Drug Monograph

A - Drug Name

temozolomide

COMMON TRADE NAME(S): Temodal®

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B - Mechanism of Action and Pharmacokinetics

Temozolomide is an imidazotetrazine derivative of the alkylating agent dacarbazine. It undergoes rapid chemical conversion in the systemic circulation at physiological pH to the active compound, MTIC (monomethyl triazeno imidazole carboxamide). Temozolomide exhibits schedule-dependent antineoplastic activity by interfering with DNA replication.

Absorption	Oral absorption: yes, 100 % (rapidly absorbed). Administration of temozolomide with food may decrease AUC.	
Distribution	Plasma concentrations are dose-dependent, while plasma clearance, volume of distribution and half-life are independent of dose. No accumulation with multiple dosing.	
	Cross blood brain barrier?	Yes
	PPB	10-20%
Metabolism	Temozolomide undergoes spontaneous hydrolysis to MTIC at physiological pH (7.4) with subsequent formation of a reactive methyl-diazonium species, and followed by further degradation to 4-amino-5-imidazole-carboxamide.	
	Active metabolites	MTIC and others

	Inactive metabolites	AIC, temozolomide acid metabolite and others
Elimination	Plasma clearance of temozolomide is independent of age, renal function, hepatic function or tobacco use. Temozolomide is eliminated primarily in the urine	
	Urine	primary
	Feces	minor
	Half-life	1.2 hours

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C - Indications and Status

Health Canada Approvals:

- Treatment of adult patients with glioblastoma multiforme or anaplastic astrocytoma, and documented evidence of recurrence or progression after standard therapy.
- Treatment of patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment.

Other Uses:

- Neuroendocrine tumours
- Ewing's sarcoma
- Melanoma

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D - Adverse Effects

Emetogenic Potential:
Moderate – Consider prophylaxis daily (> 75 mg/m2/day OR ≤ 75 mg/m2/day + concurrent RT)
Low – No routine prophylaxis; PRN recommended (≤ 75 mg/m2/day)

Extravasation Potential: Irritant

The following table contains adverse effects reported mainly in maintenance treatment for newly diagnosed glioma.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Auditory	Hearing impaired (4%)	E
Cardiovascular	Arterial thromboembolism (rare)	E
	Venous thromboembolism (2%)	E
Dermatological	Alopecia (55%)	E
	Rash (13%) (may be severe)	E
Gastrointestinal	Abdominal pain (5%)	E
	Anorexia, weight loss (27%)	E
	Constipation (22%)	E
	Diarrhea (10%)	E
	Dyspepsia (2%)	E
	Mucositis (9%)	E
	Nausea, vomiting (49%)	I
General	Delayed wound healing (1%)	E
	Edema (2%)	E
	Fatigue (61%)	E
Hematological	Myelosuppression ± infection, bleeding (14%) (severe, include opportunistic infections)	E
Hepatobiliary	↑ LFTs (2%) (may be severe)	E D
Hypersensitivity	Hypersensitivity (3%)	I
Immune	Other - other viral reactivation (hepatitis B, CMV; rare)	E D
Metabolic / Endocrine	Abnormal electrolyte(s) (1%) (↓ K)	E
	Hyperglycemia (1%)	E
	Other - diabetes insipidus (rare)	E
Musculoskeletal	Musculoskeletal pain (6%)	E
Neoplastic	Secondary malignancy	D
Nervous System	Anxiety (4%)	E
	Confusion (5%)	E
	Dizziness (5%)	E
	Dysgeusia (5%)	I
	Headache (23%)	E
	Insomnia (4%)	E

	Memory impairment (7%)	E
	Paresthesia (2%)	E
	Seizure (11%)	E
	Somnolence (2%)	E
Ophthalmic	Blurred vision (8%) (plus other eye changes)	E
Reproductive and breast disorders	Irregular menstruation (1%)	E
Respiratory	Cough, dyspnea (8%)	E
	Pneumonitis (also fibrosis, rare)	E D
Urinary	Other (2%) (urinary symptoms)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

Myelosuppression is the major dose-limiting toxicity and is generally not cumulative. There have been reports of prolonged pancytopenia, which may result in aplastic anemia (fatal in some cases).

The most common non-hematologic adverse effects associated with temozolomide were **nausea and vomiting** and were either self-limiting or readily controlled with standard antiemetic therapy. These effects were generally mild to moderate (grade 1, 2).

All patients on temozolomide should be monitored closely for **Pneumocystis carinii pneumonia (PCP).** There may be a higher incidence of PCP in patients receiving a longer dosing temozolomide regimen, or in patients receiving corticosteroids. PCP prophylaxis is required for patients receiving temozolomide concurrently with radiotherapy for the 42-day regimen. Screen patients for **HBV infection** before starting temozolomide treatment. Patients with active hepatitis B should not be treated; those with inactive disease should be closely monitored (see Monitoring).

Herpes simplex encephalitis (HSE), including fatal cases, have been reported, mainly with concomitant radiotherapy.

Potentially fatal cases of interstitial pneumonitis, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported during post-marketing.

Hepatic dysfunction may be severe and may occur several weeks after starting temozolomide or after treatment discontinuation. Fatal cases have been reported. **Hepatitis B reactivation** has been observed rarely and resulted in death in some cases.

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E - Dosing

Refer to the protocol being used. Antiemetic therapy is recommended prior to or following administration of temozolomide, especially for patients with emesis.

In general, doses of less than 100mg/m^2 should not be given except in combination with radiation treatment (RT).

PCP prophylaxis is required when used in combination with radiation.

Adults:

Newly diagnosed

Concurrent with RT (for 42-49 days):

- 75 mg/m^2 daily for 42 days (up to 49 days maximum).
- Check CBC weekly and modify according to Table 1.

THEN

Maintenance (post-RT; q 28 days x 6 cycles starting 4 weeks after completion of RT):

- Cycle 1: 150 mg/m^2 daily for 5 days.
- Cycle 2: In absence of hematologic toxicity and ≥ grade 3 of other toxicities in cycle 1, increase to 200mg/m^2 x 5 d starting from cycle 2. Otherwise, continue with 150mg/m^2 and do not escalate dose in subsequent cycles.
- CBC on day 22 and day 29 (day 1 of next cycle); modify doses as indicated in Table 2.

Recurrent/Progressive

Chemotherapy-naive:

- 200 mg/m^2 once daily for 5 days, q28d
- Modify doses as indicated in Table 2.

Previously treated:

- Cycle 1: 150 mg/m^2 daily for 5 days.
- Cycle 2: In absence of hematologic toxicity and ≥ grade 3 of other toxicities in cycle 1, increase to 200mg/m^2 x 5 d starting from cycle 2. Otherwise, continue with 150mg/m^2 and do not escalate dose in subsequent cycles.
- CBC on day 22 and day 29 (day 1 of next cycle); modify doses as indicated in Table 2.

Dosage with Toxicity:

Dose Modification for Newly Diagnosed-Concurrent RT:

- No specific dose reductions are recommended for concurrent RT phase. (Continued on next page)

Table 1: Modifications during concurrent treatment

ANC (10^9/L)		**Platelets (10^9/L)**		**Non-hematologic toxicity#**	**Action during RT**
≥0.5 to <1.5	OR	≥10 to <100	OR	Grade 2	Hold until recovery and then restart
< 0.5	OR	<10	OR	≥ Grade 3, including pneumonitis or severe rash	Discontinue during RT
				Hepatotoxicity	Assess risk/benefit before continuing treatment
				Hepatitis B or HSE	Discontinue if active disease or reactivation

except for alopecia, nausea, vomiting

(Continued on next page)

Dose Modifications for Adjuvant-Maintenance and Recurrent/Progressive disease:

- Dose levels are 200, 150 and 100 mg/m^2

Table 2: Modifications for worst toxicity in previous cycle					
ANC (10^9/L)		**Platelets (**10^9/L)		**Non-hematologic toxicity#**	**Dose for Next Cycle ****
<1	OR	< 50	OR	Grade 3	Reduce by 1 dose level*
-	OR	-	OR	Grade 4 or Recurrent Grade 3 or pneumonitis or severe rash	Discontinue
				Hepatotoxicity	Assess risk/benefit before continuing treatment
				Hepatitis B or HSE	Discontinue if active disease or reactivation

except for alopecia, nausea, vomiting

* Discontinue if < 100mg/m^2

** New cycles of temozolomide should not be started until ANC is ≥ 1.5 x 10^9/L and platelets ≥ 100 x 10^9/L and patient has recovered from ≥ grade 3 organ toxicity.

Dosage with Hepatic Impairment:

No formal studies have been performed. Population pharmacokinetics appear unchanged in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment should be monitored closely and consideration given to dose modification.

Dosage with Renal Impairment:

No formal studies have been performed. Population pharmacokinetics appear unchanged in patients with mild-moderate renal impairment. Patients with severe renal impairment should be monitored closely and consideration given to dose modification.

Dosage in the elderly:

Patients > 70 years of age appear to be at an increased risk of myelosuppression and should be monitored closely.

Dosage based on gender:

Lower clearance of temozolomide and higher incidence of grade 4 thrombocytopenia or neutropenia in females, especially in the first cycle. Monitor for toxicity.

Children:

Use of temozolomide in children has not been approved in North America. Doses used in children are similar to doses used in adults, although the AUC appears to be higher compared to adults. Pediatric patients appeared to tolerate higher plasma concentrations of temozolomide before reaching dose-limiting toxicity, which may likely be due to increased bone marrow reserves.

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F - Administration Guidelines

- It is preferable to give temozolomide on an empty stomach, at least one hour before or at least 2 hours after a meal, as this may help reduce nausea and vomiting. Alternatively, it may be given with food; however, administration timing relative to meals should be consistent.
- Capsules must not be opened or chewed, but are to be swallowed whole with a glass of water.
- If vomiting occurs after the dose is administered, do not administer a second dose.
- Store capsules at room temperature (15 to 30°C).

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G - Special Precautions

Contraindications:

- Patients with hypersensitivity to its components or to dacarbazine
- Patients with severe myelosuppression
- Patients with active hepatitis B infection

Other Warnings/Precautions:

- Patients with hepatic impairment, poor performance status, severe debilitating diseases or infection

Other Drug Properties:

- Carcinogenicity: Yes

Pregnancy and Lactation:

- Fetotoxicity: Yes
  Temozolomide is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **6 months** after the last dose.
  Impaired **fertility** in males was observed in animals; advice on cryoconservation of sperm should be sought.
- Breastfeeding: Not recommended

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H - Interactions

Coadministration of the following drugs **did not alter** the clearance of temozolomide: dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H2-receptor antagonists, or phenobarbital.

Temozolomide does not appear to affect the metabolism of drugs by CYP450, although concomitant administration with other drugs has not been fully studied. Increased myelosuppression is expected when combined with other alkylating agents.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Valproic acid	↑ toxicity	↓ clearance of temozolomide by 5%; clinically insignificant	Use with Caution
Drugs associated with aplastic anemia (e.g.	↑ risk of aplastic anemia and complicates assessment	Possibly additive	Monitor patient carefully

cotrimoxazole, carbamazepine, phenytoin)

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline then weekly for concurrent RT; Baseline then on day 1 and 22 (for q28d cycles)
Liver function tests	Baseline then each cycle (28-day cycles); Baseline then at mid-cycle (42-day cycle)
Hepatitis B screening	Baseline. If active, do not treat with temozolomide. If not active, monitor every 1-2 cycles for reactivation & continue for 6 months after treatment discontinuation.
Signs & symptoms of HSE, especially in patients with previous herpes simplex viral infections	At each visit
Clinical toxicity assessment including fatigue, constipation, infections (including opportunistic such as PCP and Hepatitis B), bleeding, nausea and vomiting, pneumonitis, hypersensitivity, thromboembolism, skin and respiratory toxicity	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)

- temozolomide

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K - References

Brada M, Judson I, Beale P, et al. Phase I dose-escalation and pharmacokinetic study of temozolomide (SCH 52365) for refractory or relapsing malignancies. Br J Cancer 1999 Nov;81(6):1022-30.

Hvizdos KM, Goa KL. Temozolomide. CNS Drugs 1999;12(3):237-43.

Product Monograph: Temozolomide (Temodal®). Merck Canada Inc., June 2017.

Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-96.

June 2021 temozolomide is ODB general benefit

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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