Cabazitaxel and Prednisolone

INDICATIONS FOR USE:

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Protocol Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabazitaxel is indicated in combination with prednisone or prednisolone for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.</td>
<td>C61</td>
<td>00101a</td>
</tr>
</tbody>
</table>

ELIGIBILITY:
- Indications as above
- ECOG status 0-2
- Adequate haematological, hepatic and renal function

EXCLUSIONS:
- Hypersensitivity to cabazitaxel, to other taxanes or any of the excipients including polysorbate 80
- Hepatic impairment (bilirubin >3xULN)
- ANC < 1.5 x 10⁹/L
- Prior radiotherapy to >40% bone marrow
- Prior radionucleotide therapy with samarium-153 or P-32 within 8 weeks or strontium-89 or radium-223 within 12 weeks

TESTS:
Baseline tests: FBC, U&Es, LFTs.

Regular tests: FBC, U&Es, LFTs.
Assessment of peripheral neuropathy.

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.
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.

Androgen ablative therapy (e.g. LHRH agonist, LHRH antagonist) should be maintained.
Cabazitaxel is administered every 21 days (average of 6 cycles) or until disease progression or unacceptable toxicity develops.
Facilities to treat anaphylaxis MUST be present when cabazitaxel is administered

<table>
<thead>
<tr>
<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>Cabazitaxel</td>
<td>25 mg/m²</td>
<td>IV*</td>
<td>250ml 0.9% NaCl or glucose 5% over 1 hour</td>
<td>Repeat every 21 days</td>
</tr>
<tr>
<td>1-21</td>
<td>Prednisolone</td>
<td>10 mg daily</td>
<td>PO</td>
<td></td>
<td>Continuous therapy</td>
</tr>
</tbody>
</table>

An in-line filter of 0.22 micrometer pore size is recommended during administration.
NON PVC infusion containers and NON polyurethane infusion sets should be used.
Final concentration of cabazitaxel in infusion solution should be between 0.10mg/ml and 0.26mg/ml.

DOSE MODIFICATIONS:
- Any dose modification should be discussed with a Consultant.
- Acceptable levels for treatment to proceed (if outside these levels defer one week or contact consultant)
  - Neutrophil count >1.5 x10⁹/L
  - Platelets >100 X 10⁹/L

Renal impairment:
No dose adjustment is necessary in patients with renal impairment, not requiring hemodialysis.

Patients presenting end stage renal disease,(Creatinine Clearance < 15ml/min/1.73m²) should be treated with caution and monitored carefully during treatment

<table>
<thead>
<tr>
<th>Renal impairment</th>
<th>Bilirubin</th>
<th>AST</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 1 to ≤ 1.5x ULN</td>
<td>or</td>
<td>&gt;1.5 x ULN</td>
</tr>
<tr>
<td></td>
<td>&gt;1.5 to ≤ 3 x ULN</td>
<td></td>
<td>*Max dose 15mg/m²</td>
</tr>
<tr>
<td></td>
<td>&gt; 3 x ULN</td>
<td></td>
<td>CI</td>
</tr>
</tbody>
</table>

* Limited efficacy data are available at this dose
Table 1: Dose modification schedule based on the grade of any adverse events

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Discontinue</th>
<th>Recommended dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged grade ≥3 neutropenia (longer than 1 week) despite appropriate treatment including G-CSF</td>
<td></td>
<td>Delay treatment until neutrophil count is &gt;1,500 cells/mm³, then reduce cabazitaxel dose from 25 mg/m² to 20 mg/m². Withdraw treatment if this recurs.</td>
</tr>
<tr>
<td>Febrile neutropenia or neutropenic infection</td>
<td></td>
<td>Delay treatment until improvement or resolution, and until neutrophil count is &gt;1,500 cells/mm³, then reduce cabazitaxel dose from 25 mg/m² to 20 mg/m². Withdraw treatment if this recurs.</td>
</tr>
<tr>
<td>Grade ≥3 diarrhoea or persisting diarrhoea despite appropriate treatment, including fluid and electrolyte replacement</td>
<td></td>
<td>Delay treatment until improvement or resolution, then reduce cabazitaxel dose from 25 mg/m² to 20 mg/m². Withdraw treatment if this recurs.</td>
</tr>
<tr>
<td>Grade &gt;2 peripheral neuropathy</td>
<td></td>
<td>Delay treatment until improvement, then reduce cabazitaxel dose from 25 mg/m² to 20 mg/m². Withdraw treatment if this recurs.</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>Discontinue</td>
<td>Withhold treatment until grade 1 then restart at 20 mg/m²</td>
</tr>
<tr>
<td>Grade 3</td>
<td></td>
<td>Replace metoclopramide pre-med with ondansetron If, despite this grade ≥3 nausea/vomiting occurs then reduce dose to 20 mg/m². Withdraw treatment if this recurs.</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
<td>Discontinue</td>
<td></td>
</tr>
</tbody>
</table>

*SUPPORTIVE CARE:*  
**EMETOGENIC POTENTIAL:** Low (Refer to local policy).

**PREMEDICATIONS:**  
Premedication 30 minutes prior to each administration:  
Antihistamine - Chlorphenamine 10mg IV  
IV Steroid – Dexamethasone 8mg IV  
H2 Antagonist – Ranitidine 50mg IV

**TAKE HOME MEDICATIONS:**  
Ondansetron 8mg orally BD for 2 days.  
Metoclopramide 10mg orally TDS PRN for 5 days.
Loperamide should be prescribed with first cycle and patients should be instructed to take at onset of diarrhoea.

OTHER SUPPORTIVE CARE:
Primary prophylaxis with G-CSF should be considered in patients with high-risk clinical features (age >65 years, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, or other serious comorbidities) that predispose them to increased complications from prolonged neutropenia.

GCSF support is recommended therapeutically, as secondary prophylaxis.

Throughout the treatment, adequate hydration of the patient needs to be ensured in order to prevent complications like renal failure.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **Hypersensitivity reactions:** All patients should be pre-medicated prior to the initiation of the infusion of cabazitaxel. Patients should be observed closely for hypersensitivity reactions especially during the first and second infusions. Severe hypersensitivity reactions require immediate discontinuation of cabazitaxel and appropriate therapy. Patients with a hypersensitivity reaction must stop treatment with cabazitaxel.

- **Neutropenia:** Most common adverse reaction of cabazitaxel. Monitoring of complete blood counts is essential on a weekly basis during cycle 1 and before each treatment cycle thereafter so that the dose can be adjusted, if needed. The dose should be reduced in case of febrile neutropenia, or prolonged neutropenia despite appropriate treatment. Patients should be re-treated only when neutrophils recover to a level $\geq 1.5 \times 10^9$ cells/L. Primary prophylaxis with G-CSF should be considered in patients with high-risk clinical features (age >65 years, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, or other serious comorbidities) that predispose them to increased complications from prolonged neutropenia. The use of G-CSF has been shown to limit the incidence and severity of neutropenia.

- **Gastrointestinal disorders:** Symptoms such as abdominal pain and tenderness, fever, persistent constipation, diarrhoea, with or without neutropenia, may be early manifestations of serious gastrointestinal toxicity and should be evaluated and
treated promptly. Cabazitaxel treatment delay or discontinuation may be necessary. Gastrointestinal (GI) hemorrhage and perforation, ileus, colitis, including fatal outcome, have been reported in patients treated with cabazitaxel. Caution is advised with treatment of patients most at risk of developing gastrointestinal complications: those with neutropenia, the elderly, concomitant use of NSAIDs, anti-platelet therapy or anti-coagulants, and patients with a prior history of pelvic radiotherapy or gastrointestinal disease, such as ulceration and GI bleeding.

- **Peripheral neuropathy:** Patients under treatment with cabazitaxel should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop. Physicians should assess for the presence or worsening of neuropathy before each treatment. Treatment should be delayed until improvement of symptoms. The dose of cabazitaxel should be reduced from 25 mg/m$^2$ to 20 mg/m$^2$ for persistent grade ≥2 peripheral neuropathy.

- **Risk of renal failure:** Renal disorders, have been reported in association with sepsis, severe dehydration due to diarrhoea, vomiting and obstructive uropathy. Renal failure including cases with fatal outcome has been observed. Adequate hydration should be ensured throughout treatment with cabazitaxel. The patient should be advised to report any significant change in daily urinary volume immediately. Serum creatinine should be measured at baseline, with each blood count and whenever the patient reports a change in urinary output. Cabazitaxel treatment should be discontinued in case of renal failure ≥ Grade 3.

- **Excipients:** The solvent contains 573.3 mg ethanol 96% (15% v/v), equivalent to 14 ml of beer or 6 ml of wine. Harmful for those suffering from alcoholism. It should be taken into account in high-risk groups such as patients with liver disease, or epilepsy.

**DRUG INTERACTIONS:**
- Concomitant medicinal products that are strong inducers or strong inhibitors of CYP3A should be avoided. However, if patients require co-administration of a strong CYP3A inhibitor, a 25% cabazitaxel dose reduction should be considered. Patients should also be counselled with regard to consumption of grapefruit juice
- Vaccination with live attenuated vaccines should be avoided.
- Current drug interaction databases should be consulted for more information.

**ATC CODE:**
Cabazitaxel - L01CD04

**REIMBURSEMENT CATEGORY:**

<table>
<thead>
<tr>
<th>NCCP Protocol: Cabazitaxel and Prednisolone</th>
<th>Published: 1/3/2013</th>
<th>Version number: 3</th>
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<tr>
<td>Tumour Group: Genitourinary</td>
<td>ISMO Contributor: Dr Maccon Keane, GUH</td>
<td></td>
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<tr>
<td>NCCP Protocol Code: 00101</td>
<td>3/32019</td>
<td>Page 5 of 6</td>
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Cabazitaxel is available for use in public hospitals and is currently available for reimbursement through the Oncology Hospital Drugs Management System (hosted by PCRS, Jan 2015).

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

**REFERENCES:**

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5/3/2013</td>
<td></td>
<td>Dr David Gallagher</td>
</tr>
<tr>
<td>2</td>
<td>1/3/2015</td>
<td>Updated treatment section to include glucose 5% as diluent, specify infusion concentration Use of NON PVC or NON polyurethane infusion containers or giving sets specified as per update to SmPC Updated exclusion criteria</td>
<td>Dr Maccon Keane</td>
</tr>
<tr>
<td>3</td>
<td>1/3/2017</td>
<td>Updated exclusion criteria with respect to hepatic impairment, updated dosing recommendations in renal and hepatic impairment</td>
<td>Prof Maccon Keane</td>
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</tbody>
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Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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