NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Temozolomide Devatis hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect
Temozolomide Devatis hard capsules contain lactose. For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

- Temozolomide Devatis 5 mg: Opaque light green cap and opaque white body with 5 mg print on it, filled with white to light pink powder; hard gelatin capsule size "3".
- Temozolomide Devatis 20 mg: Opaque rich yellow cap and opaque white body with 20 mg print on it, filled with white to light pink powder; hard gelatin capsule size "2".
- Temozolomide Devatis 100 mg: Opaque flesh cap and opaque white body with 100 mg print on it, filled with white to light pink powder; hard gelatin capsules size "1".
- Temozolomide Devatis 140 mg: Transparent light blue cap and opaque white body with 140 mg print on it, filled with white to light pink powder; hard gelatin capsule size "0".
- Temozolomide Devatis 180 mg: Opaque Swedish orange cap and opaque white body with 180 mg print on it, filled with white to light pink powder; hard gelatin capsule size "0".
- Temozolomide Devatis 250 mg: Opaque white cap and opaque white body with 250 mg print on it, filled white to with light pink powder; hard gelatin capsules size "0".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Temozolomide Devatis 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.

Temozolomide Devatis 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 Temozolomide Devatis capsules. Temozolomide Devatis 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 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 ≥100x10^9/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 150 mg/m^2 once daily for 5 days followed by 23 days without treatment. At the start of Cycle 2, the dose is escalated to 200 mg/m^2 if the CTC non-haematological toxicity for Cycle 1 is Grade ≤2 (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is ≥ 1.5x 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	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/m2 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/m2 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/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 1.5x10^9/L and platelet count exceeds 100x10^9/L. If ANC falls to <1.0x10^9/L or the platelet count is <50x10^9/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

Temozolomide Devatis 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

Temozolomide Devatis is contraindicated in patients who have a history of hypersensitivity reaction to its components or to dacarbazine (DTIC).

Temozolomide Devatis is contraindicated for use during pregnancy and in women who intend to become pregnant (see **Section 4.6 Fertility, Pregnancy and Lactation**).

Temozolomide Devatis must not be used by breastfeeding women (see **Section 4.6 Fertility, Pregnancy and Lactation**).

Temozolomide Devatis is contraindicated in patients with severe myelosuppression.

4.4 Special warnings and precautions for use

Keep this medication out of the reach of children.

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.

Thus, prophylaxis against *Pneumocystis carinii* pneumonia is required for all patients receiving concomitant Temozolomide Devatis and radiotherapy for the 42 day regimen (with a maximum of 49 days) regardless of lymphocyte count. If lymphocytopenia occurs *Pneumocystis carinii* pneumonia 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 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.

HBV reactivation
Hepatitis due to hepatitis B virus (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 Devatis. 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:

Patients with newly diagnosed glioblastoma multiforme:
- anti-emetic prophylaxis is recommended prior to the initial dose of *concomitant* Temozolomide Devatis
- 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: 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 (21 days after the first dose) or within 48 hours of that day, and weekly until ANC is above 1.5 x 10^9/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.

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 Devatis 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 Devatis is administered to these patients.

Use in the elderly

Elderly patients (>70 years of age) appear to be at increased risk of neutropenia and thombocytopenia, 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 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 Devatis 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 Devatis is contraindicated in women who intend to become pregnant, and effective contraception should be used by female patients during and for at least 6 months 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 Devatis. Temozolomide can have genotoxic effects. Therefore, men being treated with temozolomide 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 temozolomide. Semen donation is also not advised during treatment and for at least 3 months after the final dose (see **Section 5.3 Preclinical Safety Data** and **Section 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/m^2, (associated with systemic exposure below that anticipated in humans) teratogenicity and/or foetal toxicity were demonstrated. Temozolomide Devatis, 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 Temozolomide Devatis treatment and for 6 months after discontinuation of Temozolomide Devatis 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 Devatis 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 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

Adverse events	Concomitant phase		Adjuvant phase
	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	17	19	23
neuropathy	2	3	3
aphasia	1	3	2
concentration impaired	1	2	3
paresthesia	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	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 disorders			
thrombocytopenia	1	4	8
lymphopenia	0	2	1
leukopenia	0	2	2
neutropenia	0	2	3
Metabolism and nutrition disorders			
anorexia	9	19	27
vomiting	6	20	29
hyperglycemia	1	2	1
weight decrease	<1	2	3
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 disorders			
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 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 anti-emetic 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 haematologic 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 1-2 weeks. No evidence of cumulative myelosuppression was observed. Pancytopenia, leukopenia, 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 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, cases of erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome and allergic reactions, including anaphylaxis, have been reported very rarely. Drug reaction with eosinophilia and systemic symptoms has been reported with a frequency of unknown. 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 *Pneumocystis 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 and pulmonary fibrosis have been reported very rarely. Very rare cases of myelodysplastic syndrome (MDS) and secondary malignancies, including myeloid leukaemia, have also been observed. Prolonged pancytopenia, which may result in aplastic anaemia has been reported, and in some cases has resulted in a fatal outcome. Diabetes insipidus has also been reported.

Reporting of suspected adverse reactions

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 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: L01AX03

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 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)

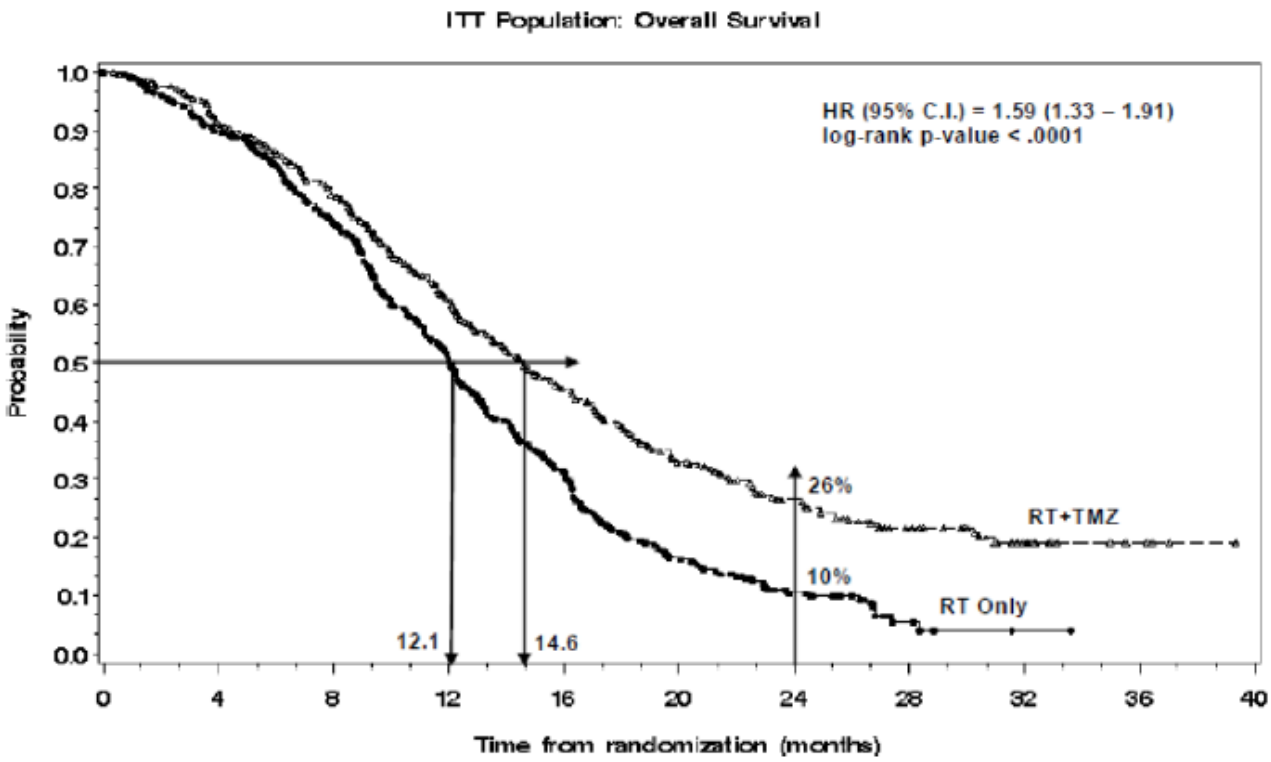

Figure 1. Kaplan-Meier Curves for Overall Survival (ITT Population; at time of randomisation; RT alone group = 286 and RT/TMZ = 287)

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 intent-to-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 ^{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, 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/m2). 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 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**.**

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 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 lactose, sodium starch glycolate type A, colloidal anhydrous silica, tartaric acid and stearic acid in a gelatin capsule shell.

Temozolomide Devatis capsule shells gelatin and titanium dioxide (E171), and are imprinted with ink.

Temozolomide Devatis 5 mg capsule shells also contain yellow iron oxide (E172) and indigotine - FD&C Blue 2 (E132).
Temozolomide Devatis 20 mg capsule shells also contain yellow iron oxide (E172).
Temozolomide Devatis 100 mg capsule shells also contain red iron oxide (E172).
Temozolomide Devatis 140 mg capsule shells also contain indigotine-FD&C Blue 2 (E132).
Temozolomide Devatis 180 mg capsule shells also contain red iron oxide (E172).

Printing ink contains shellac glaze 45% in ethanol, iron oxide black (E172), N-buthyl alcohol, purified water, propylene glycol (E1520), dehydrated ethanol, isopropyl alcohol, ammonium hydroxide 28% (E517).

Temozolomide Devatis capsules are gluten free.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life

5 mg and 20 mg strengths: 3 years
100 mg, 140 mg, 180 mg and 250 mg strengths: 4 years

6.4 Special precautions for storage

The capsules should be stored at or below 25°C.
Store in the original bottle in order to protect from moisture.
Keep the bottle tightly closed.

6.5 Nature and contents of container

Temozolomide Devatis 5 mg, 20 mg, 100 mg, 140 mg, 180 mg & 250 mg are supplied in 50 mL type III amber coloured glass bottles of 5 and 20 capsules closed with 28 diameter child-resistant white opaque closures.
Not all strengths or pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

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

Devatis Limited
Findex, 173 Spey Street, Invercargill 9810, New Zealand

Toll Free Number: 0800 887750
www.devatis.nz

9. DATE OF FIRST APPROVAL

12/12/2024

10. DATE OF REVISION OF THE TEXT

06/02/2025