Regimen Monograph

A - Regimen Name

TMZL Regimen

Temozolomide

Disease Site	Central Nervous System
Intent	Adjuvant
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 newly diagnosed patients with glioblastoma multiforme.
Supplementary Public Funding	**temozolomide** ODB - General Benefit (temozolomide)

back to top

B - Drug Regimen

temozolomide[1, 2]	150-200 mg /m²	PO	Daily, on Days 1-5

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 ≥ 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 (Stupp et al).

back to top

C - Cycle Frequency

REPEAT EVERY 28 DAYS

For a usual total of 6 cycles unless disease progression or unacceptable toxicity occurs

back to top

D - Premedication and Supportive Measures

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

back to top

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/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 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.

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.

back to top

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
• Fatigue • Alopecia	• Nausea, vomiting • Anorexia,weight loss	• Headache • Constipation • Diarrhea • Myelosuppression +/- infection (opportunistic, viral reactivation), • bleeding (may be severe) • Rash (may be severe)	• Arterial / venous thromboembolism • Hypersensitivity • Hepatotoxicity • Pneumonitis • Secondary malignancy

back to top

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)

back to top

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.

back to top

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 on day 1 and 22
- Liver function tests; Baseline then each cycle
- Hepatitis B screening; Baseline. If active, do not treat with temozolomide. If not active, monitor every 1-2 cycles (q28d 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

back to top

J - Administrative Information

Oral: Outpatient prescription for home administration

back to top

K - References

Malmström A, Grønberg BH, Marosi C, et al. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. Lancet Oncol 2012 Sep;13(9):916-26.

Stupp R, Mason WP, Van Den Bent MJ et al. Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. NEJM. March 10 2005; 352; 987-96.

Temozolomide drug monograph, Cancer Care Ontario.

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

back to top

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.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

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.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, 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.

CCO and the Formulary's content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person's use of the information in the Formulary.

back to top