Temozolomide with Radiotherapy(RT) and Adjuvant Therapy-Patients greater than 65 years

INDICATIONSFOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Adult patients greater than 65 years with newly-diagnosed glioblastomamultiformenot suitable for the standard radiotherapy regimen in combination with temozolomide.[i]	C71	00461a	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 21 days from day 1.
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 12cycles of monotherapy treatment or until disease progression or unacceptable toxicity develops.

Drug	Dose	Route	Cycle (21 days)
Temozolomide	75mg/m^2 ONCE daily concomitantly with radiotherapy	PO	Continuously with radiotherapy for 21 days
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: TemozolomideMonotherapy 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.

Temozolomide is available as 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, or 250 mg hard capsules

ELIGIBILTY:

- 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 up until and including 4 weeks after last fraction of radiotherapy (i.e. Week, 1,2,3,4,5,6,7)
- Renal and liver profile1 week and 4 weeks after last fraction of radiotherapy

TemozolomideMonotherapy Phase (Adjuvant)

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

(***** Excluding cycle 1 - the "4 weeks after the last fraction of radiotherapy" evaluation to count towards "day 1 of cycle 1" as well.)

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 (Table 1 and Table 2 below).
- If temozolomide is interrupted due to adverse events, radiotherapy should continue. When treatment with temozolomide resumes, daily doses should be taken until the last

day of radiotherapy as per the original schedule, i.e. missed doses of temozolomide will not be replaced or restored.

Table 1:Temozolomide dosing interruption or discontinuation for haematological toxicity during concomitant radiotherapy and temozolomide

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose of Temozolomide concurrently with RT
≥ 1.5	and	≥ 100	75mg/m^2
≥ 0.5 and <1.5	and/or	≥ 25 and <100	Hold until recovery then resume daily dosing at 75mg/m^2
<0.5	and/or	<25	Stop

Table 2: Temozolomide dosing interruption or discontinuation for non- haematological toxicity during concomitant radiotherapy and temozolomide

Adverse Event	Grade	Dose of Temozolomide Given Concurrently with Radiotherapy
Nausea or vomiting	3	Hold until recovery to ≤Grade 2 and then resume daily treatment at 75mg/m^2
	4	Stop
All other non-haematological adverse events (except alopecia)	2, 3	Hold until recovery to ≤Grade 1 and then resume daily treatment at 75mg/m^2
	4	Stop

TemozolomideMonotherapy 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 nausea and vomiting (≤3), 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 3: Temozolomide dose levels for Monotherapy Treatment

Dose Level	Temzolomide Dose (mg/m^2)	Remarks
-1	100	Reduction for prior toxicity
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2-12in absence of toxicity

Table 4: Temozolomidedose reduction or discontinuation for haematological toxicity during Monotherapy Treatment

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose of Temozolomide concurrently with RT
≥ 1.5	and	≥ 100	Treat on time, no dose modification
<1.5	and/or	<100	Delay start of cycle by 1 week intervals, to a maximum of 3 weeks[a], until recovery, then treat with same dose as day 1 of previous cycle
<0.5	and/or	<25	Stop
[a]If the counts have not recovered after 3 weeks then adjuvant temozolomide should be stopped			

Table 5: Temozolomide dosing interruption or discontinuation for non- haematological toxicity during monotherapy treatment

Adverse Event	Grade	Dose of Temozolomide Given Concurrently with Radiotherapy
Nausea or vomiting	3	Delay start of cycle by 1 week intervals, to a maximum of 3 weeks [b] until recovery to ≤Grade 2 and then treat with same dose as day 1 of previous cycle
	4	Stop
All other non-haematological adverse events (except alopecia)	2, 3	Delay start of cycle by 1 week intervals, to a maximum of 3 weeks [b] until recovery to ≤Grade 1 and then treat with same dose as day 1 of previous cycle
	4	Stop
[b]If not recovered after 3 weeks then adjuvant temozolomide should be stopped		

Renal and Hepatic Impairment:

Table 6: Dose modification of temozolomidein 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 temozolomidewere 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 to 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 Reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy. **(Refer to local infectious disease policy**). These patients should be considered for assessment by hepatology.
- **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. Perry JR, Laperriere N et al. Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma. NEJM 2017;7;376:1027-37

2. Temozolomide(Temodal®) Summary of Product Characteristics. Last updated: 30/10/2019 Accessed Feb 2020. Available at https://www.ema.europa.eu/en/documents/product-information/temodal-epar-product-information_en.pdf
3. 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	22/02/2018		Prof Maccon Keane
2	22/04/2020	Reviewed. Update of emetogenic potential and adverse events	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i]This regimen is outside its licensed indication in Ireland. Patients should be informed of the unlicensed nature of this indication and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be aware of their responsibility in communicating any relevant information to the patient and also in ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.