Lomustine and Bevacizumab 7.5mg/kg Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
For the treatment of recurrent malignant glioblastoma	C71	00804a	Hospital

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 on days 1 and 22 and lomustine is administered on day 1 of a 42 day cycle for up to 6 cycles.

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

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle Frequency
1	1, 22	Bevacizumab	7.5mg/kg	IV infusion	100ml NaCl 0.9% over 90mins[a, b]	Every 42 days
2	1	Lomustine[c, d]	90mg/m^2 (max. dose 160mg)	PO	n/a	Every 42 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[i] is described in the NCCP Bevacizumab Rapid Infusion Rate Guidance here.
It should not be administered as an intravenous push or bolus.

[c] Lomustine is available as 40mg capsules

[d] Lomustine is an unlicensed drug. If the drug is not to be dispensed by the hospital, then the hospital should ensure communication with the patient's community pharmacy to ensure there is no interruption in treatment

ELIGIBILITY:

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

EXCLUSIONS:

- Hypersensitivity to bevacizumab, lomustine or any of the excipients
- Recent intracranial haemorrhage
- Recent stroke or MI (less than 1 year)
- Major surgery within 4 weeks

- Imaging showing no or minimal contrast enhancement or evidence of gliomatosis cerebri
- Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies
- Pregnancy
- Breast-feeding

USE WITH CAUTION:

Use with caution in patients with:

- 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

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 as clinically indicated.
- Glucose
- Pulmonary function tests as clinically indicated for patients considered high risk of pulmonary toxicity
- 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.
- Pulmonary function tests as clinically indicated
- 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 3 and Table 4).

Haematological:

Table 1: Dose modifications for lomustine in haematological toxicity

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose
≥1.0	and	≥100	100%
<1.0	And/or	< 80	Delay lomustine treatment until ANC ≥1.0 and platelets ≥100. Consider dose reduction

Renal and Hepatic Impairment:

Table 2: Dose modification of lomustine and bevacizumab in renal and hepatic impairment

Drug	**Renal Impairment**		**Hepatic Impairment**
Bevacizumab	No studies have been performed in patients with renal impairment.		No studies have been performed in patients with hepatic impairment.
Lomustine	**CrCl (ml/min)**	**Dose**	Lack of information available. Consider dose reduction.
	>60	100%	
	45-60	75%	
	30-45	50%	
	<30	Not recommended	

Management of adverse events:

Proteinuria:

Table 3: 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 4: Dose modification 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:

Bevacizumab**:** Minimal **(Refer to local policy).**
Lomustine: Moderate to High **(Refer to local policy)**

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

OTHER SUPPORTIVE CARE:

- Lomustine can cause birth defects. Men and women are recommended to take contraceptive precautions during therapy with lomustine and for 6 months after treatment.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

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

Bevacizumab:

- **Gastrointestinal perforations:** Patients may be at an increased risk for the development of gastrointestinal perforation and gall bladder perforation when treated with bevacizumab. Intra-abdominal inflammatory process may be a risk factor for gastrointestinal perforations in patients with metastatic carcinoma of the colon or rectum, therefore, caution should be exercised when treating these patients. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation.
- **Wound healing complications:** Bevacizumab may adversely affect the wound healing process. Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experienced wound healing complications during therapy, treatment should be withheld until the wound is fully healed. Therapy should be withheld for major elective surgery for 28 days and for 7 days for minor surgery or as directed by the prescribing Consultant. Necrotising fasciitis, including fatal cases, has rarely been reported in patients treated with bevacizumab. This condition is usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Bevacizumab therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.
- **Hypertension:** An increased incidence of hypertension has been observed in patients treated with bevacizumab. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent.
    - Pre-existing hypertension should be adequately controlled before starting bevacizumab treatment. Bevacizumab may be continued in conjunction with standard anti-hypertensive therapy at physician's discretion.
    - Patients should have their blood pressure measured before each dose or more frequently if hypertension develops/worsens.
    - Any patient who develops hypertension (>150/100 mmHg) should be treated with anti-hypertensive medications, or have their pre-existing medications adjusted. Patients developing severe hypertension (>200/110 mm Hg) that is not controlled with medication should have bevacizumab discontinued.
    - It should be permanently discontinued if the patient develops hypertensive crisis or

hypertensive encephalopathy.

- **Posterior Reversible Encephalopathy Syndrome (PRES):** There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with PRES, a rare neurologic disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of bevacizumab. The safety of reinitiating therapy in patients previously experiencing PRES is not known.
- **Proteinuria:** Patients with a history of hypertension may be at increased risk for the development of proteinuria.
- **Thromboembolism:** Patients receiving bevacizumab plus chemotherapy, with a history of arterial thromboembolism or age > 65 years have an increased risk of developing arterial thromboembolic reactions during therapy. Caution should be taken when treating these patients. Therapy should be permanently discontinued in patients who develop arterial thromboembolic reactions. Patients may be at risk of developing venous thromboembolic reactions, including pulmonary embolism under bevacizumab treatment. Bevacizumab should be discontinued in patients with life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism. Patients with thromboembolic reactions ≤ Grade 3 need to be closely monitored.
- **Haemorrhage:** Patients treated with bevacizumab have an increased risk of haemorrhage, especially tumour associated haemorrhage and minor mucocutaneous haemorrhage. Bevacizumab should be used with caution in patients at risk of bleeding.
- **Aneurysms and artery dissections**: The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating bevacizumab, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Lomustine:

- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Pulmonary toxicity:** Lomustine should be administered with caution in patients with a baseline below 70% of predicted forced vital capacity (FVC) or carbon monoxide diffusing capacity (DLCO.) Baseline pulmonary function studies should be carried out and repeated as clinically indicated during treatment. Pulmonary toxicity associated with lomustine appears to be dose- related.

DRUG INTERACTIONS:

- Current drug interaction databases should be consulted for more information.
- The safety and efficacy of concomitant administration of radiotherapy and bevacizumab has not been established.

REFERENCES:

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3. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
4. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network.
5. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V4 2022. 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
6. Bevacizumab (Avastin®) Summary of product characteristics EMA. Last updated 28/01/2021. Accessed May 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information_en.pdf
7. Lomustine BCCA Drug monograph Summary of Product Characteristics. Accessed May 2023 Available at http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Lomustine_monograph.pdf

Version	Date	Amendment	Approved By
1	15/05/2023		Prof Patrick Morris

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] The rapid infusion is an unlicensed means of administration of bevacizumab for the indication 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.