CISplatin, Lomustine and vinCRIStine (CLV) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved Reimbursement Status*
Adult high-risk medulloblastoma or other primitive neuro-ectodermal tumour (PNET)	C71	00806a	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.

Lomustine, CISplatin and vinCRIStine are administered every 6 weeks for 8 cycles, starting 4 to 6 weeks after craniospinal radiotherapy (RT)

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

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Lomustine[a, b]	75mg/m^2	PO	N/A	Every 42 days
2	1	CISplatin	75mg/m^2	IV infusion	1000mL NaCl 0.9% over 1 hour (pre and post hydration therapy required)[c, d]	Every 42 days
3	1,8,15	vinCRIStine[e]	1.5mg/m^2 (max dose 2mg)	IV infusion	50mL minibag NaCl 0.9% over 15 minutes	Every 42 days

[a]Lomustine is commonly available as 40mg capsules.

[b]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

[c]**Pre and post hydration therapy required for CISplatin**
See local hospital policy recommendations.
Suggested prehydration for CISplatin therapy:

- Administer 10mmol magnesium sulphate ($MgSO_4$) ((+/-KCl 10-20mmol/L if indicated) in 1000 mL NaCl 0.9% over 60 - 120 minutes. (Refer to relevant local hospital policy for advice on administration of electrolyte infusions).

Administer CISplatin as described above
Post hydration: Administer 1000 mL 0.9% NaCl over 60 minutes.

[d]Mannitol 10% may be used as per local policy to induce diuresis, although there is no conclusive evidence that this is required. The routine use of furosemide to increase urine flow is not recommended unless there is evidence of fluid overload.

[e]vinCRIStine is a neurotoxic chemotherapeutic agent. Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer
https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/safetyreview/neurotoxicguidance.pdf

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

ELIGIBILITY:

- Indication as above
- High risk medulloblastoma or supratentorial PNET (including pinealoblastoma) such as:
  - Residual tumour greater than 1.5cm
  - Evidence of metastatic spread on neuroimaging and/or CSF analysis
  - Brainstem invasion by tumour
- ECOG 0-2
- Adequate haematologic, renal and liver profile

EXCLUSIONS:

- Hypersensitivity to lomustine, CISplatin, vinCRIStine or any of the excipients
- Age >40 years
- Significant hearing impairment/tinnitus
- Pregnancy
- Breastfeeding
- Severe renal impairment

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Pulmonary function tests as clinically indicated for patients considered high risk of pulmonary toxicity
- Audiology and creatinine clearance if clinically indicated

Regular tests:

- FBC, renal and liver profile
- Pulmonary function tests as clinically indicated for patients considered high risk of pulmonary toxicity
- Audiology if clinically indicated

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.

Haematological:

Table 1: Dose modification of lomustine in haematological toxicity

ANC (x10^9/L)		Platelets (x10^9/L)	Dose
≥1.0	and	≥100	100%
<1.0	And/or	<80	Delay until ANC ≥ 1.0 **AND** Platelets ≥ 100 Resume at 80% of original dose (Note: this will be the new 100% dose thereafter)*

*If more than two delays, consult prescribing clinician

Renal and Hepatic Impairment:

Table 2: Dose modification in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment	
Lomustine[a]	**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		
CISplatin[b]	50-59	75% of the original dose	No need for dose adjustment is expected.	
	40-49	50% of the original dose		
	<40	Not recommended		
	Haemodialysis	50% of the original dose may be considered		
vinCRIStine[c]	No need for dose adjustment is expected Haemodialysis: no need for dose adjustment is expected		**Bilirubin (micromol/L)**	**Dose**
			>51	50% of original dose

[a] Lomustine (renal and hepatic - Giraud et al 2023)
[b] CISplatin (renal and hepatic - Giraud et al 2023)
[c] vinCRIStine (renal and hepatic - Giraud et al 2023)

Management of adverse events:

Table 3: Recommended dose modifications of vinCRIStine based on neurotoxicity

Symptom	Dose of VinCRIStine
Grade 1	100%
Grade 2	Hold until recovery then reduce dose by 50%
Grade 3 and 4	Omit

SUPPORTIVE CARE:

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

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

Consider increased risk of vinca alkaloid-induced adverse effects due to inhibition of CYP3A4 by Aprepitant

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:

- Hydration pre and post CISplatin administration **(Reference local policy or see recommendations above).**

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.
- Prophylactic regimen against vinCRIStine induced constipation is recommended **(Refer to local policy)**.
- Anti-fungal prophylaxis (Avoid the concurrent use of azoles and vinCRIStine **(Refer to local policy).**

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:

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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
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6. CISplatin 1mg/mL Concentrate for Solution for Infusion. Summary of Product Characteristics. Last updated 20/19/2023. Accessed May 2024. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-081-001_20092023111244.pdf
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Version	Date	Amendment	Approved By
1	15/05/2023		Prof Patrick Morris
2	18/07/2024	Reviewed. Updated footer on treatment table. Updated Exclusions section. Updated baseline tests 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.