Cabazitaxel and prednisoLONE Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
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.	C61	00101a	ODMS

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.

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 1: Treatment schedule for Cabazitaxel 25mg/m^2 and prednisoLONE*

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Cabazitaxel	25 mg / m^2	IV[a]	250ml 0.9% NaCl over 1 hour	Repeat every 21 days
1-21	prednisoLONE	10 mg daily	PO		Continuous therapy
[a]An in-line filter of 0.22 micrometer pore size may be recommended during administration depending on brand used. 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.					

*See alternative schedule for cabazitaxel 20mg/m^2 and prednisoLONE below

ALTERNATE TREATMENT SCHEDULE:

Table 2: Treatment schedule for Cabazitaxel 20mg/m^2 and prednisoLONE

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Cabazitaxel	[i]20 mg / m^2	IV[a]	250ml 0.9% NaCl over 1 hour	Repeat every 21 days
1-21	prednisoLONE	10 mg daily	PO		Continuous therapy
[a]An in-line filter of 0.22 micrometer pore size may be recommended during administration depending on brand used 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.					

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 10^9/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

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile

Regular tests:

- FBC prior to each cycle
- Renal and liver profile prior to each cycle
- 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.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
  Recommended dose modifications are based on starting dose of 25mg/m^2 as data in patients below the 20 mg/m^2 dose are limited. Consider starting dose when making reductions.

Haematological:

Table 3: Dose modification in haematological toxicity

ANC (x10^9/L)		Platelets (x10^9/L)	Recommended dose modification
<1.5	**And**	**<100**	Delay treatment for one week until neutrophil count has recovered to >1.5x 10^9 and platelets > 100 x 10^9/L or contact clinician
Prolonged grade ≥3 neutropenia (longer than1 week) despite appropriate treatment including G-CSF			Delay treatment until neutrophil count is >1.5x 10^9L, then reduce cabazitaxel dose from 25 mg/m^2 to 20 mg/m^2. Note: A further dose reduction to 15 mg/m^2 or discontinuation of cabazitaxel may be considered on recurrence. Data in patients below the 20 mg/m^2 dose are limited.
Febrile neutropenia or neutropenic infection			

Renal and Hepatic Impairment:

Table 4: Dose modification of cabazitaxel in renal and hepatic impairment

Renal Impairment	Hepatic Impairment			
No dose adjustment is necessary in patients with renal impairment, not requiring hemodialysis. Patients presenting end stage renal disease(Creatinine Clearance < 15ml/min/1.73m^2) should be treated with caution and monitored carefully during treatment	**Bilirubin**		**AST**	**Recommended dose modification**
	> 1 to ≤ 1.5x ULN	**or**	>1.5 x ULN	20mg/m^2
	>1.5 to ≤ 3 x ULN			*Max dose 15mg/m^2
	> 3 x ULN			CI
* Limited efficacy data are available at this dose				

Management of adverse events:

Table 5: Dose modification schedule based on the grade* of any adverse events

Adverse reactions	Recommended dose modification
Grade ≥3 diarrhoea or persisting diarrhoea despite appropriate treatment, including fluid and electrolyte replacement	*Delay treatment until improvement or resolution, then reduce cabazitaxel dose from 25 mg/m^2 to 20 mg/m^2
Grade ≥2 peripheral neuropathy	*Delay treatment until improvement, then reduce cabazitaxel dose from 25 mg/m^2 to 20 mg/m^2.
<u>Stomatitis</u> Grade 3 Grade 4	 Withhold treatment until grade 1 then restart at 20 mg/m^2 Discontinue
Nausea/vomiting	Replace metoclopramide pre-med with ondansetron If, despite this, grade ≥3 nausea/vomiting occurs then reduce dose to 20 mg/m^2. Withdraw treatment if this recurs.
Hypersensitivity reactions	Discontinue
* Note: A further dose reduction to 15 mg/m^2 or discontinuation of cabazitaxel may be considered on reoccurrence. Data in patients below the 20 mg/m^2 dose are limited.	

* Common Terminology Criteria for Adverse Events v4.0 (CTC-AE).

SUPPORTIVE CARE:

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

PREMEDICATIONS: Premedication consisting of an anti-histamine, glucocorticoid and H2 antagonist should always be administered before each infusion of cabazitaxel

Table 6: Suggested pre-medications prior to cabazitaxel infusion:

Drugs	Dose	Route
Chlorphenamine	10mg	IV bolus 30 minutes prior to cabazitaxel infusion
dexAMETHasone	8mg	IV bolus 30 minutes prior to cabazitaxel infusion
Famotidine	20mg	IV bolus 30 minutes prior to cabazitaxel infusion

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.
- G-CSF 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.
- Loperamide should be prescribed with first cycle and patients should be instructed to take at onset of diarrhoea.

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 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 ≥1.5 x 10^9cells/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/m2 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 6ml 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

REFERENCES:

1. De Bono JS, Oudard S, Ozguroglu M et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after DOCEtaxel treatment: a randomised open-label trial. Lancet, 2010 Vol 376 p1147-1154
2. Eisenberger M, Hardy- Bessard AC, Kim CS et al: Phase III study comparing a reduced dose of cabazitaxel (20mg/m^2) and the currently approved dose (25mg/m^2) in post DOCEtaxel patients with metastatic castration-resistant prostate cancer – PROSELICA. J Clin Oncol 2017 35: 3198-3206
3. Cabazitaxel (Jevtana®) Summary of Product Characteristics Accessed Oct 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/jevtana-epar-product-information_en.pdf
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2022. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

Version	Date	Amendment	Approved By
1	05/03/2013		Dr David Gallagher
2	01/03/2015	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	Dr Maccon Keane
3	01/03/2017	Updated exclusion criteria with respect to hepatic impairment, updated dosing recommendations in renal and hepatic impairment	Prof Maccon Keane
4	01/02/2019	Updated to new NCCP regimen template Updated dose modifications as per SmPC update	Prof Maccon Keane
5	10/11/2020	Amended regular tests section	Prof Maccon Keane
6	10/03/2021	Reviewed. Amended premedications: added famotidine as H2 antagonist alternative	Prof Maccon Keane
7	10/11/2023	Addition of alternative treatment table for cabazitaxel 20mg/m^2. Substitution of famotidine for ranitidine in premeds table.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This is an unlicensed posology for the use cabazitaxel in Ireland. Patients should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy