New Zealand Data Sheet

1. PRODUCT NAME

Temaccord Capsules

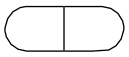
2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Temozolomide 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, 250 mg Capsules.

Excipient(s) with known effect

Temaccord capsules contain lactose. For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Strength (mg/cap)	Visual	Product Description	Capsule Size	Capsule Dimensions (mm)
5 mg		Green/White hard gelatin capsules, size '3' imprinted 'TMZ' on cap and '5' on body, containing white to light pink powder.	Size 3	approx 15.8 ± 0.4
20 mg		Yellow/White hard gelatin capsules, size '5' imprinted 'TMZ' on cap and '20' on body, containing white to light pink powder.	Size 5	approx 11.4± 0.4
100 mg		Pink/White hard gelatin capsules, size '3' imprinted 'TMZ' on cap and '100' on body, containing white to light pink powder.	Size 3	approx 15.8 ± 0.4
140 mg		Transparent Blue/White hard gelatin capsules, size '1' imprinted 'TMZ' on cap and '140' on body, containing white to light pink powder.	Size 1	approx 19.3± 0.4
180 mg		Maroon /White hard gelatin capsules, size '1' imprinted 'TMZ' on cap and '180' on body, containing white to light pink powder.	Size 1	approx 19.3± 0.4
250 mg		White/White hard gelatin capsules, size '0' imprinted 'TMZ' on cap and '250' on body, containing white to light pink powder.	Size 0	approx 21.4 ± 0.4

Temaccord 5 mg capsule is larger than Temaccord 20 mg capsule.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Temaccord capsules are indicated for the treatment of

- patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as adjuvant treatment.
- patients with recurrent high grade glioma, such as glioblastoma multiforme or anaplastic astrocytoma.

Temaccord capsules are also indicated as first line treatment for patients with advanced metastatic malignant melanoma.

4.2. Dose and method of administration

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

Dose

Adults: Newly diagnosed glioblastoma multiforme

Concomitant phase

Concomitant phase consists of temozolomide administered orally at 75mg/m^2 daily for 42 days with focal radiotherapy (60 Gy administered in 30 fractions). The concomitant phase is followed by the adjuvant phase [temozolomide for 6 cycles.]

Dose reductions are not 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 ≥ 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 concomitant treatment a complete blood count should be obtained weekly.

Temozolomide (TMZ) 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 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 of the following conditions were met: absolute neutrophil count ≥ 1.5x10^9 / L; thrombocyte count ≥100 x 10^9 / L; CTC non-haematological toxicity ≤ Grade 1 (except for alopecia, nausea, vomiting). TMZ= Temozolomide; CTC = Common Toxicity Criteria.		

Adjuvant Phase

Four weeks after completing the temozolomide capsules + Radiotherapy phase, temozolomide capsule is administered for an additional 6 cycles of adjuvant treatment. Dosage in Cycle 1 (adjuvant) is 150mg/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 ≥ 1.5x 10^9 /L, and the thrombocyte count is ≥ 100x 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 5 days of each subsequent cycle except if toxicity occurs. During treatment a complete blood count should be obtained on day 22 (21 days after the first dose of temozolomide capsules). The temozolomide capsule dose should be reduced or discontinued according to Table 3. Dose reductions during the adjuvant phase should be applied according to Tables 2 and 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 Dose Reduction or Discontinuation During Adjuvant Treatment

Toxicity	**Reduce TMZ by 1 Dose Level[a]**	**Discontinue TMZ**
Absolute Neutrophil Count	< 1.0 x 10^9/L	See footnote b
Thrombocyte Count	< 50 x 10^9/L	See footnote b
CTC Non-haematological Toxicity (except for alopecia, nausea, v omiting)	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, vomiting) recurs after dose reduction. TMZ+ Temozolomide, CTC= Common Toxicity Criteria.		

Adults: Recurrent glioblastoma multiforme, anaplastic astrocytoma or malignant melanoma

In patients previously untreated with chemotherapy, temozolomide capsules are administered orally at a dose of 200 mg/m^2 once daily for 5 days per 28-day cycle. In patients previously treated with chemotherapy, the initial dose is 150 mg/m^2 once daily, to be increased in the second cycle to 200 mg/m^2 daily providing the absolute neutrophil count (ANC) is ≥1.5 x 10^9/L and the thrombocyte count is ≥100 x 10^9/L on Day 1 of the next cycle.
Dose modifications for temozolomide capsules should be based on toxicities according to nadir ANC or platelet counts.

Children

In patients 3 years of age and older, temozolomide capsules are 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 cranio-spinal 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 toxicity.

Laboratory Parameters for dose modification in recurrent or progressive malignant glioma or malignant melanoma

Prior to dosing, the following laboratory parameters must be met: absolute neutrophil count (ANC) ≥1.5 x 10^9/L and platelets ≥100 x 10^9/L. During cyclical treatment a complete blood count must be obtained on Day 22 (21days after the first dose) or within 48 hours of that day, and weekly until ANC is above 1.5x109/L and platelet count exceeds 100 x 10^9/L. If ANC falls to <1.0 x 10^9/L or the platelet count is <50 x 10^9/L during any cycle, the next cycle should be reduced one dose level. Dose levels include 100 mg/m^2, 150 mg/m^2 and 200 mg/m^2. The lowest recommended dose is 100 mg/m^2.

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, temozolomide capsules can be continued until disease progression or for a maximum of 2 years.

Method of Administration

Temaccord 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.

4.3. Contraindications

Temaccord capsules are contraindicated in patients who have a history of hypersensitivity reaction to temozolomide, its components or to dacarbazine (DTIC).
Temaccord capsules are contraindicated for use during pregnancy (see Section 4.6).

Temaccord capsules must not be used by breastfeeding women (see Section 4.6).
Temaccord capsules are contraindicated in patients with severe myelosuppression.

4.4. Special warnings and precautions for use

Opportunistic infections and reactivation of infections

Opportunistic infections (such as Pneumocystitis jirovecii [previously Pneumocystis carinii] pneumonia) and reactivation of infections (such as HBV, CMV) have been observed during treatment with temozolomide (See section 4.8).

Patients who received concomitant temozolomide capsules and radiotherapy 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 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. Cases of fatal respiratory failure have been reported in patients using temozolomide, in particular in combination with dexamethasone or other steroids.

Meningoencephalitis herpetic

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

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. 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 reactivationduring and for several months following treatment with Temaccord. Therapy should be discontinued for patients with evidence of active hepatitis B infection.

Hepatotoxicity

Hepatic injury, including fatal hepatic failure, has been reported in patients treated with temozolomide (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).

Antiemetic therapy

Nausea and vomiting are very commonly associated with temozolomide, and anti-emetic therapy may be administered prior to or following administration

Patients with newly diagnosed glioblastoma multiforme

- anti-emetic prophylaxis is recommended prior to the initial dose of concomitant temozolomide capsules
- anti-emetic 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 anti-emetic 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: ANC ≥ 1.5 x 10^9/l and platelet count ≥ 100 x 10^9/l. A complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until ANC > 1.5 x 10^9/l and platelet count > 100 x 10^9/l. If ANC falls to < 1.0 x 10^9/l or the platelet count is < 50 x 10^9/l during any cycle, the next cycle should be reduced one dose level (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.

All Patients

Keep this medication out of the reach of children.

Use in Patients with Hepatic or Renal Dysfunction

No data are available on the administration of temozolomide in patients with hepatic or renal dysfunction.

Based on the pharmacokinetic properties of temozolomide, it is unlikely that dose reductions are required in patients with severe hepatic or renal dysfunction. However, caution should be exercised when temozolomide is administered in these patients.

Use in children

There is no clinical experience with the use of temozolomide in children under the age of 3 years with glioblastoma multiforme. There is limited experience in children over the age of 3 years with glioma.

Melanoma

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

Use in Elderly Patients

Elderly patients (>70 years of age) appear to be at increased risk of neutropenia and thombocytopenia, compared with younger patients. Therefore, special care should be taken when temozolomide is administered in elderly patients.

Male patients

Men being treated with temozolomide 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

The capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take them (See Section 6.1).

4.5. Interaction with other medicines and other forms of interaction

Administration of temozolomide capsules 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 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 capsules in combination with other myelosuppressive agents may increase the likelihood of myelosuppression.

No studies have been conducted to determine the effect of temozolomide on the metabolism or elimination of other medicinal products. However, since temozolomide 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).

Administration of temozolomide 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, Temaccord should be administered without food (See section 4.2).

4.6. Fertility, pregnancy and lactation

Use in Pregnancy

(Category D)
Cytotoxic agents can produce spontaneous abortion, foetal loss and birth defects. There are no studies in pregnant women. In preclinical studies in rats and rabbits administered 150 mg/m2 , (associated with systemic exposure below that anticipated in humans) teratogenicity and/or foetal toxicity were demonstrated. Temaccord, 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 foetus. Women of childbearing potential should be advised to avoid pregnancy if they are going to receive Temaccord treatment and for 6 months after discontinuation of Temaccord therapy. Temaccord capsules are contraindicated in women who intend to become pregnant, and effective contraception should be used in female patients during and for at least 6 months after treatment with temozolomide (see Section 4.3).

Breast-feeding

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

Fertility

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.

Use in men

Effective contraception should be used by male patients treated with Temaccord. Temozolomide can have genotoxic effects. Therefore, men being treated with Temaccord are advised not to father a child for at least 3 months after receiving the final dose and to seek advice on cryoconservation of spermatozoa prior to treatment because of the possibility of irreversible impairment in fertility due to therapy with Temaccord. Semen donation is also not advised during treatment and for at least 3 months after the final dose.

4.7. Effects on ability to drive and use machines

The ability to drive and use machinery may be impaired in patients treated with Temaccord capsules due to fatigue and somnolence.

4.8. Undesirable effects

Newly diagnosed glioblastoma multiforme

Table 4: Treatment Emergent Adverse Events with an incidence of 2% or greater observed more frequently in the TMZ arm than the RT arm during the concomitant phase and corresponding adverse events in the adjuvant phase.

Table 4	Concomitant phase		Adjuvant phase
Adverse event	**Radiotherapy 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 neuropathy	17	19	23
aphasia	2	3	3
concentration impaired	1	3	2
paresthesia	1	2	3
balance impaired NOS	1	2	2
consciousness decrease	1	2	2
somnolence	<1	2	<1
	<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	2
haemorrhage NOS	<1	2	3
Renal and urinary disorders			
micturition frequency	1	2	<1
urinary incontinence	1	2	2
Blood and the 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
weight decrease	<1	2	3
hyperglycaemia	1	2	1
Skin and subcutaneous tissue disorders			
alopecia	63	69	55
rash	15	19	13
pruritus	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

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

Adverse Effects in patients with recurrent anaplastic astrocytoma, glioblastoma multiforme or malignant melanoma Very Common (≥10%); Common (≥1% and <10%)	
Neurological Very common Common	 Fatigue, headache Somnolence, asthenia, dizziness, paraesthesia
Gastrointestinal Very common Common	 Nausea, vomiting, constipation, anorexia Diarrhoea, abdominal pain, dyspepsia, taste perversion
Haematological Very Common Common	 Thrombocytopenia, neutropenia Anemia, 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 (42%) and vomiting (35%). These effects were usually Grade 1 or 2 (mild to moderate in severity) and were either self-limiting or readily controlled with standard anti-emetic therapy. The incidence of severe nausea and vomiting was 4%. There is no information on the risk of second malignancies. 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 haematologic origin) are consistent with the results from studies in adults as well as the underlying disease.

Laboratory Results

In adult patients, myelosuppression was common with Grade 3 or 4 thrombocytopenia and neutropenia occurred 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 1-2 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 <500 cells/µL), 12% versus 5%, and thrombocytopenia (<20,000 cells/µL), 9% versus 3%, in women vs. men in the first cycle of therapy. In a 400-subject recurrent glioma data set, Grade 4 neutropenia occurred in 8% of female versus 4% of male subjects and Grade 4 thrombocytopenia in 8% of female 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.

In children the incidence of myelosuppression 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. Myelosuppression was usually transient and reversible with cessation of temozolomide treatment.

Post-Marketing experience with temozolomide

During the marketing of temozolomide capsules, 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 reported. There have been reported cases of hepatotoxicity including elevations of liver enzymes, hyperbilirubinaemia, cholestasis and hepatitis.

Rarely, cases of opportunistic infections including *Pneumocystis* jirovecii pneumonia (PCP) and both primary and reactivated cytomegalovirus (CMV) infection have been reported. Cases of herpes simplex encephalitis, including fatal cases, have been reported. Cases of sepsis have also been reported. Cases of interstitial pneumonitis/pneumonitis and pulmonary fibrosis have been reported very rarely.

Very rare cases of myelodysplastic syndrome (MDS) and secondary malignancies, including myeloid leukaemia, have been reported in patients treated with regimens that included temozolomide. Prolonged pancytopenia, which may result in aplastic anaemia has been reported very rarely, in some cases with a fatal outcome. Diabetes insipidus has also been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected reactions https://pophealth.my.site.com/carmreportnz/s/}

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 at any dose but is expected to be more severe at higher doses. An overdose of 2,000 mg per day for 5 days was taken by one patient and the adverse events reported were pancytopenia, pyrexia, multi-organ failure and death. There are reports of patients who have taken more than 5 days of treatment (up to 64 days) with adverse events reported including bone marrow suppression, with or without infection, in some cases severe and prolonged and resulting in death. In the event of an overdose, haematologic evaluation is needed. Supportive measures should be provided as necessary.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents; ATC code: L01A X03

Mechanism of action

Temozolomide is an imidazotetrazine alkylating agent with antitumour 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 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 trials

Newly diagnosed Glioblastoma Multiforme

Five hundred and seventy-three patients were randomized 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 - 200 mg/m^2) on day 1 -5 of every 28-day cycle for 6 cycles, starting 4 weeks after the end of RT. Patients in the control arm received RT only. *Pneumocysitis* jirovecii pneumonia (PCP) prophylaxis was required during RT and combined temozolomide therapy regardless of lymphocyte count. If lymphocytopenia occurred, PCP prophylaxis continued during RT/TMZ until lymph recovery to a lymphocyte count less than or equal to grade 1.

The trial excluded patients below 18 yrs old and greater than 70 yrs old and those with a 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 % CI for HR=1.33-1.91) with a log-rank p <0.0001 in favor of the temozolomide arm. The estimated probability of surviving 2 years or more (26 % vs 10 %) 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. (Figure 1)

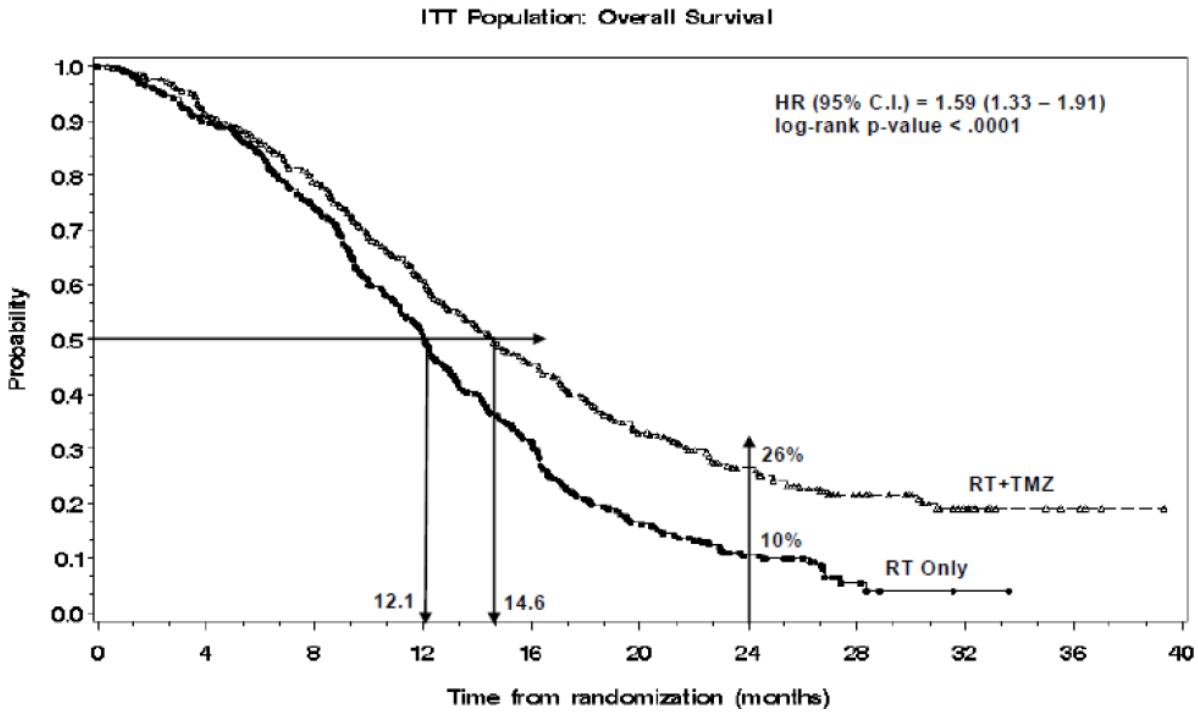


Figure 1 Kaplan-Meier Curves for Overall Survival (ITT Population; at time of randomisation; RT alone group = 286 and RT/TMZ = 287)

Recurrent Glioblastoma multiforme

Data on clinical efficacy in patients with glioblastoma multiforme (Karnofsky performance status [KPS] ≥70), progressive or recurrent after surgery and radiotherapy, were based on two clinical trials. One was a non-comparative trial in 138 patients (29% received prior chemotherapy) and the other was a randomised reference controlled trial of temozolomide and procarbazine in a total of 120 patients (37.5% 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 noncomparative trial, the PFS at 6 months was 19%, the median

progression-free survival 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 6 month PFS was significantly greater for temozolomide (20%, 95% confidence interval, CI: 9-30%) than for procarbazine (10%, 95% CI: 2-18%) 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 6 months the fraction of surviving patients was significantly higher in the temozolomide arm (66%, 95% CI: 54-78%) compared with the procarbazine arm (51%, 95% CI: 38-64%).

The study has 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 patients with anaplastic astrocytoma at first relapse (60% received prior chemotherapy), the 6 month progression-free survival was 46%. The median progression-free survival 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 6-month event-free survival for the ITT population was 44% with a median event-free survival of 4.6 months, which was similar to the results for the progression-free survival. For the eligible histology population, the efficacy results were similar. Achieving a radiologic objective response or maintaining progression-free status was strongly associated with maintained or improved quality of life.

Metastatic melanoma

The pivotal trial involving 305 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 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 temozolomide 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 temozolomide compared to DTIC (1.9 months vs. 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/m2 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

Preclinical data suggest that temozolomide crosses the blood-brain barrier rapidly and is present in the cerebrospinal fluid. 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). Plasma concentrations increase in a dose-related manner. Plasma clearance, volume of distribution and half-life are independent of dose. Temozolomide demonstrates low protein binding (10% to 20%), and thus is not expected to interact with highly protein bound agents. After oral administration of ^{14}C-labelled temozolomide, mean faecal excretion of ^{14}C over 7 days post-dose was 0.8% indicating complete absorption. Following oral administration approximately 5% to 10% of the dose is recovered unchanged in the urine over 24 hours, and the remainder excreted as AIC (4-amino-5-imdazole-carboxamide hydrochloride) or unidentified polar metabolites. The bioavailability of temozolomide is approximately 100%.

Administration of temozolomide with food resulted in a 33% decrease in C_{max} and a 9% decrease in AUC. As it cannot be excluded that the change in C_{max} is clinically significant, Temaccord should not be administered with food.

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

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

Toxicology

Single-dose toxicity studies of temozolomide were conducted in mice, rats and dogs. Estimated LD_{50} doses by the oral route were moderately higher in the rat (approximately 1900 mg/m^2) than in the mouse (approximately 1000 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 (5-day dosing, 23 days non-treatment), 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, central nervous system (CNS) and retina. Temozolomide appears to be more toxic to the rat and dog 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 leukocytes and platelets appear to be sensitive indicators of toxicity in both rats and dogs. During intervals when dosing is discontinued, significant evidence of recovery from most 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.

Carcinogenicity

No long term carcinogenicity studies have been conducted, but evidence of **the** 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 tumourigenic potential is not unexpected and has been observed with other alkylating agents, including those producing MTIC.

Mutagenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

The inactive ingredients are anhydrous lactose, sodium starch glycollate Type A, stearic acid, tartaric acid and colloidal anhydrous silica in a gelatin capsule shell.

Temaccord capsule shells contain titanium dioxide (E171) and gelatin, and are imprinted with TekPrint SW-9008 Black Ink.

Temaccord 5 mg capsule shells also contain iron oxide Yellow (E172) and FD&C Blue 2 (E132).
Temaccord 20 mg capsule shells also contain iron oxide Yellow (E172).
Temaccord 100 mg capsule shells also contain iron oxide Red (E172).
Temaccord 140 mg capsule shells also contain FD&C Blue 2 (E132).
Temaccord 180 mg capsule shells also contain iron oxide Red (E172) and iron oxide Yellow (E172).

Allergen statement: Contains lactose, sugars and sulfites. Gluten free.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at or below 25°C. Keep in a dry place.

6.5. Nature and contents of container

Temaccord capsules are presented in Amber glass bottles containing 5 or 20 capsules or sachet packs containing 5 or 20 capsules individually sealed in sachets.

Not all strengths or pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Do not open the capsules. If a capsule becomes damaged, avoid contact of the powder contents with skin or mucous membrane.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

Douglas Pharmaceuticals Ltd
P O Box 45 027
Auckland 0651
New Zealand
Phone: (09) 835 0660

9. DATE OF FIRST APPROVAL

28 October 2010

10. DATE OF REVISION OF THE TEXT

26 February 2025

Summary table of changes

Section Changed	Summary of new information
Various	Use of SI nomenclature for active and editorial/spelling corrections
4.4	Revised name of Pneumocystitis carinii to Pneumocystitis jirovecii, addition of information on meningoencephalitis herpetic, HBV, hepatoxicity, malignancies, Laboratory parameters, use in males and lactose
4.5	Addition of information on lack metabolism interactions and information on food effect.
4.6	Revised Use in pregnancy information to match the innovator.
4.8	Information on use in children, revised name of Pneumocystitis carinii to Pneumocystitis jirovecii, added further information on pancytopenia and diabetes insipidus. Revised website for AE reporting
5.1	Added information on clinical trials in children
5.2	Added information on pharmacokinetics in children
5.3	Updated information on toxicity in rats and dogs
6.1	Added allergen statement.