INDICATIONS FOR USE:

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Regimen Code</th>
<th>*Reimbursement Indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locally advanced or metastatic transitional cell carcinoma (TCC) of the urothelium</td>
<td>C67</td>
<td>00333a</td>
<td></td>
</tr>
</tbody>
</table>

*If a reimbursement indicator (e.g. ODMS, CDS) is not defined, the drug and its detailed indication have not been assessed through the formal HSE reimbursement process.

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.

Methotrexate is administered on day 1 and vinBLAstine, DOXOrubicin and CISplatin on day 2 once every 14 days until disease progression or unacceptable toxicity develops.

Granulocyte-Colony stimulating factor (G-CSF) is administered on day 3, 4, 5 6 & 7 of every 14 day cycle.

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>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Methotrexate</td>
<td>30mg/m²</td>
<td>IV Bolus</td>
<td></td>
<td>Every 14 days</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td><em>VinBLAstine</em></td>
<td>3mg/m²</td>
<td>IV infusion</td>
<td>50ml 0.9% NaCl over 15 min</td>
<td>Every 14 days</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>DOXOrubicin</td>
<td>30mg/m²</td>
<td>IV Bolus</td>
<td></td>
<td>Every 14 days</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td><em>CISplatin</em></td>
<td>70mg/m²</td>
<td>IV infusion</td>
<td>500ml 0.9% NaCl over 60-120mins</td>
<td>Every 14 days</td>
</tr>
</tbody>
</table>

*VinBLAstine is a neurotoxic chemotherapeutic agent. Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer

*Lifetime cumulative dose of DOXOrubicin is 450mg/m²
In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors outlined below and to the age of the patient.

\[ \text{Risk Factors:} \]

Pre and post hydration therapy required for CISplatin
See local hospital policy recommendations.
Suggested prehydration for CISplatin therapy:
1. Administer 10mmol magnesium sulphate (MgSO₄) \((+/-KCl 20mmol/L \text{ if indicated})\) in 1000ml sodium chloride 0.9% over 60 minutes.
2. Administer CISplatin as described above
3. Post hydration: Administer 1000 ml 0.9% NaCl over 60mins
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.

ELIGIBILITY:
- Indications as above
- ECOG 0-1

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NCCP Chemotherapy Regimen

EXCLUSIONS:
- Hypersensitivity to methotrexate, vinBLAS, DOXorubicin, CISplatin or any of the excipients
- Congestive heart failure (LVEF < 50%) or other significant heart disease
- Moderate/severe renal impairment (creatinine clearance < 60 mL/min)
- Pregnancy and Lactation
- Pre-existing neuropathies ≥ grade 2
- Significant hearing impairment/tinnitus

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

TESTS:
Baseline tests:
FBC, Renal and liver profile
ECG
MUGA or ECHO (LVEF > 50% to administer doxorubicin) if >65 years or if clinically indicated.
Audiology and creatinine clearance if clinically indicated

Regular tests:
FBC, Renal and liver profile prior to each cycle
If clinically indicated MUGA scan or ECG

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 for haematological toxicity

<table>
<thead>
<tr>
<th>ANC (x10⁹ /L)</th>
<th>Platelets (x10⁹ /L)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1.5</td>
<td>≥100</td>
<td>100% Dose</td>
</tr>
<tr>
<td>&lt;1.5</td>
<td>&lt;100</td>
<td>Hold*</td>
</tr>
</tbody>
</table>

Febrile neutropenia or ANC < 0.5 for 5-7 days
Thrombocytopenic bleeding or platelets < 25

Hold *then 75% of previous dose

*Do not start a new cycles until ANC ≥1.5 x 10⁹/L and platelets ≥100 x10⁹/L
Renal and Hepatic Impairment:

### Table 2: Dose modifications 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>Cr Cl (ml/min)</td>
<td>Dose</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>&gt;80</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>65%</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>&lt;30</td>
<td></td>
</tr>
<tr>
<td>vinBLAStine</td>
<td>No dose reduction necessary</td>
<td>Bilirubin (micromol/L)</td>
</tr>
<tr>
<td></td>
<td>26–51</td>
<td>or</td>
</tr>
<tr>
<td></td>
<td>&gt;51</td>
<td>and</td>
</tr>
<tr>
<td></td>
<td>&gt;51</td>
<td>and</td>
</tr>
<tr>
<td>DOXOrubicin</td>
<td>No dose reduction required. Clinical decision in severe impairment.</td>
<td>Bilirubin (micromol/L)</td>
</tr>
<tr>
<td></td>
<td>20–51</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>51–85</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>&gt;85</td>
<td>Omit</td>
</tr>
<tr>
<td>CISplatin</td>
<td>GFR (ml/min)</td>
<td>Dose</td>
</tr>
<tr>
<td></td>
<td>≥60</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>45–59</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>&lt;45</td>
<td>Consider cisplatin</td>
</tr>
</tbody>
</table>

Management of adverse events:

### Table 3: Dose Modification of MVAC Therapy for Adverse Events

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Recommended dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurotoxicity</td>
<td></td>
</tr>
<tr>
<td>Grade 2 present at start of next cycle</td>
<td>Reduce dose of CISplatin and vinBLAStine by 25% dose.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Discontinue CISplatin and vinBLAStine</td>
</tr>
</tbody>
</table>

**SUPPORTIVE CARE:**

**EMETOGENIC POTENTIAL:**
Day 1 Low (Methotrexate)
Day 2 High *(Refer to local policy).*

**PREMEDICATIONS:** None usually required

**OTHER SUPPORTIVE CARE:**

- Hydration prior and post CISplatin administration *(Reference local policy or see recommendations above).* Patient should be encouraged to drink large quantities of liquids for 24 hours after the CISplatin infusion to ensure adequate urine secretion.

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• Prophylactic laxatives may be required to prevent constipation related to the use of vinca alkaloids.

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.
• **Pleural effusion or ascites:** Methotrexate should be used with caution in patients with pleural effusions or ascites, as methotrexate may accumulate in third space fluid compartments.
• **Extravasation:** vinBLASTine is a vesicant. DOXOrubicin may cause pain and tissue necrosis if extravasated. (Refer to local extravasation guidelines).
• **Cardiac Toxicity:** DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction.
• **Hypersensitivity:** Hypersensitivity reactions have been reported with CISplatin.
• **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:**

• NSAIDs may decrease the clearance of methotrexate by decreasing its renal perfusion and tubular secretion thus increasing its toxicity.
• Sulphonamides and penicillins may displace bound methotrexate from plasma protein increasing serum methotrexate levels and its toxicity.
• Concomitant administration of drugs that cause folate deficiency may lead to increased methotrexate toxicity.
• Ciprofloxacin may inhibit renal tubular transport of methotrexate, increasing serum methotrexate levels and its toxicity.
• Probenecid may inhibit renal excretion of methotrexate, increasing serum methotrexate levels and its toxicity.
• Co-administration of CISplatin has been reported to cause higher plasma concentrations of vinBLASTine.
• Erythromycin may increase the toxicity of vinBLASTine.
• Concurrent administration of calcium channel blockers with DOXOrubicin should be avoided as they may decrease the clearance of DOXOrubicin.
• CISplatin may potentiate the nephrotoxic and ototoxic effects of loop diuretics and aminoglycosides so concurrent use should be avoided.
• Current drug interaction databases should be consulted for more information.

**ATC CODE:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>ATC Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>L01BA01</td>
</tr>
<tr>
<td>vinBLASTine</td>
<td>L01CA01</td>
</tr>
<tr>
<td>DOXOrubicin</td>
<td>L01DB01</td>
</tr>
</tbody>
</table>

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NCCP Chemotherapy Regimen

NCCP Regimen: Methotrexate, VinBLAStine, DOXORubicin and CISplatin (MVAC)-14 days Therapy

Published: 20/06/2016
Review: 11/12/2019
Version number: 2

Tumour Group: Genitourinary
NCCP Regimen Code: 0033

ISM0 Contributor: Prof Maccon Keane

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REFERENCES:
4. Nephrotoxicity Associated with CISplatin EviQ ID: 184 v.3
   https://www.uptodate.com/contents/CISplatin-nephrotoxicity?source=search_result&search=CISplatin%20hydration&selectedTitle=1~150
   Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0437-005-003_22042013144145.pdf3.

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20/06/2016</td>
<td>Updated with new NCCP regimen format, updated with revised CISplatin hydration regimen recommendations</td>
<td>Prof Maccon Keane</td>
</tr>
<tr>
<td>2</td>
<td>11/12/2017</td>
<td></td>
<td>Prof Maccon Keane</td>
</tr>
</tbody>
</table>

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.
NCCP Chemotherapy Regimen

NCCP Regimen: Methotrexate, VinBLAStine, DOXOribucin and CISplatin (MVAC)-14 days Therapy

Published: 20/06/2016
Review: 11/12/2019
Version number: 2

Tumour Group: Genitourinary
NCCP Regimen Code: 00333

Cardiotoxicity is a risk associated with anthracycline therapy that may be manifested by early (acute) or late (delayed) effects.

Risk factors for developing anthracycline-induced cardiotoxicity include:
- high cumulative dose, previous therapy with other anthracyclines or anthracenediones
- prior or concomitant radiotherapy to the mediastinal/pericardial area
- pre-existing heart disease
- concomitant use of other potentially cardiotoxic drugs

In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors above and to the age of the patient.