

# Temozolomide Capsules

**TemoRel™**

## Composition:

### Each Temozolomide-20 capsule contains:

Temozolomide ..... 20 mg

### Each Temozolomide-100 capsule contains:

Temozolomide ..... 100 mg

### Each Temozolomide-250 capsule contains:

Temozolomide ..... 250 mg

Approved colours used in capsule shell.

## Description

Temozolomide is a prodrug, orally administered alkylating agent of the imidazotetrazine class, rapidly and completely absorbed and, at physiological pH, spontaneously hydrolyzed into the active metabolite. The chemical name of temozolomide is 3,4-dihydro-3-methyl-4-oxoimidazo [5,1-d]-[4,5-c]tetra-8-carboxamide. The material is a white to light tan/white pink powder with a molecular formula of C<sub>5</sub>H<sub>7</sub>N<sub>3</sub>O<sub>4</sub> and a molecular weight of 194.15. The molecule is stable at acidic pH (<5), and labile at pH >7, hence temozolomide can be administered orally.

## Pharmacology

Reaction of water with the electropositive C4 atom of temozolomide opens the heterocyclic ring, releasing MTIC and carbon dioxide. MTIC is unstable and degrades into methyl diazonium ion, a reactive methylating compound. The pharmacological activity of temozolomide is due to the cytotoxic effects of the degradation product, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC). MTIC blocks cellular replication by inhibition of deoxyribonucleic acid (DNA) methylation. Peak plasma concentrations are achieved within one hour after oral administration. Bioavailability is 96%. A high fat meal reduces peak plasma concentrations by 32%; the time to peak plasma concentrations are delayed by 1.15 hours and the extent of absorption by 9%.

The pharmacokinetics of temozolomide are linear with dose. Temozolomide half-life is 1.5–1.8 hours. Clearance is 200–290 mL/min. Temozolomide and its metabolites are primarily excreted in the urine. Approximately 6% of the dose is excreted unchanged in the urine. Women have a 5% lower clearance than men.

## Indications

Temozolomide capsules are indicated for the treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment. Temozolomide capsules are indicated for the treatment of adult patients with refractory anaplastic astrocytoma, i.e. patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine.

## Dosage and administration

Dosage of temozolomide capsules must be adjusted according to nadir neutrophil and platelet counts in the previous cycle and the neutrophil and platelet counts at the time of initiating the next cycle. For temozolomide dosage calculations based on body surface area (BSA), see Table 1.

**Table 1: Daily dose calculations by body surface area (BSA)**

Total BSA (m <sup>2</sup> )	75 mg/m <sup>2</sup> (mg daily)	150 mg/m <sup>2</sup> (mg daily)	200 mg/m <sup>2</sup> (mg daily)
1.0	75	150	200
1.1	82.5	165	220
1.2	90	180	240
1.3	97.5	195	260
1.4	105	210	280
1.5	112.5	225	300
1.6	120	240	320
1.7	127.5	255	340
1.8	135	270	360
1.9	142.5	285	380
2.0	150	300	400
2.1	157.5	315	420
2.2	165	330	440
2.3	172.5	345	460
2.4	180	360	480
2.5	187.5	375	500

## Patients with newly diagnosed high grade glioma Concomitant phase

Temozolomide is administered orally at 75 mg/m<sup>2</sup> daily for 42 days concomitant with focal radiotherapy (60 Gy administered in 30 fractions) followed by maintenance for 6 cycles. The temozolomide dose should be continued throughout the 42 day concomitant period up to 49 days if all of the following conditions are met: absolute neutrophil count  $1.5 \times 10^7/L$  platelet count  $100 \times 10^9/L$ , common toxicity criteria (CTC) non-hematological toxicity Grade 1 (except for alopecia, nausea and vomiting).

During treatment a complete blood count should be obtained weekly. Temozolomide dosing should be interrupted or discontinued during concomitant phase according to the hematological and non-hematological toxicity criteria.

PCP prophylaxis is required during the concomitant administration of temozolomide and radiotherapy and should be continued in patients who develop lymphocytopenia until recovery from lymphocytopenia (CTC grade 1).

## Maintenance phase cycle 1

Four weeks after completing the temozolomide + RT (radiotherapy) phase, temozolomide is administered for an additional 6 cycles of maintenance treatment. Dosage in cycle 1 (maintenance) is 150 mg/m<sup>2</sup> once daily for 5 days followed by 23 days without treatment.

## Cycles 2-6

At the start of cycle 2, the dose is escalated to 200 mg/m<sup>2</sup>, if the CTC non-hematological toxicity for cycle 1 is Grade 2 (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is  $1.5 \times 10^7/L$ , and the platelet count is  $100 \times 10^9/L$ . The dose remains at 200 mg/m<sup>2</sup> per day for the first 5 days of each subsequent cycle except if toxicity occurs. If the dose was not escalated at cycle 2, escalation should not be done in subsequent cycles.

## Dose reduction or discontinuation during maintenance

During treatment a complete blood count should be obtained on day 22 (21 days after the first dose of temozolomide) or within 48 hours of that day, and weekly until the ANC is above  $1.5 \times 10^7/L$  (1,500/ $\mu$ L) and the platelet count exceeds  $100 \times 10^9/L$  (100,000/ $\mu$ L). The next cycle of temozolomide should not be started until the ANC and platelet count exceed these levels.

Dose reductions during the next cycle should be based on the lowest blood counts and worst non-hematologic toxicity during the previous cycle.

## Patients with refractory anaplastic astrocytoma

For adults the initial dose is 150 mg/m<sup>2</sup> orally once daily for 5 consecutive days per 28-day treatment cycle. For adult patients, if both the nadir and day of dosing (Day 29, Day 1 of next cycle) ANC are  $1.5 \times 10^7/L$  (1,500/ $\mu$ L) and both the nadir and Day 29, Day 1 of next cycle platelet counts are  $100 \times 10^9/L$  (100,000/ $\mu$ L), the temozolomide dose may be increased to 200 mg/m<sup>2</sup>/day for 5 consecutive days per 28-day treatment cycle. During treatment, 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 the ANC is above  $1.5 \times 10^7/L$  (1,500/ $\mu$ L) and the platelet count exceeds  $100 \times 10^9/L$  (100,000/ $\mu$ L). The next cycle of temozolomide should not be started until the ANC and platelet count exceed these levels. If the ANC falls to  $1.0 \times 10^7/L$  (1,000/ $\mu$ L) or the platelet count is  $50 \times 10^9/L$  (50,000/ $\mu$ L) during any cycle, the next cycle should be reduced by 50 mg/m<sup>2</sup>, but not below 100 mg/m<sup>2</sup>, the lowest recommended dose. Temozolomide therapy can be continued until disease progression.

## Contraindications

Temozolomide is contraindicated in patients with a history of hypersensitivity to dacarbazine. Patients receiving immunosuppressive chemotherapy should not receive vaccination with live vaccines.

## Adverse effects

The most frequently occurring adverse effects were nausea, vomiting, headache, and fatigue. Most adverse effects were self-limiting, and the nausea and vomiting were controlled with antiemetics. The incidence of grade 3 or 4 nausea occurred in 10%, and vomiting occurred in 6%.

The dose-limiting toxicity of temozolomide is myelosuppression. The median nadirs in temozolomide studies occurred at 28 days (range 1 to 44 days) for neutrophils and 26 days (range 22 to 40 days) for platelets. The myelosuppression is the most common dose-limiting adverse event. The average time for the absolute neutrophil count (ANC) and platelet count to return to normal from the nadir was 14 days.

Temozolomide may induce hypercoagulability. Pulmonary emboli and venous thrombosis were observed however, it is possible those events may have been associated with the disease being treated rather than the treatment.

## Drug interactions

Administration of valproic acid decreases oral clearance of temozolomide by about 5%. The clinical implication of this effect is not known.

## Warnings

Patients treated with temozolomide capsules may experience myelosuppression. Prior to dosing, patients must have an absolute neutrophil count (ANC)  $1.5 \times 10^7/L$  and a platelet count  $100 \times 10^9/L$ . A complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above  $1.5 \times 10^7/L$  and platelet count exceeds  $100 \times 10^9/L$ .

## Precautions

Patients with severe hepatic or renal impairment: Caution should be exercised when temozolomide capsules are administered to patients with severe renal impairment. Temozolomide has not been studied in patients on dialysis. Caution should be exercised when temozolomide is administered to patients with severe hepatic impairment.

## Carcinogenesis, Mutagenesis, and Impairment of Fertility:

Standard carcinogenicity studies were not conducted with temozolomide. According to published data, in rats treated with 200 mg/m<sup>2</sup> temozolomide (equivalent to the maximum recommended daily human dose) on 5 consecutive days every 28 days for 3 cycles, mammary carcinomas were found in both males and females. Temozolomide was mutagenic in vitro in bacteria (Ames assay) and clastogenic in mammalian cells (human peripheral blood lymphocyte assays).

## Pregnancy

Temozolomide may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with temozolomide capsules.

## Nursing mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from temozolomide capsules, patients receiving temozolomide should discontinue nursing.

## Pediatric use

Temozolomide effectiveness in children has not been demonstrated.

## Overdosage

Dose-limiting toxicity was hematologic and was reported with any dose but is expected to be more severe at higher doses. In the event of an overdose, hematologic evaluation is needed. Supportive measures should be provided as necessary.

## Preparation

Temozolomide is supplied as 20 mg, 100 mg and 250 mg capsules for oral consumption.

## Shelf life

Two years from the date of manufacturing.



Manufactured and Marketed by:  
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