1. NAME OF THE MEDICINAL PRODUCT

Temodal® 5, 20, 100 or 250 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 5, 20, 100 or 250 mg temozolomide.

Excipient(s) with known effect:
Each Temodal 5 mg capsule contains 132.8 mg of anhydrous lactose.
Each Temodal 20 mg capsule contains 182.2 mg of anhydrous lactose
Each Temodal 100 mg capsule contains 175.7 mg of anhydrous lactose
Each Temodal 250 mg capsule contains 154.3 mg of anhydrous lactose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule.

Temodal 5 mg 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.
Temodal 20 mg 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.
Temodal 100 mg 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.
Temodal 250 mg 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 capsules are 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.
- Temodal capsules are also indicated as first line treatment for adult patients with advanced metastatic malignant melanoma.

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^2 daily for 42 days concomitant with focal radiotherapy (60 Gy administered in 30 fractions). No dose reductions are recommended, but delay or discontinuation of 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) ≥ 1.5 x 10^9/l
- thrombocyte count ≥ 100 x 10^9/l
- common toxicity criteria (CTC) non-haematological toxicity ≤ Grade 1 (except for alopecia, nausea and vomiting).

During treatment a complete blood count should be obtained weekly. 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.

Table 1. TMZ dosing interruption or discontinuation during concomitant radiotherapy and TMZ

Toxicity	TMZ interruption[a]	TMZ discontinuation
Absolute neutrophil count	≥ 0.5 and < 1.5 x 10^9/l	< 0.5 x 10^9/l
Thrombocyte count	≥ 10 and < 100 x 10^9/l	< 10 x 10^9/l
CTC non-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 ≥ 1.5 x 10^9/l; thrombocyte count ≥ 100 x 10^9/l; CTC non-haematological toxicity ≤ 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^2 once daily for 5 days followed by 23 days without treatment. At the start of Cycle 2, the dose is escalated to 200 mg/m^2 if the CTC non-haematological toxicity for Cycle 1 is Grade ≤ 2 (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is ≥ 1.5 x 10^9/l, and the thrombocyte count is ≥ 100 x 10^9/l. If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles. Once escalated, the dose remains at 200 mg/m^2 per day for the first 5 days of each subsequent cycle except if toxicity occurs. Dose reductions and discontinuations during the monotherapy phase should be applied according to Tables 2 and 3.

During treatment a complete blood count should be obtained on Day 22 (21 days after the first dose of TMZ). The dose should be reduced or administration discontinued according to Table 3.

Table 2. TMZ dose levels for monotherapy treatment		
Dose level	TMZ dose (mg/m^2/day)	Remarks
–1	100	Reduction for prior toxicity
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2-6 in absence of toxicity

Table 3. TMZ dose reduction or discontinuation during monotherapy treatment		
Toxicity	Reduce TMZ by 1 dose level[a]	Discontinue TMZ
Absolute neutrophil count	< 1.0 x 10^9/l	See footnote b
Thrombocyte count	< 50 x 10^9/l	See footnote b
CTC non-haematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4[b]

a: TMZ dose levels are listed in Table 2.
b: TMZ is to be discontinued if:

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

Adult and paediatric patients 3 years of age or older with recurrent or progressive malignant glioma (Recurrent glioblastoma multiforme or anaplastic astrocytoma):
A treatment cycle comprises 28 days. In patients previously untreated with chemotherapy, TMZ is administered orally at a dose of 200 mg/m^2 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^2 once daily, to be increased in the second cycle to 200 mg/m^2 once daily, providing the absolute neutrophil count (ANC) is ≥ 1.5 x 10^9/L and the platelet count is ≥ 100 x 10^9/L on Day 1 of the next cycle.

Dose modification for TEMODAL should be based on toxicities according to nadir ANC or platelet counts.

Adults: Metastatic malignant melanoma

For patients with metastatic malignant melanoma, the recommended dose is 200 mg/m^2 once daily for 5 days per 28-day cycle.

Paediatric patients: Recurrent glioblastoma multiforme or anaplastic astrocytoma

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

In patients with recurrent glioblastoma multiforme/anaplastic astrocytoma or metastatic melanoma, TEMODAL can be continued until disease progression or for a maximum of 2 years.

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 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).

Women who are pregnant, who intend to become pregnant or breast feeding women

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 ≤ 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 mg/m^2, 150 mg/m^2, and 200 mg/m^2. The lowest recommended dose is 100 mg/m^2.

Paediatric population

Anaplastic astrocytoma/Glioblastoma multiforme:
There is no clinical experience with use of TMZ in children under the age of 3 years. Experience in older children (over the age of 3 years) and adolescents with glioma is very limited (see sections 4.2 and 5.1).

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

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.

Female patients

Women of childbearing potential have to use effective contraception to avoid pregnancy while they are receiving TMZ, and for at least 6 months following completion of treatment.

Male patients

Men being treated with TMZ should be advised not to father a child for at least 3 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, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

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_{max} and a 9% decrease in area under the curve (AUC).
As it cannot be excluded that the change in C_{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^2 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 have to use effective contraception to avoid pregnancy while they are receiving TMZ, and for at least 6 months following completion of treatment.

Male fertility

TMZ can have genotoxic effects. Therefore, men being treated with it should use effective contraceptive measures and be advised not to father a child for at least 3 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

Summary of the safety profile

Clinical trial experience

In patients treated with TMZ in clinical trials, the most common adverse reactions were nausea, vomiting, constipation, anorexia, headache, fatigue, convulsions, and rash. Most haematologic adverse reactions were reported commonly; the frequency of Grade 3-4 laboratory findings is presented after Table 4.

For patients with recurrent or progressive glioma, nausea (43 %) and vomiting (36 %) 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 %.

Tabulated list of adverse reactions
Adverse reactions observed in clinical studies and reported from post-marketing use of TMZ are listed in Table 4. These reactions are classified according to System Organ Class and frequency. Frequency groupings are defined according to the following convention: Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥1/10,000 to <1/1,000); Very rare

(<1/10,000); Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 4. Adverse reactions in patients treated with temozolomide	
Infections and infestations	
Common:	Infections, herpes zoster, pharyngitis[a], candidiasis oral
Uncommon:	Opportunistic infection (including PCP), sepsis[†], meningoencephalitis herpetic[†], CMV infection, CMV reactivation, hepatitis B virus[†], herpes simplex, infection reactivation, wound infection, gastroenteritis[b]
Neoplasm benign, malignant, and unspecified	
Uncommon:	Myelodysplastic syndrome (MDS), secondary malignancies, including myeloid leukaemia
Blood and lymphatic system disorders	
Common:	Febrile neutropenia, neutropenia, thrombocytopenia, lymphopenia, leukopenia, anaemia
Uncommon:	Prolonged pancytopenia, aplastic anaemia[†], pancytopenia, petechiae
Immune system disorders	
Common:	Allergic reaction
Uncommon:	Anaphylaxis
Endocrine disorders	
Common:	Cushingoid[c]
Uncommon:	Diabetes insipidus
Metabolism and nutrition disorders	
Very common:	Anorexia
Common:	Hyperglycaemia
Uncommon:	Hypokalaemia, alkaline phosphatase increased
Psychiatric disorders	
Common:	Agitation, amnesia, depression, anxiety, confusion, insomnia
Uncommon:	Behaviour disorder, emotional lability, hallucination, apathy
Nervous system disorders	
Very common:	Convulsions, hemiparesis, aphasia/dysphasia, headache
Common:	Ataxia, balance impaired, cognition impaired, concentration impaired, consciousness decreased, dizziness, hypoesthesia, memory impaired, neurologic disorder, neuropathy[d], paraesthesia, somnolence, speech disorder, taste perversion, tremor
Uncommon:	Status epilepticus, hemiplegia, extrapyramidal disorder, parosmia, gait abnormality, hyperaesthesia, sensory disturbance, coordination abnormal
Eye disorders	
Common:	Hemianopia, vision blurred, vision disorder[e], visual field defect, diplopia, eye pain
Uncommon:	Visual acuity reduced, eyes dry

Table 4. Adverse reactions in patients treated with temozolomide	
Ear and labyrinth disorders	
Common:	Deafness[f], vertigo, tinnitus, earache[g]
Uncommon:	Hearing impairment, hyperacusis, otitis media
Cardiac disorders	
Uncommon:	Palpitation
Vascular disorders	
Common:	Haemorrhage, embolism pulmonary, deep vein thrombosis, hypertension
Uncommon:	Cerebral haemorrhage, flushing, hot flushes
Respiratory, thoracic and mediastinal disorders	
Common:	Pneumonia, dyspnoea, sinusitis, bronchitis, coughing, upper respiratory infection
Uncommon:	Respiratory failure[†], interstitial pneumonitis/pneumonitis, pulmonary fibrosis, nasal congestion
Gastrointestinal disorders	
Very common:	Diarrhoea, constipation, nausea, vomiting
Common:	Stomatitis, abdominal pain[h], dyspepsia, dysphagia
Uncommon:	Abdominal distension, faecal incontinence, gastrointestinal disorder, haemorrhoids, mouth dry
Hepatobiliary disorders	
Uncommon:	Hepatic failure[†], hepatic injury, hepatitis, cholestasis, hyperbilirubinemia
Skin and subcutaneous tissue disorders	
Very Common:	Rash, alopecia
Common:	Erythema, dry skin, pruritus
Uncommon:	Toxic epidermal necrolysis, Stevens-Johnson syndrome, angioedema, erythema multiforme, erythroderma, skin exfoliation, photosensitivity reaction, urticaria, exanthema, dermatitis, sweating increased, pigmentation abnormal
Not known:	Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders	
Common:	Myopathy, muscle weakness, arthralgia, back pain, musculoskeletal pain, myalgia
Renal and urinary disorders	
Common:	Micturition frequency, urinary incontinence
Uncommon:	Dysuria
Reproductive system and breast disorders	
Uncommon:	Vaginal haemorrhage, menorrhagia, amenorrhoea, vaginitis, breast pain, impotence
General disorders and administration site conditions	
Very common:	Fatigue
Common:	Fever, influenza-like symptoms, asthenia, malaise, pain, oedema, oedema peripheral[i]

Table 4. Adverse reactions in patients treated with temozolomide	
Uncommon:	Condition aggravated, rigors, face oedema, tongue discolouration, thirst, tooth disorder
Investigations	
Common:	Liver enzymes elevation[j], weight decreased, weight increased
Uncommon:	Gamma-glutamyltransferase increased
Injury, poisoning and procedural complications	
Common:	Radiation injury[k]

[a] Includes pharyngitis, nasopharyngeal pharyngitis, pharyngitis Streptococcal
[b] Includes gastroenteritis, gastroenteritis viral
[c] Includes cushingoid, Cushing syndrome
[d] Includes neuropathy, peripheral neuropathy, polyneuropathy, peripheral sensory neuropathy, peripheral motor neuropathy
[e] Includes visual impairment, eye disorder
[f] Includes deafness, deafness bilateral, deafness neurosensory, deafness unilateral
[g] Includes earache, ear discomfort
[h] Includes abdominal pain, abdominal pain lower, abdominal pain upper, abdominal discomfort
[i] Includes oedema peripheral, peripheral swelling
[j] Includes liver function test increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzymes increased
[k] Includes radiation injury, radiation skin injury
[†] Including cases with fatal outcome

Newly-diagnosed glioblastoma multiforme

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 (anaplastic astrocytoma, glioblastoma multiforme) or malignant melanoma

Laboratory results

In adult patients, myelosuppression was common with grade 3 or 4 thrombocytopenia and neutropenia observed in 19% and 17% of patients respectively treated for glioma and 20% and 22% respectively of patients with metastatic melanoma. This led to hospitalisation and/or discontinuation of TEMODAL in 8% and 4% respectively of patients with glioma and 3% and 1.3% respectively of those with melanoma. Myelosuppression was predictable (usually within the first few cycles, with the nadir between Day 21 and Day 28), and recovery was rapid, usually within 1-2 weeks. No evidence of cumulative myelosuppression was observed. Pancytopenia, leukopenia, and anaemia have also been reported. Lymphopenia has also been reported.
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 10^9/l), 12% *vs* 5%, and thrombocytopenia (< 20 x 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.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il

4.9 Overdose

Doses of 500, 750, 1,000, and 1,250 mg/m^2 (total dose per cycle over 5 days) have been evaluated clinically in patients. Dose-limiting toxicity was haematological and was reported 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^6 position of guanine with additional alkylation also occurring at the N^7 position. Cytotoxic lesions that develop subsequently are thought to involve aberrant repair of the methyl adduct.

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^2) once daily, starting the first day of RT until the last day of RT, for 42 days (with a maximum of 49 days). This was followed by monotherapy TMZ (150 - 200 mg/m^2) on Days 1 - 5 of every 28-day cycle for up to 6 cycles, starting 4 weeks after the end of RT. Patients in the control arm received RT only. *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis was required during RT and combined TMZ therapy. PCP prophylaxis was given regardless of lymphocyte count and was continued during RT/TMZ until lymph recovery to less than or equal to grade 1.

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).

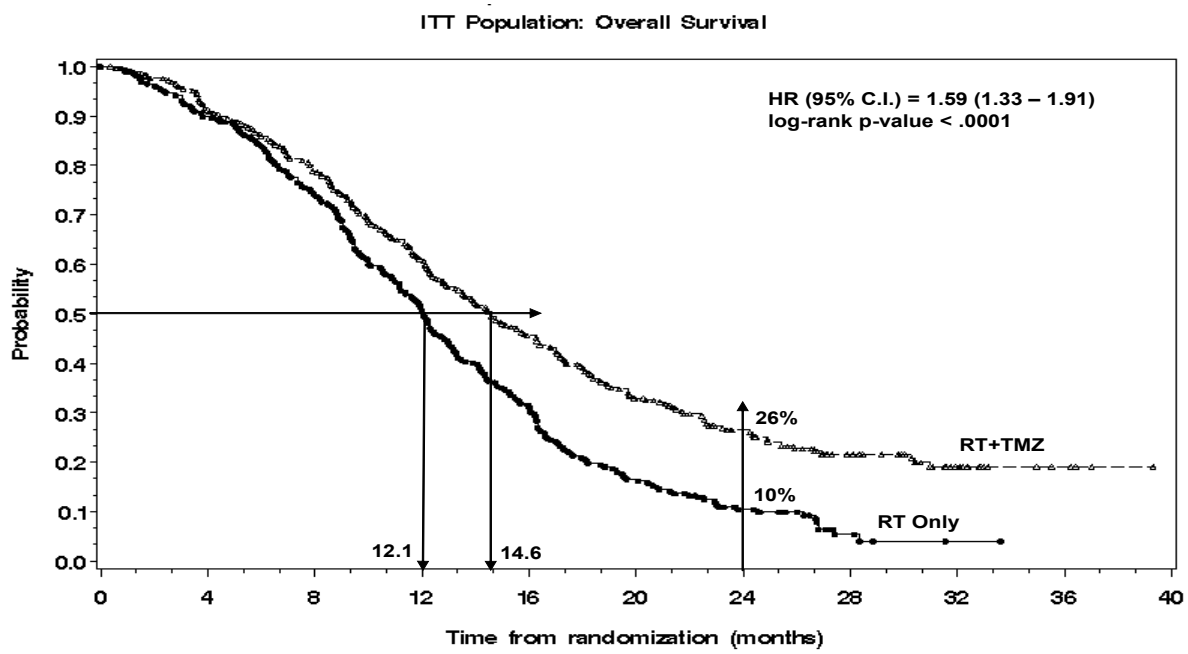

Figure 1 Kaplan-Meier curves for overall survival (intent-to-treat population)

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] ≥ 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 ≥ 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.

Metastatic Melanoma

The pivotal trial involving 305 adult patients with advanced metastatic melanoma at first presentation of metastatic disease was a large multicentre randomised phase III trial comparing the efficacy of TEMODAL (156 patients) with the standard treatment, dacarbazine (DTIC, 149 patients). Patients were balanced in regard to demographics and disease characteristics between the two treatment groups. Patients may not have had previous treatment for metastatic melanoma and may not have had brain metastases from melanoma. The primary endpoint was overall survival. Progression-free survival and response rate were secondary endpoints.

Median overall survival was longer for patients treated with TEMODAL compared to patients treated with DTIC (7.7 vs. 6.4 months respectively, p=0.2). Median progression-free survival was statistically significantly longer with TEMODAL compared to DTIC (1.9 months vs. 1.5 months respectively, p=0.012). The overall response rate was 13.5 % for TEMODAL and 12.1 % for DTIC.

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-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^6 and N^7 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.

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 ^{14}C-labelled TMZ, mean faecal excretion of ^{14}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}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^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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
anhydrous lactose,
sodium starch glycolate,
stearic acid,
tartaric acid,
colloidal anhydrous silica.

Capsule shell:
gelatin,
titanium dioxide,
sodium lauryl sulfate,
yellow iron oxide [for Temodal 5 and 20 mg],
FD & C Blue 2 [for Temodal 5 mg]
Red Iron oxide [for Temodal 100 mg]

Printing ink:
shellac,
anhydrous ethyl alcohol
isopropyl alcohol
n-butyl alcohol
propylene glycol,
purified water,
ammonium hydroxide,
potassium hydroxide,
black iron oxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaing material.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Sachet presentation

Sachets are composed of linear low density polyethylene (innermost layer), aluminium and polyethylene terephthalate.
Each sachet contains 1 capsule and is dispensed in a cardboard carton.
The carton contains 5 or 20 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. License numbers:
Temodal 5 mg: 120.28.30114
Temodal 20 mg: 120.29.30115
Temodal 100 mg: 120.30.30116
Temodal 250 mg: 120.31.30119

8. MANUFACTURER
Orion Corporation, Turko, Finland for Merck Sharp & Dohme Corp., NJ, USA

9. LICENSE HOLDER
Merck Sharp & Dohme (Israel – 1996) Company Ltd., P.O.Box 7121, Petah-Tikva 49170.

Revised in August 2021 according to MOHs guidelines.