Etoposide and CISplatin 20mg/m^2 (EP) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Indicator
Treatment of good prognosis (IGCCCG criteria) metastatic germ cell tumours (both non-seminoma and seminoma)	C62	00301a	

If a reimbursement indicator (e.g. ODMS, CDS[i]) is not defined, the drug and its detailed indication have not gone through the formal reimbursement process as legislated for in the Health (Pricing and Supply of Medical Goods) Act 2013.

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.

Treatment with etoposide and CISplatin is administered on 5 consecutive days (days 1-5), of a 21 day cycle and repeated for 4 cycles or until disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Admin Order	Day	Drug	Dose	Route	Diluent & Rate
1	1-5	Etoposide	100mg/m^2	IV infusion	1000ml 0.9% NaCl over 30-120 minutes[b]
2	1-5	CISplatin	20mg/m^2	IV infusion	500 to 1000ml 0.9% NaCl over 1 hour (Pre hydration therapy required)[a]
[a]Prehydration therapy required prior to CISplatin See local hospital policy recommendations. Suggested prehydration for CISplatin therapy: Administer 10mmol magnesium sulphate ($MgSO_4$) in 1000 mL sodium chloride 0.9% over 60 minutes. Administer CISplatin as described above					
[b]Hypotension following rapid IV administration has been reported. Longer infusion times may be required based on the patient's tolerance					

ELIGIBILTY:

- Indications as above
- ECOG status 0-3

EXCLUSIONS:

- Hypersensitivity to etoposide, CISplatin or any of the excipients.
- CISplatin
  - Pre existing neuropathies ≥ grade 2
  - Creatinine clearance < 40 mL/min
  - Significant hearing impairment/tinnitus
- Severe liver impairment (etoposide)

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, U&Es, LFTs, creatinine
- Consider sperm banking for appropriate patients prior to initiation of therapy

Regular tests:

- FBC weekly during treatment
- U&Es, LFTs, creatinine prior to each treatment 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

Haematological:

- Delay and dose reductions are not recommended as the efficacy of this treatment may be greatly compromised.
- All delays to treatment must be approved by prescribing consultant.
- Prophylactic use of G-CSF is not recommended.
- G-CSF is indicated in patients receiving their second or subsequent cycle of BEP who have had an episode of neutropenic fever or who have not recovered their neutrophil count by Day 5.

Renal and Hepatic Impairment:

Table 2: Dose modification in renal and hepatic impairment

Drug	Renal impairment		Hepatic Impairment			
Etoposide	**Cr Cl (ml/min)**	**Dose**	**Bilirubin (micromol/L)**		**AST (Units/L)**	**Dose Etoposide**
	>50	100%				
	15-50	75%	26-51	or	60-180	*50%
	Subsequent dosing should be based on patient tolerance and clinical effect. Data are not available in patients with CrCl < 15ml/min and further dose reductions should be considered in these patients.		>51	or	>180	Clinical decision
CISplatin	**GFR (ml/min)**	**Dose of CISplatin**	**No dose reduction necessary**			
	≥ 60	100%				
	*45-59	75%				
	<45	Hold CISplatin or delay with additional IV fluids				
**Due to the curative intent of this chemotherapy regimen , in cases where Cr Cl falls between 45-59ml/min it may be appropriate to maintain dose of CISplatin but with extra hydration, longer infusion time and daily Creatinine measurements at the discretion of the prescribing consultant.*						

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

CISplatin High
Etoposide Low (**Refer to local policy).**

PREMEDICATIONS:

Hydration prior to CISplatin administration **(Reference local policy or see recommendations above).**

OTHER SUPPORTIVE CARE:

No specific recommendations

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

- **Hypersensitivity:** Hypersensitivity reactions have been reported with etoposide and CISplatin. Monitor infusion of etoposide for the first 15 minutes for signs of hypotension.
- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately. Avoid aminoglycoside antibiotics.
- **Renal Toxicity**: Nephrotoxicity is common with CISplatin. Strongly encourage oral hydration. If oral hydration is not possible (e.g. excessive nausea), IV hydration is indicated. Avoid nephrotoxic drugs such as aminoglycoside antibiotics where possible. Where treatment with nephrotoxic drugs must be used, monitor renal function.
- **Ototoxicity and sensory neural damage**: These are associated with CISplatin therapy. They should be

assessed by history prior to each cycle.

DRUG INTERACTIONS:

- CISplatin may potentiate the nephrotoxic and ototoxic effects of loop diuretics and aminoglycosides so concurrent use should be avoided.
- Concomitant CISplatin therapy is associated with reduced total body clearance of etoposide.
- CYP3A4 inducers may increase the clearance of etoposide.
- CYP3A4 and p-gp inhibitors may decrease the clearance of etoposide
- Current drug interaction databases should be consulted for more information

ATC CODE:

CISplatin	L01XA01
Etoposide	L01CB01

REFERENCES:

1. Culine, S., P. Kerbrat, A. Kramar, et al. Refining the optimal chemotherapy regimen for good-risk metastatic nonseminomatous germ-cell tumors: a randomized trial of the Genito-Urinary Group of the French Federation of Cancer Centers (GETUG T93BP). Ann Oncol 2007;18(5):917-924.
2. Einhorn LH, Williams SD, Loehrer PJ, et al. Evaluation of optimal duration of chemotherapy in favorable-prognosis disseminated germ cell tumors: a Southeastern Cancer Study Group protocol. J Clin Oncol 1989; 7:387-91
3. CISplatin 1mg/ml Concentrate for Solution for Infusion. Summary of Product Characteristics Accessed July 2017. Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0749-119-002_06062013115044.pdf
4. Etoposide 20 mg/ml Concentrate for Solution for Infusion Summary of Product Characteristics Accessed July 2017 Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA1809-020-001_07102015115038.pdf

Version	Date	Amendment	Approved By
1	08/04/2016		Dr Maccon Keane
2	20/09/2019	Updated with new NCCP regimen template	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/