New Zealand Data Sheet

1. PRODUCT NAME

Temaccord Capsules

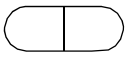
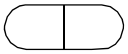
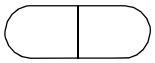
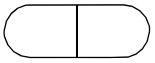
2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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-haemotological toxicity ≤ Grade 1 (except for alopecia, nausea and vomiting). During concomitant 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 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 capsules 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 capsule is administered orally at a dose of 200 mg/m^2 once daily for 5 days per 28-day cycle. In patients previously treated with chemotherapy, the initial dose is 150 mg/m^2 once daily, to be increased in the second cycle to 200 mg/m^2 daily providing the absolute neutrophil count (ANC) is ≥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 capsule 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 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 haematologic toxicity.

Laboratory Parameters for does 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/Land 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, thenext 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

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 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.

Antiemetic therapy

Nausea and vomiting are very commonly associated with Temozolomide and guidelines are provided:

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.

All Patients

Keep this medication out of the reach of children.

Use in Patients with Hepatic or Renal Dysfunction

The pharmacokinetics of temozolomide were comparable in patients with normal hepatic function and in those with mild or moderate hepatic dysfunction. No data are available on the administration of Temozolomide in patients with severe hepatic dysfunction (Child's Class III) or with 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.
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.

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.

4.6. Fertility, pregnancy and lactation

Pregnancy

Temaccord capsules are 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).

There are no studies in pregnant women. In preclinical studies in rats and rabbits administered 150 mg/m2, teratogenicity and/or foetal toxicity were demonstrated. Temozolomide capsules, 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 while they are receiving Temozolomide and for the 6 months after discontinuation of Temozolomide therapy.

Breast-feeding

It is not known whether temozolomide is excreted in human milk; thus, 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 Temozolomide. Temozolomide 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 infertility due to therapy with temozolomide (see Section 5.3).

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 rash pruritus	 63 15 1	 69 19 4	 55 13 5
Psychiatric disorders insomnia	 3	 5	 4
Respiratory, thoracic and mediastinal dyspnoea coughing	 3 1	 4 5	 5 8
Investigation SGPT 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, paresthesia
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.

Laboratory Results

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.

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 carinii* pneumonia (PCP) have been reported. Cases of herpes simplex encephalitis, including fatal cases, have been reported. Cases of interstitial pneumonitis/pneumonitis have been reported very rarely.

Very rare cases of myelodysplastic syndrome (MDS) and secondary malignancies, including myeloidleukaemia, have been reported in patients treated with regimens that included Temozolomide. Prolonged pancytopenia, which may result in aplastic anaemia has been reported very rarely.

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://nzphvc.otago.ac.nz/reporting/

4.9. Overdose

Doses of 500, 750, 1,000, and 1,250 mg/m2 (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 aberrantrepair 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 carinii* 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 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)

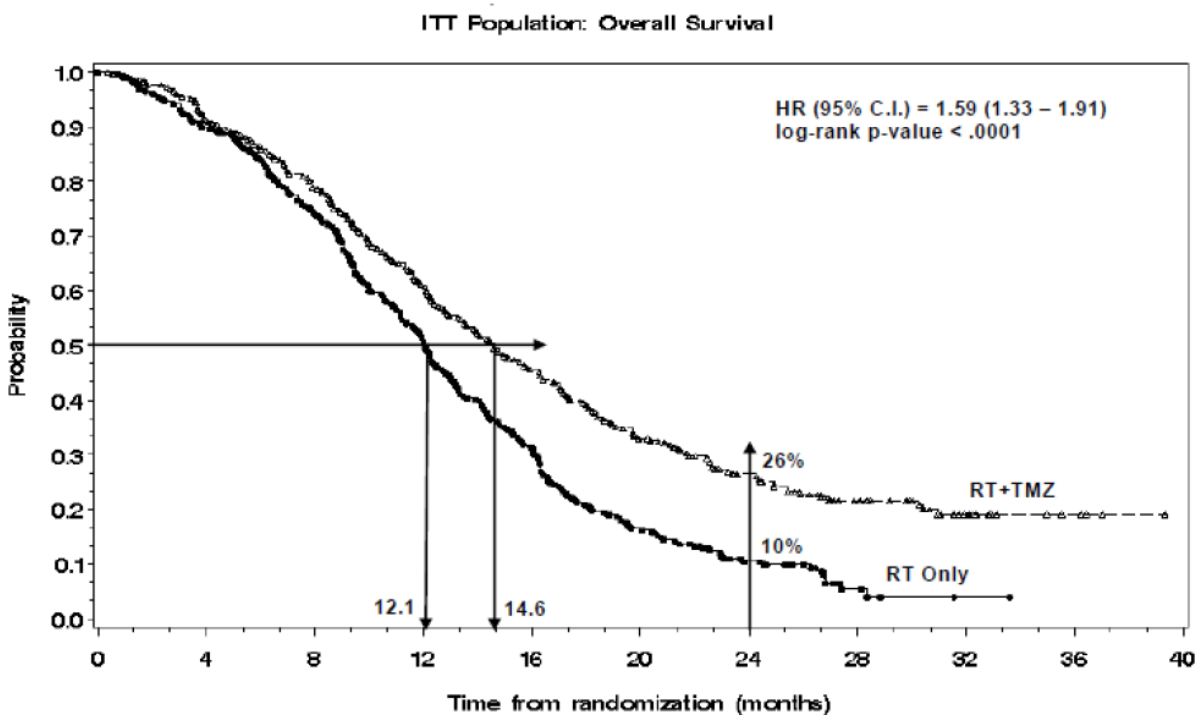


Figure 1 Kaplan-Meier Curves for Overall Survival (ITT Population; at time of randomisation; RT alone group = 286 and RT/TMZ = 287)

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 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 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 intentto-treat 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.

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 14C-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, Temozolomide 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.

Paediatric patients had a higher AUC than adult patients; however, the maximum tolerated dose (MTD) was 1000 mg/m^2 per cycle both in children and in adults.

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. Temozolomide is 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. Dose-related reductions in leukocytes andplatelets 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**.**

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 tumourigenic potential is notunexpected 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).

Temaccord capsules are 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

23 September 2019

Summary table of changes

Section Changed	Summary of new information
6.1	Correction of excipient content for 250 mg capsule