

Regimen Monograph

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A - Regimen Name

TMZL Regimen

Temozolomide

Disease Site Central Nervous System

Intent Palliative

Regimen Category **Evidence-Informed :**

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses Treatment of adult patients with glioblastoma multiforme or anaplastic astrocytoma, and documented evidence of recurrence or progression after standard therapy

Supplementary Public Funding [temozolomide](#)
ODB - General Benefit (temozolomide)

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B - Drug Regimen

In patients without prior chemotherapy¹:

| | | | |
|------------------------------|------------------------|----|--------------------|
| temozolomide | 200 mg /m ² | PO | Daily, on Days 1-5 |
|------------------------------|------------------------|----|--------------------|

In patients with prior chemotherapy²:

| | | | |
|------------------------------|------------------------|----|--------------------|
| temozolomide | 150 mg /m ² | PO | Daily, on Days 1-5 |
|------------------------------|------------------------|----|--------------------|

Alternative Schedule:

| | | | |
|---|-----------------------|----|------------------|
| temozolomide ³ | 50 mg /m ² | PO | Continuous daily |
|---|-----------------------|----|------------------|

¹ Outpatient prescription in multiples of 5mg, 20mg, 100mg, 140mg and 250mg capsules.

² Start with 150 mg/m² in cycle 1. For cycle 2: In absence of hematologic toxicity and \geq grade 3 of other toxicities in cycle 1, increase to 200mg/m² x 5 d starting from cycle 2. Otherwise, continue with 150mg/m² and do not escalate dose in subsequent cycles.

³ See Perry et al, 2010

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C - Cycle Frequency

For 150-200 mg/m² daily on days 1-5:

REPEAT EVERY 28 DAYS

Until evidence of disease progression or unacceptable toxicity

For 50 mg/m² daily dosing:

CONTINUOUS TREATMENT

Until evidence of disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate – Consider prophylaxis daily ($> 75 \text{ mg/m}^2$ OR $\leq 75 \text{ mg/m}^2/\text{day} + \text{RT}$)
 Low – No routine prophylaxis; PRN recommended ($\leq 75 \text{ mg/m}^2/\text{day}$)

Other Supportive Care:

- Antiemetic therapy is recommended prior to or following administration of temozolomide, especially for patients with emesis.
- Consider PCP prophylaxis, especially for patients on concurrent corticosteroids.

Also refer to [CCO Antiemetic Recommendations](#).

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations have been adapted from clinical trials or product monographs and could be considered.

Dosage with toxicity

Dose Modifications for **every-4 week** dosing: Dose levels are 200, 150 and 100 mg/m^2

| Table 2: Modifications for worst toxicity in previous cycle | | | | | |
|---|----|-------------------------------|----|--|---|
| ANC ($10^9/\text{L}$) | | Platelets ($10^9/\text{L}$) | | 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 |
| <p># except for alopecia, nausea, vomiting * Discontinue if $< 100\text{mg}/\text{m}^2$ ** New cycles should not be started until ANC is $\geq 1.5 \times 10^9/\text{L}$ and platelets $\geq 100 \times 10^9/\text{L}$ and patient has recovered from \geq grade 3 organ toxicity.</p> | | | | | |

Dose modifications for **50mg/m² PO daily** dosing:

| Hematologic toxicity (counts x 10 ⁹ /L) | | Non-hematologic toxicity | Dose for next cycle |
|--|----|---|---|
| ANC <1 OR platelets <100 | OR | Grade 3 [#] | Hold until resolved** |
| As above, recurrent or persistent for > 6 weeks | OR | As above, recurrent or persistent for > 6 weeks | Discontinue |
| | | Grade 4 or pneumonitis or severe rash | Discontinue |
| | | Hepatotoxicity | Assess risk/benefit before continuing treatment |
| Hematologic toxicity (counts x 10 ⁹ /L) | | Non-hematologic toxicity | Dose for next cycle |
| | | Hepatitis B or HSE | Discontinue if active disease or reactivation |
| <p># except for alopecia, nausea, vomiting **Treatment should restart if ANC $1.5 \times 10^9/\text{L}$ and platelets $\geq 100 \times 10^9/\text{L}$ and non-hematological toxicities have resolved.</p> | | | |

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.

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.

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F - Adverse Effects

Refer to [temozolomide](#) drug monograph(s) for additional details of adverse effects

| Very common (≥ 50%) | Common (25-49%) | Less common (10-24%) | Uncommon (< 10%), but may be severe or life-threatening |
|---|---|---|--|
| <ul style="list-style-type: none"> • Fatigue • Alopecia | <ul style="list-style-type: none"> • Nausea, vomiting • Anorexia, weight loss | <ul style="list-style-type: none"> • Headache • Constipation • Diarrhea • Myelosuppression +/- infection (opportunistic, viral reactivation), • bleeding (may be severe) • Rash (may be severe) | <ul style="list-style-type: none"> • Arterial / venous thromboembolism • Hypersensitivity • Hepatotoxicity • Pneumonitis • Secondary malignancy |

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G - Interactions

Refer to [temozolomide](#) drug monograph(s) for additional details

- 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.
- Monitor closely when used with drugs associated with aplastic anemia (e.g. cotrimoxazole, carbamazepine)

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H - Drug Administration and Special Precautions

Refer to [temozolomide](#) drug monograph(s) for additional details

Administration

- 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).

Contraindications

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

Warnings/precautions

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

Pregnancy & lactation

- Temozolomide is not recommended for use in pregnancy or breastfeeding. 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.

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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

- CBC; Baseline then weekly for concurrent RT; Baseline then on day 1 and 22 (for q28d cycles); baseline then weekly (continuous daily dosing)
- Liver function tests; Baseline then each cycle (q28day cycles); baseline then every 3 weeks (continuous daily dosing)
- 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 herpes simplex encephalitis (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 - Administrative Information

Oral: Outpatient prescription for home administration

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K - References

Brada M, Stenning S, Gabe R, et al. Temozolomide versus procarbazine, lomustine, and vincristine in recurrent high-grade glioma. *J Clin Oncol* 2010;28(30):4601-8.

Perry JR, Bélanger K, Mason WP, et al. Phase II trial of continuous dose-intense temozolomide in

recurrent malignant glioma: RESCUE study. J Clin Oncol 2010 Apr 20;28(12):2051-7.

Temozolomide drug monograph, Cancer Care Ontario.

Yung W, Albright R, Olson J et al. A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse . Br J Cancer. 2000 Sep;83(5):588-93.

PEBC Advice Documents or Guidelines

- [Endorsement of the 2017 European Association for Neuro-Oncology Guideline on the Diagnosis and Treatment of Adult Astrocytic and Oligodendroglial Gliomas](#)

June 2021 temozolomide is ODB General Benefit

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

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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The format and content of the drug monographs, regimen monographs, appendices and symptom management

information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

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