Temozolomide with Radiotherapy (RT) and Adjuvant Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) followed by adjuvant treatment commencing 4 weeks after completion of chemoradiation	C71	00334a	CDS

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Temozolomide is administered orally once daily with concomitant radiotherapy for 6 weeks.
Four weeks after completion of the temozolomide and radiotherapy concomitant phase:
Temozolomide is administered orally once daily on days 1-5 of a 28 day cycle for up to 6 cycles of monotherapy treatment or until disease progression or unacceptable toxicity develops.

Drug	Dose	Route	Cycle
Temozolomide	75mg/m^2 ONCE daily concomitantly with radiotherapy	PO	Continuously with radiotherapy for 6 weeks
PJP prophylaxis **(Refer to local policy)** is required when temozolomide is administered with concomitant radiotherapy			

4 WEEK BREAK FOLLOWED BY:

Day	Drug	Dose	Route	Cycle (28 days)
1-5	Temozolomide	150mg/m^2 ONCE daily	PO	1
1-5	Temozolomide	200mg/m^2 ONCE daily *	PO	2-6

*** See Dose Modifications: Temozolomide Monotherapy Phase below**

Temozolomide hard capsules should be administered in the fasting state.
The capsules must be swallowed whole with a glass of water and must not be opened or chewed.
If vomiting occurs after the dose is administered, a second dose should not be administered that day

If a dose is missed, the patient should make up that dose, unless the next dose is due within 12 hours.

ELIGIBILITY:

- Indications as above
- ECOG 0-2
- Adequate renal and hepatic function

EXCLUSIONS:

- Patients with hypersensitivity to temozolomide or any of its listed excipients
- Hypersensitivity to dacarbazine
- Severe myelosuppression
- Creatinine > 1.5 x ULN
- Significant hepatic dysfunction
- Pregnancy or lactation

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- Blood, renal and liver profile
- Glucose
- Virology screen -Hepatitis B (HBsAg, HBcoreAb)

*(Reference Adverse Events/Regimen Specific Complications for information on Hepatitis B reactivation)

Regular tests:

Temozolomide and Concomitant Radiotherapy (RT)

- Blood profile weekly
- Renal and liver profile before week 4

Temozolomide Monotherapy Phase (Adjuvant)

- Blood, renal and liver profile every 28 days (at day 1 of each cycle)

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

Temozolomide and Concomitant Radiotherapy (RT)

- Any dose modification should be discussed with a Consultant.
- No dose reductions are recommended, but delay or discontinuation of temozolomide administration should be decided weekly according to haematological and non-haematological toxicity criteria.
- Temozolomide administration can be continued throughout the 42day concomitant period (up to 49 days) if all of the following conditions are met:
  - absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
  - platelet count ≥ 100 x 10^9/L
  - common toxicity criteria (CTC) non-haematological toxicity ≤ Grade 1 (except for alopecia, nausea and vomiting).
- During treatment with concomitant RT a complete blood count should be obtained weekly.
- Temozolomide administration should be temporarily interrupted or permanently discontinued during the 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 radiotherapy and temozolomide

Toxicity	Temozolomide Interruption	Temozolomide Discontinuation
ANC	≥ 0.5 and <1.5 x 10^9/L	< 0.5 x 10^9/L
Platelets	≥ 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

Temozolomide Monotherapy Phase

- Any dose modification should be discussed with a Consultant
- Dose in Cycle 1 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 ≥ 1.5 x 10^9/L, and the platelet count is ≥ 100 x 10^9/L.
- If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles.
- Once escalated, the dose remains at 200 mg/m^2 per day for the first 5 days of each subsequent cycle except if toxicity occurs.

Table 2: Temozolomide dose levels for Monotherapy Treatment

Dose Level	Temozolomide Dose (mg/m^2)	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 monotherapy treatment

Toxicity	Reduce temozolomide by 1 dose level[a]	Discontinue Temozolomide
ANC	< 1 x 10^9/L	See footnote b
Platelets	< 50 x 10^9/L	See footnote b
CTC non-haematological toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4[b]

[a]Temozolomide dose levels are listed in Table 2.

[b] Temozolomide is to be discontinued if:

- dose level -1 (100 mg/m^2) still results in unacceptable toxicity
- the same Grade 3 non-haematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction.

Renal and Hepatic Impairment:

Table 4: Dose modification of temozolomide in renal and hepatic impairment

Renal Impairment	Hepatic Impairment
No data are available on the administration of temozolomide in patients with renal impairment. Caution should be exercised when temozolomide is administered in these patients	• The pharmacokinetics of temozolomide were comparable in patients with normal hepatic function and in those with mild or moderate hepatic impairment. • No data are available on the administration of temozolomide in patients with severe hepatic impairment (Child's Class C). • Based on the pharmacokinetic properties of temozolomide, it is unlikely that dose reductions are required in patients with severe hepatic impairment. However, caution should be exercised when temozolomide is administered in these patients.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Moderate- High (**Refer to local policy).**

PREMEDICATIONS: None

OTHER SUPPORTIVE CARE:

PJP prophylaxis during concomitant phase **(Refer to local policy)**

Temozolomide can have genotoxic effects. Therefore, men being treated with it should be advised not to father a child up to 6 months after receiving the last dose and to seek advice on cryoconservation of sperm prior to treatment, because of the possibility of irreversible infertility due to therapy with temozolomide.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Opportunistic infections and reactivation of infections**: Opportunistic infections (such as Pneumocystis jirovecii pneumonia) and reactivation of infections (such as HBV, CMV) have been observed during the treatment with temozolomide.
- **Pneumocystis jirovecii pneumonia (PJP):** Patients who received concomitant temozolomide and RT in a pilot trial for the prolonged 42-day schedule were shown to be at particular risk for developing PJP. Thus, prophylaxis against PJP is required for all patients receiving concomitant temozolomide and RT for the 42-day regimen (with a maximum of 49 days) regardless of lymphocyte count. If lymphopenia occurs, they are to continue the prophylaxis until recovery of lymphopenia to grade ≤ 1. There may be a higher occurrence of PJP 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 PJP, regardless of the regimen. Cases of fatal respiratory failure have been reported in patients using temozolomide, in particular in combination with dexamethasone or other steroids.
- **Hepatitis B Virus (HBV):** Hepatitis due to HBV reactivation, in some cases resulting in death, has been reported. Experts in liver disease should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease). During treatment patients should

be monitored and managed appropriately.

- **Hepatotoxicity:** Hepatic injury, including fatal hepatic failure, has been reported 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.

DRUG INTERACTIONS:

- No studies have been conducted to determine the effect of temozolomide on the metabolism or elimination of other medicinal products.
- Since temozolomide does not undergo hepatic metabolism and exhibits low protein binding, it is unlikely that it would affect the pharmacokinetics of other medicinal products
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Temozolomide - L01AX03

REFERENCES:

1. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352(10):987-96.
2. Stupp R, Hegi M. & Mason W. et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol. 2009:10 (5):459-66.
3. Temodal ® Summary of Product Characteristics Accessed June 2020. Available at https://www.ema.europa.eu/en/documents/product-information/temodal-epar-product-information_en.pdf
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V2 2019. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

Version	Date	Amendment	Approved By
1	20/06/2016		Prof Maccon Keane
2	20/06/2018	Updated with new NCCP regimen template and clarified treatment table	Prof Maccon Keane
3	15/07/2020	Regimen review Updated emetogenic potential	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.