CISplatin, Lomustine and vinCRIStine (CLV) Therapy

INDICATIONS FOR USE:

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

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 mins	Every 42 days

[a]Lomustine is 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 sodium chloride 0.9% over 60 minutes.

Administer CISplatin as described above
Post hydration: Administer 1000 ml 0.9% NaCl over 60mins

[d]Mannitol 10% may be used to 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

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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

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 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.

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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	**CrCl (ml/min)**	**Dose**	Lack of information available. Consider dose reduction.			
	>60	100%				
	45-60	75%				
	30-45	50%				
	<30	Not recommended				
CISplatin	≥60	100%	No dose modifications for hepatic impairment			
	45-60	75%				
	<45	Hold CISplatin or delay with additional IV fluids				
vinCRIStine	No dose reduction necessary		**Bilirubin (micromol/L)**		**AST/ALT (Units/L)**	**Dose**
			26-51	Or	60-180	50%
			>51	And	Normal	50%
			>51	And	>180	Omit

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

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SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

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)**.

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.

Lomustine

- **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 ($DL_{CO.}$) 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.

CISplatin

- Renal toxicity is common with CISplatin. Encourage oral hydration.
- Ototoxicity and sensory neural damage should be assessed by history prior to each cycle**.**

vinCRIStine

- **Peripheral neuropathy:** vinCRIStine may cause peripheral neuropathy which is dose related and cumulative, requiring monitoring before each dose is administered. The presence of pre-existing neuropathies or previous treatment with other neurotoxic drugs may increase risk of peripheral neuropathy. Patients with mild peripheral neuropathy can usually continue to receive full doses of vinCRIStine, but when symptoms increase in severity and interfere with neurologic function, dose reduction or discontinuation of the drug may be necessary. The natural history following discontinuation of treatment is gradual improvement, which may take up to several months.
- **Extravasation:** vinCRIStine causes pain and possible tissue necrosis if extravasated **(Refer to local policy).**

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DRUG INTERACTIONS:

- Current drug interaction databases should be consulted for more information.
- Avoid concurrent use of CISplatin with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive nephrotoxicity. If necessary monitor renal function closely.
- Concurrent administration of vinCRIStine with allopurinol, pyridoxine or isoniazid may increase the incidence of cytotoxic induced bone marrow depression.
- CYP3A4 enzyme inducers may increase the clearance of vinCRIStine.
- CYP3A4 enzyme inhibitors may decrease the clearance of vinCRIStine.
- Consider increased risk of vinca alkaloid-induced adverse effects due to inhibition of CYP3A4 by aprepitant

REFERENCES:

1. Packer RJ, et al. Outcome for children with medulloblastoma treated with radiation and cisplatin, CCNU, and vincristine chemotherapy. J Neurosurg 1994;81:690-8.
2. Packer RJ, et al. Treatment of Children With Medulloblastomas With Reduced-Dose Craniospinal Radiation Therapy and Adjuvant Chemotherapy: A Children's Cancer Group Study. J Clin Oncol 1999;(17)2127-2127
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. 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
6. Lomustine BCCA Drug monograph Summary of Product Characteristics. Accessed January 2023 Available at http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Lomustine_monograph.pdf
7. CISplatin 1mg/ml Concentrate for Solution for Infusion. Summary of Product Characteristics Accessed May 2023. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-199-001_24102022175647.pdf
8. vinCRIStine Summary of Product Characteristics Last updated: October 2021. . Accessed May 2023. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-232-001_21092022164804.pdf

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1	15/05/2023		Prof Patrick Morris

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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