

## Lomustine and Bevacizumab 7.5mg/kg Therapy

### INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved Reimbursement Status*
For the treatment of recurrent malignant glioblastoma	C71	00804a	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 patient's 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 90minutes <sup>a, b</sup>	Every 42 days
2	1	Lomustine <sup>c, d</sup>	90mg/m <sup>2</sup> (max. dose 160mg)	PO	N/A	Every 42 days

<sup>a</sup> Flush line with NaCl 0.9% pre and post bevacizumab dose as it should not be mixed with glucose solutions.

<sup>b</sup> 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<sup>1</sup> is described in the NCCP Bevacizumab Rapid Infusion Rate Guidance [here](#). It should not be administered as an intravenous push or bolus.

<sup>c</sup> Lomustine is commonly available as 40mg capsules.

<sup>d</sup> 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.

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

### 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

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- 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
- Breastfeeding

## 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
- 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 as clinically indicated
  - Blood 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.)

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**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 <sup>9</sup> /L)		Platelets (x 10 <sup>9</sup> /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 bevacizumab<sup>a</sup> and lomustine<sup>b</sup> in renal and hepatic impairment**

Table 2: Dose modification of bevacizumab <sup>a</sup> and lomustine <sup>b</sup> in renal and hepatic impairment			
Drug	Renal Impairment		Hepatic Impairment
Bevacizumab	No need for dose adjustment is expected.  Haemodialysis: No need for dose adjustment is expected.		No need for dose adjustment is expected
Lomustine	CrCl (mL/min)	Dose	Mild and moderate: no need for dose adjustment is expected.  Severe: not recommended.
	>50	No dose adjustment is needed	
	30-50	75% of the original dose	
	<30	Not recommended	
	Haemodialysis	Not recommended	

<sup>a</sup> Bevacizumab (renal and hepatic - Giraud et al 2023);  
<sup>b</sup> Lomustine (renal and hepatic - Giraud et al 2023)

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## 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
<b>Hypertension</b>	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
<b>Grade 4 Proteinuria</b>		Discontinue bevacizumab
<b>Tracheoesophageal (TE) fistula or any Grade 4 fistula</b>		Discontinue bevacizumab
<b>Grade 4 Thromboembolic events</b>		Discontinue bevacizumab
<b>Haemorrhagic event ≥ Grade 3</b>		Discontinue bevacizumab
<b>Gastrointestinal Perforation</b>		Discontinue bevacizumab
*Uncontrolled hypertension for initiating bevacizumab is defined as sustained BP>150/100mmHg while receiving anti-hypertensive medication		

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## SUPPORTIVE CARE:

**EMETOGENIC POTENTIAL:** As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT)  
Induced Nausea and Vomiting linked [here](#)

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

- 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:

Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

## REGIMEN SPECIFIC COMPLICATIONS:

- Consider rare risk of pulmonary fibrosis

## 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. Wick W, et al. Lomustine and Bevacizumab in Progressive Glioblastoma. N Engl J Med 2017; 377:1954-1963. Available at <https://www.nejm.org/doi/full/10.1056/nejmoa1707358>
3. 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/>
4. 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>
5. Bevacizumab (Avastin®) Summary of product characteristics EMA. Last updated 17/03/2023.. Accessed March 2024. Available at: [https://www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information_en.pdf)

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6. Lomustine Summary of Product Characteristics. Accessed March 2024. Last updated January 2024. Available at: [https://www.medac.eu/fileadmin/user\\_upload/medac-eu/SPCs/common\\_SPCs/Lomustine\\_medac-spc-common.pdf](https://www.medac.eu/fileadmin/user_upload/medac-eu/SPCs/common_SPCs/Lomustine_medac-spc-common.pdf)

Version	Date	Amendment	Approved By
1	15/05/2023		Prof Patrick Morris
2	18/07/2024	Reviewed. Updated footer on treatment table. Updated cautions section. Updated dose modifications for renal and hepatic impairment in line with Giraud et al, 2023. Updated in line with NCCP standardisation. Added Regimen Specific Complications section.	Prof Patrick Morris

Comments and feedback welcome at [oncologydrugs@cancercontrol.ie](mailto:oncologydrugs@cancercontrol.ie).

<sup>i</sup> 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.

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