AUSTRALIAN PRODUCT INFORMATION

TEMIZOLE 5/20/100/140/180/250

temozolomide capsules

1 NAME OF THE MEDICINE

Temozolomide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each TEMIZOLE capsule contains 5 mg, 20 mg, 100 mg, 140 mg, 180 mg or 250 mg of temozolomide as the active ingredient.

Excipients with known effect: contains sugars (as lactose).

For the full list of excipients, see section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

TEMIZOLE 5 mg: green and white hard capsules, printed in black ink with "TMZ" on the cap and "5" on the body.

TEMIZOLE 20 mg: yellow and white hard capsules, printed in black ink with "TMZ" on the cap and "20" on the body.

TEMIZOLE 100 mg: pink and white hard capsules, printed in black ink with "TMZ" on the cap and "100" on the body.

TEMIZOLE 140 mg: blue and white hard capsules, printed in black ink with "TMZ" on the cap and "140" on the body.

TEMIZOLE 180 mg: maroon and white hard capsules, printed in black ink with "TMZ" on the cap and "180" on the body.

TEMIZOLE 250 mg: white hard capsules, printed in black ink with "TMZ" on the cap and "250" on the body.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as adjuvant treatment.

Treatment of recurrence of anaplastic astrocytoma and glioblastoma multiforme following standard therapy.

TEMIZOLE is also indicated as a first-line treatment for patients with advanced metastatic malignant melanoma.

4.2 DOSE AND METHOD OF ADMINISTRATION

Antiemetic therapy may be administered prior to or following administration of temozolomide.

Temozolomide should be administered in the fasting state at least one hour before a meal. If vomiting occurs after the dose is administered, a second dose should not be administered that day. Temozolomide capsules must not be opened or chewed but are to be swallowed whole with a glass of water. If a capsule becomes damaged, avoid contact of the powder contents with skin or mucous membrane.

Adult Patients with Newly Diagnosed Glioblastoma Multiforme

Concomitant Phase

Temozolomide is administered orally at 75 mg/m^2 daily for 42 days concomitant with focal radiotherapy (60 Gy administered in 30 fractions) followed by adjuvant temozolomide for six cycles. No dose reductions are recommended; however, dose interruptions may occur based on patient tolerance. The temozolomide dose can be continued throughout the 42 day concomitant period up to 49 days (if needed due to radiotherapy interruption) if all of the following conditions are met: Absolute Neutrophil Count (ANC) greater than or equal to 1.5 x 10^9/L, thrombocyte count greater than or equal to 100 x 10^9/L, common toxicity criteria (CTC) non-haematological toxicity less than or equal to grade 1 (except for alopecia, nausea and vomiting). During treatment a complete blood count should be obtained weekly. Temozolomide dosing should be interrupted or discontinued during concomitant phase according to the haematological and non-haematological toxicity criteria as noted in Table 1.

Table 1: Temozolomide (TMZ) Dosing Interruption or Discontinuation During Concomitant Focal Radiotherapy and Temozolomide

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 could be continued when all the following conditions were met: absolute neutrophil count ≥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).

Adjuvant Phase

Four weeks after completing the temozolomide + radiotherapy phase, temozolomide is administered for an additional six cycles of adjuvant treatment. Dosage in cycle 1 (adjuvant) is 150 mg/m^2 once daily for five 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 less than or equal to 2 (except for alopecia, nausea and vomiting), ANC is greater than or equal to 1.5 x 10^9/L and the thrombocyte count is greater than or equal to 100 x 10^9/L. If the dose was not escalated at cycle 2, escalation should not be done in subsequent cycles. The dose remains at 200 mg/m^2 per day for the first five days of each subsequent cycle except if toxicity occurs. Dose reductions during the adjuvant phase should be applied according to Tables 2 and 3.

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

Table 2: Temozolomide Dose Levels for Adjuvant Treatment

Dose Level	Dose (mg/m^2/day)	Remarks
-1	100	Reduction for prior toxicity
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2-6 in absence of toxicity

Table 3: Temozolomide (TMZ) Dosing Interruption or Discontinuation During Adjuvant 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-haemotological toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4[b]

a TMZ dose levels are listed in Table 2.

b TMZ is to be discontinued if dose reduction to <100 mg/m^2 is required or if the same Grade 3 non-haematological toxicity (except for alopecia, nausea and vomiting) recurs after dose reduction; CTC = common toxicity criteria.

Adults with Recurrent Glioblastoma Multiforme or Anaplastic Astrocytoma

In recurrent adult patients previously untreated with chemotherapy, temozolomide is administered orally at a dose of 200 mg/m^2 once daily for five days per 28 day cycle. For those previously treated with chemotherapy, the initial dose is 150 mg/m^2 once daily, to be increased in the second cycle to 200 mg/m^2 daily providing the ANC is greater than or equal to 1.5 x 10^9/L and the platelet count is greater than or equal to 100 x 10^9/L on day 1 of the next cycle.

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

Adults with Metastatic Malignant Melanoma

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

Paediatric Patients with Recurrent Glioblastoma Multiforme or Anaplastic Astrocytoma

In patients 3 years of age or older, temozolomide is administered orally at a dose of 200 mg/m^2 once daily for five 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 five days, with escalation to 200 mg/m^2 once daily at the next cycle if there is no toxicity.

The efficacy of temozolomide for the treatment of recurrent glioblastoma multiforme in patients who received the drug as concomitant/adjuvant treatment has not been established.

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

4.3 CONTRAINDICATIONS

History of hypersensitivity reaction to components of temozolomide or to dacarbazine (DTIC).

Use during pregnancy and in women who intend to become pregnant (see section 4.6 Fertility, Pregnancy and Lactation – Use in Pregnancy).

Must not be used by breastfeeding women (see section 4.6 Fertility, Pregnancy and Lactation – Use in Lactation).

Severe myelosuppression.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Pneumocystis Carinii Pneumonia

Patients who received concomitant temozolomide and radiotherapy in a pilot trial for the prolonged 42 day schedule were shown to be at particular risk for developing *Pneumocystis carinii* pneumonia (PCP).

Thus, prophylaxis against PCP is required for all patients receiving concomitant temozolomide and radiotherapy for the 42 day regimen (with a maximum of 49 days) regardless of lymphocyte count. If lymphocytopenia occurs PCP prophylaxis should continue to a lymphocyte count less than or equal to grade 1.

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

Hepatotoxicity

Hepatic injury, including fatal hepatic failure, has been reported very rarely in patients treated with temozolomide. Baseline liver function tests should be performed prior to treatment initiation. If abnormal, physicians should assess the benefit/risk prior to initiating temozolomide including the potential for fatal

hepatic failure. For patients on a 42-day treatment cycle, liver function tests should be repeated midway through this cycle. For all 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.

HBV Reactivation

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

Antiemetic Therapy

Nausea and vomiting are very commonly associated with temozolomide and guidelines are provided as follows.

Patients with Newly Diagnosed Glioblastoma Multiforme

Antiemetic prophylaxis is recommended prior to the initial dose of concomitant temozolomide.

Antiemetic prophylaxis is strongly recommended during the adjuvant phase.

Patients with Recurrent Glioma

Patients who have experienced severe (grade 3 or 4) vomiting in previous treatment cycles may require antiemetic therapy.

Myelosuppression

Temozolomide causes myelosuppression. Patients treated with temozolomide may also experience prolonged pancytopenia. This may result in aplastic anaemia, which in some cases has resulted in a fatal outcome. In some cases, exposure to concomitant medications associated with aplastic anaemia, including carbamazepine, phenytoin and sulfamethoxazole/trimethoprim complicates assessment. Prior to dosing, the following laboratory parameters must be met: absolute neutrophil count (ANC) of $> 1.5 \times 10^9$/L and platelets of $> 100 \times 10^9$/L. During cyclical treatment a complete blood count must be obtained on day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until ANC is above 1.5×10^9/L and platelet count exceeds 100×10^9/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. Dose levels include 100, 150 and 200 mg/m^2. The lowest recommended dose is 100 mg/m^2.

All Patients

Keep this medication out of the reach of children.

Use in Hepatic Impairment

No data are available on the administration of temozolomide in patients with hepatic dysfunction. Based on the pharmacokinetic properties of temozolomide, it is unlikely that dose reductions are required in such patients. However, caution should be exercised when temozolomide is administered to these patients.

Use in Renal Impairment

No data are available on the administration of temozolomide in patients with renal dysfunction. Based on the pharmacokinetic properties of temozolomide, it is unlikely that dose reductions are required in such patients. However, caution should be exercised when temozolomide is administered to these patients.

Use in the Elderly

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

Paediatric Use

Anaplastic Astrocytoma/glioblastoma Multiforme

There is limited experience in children over the age of 3 years with glioma (see section 5.1 Pharmacodynamic Properties – Clinical Trials). There is no clinical experience with use of temozolomide in children under the age of 3 years.

Melanoma

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

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Administration of temozolomide with ranitidine did not result in clinically significant alterations in the extent of absorption of temozolomide. Co-administration of dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H_2-receptor antagonists or phenobarbital (phenobarbitone) did not alter the clearance of temozolomide. Co-administration with valproic acid was associated with a small but statistically significant decrease in clearance of temozolomide.

Use of temozolomide in combination with other alkylating agents or O^6-alkylguanine-DNA alkyltransferases may increase the likelihood of myelosuppression and general toxicity.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Temozolomide is contraindicated in women who intend to become pregnant, and effective contraception should be used in both male and female patients during and for a prolonged period after treatment with temozolomide (see section 4.3 Contraindications and section 4.6 Fertility, Pregnancy and Lactation).

Use in Men

Effective contraception should be used by male patients treated with temozolomide as it can have genotoxic effects. Therefore, men being treated with temozolomide are advised not to father a child and to seek advice on cryoconservation of spermatozoa prior to treatment because of the possibility of irreversible impairment in fertility due to therapy with temozolomide (see section 4.6 Fertility, Pregnancy and Lactation - Effects on Fertility and section 5.3 Preclinical Safety).

Use in Pregnancy

Pregnancy category: D

Cytotoxic agents can produce spontaneous abortion, fetal loss and birth defects. There are no studies in pregnant women. In nonclinical studies in rats and rabbits administered 50 mg/m^2, (associated with systemic exposure below that anticipated in humans) teratogenicity and/or fetal toxicity were demonstrated. Temozolomide, therefore, 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 fetus. Women of childbearing potential should be advised to avoid pregnancy if they are going to receive temozolomide treatment and for six months after discontinuation of therapy.

Use in Lactation

It is not known whether temozolomide is excreted in human milk. A peri/postnatal study in rats found that treatment with temozolomide at doses of greater than 25 mg/m^2/day decreased pup growth and retarded development. Given its potential adverse effects in the newborn, temozolomide must not be used by breastfeeding women.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Temozolomide may influence the ability to drive and use machines due to fatigue and somnolence (see section 4.8 Adverse Effects (Undesirable Effects)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Newly Diagnosed Glioblastoma Multiforme

See Table 4.

Table 4: Treatment Emergent Adverse Events with an Incidence of 2% or Greater Observed More Frequently in the Temozolomide (TMZ) Arm than the Focal Radiotherapy (RT) Arm During the Concomitant Phase, and Corresponding Adverse Events in the Adjuvant Phase

Adverse Events	Concomitant Phase		Adjuvant Phase
	RT alone concomitant n = 285 (%)	RT + TMZ concomitant n = 288 (%)	TMZ adjuvant therapy n = 224 (%)
Musculoskeletal and connective tissue disorders			
Muscle weakness	1	3	3
Arthralgia	1	2	6
Nervous system disorders			
Headache	17	19	23
Neuropathy	2	3	3
Aphasia	1	3	2
Concentration impaired	1	2	3
Paraesthesia	1	2	2
Balance impaired NOS	1	2	2
Consciousness decrease	< 1	2	< 1
Somnolence	< 1	2	2
General disorders and administration site conditions			
Fatigue	49	54	61
Radiation injury NOS	4	7	2
Fever	1	4	4
Allergic reaction	2	5	3
Taste perversion	2	6	5
Face oedema	1	3	1
Pain	1	2	2
Ear and labyrinth disorders			
Hearing impairment	1	3	4
Gastrointestinal disorders			
Nausea	16	36	49
Constipation	6	18	22
Dyspepsia	2	3	2
Diarrhoea	3	6	10
Stomatitis	5	7	9
Abdominal pain	1	2	5
Dysphagia	1	2	3
Vascular disorders			
Oedema legs	1	2	< 1
Haemorrhage NOS	< 1	2	2
Blood and lymphatic system			
Thrombocytopenia	1	4	8
Lymphopenia	0	2	1

Leucopenia	0	2	2
Neutropenia	0	2	3
Metabolism and nutrition disorders			
Anorexia	9	19	27
Vomiting	6	20	29
Hyperglycaemia	1	2	1
Weight decrease	< 1	2	3
Skin and subcutaneous tissue disorders			
Alopecia	63	69	55
Rash	15	19	13
Pruritis	1	4	5
Psychiatric disorders			
Insomnia	3	5	4
Respiratory, thoracic and mediastinal			
Dyspnoea	3	4	5
Coughing	1	5	8
Investigation			
ALT increased	2	4	2

Patients with Recurrent Anaplastic Astrocytoma, Glioblastoma Multiforme or Malignant Melanoma

The frequency of adverse drug reactions reported in clinical trials or spontaneously is listed below and classified according to body system. Frequency estimates: Very common (≥10 %), Common (≥1% and <10%).

Neurological

Very common: fatigue, headache.

Common: somnolence, asthenia, dizziness, paraesthesia.

Gastrointestinal

Very common: nausea, vomiting, constipation, anorexia.

Common: diarrhoea, abdominal pain, dyspepsia, taste perversion.

Haematological

Very common: thrombocytopenia, neutropenia.

Common: anaemia, leucopenia.

Dermatological

Common: rash, alopecia, pruritus, petechiae.

Respiratory

Common: dyspnoea.

General

Common: fever, pain, malaise, weight decrease, rigors.

In clinical trials, the most frequently occurring undesirable effects were gastrointestinal disturbances, specifically nausea (43%) and vomiting (36%). These effects were usually grade 1 or 2 (mild to moderate in severity) and were either self-limiting or readily controlled with standard antiemetic therapy. The incidence of severe nausea and vomiting was 4%. Severe myelosuppression, predominantly thrombocytopenia, was

dose limiting and occurred in 7% of all patients. Anaemia was reported in 5% of patients. Severe neutropenia and leucopenia occurred in 3 and 2% of patients, respectively.

In children, the incidence of the more common adverse events (nausea, vomiting, various CNS events and those of haematological origin) are consistent with the results from studies in adults as well as the underlying disease.

Myelosuppression

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 temozolomide in 8 and 4%, respectively, of patients with glioma and 3 and 1.3%, respectively, of those with melanoma. Myelosuppression was predictable (usually within the first few cycles, with the nadir between day 21 and 28), and recovery was rapid, usually within one to two weeks. No evidence of cumulative myelosuppression was observed. Pancytopenia, leucopenia and anaemia have also been reported. Lymphopenia has also been reported very commonly.

In a population pharmacokinetics analysis of clinical trial experience, there were 101 female and 169 male subjects for whom nadir neutrophil counts were available and 110 female and 174 male subjects for whom nadir platelet counts were available. There were higher rates of grade 4 neutropenia (ANC $< 0.5 \times 10^9$/L) (12 versus 5%) and thrombocytopenia ($< 20 \times 10^9$/L) (9 versus 3%), in women versus men in the first cycle of therapy. In a 400 subject recurrent glioma data set, grade 4 neutropenia occurred in 8% of female versus 4% of male subjects and grade 4 thrombocytopenia in 8% of female versus 3% of male subjects in the first cycle of therapy. In a study of 288 subjects with newly diagnosed glioblastoma multiforme, grade 4 neutropenia occurred in 3% of female versus 0% of male subjects and grade 4 thrombocytopenia in 1% of female versus 0% of male subjects in the first cycle of therapy.

In children the incidence of myelosupression was similar to that seen in adults. In the phase II clinical trial, the incidences of grade 4 thrombocytopenia and neutropenia were 16 and 11%, respectively. Myelosupression was usually transient and reversible with cessation of temozolomide treatment.

Post-marketing Experience with Temozolomide

During the marketing of temozolomide, allergic reactions, including anaphylaxis, have been reported very rarely. Very rare cases of erythema multiforme, toxic epidermal necrolysis and Stevens-Johnson syndrome have also been observed. There have been reported cases of hepatotoxicity including elevations of liver enzymes, hyperbilirubinaemia, cholestasis and hepatitis. Hepatic injury, including fatal hepatic failure, has been reported very rarely (see section 4.4 Special Warnings and Precautions for Use).

Rare cases of opportunistic infections including *Pneymocystis carinii* pneumonia (PCP) and both primary and reactivated cytomegalovirus (CMV) infection have been reported. Cases of reactivation of hepatitis B infections, including some cases with fatal outcomes have also been reported (see section 4.4 Special Warnings and Precautions for Use). Cases of herpes simplex encephalitis, including cases with fatal outcomes, have also been reported. Cases of sepsis have also been reported. Cases of interstitial pneumonitis/pneumonitis have been reported very rarely. Very rare cases of myelodysplastic syndrome (MDS) and secondary malignancies, including myeloid leukaemia, have been reported in patients treated with regimens that included temozolomide. Prolonged pancytopenia which may result in aplastic anaemia has been reported and in some cases resulted in a fatal outcome. Diabetes insipidus has also been reported.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Doses of 500, 750, 1,000 and 1,250 mg/m^2 (total dose per cycle over five days) have been evaluated clinically in patients. Dose limiting toxicity was haematological and was reported at any dose but is expected to be more severe at higher doses. An overdose of 2,000 mg per day for five days was taken by one patient and the adverse events reported were pancytopenia, pyrexia, multiorgan failure and death.

There are reports of patients who have taken more than five 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Temozolomide is an imidazotetrazine alkylating agent with anti-tumour activity. It undergoes rapid chemical conversion in the systemic circulation at physiological pH to the active compound, monomethyl triazeno imidazole carboxamide (MTIC). The cytotoxicity of MTIC is thought to be due primarily to alkylation at the O6 position of guanine with additional alkylation also occurring at the N7 position. Cytotoxic lesions that develop subsequently are thought to involve aberrant repair of the methyl adduct.

Single dose toxicity studies of temozolomide were conducted in mice, rats and dogs. Estimated LD50 doses by the oral route were moderately higher in the rat (approximately 1,900 mg/m^2) than in the mouse (approximately 1,000 mg/m^2). The minimum lethal dose in dogs was 600 mg/m^2. In the single dose studies, clinical signs of toxicity and death were generally delayed, reflecting a delayed toxicity to tissues that normally proliferate more rapidly resulting in general deterioration of organ function; toxicity is consistent with that expected of an alkylating agent.

Temozolomide is rapidly absorbed following oral administration. Systemic exposure at the therapeutic dose level in humans is similar to that of the rat and dog.

Single cycle (five-day dosing, 23 days nontreatment), three and six cycle toxicity studies were conducted in rats and dogs. In multiple cycle studies, the primary targets of toxicity included bone marrow, lymphoreticular system, testes and gastrointestinal tract with evidence of toxic effects on the lung, liver, kidney, thyroid gland, urinary bladder, CNS and retina. Temozolomide appears to be more toxic to rats and dogs than to humans, as the therapeutic dose regimen (200 mg/m^2), which has been well tolerated in humans, approximates the minimum lethal dose following multiple doses in both rats and dogs. At this dose level, the plasma area under the curve (AUC) for temozolomide in rats was similar to that anticipated in adult patients and about 60% of that in children; the corresponding value in dogs was about 65 and 40% of that in adult and paediatric patients, respectively. Dose related reductions in leucocytes and platelets appear to be sensitive indicators of toxicity in both rats and dogs. During intervals when dosing is discontinued, significant evidence of recovery from most haematological, biochemical and histopathological changes occurs. However, due to the delayed toxicity of temozolomide, patients should be closely monitored throughout the whole treatment cycle, including the nontreatment period.

Clinical Trials

<u>Newly Diagnosed Glioblastoma Multiforme</u>

573 patients were randomised to receive either temozolomide (TMZ) + focal radiotherapy (RT) (n = 287) or focal RT alone (n = 286). Patients in the temozolomide + RT arm received concomitant temozolomide (75 mg/m^2) once daily, starting the first day of RT until the last day of RT, for 42 days (with a maximum of 49 days). This was followed by adjuvant temozolomide (150 to 200 mg/m^2) on day 1 to 5 of every 28 day cycle

for six cycles, starting four weeks after the end of RT. Patients in the control arm received RT only. *Pneumocystis carinii* pneumonia (PCP) prophylaxis was required during RT and combined temozolomide therapy. 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.

The trial excluded patients below 18 years old and greater than 70 years old. Also excluded were patients with a World Health Organization (WHO) PS (performance status) greater than 2 and who had received prior chemotherapy or radiotherapy.

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

The hazard ratio (HR) for overall survival was 1.59 (95% confidence interval (CI) for HR = 1.33 to 1.91) with a log rank $p < 0.0001$ in favour of the temozolomide arm. The estimated probability of surviving two years or more (26 versus 10%) was higher for the RT + temozolomide arm. The addition of concomitant and adjuvant temozolomide to radiotherapy in the treatment of patients with newly diagnosed GBM demonstrated a statistically significant improved overall survival compared with radiotherapy alone (see Figure 1).

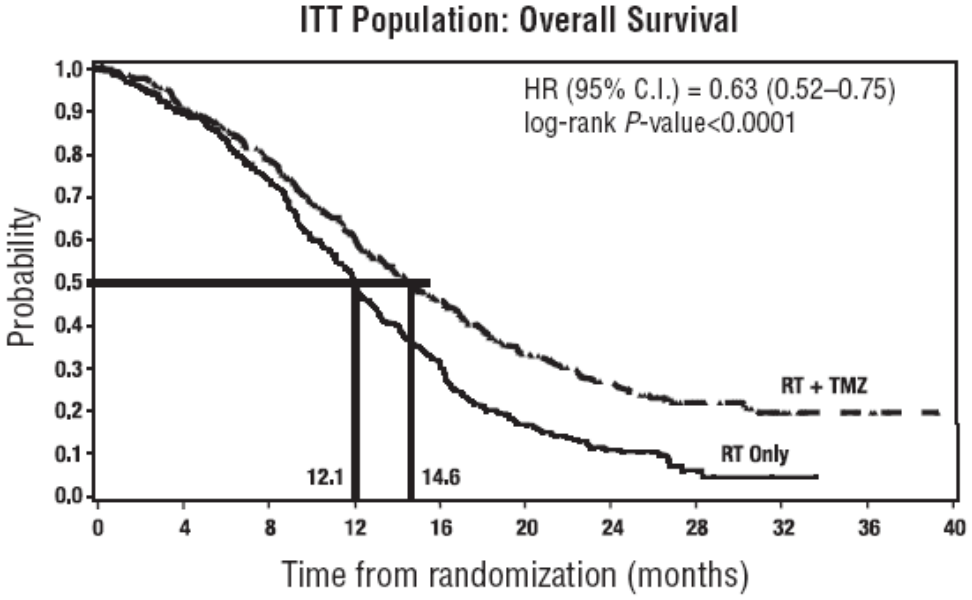


Figure 1: Kaplan-Meier curves for overall survival (ITT population).

Recurrent Glioblastoma Multiforme

Data on clinical efficacy in patients with glioblastoma multiforme (Karnofsky performance status (KPS) greater than or equal to 70), progressive or recurrent after surgery and radiotherapy, were based on two clinical trials. One was a noncomparative trial in 138 patients (29% received prior chemotherapy) and the other was a randomised reference controlled trial of temozolomide and procarbazine in a total of 120 patients (37.5% received prior treatment with nitrosourea based chemotherapy). In both trials, the primary endpoint was progression free survival (PFS) defined by magnetic resonance imaging (MRI) scans or neurological worsening. In the noncomparative trial, the PFS at six months was 19%, the median PFS was 2.1 months and the median overall survival was 5.4 months. The objective response rate based on MRI scans was 8%.

In the randomised trial, the six month PFS was significantly greater for temozolomide (20%, 95% CI: 9 to 30%) than for procarbazine (10%, 95% CI: 2 to 18%) with median PFS of 3.5 and 1.9 months, respectively (log rank, $p = 0.015$). The median survival was 7.7 and 6.1 months for temozolomide and procarbazine, respectively (log rank, p =0 .61). At six months the fraction of surviving patients was significantly higher in

the temozolomide arm (66%, 95% CI: 54 to 78%) compared with the procarbazine arm (51%, 95% CI: 38 to 64%). The study has later been completed (225 patients) and results reinforce those of the interim report.

Anaplastic Astrocytoma

In a multicentre, global, prospective phase II trial evaluating the safety and efficacy of temozolomide in the treatment of 162 adult patients with anaplastic astrocytoma at first relapse (60% received prior chemotherapy), the six month PFS was 46%. The median PFS was 5.4 months and 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 (ITT) population. Including 43 stable disease responses, the response rate was 61%. The six 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 PFS. 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 temozolomide (156 patients) with the standard treatment, dacarbazine (DTIC, 149 patients). Patients were balanced regarding 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. PFS and response rate were secondary endpoints.

Median overall survival was longer for patients treated with temozolomide compared to patients treated with DTIC (7.7 versus 6.4 months, respectively, $p = 0.2$). Median PFS was statistically significantly longer with temozolomide compared to DTIC (1.9 versus 1.5 months, respectively, $p = 0.012$). The overall response rate was 13.5% for temozolomide and 12.1% for DTIC.

Paediatric Patients

Temozolomide capsules have been studied in two open label phase II studies in paediatric patients with advanced recurrent CNS malignancies at a dose of 160 to 200 mg/m^2 daily for five days every 28 days. In a phase I trial, 29 patients with recurrent brainstem glioma and 34 patients with recurrent high-grade astrocytoma were enrolled. All patients had been previously treated with standard radiation therapy, while 50% of high-grade astrocytoma patients and 31% of brainstem glioma patients had previously received chemotherapy. The objective response rate, based on a central review of all subjects deemed to have eligible histologies, (16 brain stem glioma and 26 high grade astrocytoma subjects), was 0% for brain stem glioma subjects although 19% achieved stable disease; responses were documented in 12% of high grade astrocytoma subjects while 15% had stable disease. Based on investigator reviews, three patients with brain stem glioma had a partial response (10%) and an additional 14 patients had stable disease (48%). Eleven patients with high grade astrocytoma had a partial response (32%) and an additional seven patients had stable disease (21%). For all subjects, the median time to progression in the high-grade astrocytoma arm was 2.9 months and the median time to progression in the brain stem glioma arm was 2.8 months.

In the phase II open label study, 117/122 patients treated for various recurrent CNS malignancies were evaluable for efficacy with an overall response rate of 5%. Of 23 patients with high grade astrocytomas seven patients (19%) had stable disease after two cycles. Disease progressed thereafter (cycle 3, 4, 5, 6, 7, 8 and 9, respectively); however, one patient had a partial response. In 16 patients with brainstem gliomas, six had stable disease after two cycles, but disease progressed in all patients by the end of the fifth cycle, with no further response.

No clinical trials have been conducted in patients under 18 years of age with malignant melanoma.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

After oral administration to adult patients, temozolomide is absorbed rapidly with peak concentrations reached as early as 20 minutes post-dose (mean times between 0.5 and 1.5 hours). After oral administration of ^{14}C-labelled temozolomide, mean faecal excretion of ^{14}C over seven days postdose was 0.8% indicating complete absorption.

Administration of temozolomide with food resulted in a 33% decrease in C_{max}, an increase in T_{max} from about one to two hours and a 9% decrease in AUC. As it cannot be excluded that the change in C_{max} is clinically significant, temozolomide should not be administered with food.

Distribution

Preclinical data suggest that temozolomide crosses the blood brain barrier rapidly and is present in the cerebrospinal fluid. Plasma concentrations increase in a dose related manner. Temozolomide demonstrates low protein binding (10 to 20%), and thus is not expected to interact with highly protein bound agents.

Metabolism

The maximum tolerated dose (MTD) was 1,000 mg/m^2 per cycle both in children and in adults.

Plasma clearance, volume of distribution and half-life are independent of dose.

Excretion

Following oral administration approximately 5 to 10% of the dose is recovered unchanged in the urine over 24 hours, and the remainder excreted as AIC (4-amino-5-imidazole- carboxamide hydrochloride) or unidentified polar metabolites.

Pharmacokinetics in Special Populations

In relation to adults, analysis of population-based pharmacokinetics of temozolomide revealed that plasma clearance was independent of age, renal function, hepatic function or tobacco use.

Paediatric Patients

Among paediatric age groups 3 to 12 and > 12 to 16 years, dose normalised C_{max} and AUC value were the same. Similarly, clearance, volume of distribution and half-life were not different between the two paediatric age groups. Mean dose normalised AUC was approximately 30% higher in paediatric patients than in adult patients. Volume of distribution and clearance appeared lower in paediatric patients compared to adult patients. Terminal phase half-life was the same in adults and children.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Temozolomide was genotoxic in assays for gene mutations (*Salmonella typhimurium* and *Eschericia coli*) and chromosomal changes (human blood lymphocytes).

Pathological lesions of necrosis, degeneration, hypospermatogenesis and presence of syncytial cells and immature/abnormal spermatozoa in the testes, epididymis and seminal vesicles have been observed in the mouse, rat and dog at systemic exposure levels to temozolomide well within the anticipated human exposure. Decreased ovarian weight was noted in rats at temozolomide exposure comparable to that anticipated clinically. The reversibility of these changes has not been investigated, but no evidence of recovery was noted during the 23 day non-treatment period.

Carcinogenicity

No long-term carcinogenicity studies have been conducted, but evidence of carcinogenic potential of temozolomide was observed in the three and six cycle studies in rats. Neoplasms observed in the rat studies

included mammary carcinoma, keratoacanthoma of the skin, basal cell adenoma and a variety of mesenchymal neoplasms. These neoplasms occurred at systemic exposure to temozolomide less than that anticipated clinically. No tumours or preneoplastic changes were observed in the dog studies of up to six cycles. Considering that temozolomide is a prodrug of the alkylating agent MTIC, its tumorigenic potential is not unexpected and has been observed with other alkylating agents, including those producing MTIC.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The capsules also contain colloidal anhydrous silica, lactose, sodium starch glycollate, stearic acid and tartaric acid. The capsule shells contain gelatin, indigo carmine (5 mg and 140 mg only), iron oxide red (100 mg and 180 mg only), iron oxide yellow (5 mg, 20 mg and 180 mg only), purified water, sodium lauryl sulfate (250 mg only) and titanium dioxide. The ink present on the capsules is TekPrint SW-9008 Black Ink (Proprietary Ingredient: 2328).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Store in original container.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: bottle (glass type III coloured) with PP child resistant closure

Pack sizes: 5, 15

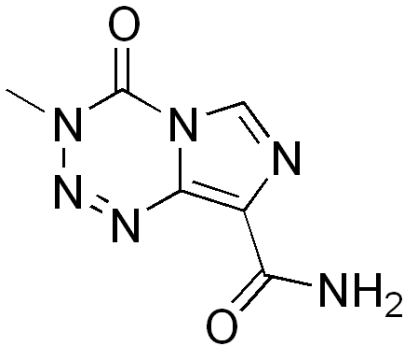
Some strengths, pack sizes and/or pack types may not be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



Temozolomide is a white to pale brown/pink, crystalline powder which is odourless or almost odourless and hygroscopic. It is slightly soluble in water (3.1 mg/mL), methanol (4.4 mg/mL) and ethanol (0.6 mg/mL).

Chemical name: 4-methyl-5-oxo- 2,3,4,6,8-pentazabicyclo [4.3.0] nona-2,7,9-triene- 9-carboxamide

Molecular formula: $C_6H_6N_6$

Molecular weight: 194.15

CAS Number

85622-93-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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www.mylan.com.au

Phone: 1800 314 527

9 DATE OF FIRST APPROVAL

19/07/2011

10 DATE OF REVISION

20/07/2020

Summary Table of Changes

Section Changed	Summary of New Information
All	Reformat of PI to align to TGA's Form for Providing Product Information
2; 3; 4.2; 4.3; 4.4; 4.6; 4.8; 5.1; 5.2; 5.3; 6.1; 6.4; 6.5; 6.7; 9	Editorial changes
4.5; 6.1	Update to ingredient names for international harmonisation
8	Update to sponsor information following transfer
4.4; 4.8	Inclusion of information relating to hepatotoxicity
4.4; 4.8	Inclusion of information relating to hepatitis B virus reactivation
4.6	Update to pregnancy warning
4.7	Update to ability to drive, use of machinery information
4.8	Inclusion of information relating to the following AEs: *pneumocystis carinii* pneumonia, cytomegalovirus, herpes simplex encephalitis, sepsis, diabetes insipidus

temizole_pi\Jul20/01