Bevacizumab 5mg/kg Monotherapy – 14 Day[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of recurrent malignant glioblastoma multiforme	C71	00813a	N/A

* This is for post 2012 indications only

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.

Bevacizumab is administered every 14 days until disease progression or unacceptable toxicity occurs.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Bevacizumab	5mg/kg	IV infusion	100mL NaCl 0.9% over 90 minutes[a, b]	Every 14 days
[a]Flush line with NaCl 0.9% pre and post bevacizumab dose as it should not be mixed with glucose solutions.					
[b]The initial dose of bevacizumab should be delivered over 90 minutes as an intravenous infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes. Alternatively, the unlicensed use of shorter infusion times is described in the NCCP Bevacizumab Rapid Infusion Rate Guidance here[ii]. It should not be administered as an intravenous push or bolus.					

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

ELIGIBILITY:

- Indication as above
- ECOG 0-2
- Adequate hematologic, renal and hepatic function

EXCLUSIONS:

- Hypersensitivity to bevacizumab or any of the excipients
- Pregnancy and breastfeeding
- Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies
- Recent intracranial haemorrhage
- Imaging showing no or minimal contrast enhancement or evidence of gliomatosis cerebri
- Recent stroke or MI (less than 1 year)
- Major surgery within 4 weeks

USE WITH CAUTION:

- Previous pelvic radiotherapy
- Pre-existing uncontrolled hypertension
- Clinically significant cardiovascular disease
- Renal disease including proteinuria
- Bleeding/Clotting disorders
- Previous anthracycline exposure
- History of significant venous thromboembolism
- Recent (less than 6 months) arterial thromboembolic events
- Prior radiation to the chest wall or other serious medical illness
- Surgical procedure or complications that could lead to increased risk of fistulation or perforation
- Underlying condition that could lead to increased risk of fistulation or perforation

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile,
- Dipstick urinalysis for protein,
- Blood pressure measurement, cardiac assessment including history and physical exam.
- ECHO should be considered in patients who have had chest wall radiation or prior treatment with an anthracycline.
- INR if clinically indicated*

*(For patients on warfarin, weekly INR until stable warfarin dose established, then INR prior to each cycle)

Regular tests:

- FBC, renal and liver profile, dipstick urinalysis for protein.
- Blood pressure prior to each cycle and post treatment.
- INR if clinically indicated*

*(For patients on warfarin, weekly INR until stable warfarin dose established, then INR prior to 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:

- Any dose modification should be discussed with a Consultant.
- Bevacizumab dose reduction for adverse events is not recommended (SmPC). If indicated, bevacizumab therapy should either be permanently discontinued or temporarily suspended until toxicity resolves (Table 2 and Table 3)

Renal and Hepatic Impairment:

Table 1: Dose modification of bevacizumab in renal and hepatic impairment

Drug	Renal Impairment	Hepatic Impairment
Bevacizumab	Renal impairment: no need for dose adjustment is expected Haemodialysis: no need for dose adjustment is expected	Hepatic impairment: no need for dose adjustment is expected
Renal and hepatic dose recommendations from Giraud et al 2023		

Management of adverse events:

Proteinuria:

Table 2: Dose modifications of bevacizumab for proteinuria

Degree of proteinuria	**Action**
Neg or 1+ dipstick or less than 1 g/L laboratory urinalysis for protein	Administer bevacizumab dose as scheduled
2+ or 3+ dipstick or greater than or equal to 1 g/L laboratory urinalysis for protein	Administer bevacizumab dose as scheduled. Collect 24-hour urine for determination of total protein within 3 days before the next scheduled bevacizumab administration. Adjust bevacizumab treatment based on the table below
If urine dipstick shows 4+ at baseline or during treatment	Withhold bevacizumab and proceed with 24 hour urine collection
24-hour urine total protein (g/24hr)	**Action**
less than or equal to 2	Proceed
greater than 2 to 4	Hold dose and recheck 24 hour urine every 2 weeks, resume therapy when less than or equal to 2g/24hour
greater than 4	Discontinue Therapy

Table 3: Dose modifications of bevacizumab for adverse events

Adverse reactions		Recommended dose modification
Hypertension	Uncontrolled* or symptomatic hypertension on Day 1	Withhold bevacizumab treatment and start antihypertensive therapy or adjust pre-existing medication
	Grade 2-3 hypertension	Initiate antihypertensive therapy and consider interruption of bevacizumab until controlled
	Grade 4 hypertension or persisting grade 3 hypertension	Discontinue bevacizumab
Grade 4 Proteinuria		Discontinue bevacizumab
Tracheoesophageal (TE) fistula or any Grade 4 fistula		Discontinue bevacizumab
Grade 4 Thromboembolic events		Discontinue bevacizumab
Haemorrhagic event ≥ Grade 3		Discontinue bevacizumab
Gastrointestinal Perforation		Discontinue bevacizumab
*Uncontrolled hypertension for initiating bevacizumab is defined as sustained BP>150/100mmHg while receiving anti-hypertensive medication		

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL

- As outlined in NCCP Classification Document for Systemic Anti Cancer Therapy (SACT) Induced Nausea and Vomiting linked here

Bevacizumab : Minimal (**Refer to local policy).**

For information:
Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - link here
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - link here

PREMEDICATIONS: None usually required unless the patient has had a previous hypersensitivity.

OTHER SUPPORTIVE CARE: Anti-diarrhoeal treatment may be required **(Refer to local policy).**

ADVERSE EFFECTS

- Please refer to the relevant Summary of Product Characteristics (SmPC)

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

REFERENCES:

1. Gleeson JP, et al. Similar overall survival with reduced vs. standard dose bevacizumab monotherapy in progressive glioblastoma. Cancer Med 2020;9(2):469-475
2. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
3. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. 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
4. Bevacizumab (Avastin®) Summary of product characteristics EMA. Last updated 28/01/2021. Accessed March 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	02/05/2023		Prof Patrick Morris
2	24/07/2024	Regimen reviewed. Updated cautions section. Updated renal and hepatic dose modifications to align with Giraud et al 2023. Adverse Effects and Drug Interactions sections removed and replaced with standard wording.	Prof Patrick Morris

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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[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

[ii] The rapid infusion is an unlicensed means of administration of bevacizumab for the indications described above, in Ireland. Patients should be informed of this 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 fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" means of administration has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy