Bleomycin, Etoposide and CISplatin (BEP) Therapy

INDICATIONS FOR USE:

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Regimen Code</th>
<th>Reimbursement Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant treatment of high risk (vascular invasion carcinoma) stage 1 nonseminoma germ cell tumour</td>
<td>C62</td>
<td>00300a</td>
<td>Hospital</td>
</tr>
<tr>
<td>Metastatic germ cell tumours of the testis</td>
<td>C62</td>
<td>00300b</td>
<td>Hospital</td>
</tr>
<tr>
<td>Advanced stage or metastatic germ cell tumours (dygserminoma) of the ovaries</td>
<td>C56</td>
<td>00300c</td>
<td>Hospital</td>
</tr>
<tr>
<td>Extra-gonadal germ cell tumours</td>
<td>C56/C62</td>
<td>00300d</td>
<td>Hospital</td>
</tr>
</tbody>
</table>

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.

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.

<table>
<thead>
<tr>
<th>Admin Order</th>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1, 8 and 15</td>
<td>#Bleomycin</td>
<td>300,000 International Units</td>
<td>IV Bolus or IM&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1-5</td>
<td>Etoposide</td>
<td>100mg/m²</td>
<td>IV infusion</td>
<td>1000ml 0.9% NaCl over 60 minutes&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>1-5</td>
<td>CISplatin</td>
<td>20mg/m²</td>
<td>IV infusion</td>
<td>1000ml 0.9% NaCl over 1 hour (Prehydration therapy required)&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Bleomycin dosing should only be expressed in terms of international units.

<sup>d</sup>Lifetime cumulative dose of bleomycin is 400,000 international units (bleomycin has been associated with severe and life threatening respiratory complications. The total cumulative dose of bleomycin should NOT exceed 400,000 international units. The risk of pulmonary toxicity increases beyond a cumulative dose of 300,000 international units. Check the cumulative dose prior to each treatment).

<sup>e</sup>Prehydration therapy required for CISplatin

See local hospital policy recommendations.

Suggested prehydration for CISplatin therapy:

1. Administer 10mmol magnesium sulphate (MgSO<sub>4</sub>) (+/-KCl 10-20mmol/L if indicated) in 1000 mL sodium chloride 0.9% over 60 minutes.

Administer CISplatin as described above.

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The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient’s care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE’s terms of use available at [http://www.hse.ie/eng/Disclaimer](http://www.hse.ie/eng/Disclaimer).

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ELIGIBILITY:
- 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, renal and liver profile, creatinine
- Pulmonary function tests (PFTs) and Chest X-ray prior to bleomycin
- Consider sperm banking for appropriate patients prior to initiation of therapy
- Consider Audiometry testing

Regular tests:
- FBC weekly during treatment
- Renal and liver profile, 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 1: Dose modification in renal and hepatic impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal Impairment</th>
<th>Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CrCl (ml/min)</td>
<td>Dose</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>&gt;50</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>10-50</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>&lt;10</td>
<td>50%</td>
</tr>
</tbody>
</table>

Subsequent dosing should be based on patient tolerance and clinical effect.

Etoposide
- CrCl (ml/min) >50: 100%
- 15-50: 75%
- <15: 50%

Subsequent dosing should be based on patient tolerance and clinical effect.

CISplatin
- CrCl (ml/min) ≥ 60: 100%
- *45-59: 75%
- <45: Hold CISplatin or delay with additional IV fluids

*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:
Bleomycin: Minimal (Refer to local policy)
Etoposide: Low (Refer to local policy)
CISplatin: High (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.
- **Otoxicity 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.
REFERENCES:


<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>08/04/2016</td>
<td></td>
<td>Dr Maccon Keane</td>
</tr>
<tr>
<td>2</td>
<td>27/09/2017</td>
<td>Updated with new NCCP regimen template</td>
<td>Prof Maccon Keane</td>
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<tr>
<td>3</td>
<td>06/12/2017</td>
<td>Updated with revised CISplatin hydration regimen recommendations</td>
<td>Prof Maccon Keane</td>
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<tr>
<td>4</td>
<td>20/11/2019</td>
<td>Reviewed. Standardised treatment table and renal dose modifications.</td>
<td>Prof Maccon Keane</td>
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<tr>
<td>5</td>
<td>11/11/2020</td>
<td>Updated baseline tests</td>
<td>Prof Maccon Keane</td>
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<tr>
<td>6</td>
<td>22/10/2021</td>
<td>Removed reference to bleomycin mg dosing. Updated emetogenic potential.</td>
<td>Prof Maccon Keane</td>
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Comments and feedback welcome at oncologydrugs@cancercontrol.ie.