Bleomycin, Etoposide and CISplatin (BEP) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Indicator
Adjuvant treatment of high risk (vascular invasion carcinoma) stage 1 nonseminoma germ cell tumour	C62	00300a	
Metastatic germ cell tumours of the testis	C62	00300b	
Advanced stage or metastatic germ cell tumours (dysgerminoma) of the ovaries	C56	00300c	
Extra-gonadal germ cell tumours	C56/C62	00300d	

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 days 1-5, and treatment with bleomycin is administered on days 1, 8 and 15 of a 21 day cycle.

For good risk patients - 3 cycles are administered,
For intermediate to poor risk patients - 4 cycles are administered

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

Admin Order	Day	Drug	Dose	Route	Diluent & Rate
1	1, 8 and 15	Bleomycin	[a]30,000 IU (30mg)	IV Bolus Or IM[b]	
2	1-5	Etoposide	100mg/m^2	IV infusion	1000ml 0.9% NaCl over 30-120 minutes[c]
3	1-5	CISplatin	20mg/m^2	IV infusion	500 to 1000ml 0.9% NaCl over 1 hour (Pre hydration therapy required) [d]

Bleomycin dosing may be referred to in IU or in mg. 1,000IU = 1mg

[a]**The total cumulative dose of bleomycin should NOT exceed 400,000 international units (400mg).**
The risk of pulmonary toxicity increases beyond a cumulative dose of 300,000 international units (300mg).

[b]For IM injection dose is dissolved in up to 5ml 0.9% NaCl. If pain occurs at the site of injection a 1% solution of lignocaine may be used as a solvent (6)

[c]Hypotension following rapid IV administration has been reported.
Longer infusion times may be required based on the patient's tolerance

[d]Prehydration therapy is required prior to CISplatin (See local hospital policy recommendations).
Suggested prehydration for CISplatin therapy:

1. Administer 10mmol magnesium sulphate ($MgSO_4$) in 1000 mL sodium chloride 0.9% over 60 minutes.

Administer CISplatin as described above

ELIGIBILTY:

- Indications as above
- ECOG status 0-3

EXCLUSIONS:

- Hypersensitivity to bleomycin, etoposide, CISplatin or any of the excipients.
- Bleomycin is contraindicated in patients with acute pulmonary infection or chest X rays suggesting diffuse fibrotic changes or greatly reduced lung function
- 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
- Pulmonary function tests (PFTs) and Chest X-ray prior to bleomycin
- 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
- Chest X-ray prior to each cycle
- PFTs as 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:

- 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			
Bleomycin	**CrCl (ml/min)**	**Dose**	No dose recommendations available in SmPC, clinical decision			
	>50	100%				
	10-50	75%				
	<10	50%				
Etoposide	**CrCl (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.*

Bleomycin Induced Lung Toxicity:

- Bleomycin can be associated with the development of life-threatening pulmonary toxicity.
- Bleomycin should be discontinued in patients demonstrating clinical or radiographic evidence of pulmonary injury or significant deterioration of pulmonary diffusion capacity.
- Do not reintroduce bleomycin to patients with any bleomycin-induced lung injury.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Days 1-5 High

Days, 8 15 Minimal (**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.

- **Pulmonary toxicity**: Bleomycin: may cause severe and life threatening pulmonary toxicity. Pulmonary toxicity of bleomycin is both dose-related and age-related. It may also occur when lower doses are administered, especially in elderly patients, patients with reduced kidney function, pre-existing lung disease, previous or concurrent radiotherapy to the chest and in patients who need administration of oxygen. It is significantly enhanced by thoracic radiation and by hyperoxia used during surgical anaesthesia.
- **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:

- Bleomycin causes sensitization of lung tissue to oxygen. If oxygen is required the use of low concentration (e.g. 25%) is recommended. Fluid replacement should be carefully monitored with emphasis on administration of colloid rather than crystalloid to avoid interstitial pulmonary oedema.
- 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:

Bleomycin	L01DC01
CISplatin	L01XA01
Etoposide	L01CB01

REFERENCES:

1. 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
2. Williams S, Birch R, Einhorn LH et al. Treatment of disseminated germ-cell tumors with CISplatin, bleomycin, and either vinblastine or etoposide. N Engl J Med, 1987; 316: 1435-1440
3. de Wit R, Roberts JT, Wilkinson P, et al. Final analysis demonstrating the equivalence of 3 BEP vs 4 cycles and the 5 day schedule vs 3 days per cycle in good prognosis germ cell cancer. An EORTC/MRC phase III study. Proc Am Soc Clin Oncol 2000;19a:326a (abstract 1281).
4. Nichols et al. Randomized comparison of CISplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: an Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B Study. J Clin Oncol 1998; Vol 16 (No.4): 1287-1293
5. Williams SD, Blessing JA, Hatch KD et al. Chemotherapy of advanced dysgerminoma: trials of the Gynecologic Oncology Group. J Clin Oncol 1991;9(11):1950-1955.
6. Bleomycin, etoposide, and CISplatin (BEP) chemotherapy for germ cell tumors. UptoDate. January 2016
7. Bleo-Kyowa Summary of Product Characteristics Accessed September 2017. Available at http://www.medicines.org.uk/emc/medicine/26918
8. CISplatin 1mg/ml Concentrate for Solution for Infusion. Summary of Product Characteristics Accessed September 2017. Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0749-119-002_06062013115044.pdf
9. Etoposide 20 mg/ml Concentrate for Solution for Infusion Summary of Product Characteristics Accessed September 2017Available 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	27/09/2017	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/