctor **immediately** if this occurs.

Very rare cases of lung side effects have been observed with Temodal. Patients usually present with shortness of breath and cough. Tell your doctor if you notice any of these symptoms.

In very rare cases, patients taking Temodal and medicines like it may have a small risk of developing secondary cancers, including leukaemia.

New or reactivated (recurring) cytomegalovirus infections and reactivated hepatitis B virus infections have been uncommonly reported. Cases of brain infections caused by herpes virus (meningoencephalitis herpetic), including fatal cases, have been uncommonly reported. Cases of sepsis (when bacteria and their toxins circulate in the blood and start to damage the organs) have been uncommonly reported.

Cases of diabetes insipidus have been uncommonly reported. Symptoms of diabetes insipidus include passing a lot of urine and feeling thirsty.

**Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

**5. How to store Temodal**

Keep this medicine out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

Do not use this medicine after the expiry date which is stated on the label and carton. The expiry date refers to the last day of that month.

Bottle presentation

Do not store above 30 °C.

Store in the original bottle in order to protect from moisture.

Keep the bottle tightly closed.

Sachet presentation

Do not store above 30 °C

Tell your pharmacist if you notice any change in the appearance of the capsules.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

### What Temodal contains

The active substance is temozolomide.

*Temodal 5 mg hard capsules:* Each capsule contains 5 mg temozolomide.

*Temodal 20 mg hard capsules:* Each capsule contains 20 mg temozolomide.

*Temodal 100 mg hard capsules:* Each capsule contains 100 mg temozolomide.

*Temodal 140 mg hard capsules:* Each capsule contains 140 mg temozolomide.

*Temodal 180 mg hard capsules:* Each capsule contains 180 mg temozolomide.

*Temodal 250 mg hard capsules:* Each capsule contains 250 mg temozolomide.

The other ingredients are:

#### capsule content:

anhydrous lactose, colloidal anhydrous silica, sodium starch glycolate type A, tartaric acid, stearic acid (see section 2 "Temodal contains lactose").

#### capsule shell:

*Temodal 5 mg hard capsules:* gelatin, titanium dioxide (E 171), sodium laurilsulfate, yellow iron oxide (E 172), indigo carmine (E 132).

*Temodal 20 mg hard capsules:* gelatin, titanium dioxide (E 171), sodium lauril sulfate, yellow iron oxide (E 172),

*Temodal 100 mg hard capsules:* gelatin, titanium dioxide (E 171), sodium lauril sulfate, red iron oxide (E 172),

*Temodal 140 mg hard capsules:* gelatin, titanium dioxide (E 171), sodium lauril sulfate, indigo carmine (E 132),

*Temodal 180 mg hard capsules:* gelatin, titanium dioxide (E 171), sodium lauril sulfate, yellow iron oxide (E 172), and red iron oxide (E 172),

*Temodal 250 mg hard capsules:* gelatin, titanium dioxide (E 171), sodium lauril sulfate.

#### printing ink:

shellac, propylene glycol, purified water, ammonium hydroxide, potassium hydroxide, and black iron oxide (E 172).

### What Temodal looks like and contents of the pack

*Temodal 5 mg hard capsules* have an opaque white body, an opaque green cap, and are imprinted with black ink.

*Temodal 20 mg hard capsules* have an opaque white body, an opaque yellow cap, and are imprinted with black ink.

*Temodal 100 mg hard capsules* have an opaque white body, an opaque pink cap, and are imprinted with black ink.

*Temodal 140 mg hard capsules* have an opaque white body, a blue cap, and are imprinted with black ink.

*Temodal 180 mg hard capsules* have an opaque white body, an opaque orange cap, and are imprinted with black ink.

*Temodal 250 mg hard capsules* have an opaque white body and cap, and are imprinted with black ink.

### Bottle presentation

The hard capsules for oral use are dispensed in amber glass bottles containing 5 or 20 capsules.

The carton contains 1 bottle.

Sachet presentation

The hard capsules (capsules) for oral use are individually sealed in sachets and dispensed in cartons containing 5 or 20 hard capsules.

Not all pack sizes may be marketed.

### **Marketing Authorisation Holder and Manufacturer**

Marketing Authorisation Holder:

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN Haarlem  
The Netherlands

Manufacturer: SP Labo N.V., Industriepark 30, B-2220 Heist-op-den-Berg, Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

#### **Belgique/België/Belgien**

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#### **Lietuva**

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**This leaflet was last revised in**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>.

## Package Leaflet: Information for the user

### Temodal 2.5 mg/ml powder for solution for infusion temozolomide

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Temodal is and what it is used for
2. What you need to know before you use Temodal
3. How to use Temodal
4. Possible side effects
5. How to store Temodal
6. Contents of the pack and other information

#### **1. What Temodal is and what it is used for**

Temodal contains a medicine called temozolomide. This medicine is an antitumour agent.

Temodal is used for the treatment of specific forms of brain tumours:

- in adults with newly-diagnosed glioblastoma multiforme. Temodal is first used together with radiotherapy (concomitant phase of treatment) and after that alone (monotherapy phase of treatment).
- in children 3 years and older and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma. Temodal is used in these tumours if they return or get worse after standard treatment.

#### **2. What you need to know before you use Temodal**

##### **Do not use Temodal**

- if you are allergic to temozolomide or any of the other ingredients of this medicine (listed in section 6).
- if you have had an allergic reaction to dacarbazine (an anticancer medicine sometimes called DTIC). Signs of allergic reaction include feeling itchy, breathlessness or wheezing, swelling of the face, lips, tongue or throat.
- if certain kinds of blood cells are severely reduced (myelosuppression), such as your white blood cell count and platelet count. These blood cells are important for fighting infection and for proper blood clotting. Your doctor will check your blood to make sure you have enough of these cells before you begin treatment.

##### **Warnings and precautions**

Talk to your doctor, pharmacist or nurse before using Temodal,

- as you should be observed closely for the development of a serious form of chest infection called *Pneumocystis jirovecii* pneumonia (PCP). If you are a newly-diagnosed patient (glioblastoma multiforme) you may be receiving Temodal for 42 days in combination with radiotherapy. In this case, your doctor will also prescribe medicine to help you prevent this type of pneumonia (PCP).

- if you have ever had or might now have a hepatitis B infection. This is because Temodal could cause hepatitis B to become active again, which can be fatal in some cases. Patients will be carefully checked by their doctor for signs of this infection before treatment is started.
- if you have low counts of red blood cells (anaemia), white blood cells and platelets, or blood clotting problems before starting the treatment, or if you develop them during treatment. Your doctor may decide to reduce the dose, interrupt, stop or change your treatment. You may also need other treatments. In some cases, it may be necessary to stop treatment with Temodal. Your blood will be tested frequently during treatment to monitor the side effects of Temodal on your blood cells.
- as you may have a small risk of other changes in blood cells, including leukaemia.
- if you have nausea (feeling sick in your stomach) and/or vomiting which are very common side effects of Temodal (see section 4), your doctor may prescribe you a medicine (an anti-emetic) to help prevent vomiting.
- if you develop fever or symptoms of an infection, contact your doctor immediately.
- if you are older than 70 years of age, you might be more prone to infections, bruising or bleeding.
- if you have liver or kidney problems, your dose of Temodal may need to be adjusted.

### **Children and adolescents**

Do not give this medicine to children under the age of 3 years because it has not been studied. There is limited information in patients over 3 years of age who have used Temodal.

### **Other medicines and Temodal**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

### **Pregnancy, breast-feeding and fertility**

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine. This is because you must not be treated with Temodal during pregnancy unless clearly indicated by your doctor.

Effective contraceptive precautions must be taken by **both male and female patients** who are using Temodal (see also “Male fertility” below).

You should stop breast-feeding while receiving treatment with Temodal.

### **Male fertility**

Temodal may cause permanent infertility. Male patients should use effective contraception and not father a child for up to 6 months after stopping treatment. It is recommended to seek advice on conservation of sperm prior to treatment.

### **Driving and using machines**

Temodal may make you feel tired or sleepy. In this case, do not drive or use any tools or machines or cycle until you see how this medicine affects you (see section 4).

### **Temodal contains sodium**

This medicine contains 2.4 mmol sodium per vial. This should be taken into consideration by patients on a controlled sodium diet.

## **3. How to use Temodal**

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will work out your dose of Temodal. This is based on your size (height and weight) and if you have a recurrent tumour and have had chemotherapy treatment in the past.

You may be given other medicines (anti-emetics) to take before and/or after receiving Temodal to prevent or control nausea and vomiting.

*Patients with newly-diagnosed glioblastoma multiforme:*

If you are a newly-diagnosed patient, treatment will occur in two phases:

- treatment together with radiotherapy (concomitant phase) first
- followed by treatment with only Temodal (monotherapy phase).

During the concomitant phase, your doctor will start Temodal at a dose of 75 mg/m<sup>2</sup> (usual dose). You will receive this dose every day for 42 days (up to 49 days) in combination with radiotherapy. The Temodal dose may be delayed or stopped, depending on your blood counts and how you tolerate your medicine during the concomitant phase.

Once the radiotherapy is completed, you will interrupt treatment for 4 weeks. This will give your body a chance to recover.

Then, you will start the monotherapy phase.

During the monotherapy phase, the dose and way you receive Temodal in this phase will be different. Your doctor will work out your exact dose.

There may be up to 6 treatment periods (cycles). Each one lasts 28 days.

You will receive your new dose of Temodal alone once daily for the first 5 days of each cycle. The first dose will be 150 mg/m<sup>2</sup>. Then you will have 23 days without Temodal. This adds up to a 28-day treatment cycle.

After Day 28, the next cycle will begin. You will again receive Temodal once daily for 5 days followed by 23 days without Temodal.

The Temodal dose may be adjusted, delayed or stopped depending on your blood counts and how you tolerate your medicine during each treatment cycle.

*Patients with tumours that have returned or worsened (malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma) receiving Temodal only:*

A treatment cycle with Temodal lasts 28 days.

You will receive Temodal alone once daily for the first 5 days. This daily dose depends on whether or not you have received chemotherapy before.

If you have not been previously treated with chemotherapy, your first dose of Temodal will be 200 mg/m<sup>2</sup> once daily for the first 5 days. If you have been previously treated with chemotherapy, your first dose of Temodal will be 150 mg/m<sup>2</sup> once daily for the first 5 days.

Then, you will have 23 days without Temodal. This adds up to a 28 day treatment cycle.

After Day 28, the next cycle will begin. You will again receive Temodal once daily for 5 days, followed by 23 days without Temodal.

Before each new treatment cycle, your blood will be tested to see if the Temodal dose needs to be adjusted. Depending on your blood test results, your doctor may adjust your dose for the next cycle.

**How Temodal is given**

Temodal will be given to you by your doctor in a drip into a vein (intravenous infusion), only over approximately 90 minutes. No infusion site other than a vein is acceptable.

**If you use more Temodal than you should**

Your medicine is given to you by health care professionals. It is therefore unlikely that you will receive more Temodal than you should. However, if you do, the doctor or nurse will treat you accordingly.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

#### 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Contact your doctor **immediately** if you have any of the following:

- a severe allergic (hypersensitive) reaction (hives, wheezing or other breathing difficulty),
- uncontrolled bleeding,
- seizures (convulsions),
- fever,
- chills,
- severe headache that does not go away.

Temodal treatment can cause a reduction in certain kinds of blood cells. This may cause you to have increased bruising or bleeding, anaemia (a shortage of red blood cells), fever, and reduced resistance to infections. The reduction in blood cell counts is usually short-lived. In some cases, it may be prolonged and may lead to a very severe form of anaemia (aplastic anaemia). Your doctor will monitor your blood regularly for any changes, and will decide if any specific treatment is needed. In some cases, your Temodal dose will be reduced or treatment stopped.

Side effects from clinical studies:

##### Temodal powder for solution for infusion

In addition to the side effects listed below, the following may also occur with the use of Temodal powder for solution for infusion: pain, irritation, itching, warmth, swelling or redness at the injection site; also bruising (haematoma).

##### Temodal in combination treatment with radiotherapy in newly-diagnosed glioblastoma

Patients receiving Temodal in combination with radiotherapy may experience different side effects than patients using Temodal alone. The following side effects may occur, and may require medical attention.

**Very common (may affect more than 1 in 10 people):** loss of appetite, headache, constipation (difficulty passing stools), nausea (feeling sick in your stomach), vomiting, rash, hair loss, tiredness.

**Common (may affect up to 1 in 10 people):** oral infections, wound infection, reduced number of blood cells (neutropenia, thrombocytopenia, lymphopenia, leukopenia), increased sugar in the blood, loss of weight, change in mental status or alertness, anxiety/depression, sleepiness, difficulty speaking, impaired balance, dizziness, confusion, forgetfulness, difficulty concentrating, inability to fall asleep or stay asleep, tingling sensation, bruising, shaking, abnormal or blurry vision, double vision, hearing impairment, shortness of breath, cough, blood clot in the legs, fluid retention, swollen legs, diarrhoea, stomach or abdominal pain, heartburn, upset stomach, difficulty swallowing, dry mouth, skin irritation or redness, dry skin, itching, muscle weakness, painful joints, muscle aches and pains, frequent urination, difficulty with holding your urine, allergic reaction, fever, radiation injury, face swelling, pain, abnormal taste, abnormal liver function tests.

**Uncommon (may affect up to 1 in 100 people):** flu-like symptoms, red spots under the skin, low potassium level in the blood, weight gain, mood swings, hallucination and memory impairment, partial paralysis, impaired coordination, impaired sensations, partial loss of vision, dry or painful eyes, deafness, infection of the middle ear, ringing in the ears, earache, palpitations (when you can feel your heart beat), blood clot in the lung, high blood pressure, pneumonia, inflammation of your sinuses, bronchitis, a cold or the flu, swollen stomach, difficulty controlling your bowel movements, haemorrhoids, peeling skin, increased skin sensitivity to sunlight, change in skin colour, increased

sweating, muscle damage, back pain, difficulty in urinating, vaginal bleeding, sexual impotence, absent or heavy menstrual periods, vaginal irritation, breast pain, hot flushes, shivering, discolouration of your tongue, change in your sense of smell, thirst, tooth disorder.

*Temodal monotherapy in recurrent or progressive glioma*

The following side effects may occur, and may require medical attention.

**Very common (may affect more than 1 in 10 people):** reduced number of blood cells (neutropenia or lymphopenia, thrombocytopenia), loss of appetite, headache, vomiting, nausea (feeling sick in your stomach), constipation (difficulty passing stools), tiredness.

**Common (may affect up to 1 in 10 people):** loss of weight, sleepiness, dizziness, tingling sensation, shortness of breath, diarrhoea, abdominal pain, upset stomach, rash, itching, hair loss, fever, weakness, shivering, feeling unwell, pain, change in taste.

**Uncommon (may affect up to 1 in 100 people):** reduced blood cell counts (pancytopenia, anaemia, leukopenia).

**Rare (may affect up to 1 in 1,000 people):** cough, infections including pneumonia.

**Very rare (may affect up to 1 in 10,000 people):** skin redness, urticaria (hives), skin eruption, allergic reactions.

Other side effects:

Cases of elevations of liver enzymes have been commonly reported. Cases of increased bilirubin, problems with bile flow (cholestasis), hepatitis and injury to the liver, including fatal liver failure, have been uncommonly reported.

Very rare cases of severe rash with skin swelling, including on the palms of the hands and soles of the feet, or painful reddening of the skin and/or blisters on the body or in the mouth have been observed. Tell your doctor **immediately** if this occurs.

Very rare cases of lung side effects have been observed with Temodal. Patients usually present with shortness of breath and cough. Tell your doctor if you notice any of these symptoms.

In very rare cases, patients receiving Temodal and medicines like it may have a small risk of developing secondary cancers, including leukaemia.

New or reactivated (recurring) cytomegalovirus infections and reactivated hepatitis B virus infections have been uncommonly reported. Cases of brain infections caused by herpes virus (meningoencephalitis herpetic), including fatal cases, have been uncommonly reported. Cases of sepsis (when bacteria and their toxins circulate in the blood and start to damage the organs) have been uncommonly reported.

Cases of diabetes insipidus have been uncommonly reported. Symptoms of diabetes insipidus include passing a lot of urine and feeling thirsty.

**Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Temodal

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).

Once your medicine is prepared for infusion (reconstituted), the solution may be stored at room temperature (25°C) for up to 14 hours, including infusion time.

The reconstituted solution should not be used if discolouration or particulate matter is observed.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

### What Temodal contains

The active substance is temozolomide. Each vial contains 100 mg temozolomide. After reconstitution, each ml solution for infusion contains 2.5 mg of temozolomide.

The other ingredients are mannitol (E421), threonine, polysorbate 80, sodium citrate (for pH-adjustment) and hydrochloric acid concentrated (for pH-adjustment) (see section 2).

### What Temodal looks like and contents of the pack

The powder for solution for infusion is a white powder. Temodal is available in a glass vial, with a butyl rubber stopper and aluminium seal with a flip-off bonnet.

Each pack contains 1 vial of 100 mg temozolomide.

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**This leaflet was last revised in****Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>.

The following information is intended for medical or health care professional use only:

Caution must be exercised in handling Temodal 2.5 mg/ml powder for solution for infusion. The use of gloves and aseptic technique is required. If Temodal 2.5 mg/ml comes into contact with skin or mucosa, it should be washed immediately and thoroughly with soap and water.

Each vial must be reconstituted with 41 ml sterilised water for injections. The resulting solution contains 2.5 mg/ml TMZ. The vials should be gently swirled and not shaken. The solution should be inspected and any vial containing visible particulate matter should not be used. Reconstituted product must be used within 14 hours, including infusion time.

A volume up to 40 ml reconstituted solution should be withdrawn, according to the total prescribed dose and transferred into an empty 250 ml infusion bag (PVC or polyolefin). The pump tubing should be attached to the bag, the tubing purged and then capped. Temodal 2.5 mg/ml must be administered by intravenous infusion **only** over a period of 90 minutes.

Temodal 2.5 mg/ml powder for solution for infusion may be administered in the same IV line with 0.9% Sodium Chloride injection. It is incompatible with dextrose solutions. In absence of additional data this medicinal product must not be mixed with other medicinal products or infused simultaneously through the same intravenous line.

This medicinal product is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.