Cabazitaxel Accord for the treatment of patients with metastatic castration resistant prostate cancer (mCRPC) previously treated with a docetaxel containing regimen

General information [1]

Drug description	Indication
Cabazitaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells.	Cabazitaxel Accord in combination with prednisone or prednisolone is indicated for the treatment of adult patients with mCRPC previously treated with a docetaxel containing regimen.

Current treatment [2]

For men with mCRPC who have received prior taxane chemotherapy (docetaxel), NICE recommends:

- Abiraterone in combination with prednisone or prednisolone is recommended as an option for the treatment of mCRPC in adults, in which the disease has progressed on or after one docetaxel-containing chemotherapy regimen
- Enzalutamide is recommended as an option for treating metastatic hormone-relapsed prostate cancer in adults whose disease has progressed during or after docetaxel-containing chemotherapy
- Cabazitaxel in combination with prednisone or prednisolone is recommended as an option for treating metastatic hormone-relapsed prostate cancer in people whose disease has progressed during or after docetaxel chemotherapy, only if: the person has an ECOG performance status 0 or 1; the person has had 225 mg/m² or more of docetaxel; treatment with cabazitaxel is stopped when the disease progresses or after a maximum of 10 cycles (whichever happens first).

Regulatory status

EMA [1]

Approval status for this indication: On 30 April 2020, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Cabazitaxel Accord. Cabazitaxel Accord will be available as a 20 mg/ml concentrate for solution for infusion.

Date of issue of marketing authorisation valid throughout the European Union: **28/08/2020.**

Cabazitaxel Accord is a hybrid medicine of Jevtana® which has been authorised in the EU since 17 March 2011. Cabazitaxel Accord contains the same active substance as Jevtana, but it is available in a different formulation.

The full indication is:

Cabazitaxel Accord in combination with prednisone or prednisolone is indicated for the treatment of adult patients with mCRPC previously treated with a docetaxel containing regimen.

Other indications: none

- ✓ **Medicine under additional monitoring**
- ✓ **Generic medicine**

FDA [3]

Approval status for this indication: 09/2017: Jevtana® is indicated in combination with prednisone for treatment of patients with mCRPC previously treated with a docetaxel-containing treatment regimen.

Recommended Dose: Jevtana® 20 mg/m² administered every three weeks as a one-hour intravenous infusion in combination with oral prednisone 10 mg administered daily throughout Jevtana® treatment. A dose of 25 mg/m² can be used in select patients at the discretion of the treating healthcare provider.

Other indications: none

Costs

Currently no cost information available.

Premedication [4]

The recommended premedication regimen should be performed at least 30 minutes prior to each administration of cabazitaxel with the following intravenous medicinal products to mitigate the risk and severity of hypersensitivity:

- antihistamine (dexchlorpheniramine 5 mg or diphenhydramine 25 mg or equivalent),
- corticosteroid (dexamethasone 8 mg or equivalent), and
- H2 antagonist (ranitidine or equivalent).

Antiemetic prophylaxis is recommended and can be given orally or intravenously as needed.

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

Special warnings and precautions for use [4]

- 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.
  - Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of cabazitaxel, thus facilities and equipment for the treatment of hypotension and bronchospasm should be available.
  - Severe reactions can occur and may include generalized rash/erythema, hypotension and bronchospasm.
  - Severe hypersensitivity reactions require immediate discontinuation of cabazitaxel and appropriate therapy.
  - Patients with a hypersensitivity reaction must stop treatment with cabazitaxel.
- Bone marrow suppression:
  - Bone marrow suppression manifested as neutropenia, anaemia, thrombocytopenia, or pancytopenia may occur.
- Risk of neutropenia:
  - Patients treated with cabazitaxel may receive prophylactic G-CSF, as per American Society of Clinical Oncology (ASCO) guidelines and/or current institutional guidelines, to reduce the risk or manage neutropenia complications (febrile neutropenia, prolonged neutropenia or neutropenic infection).
  - 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.
  - Neutropenia is the 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 ≥ 1,500/mm^3.
- 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.
  - Risk of nausea, vomiting, diarrhoea and dehydration:
    - If patients experience diarrhoea following administration of cabazitaxel they may be treated with commonly used anti-diarrhoeal medicinal products. Appropriate measures should be taken to re-hydrate patients. Diarrhoea can occur more frequently in patients that have received prior abdomino-pelvic radiation. Dehydration is more common in patients aged 65 or older. Appropriate measures should be taken to rehydrate patients and to monitor and correct serum electrolyte levels, particularly potassium. Treatment delay or dose reduction may be necessary for grade ≥ 3 diarrhoea.
    - If patients experience nausea or vomiting, they may be treated with commonly used anti-emetics.
  - Risk of serious gastrointestinal reactions:
    - 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:
  - Cases of peripheral neuropathy, peripheral sensory neuropathy (e.g., paraesthesias, dysaesthesias) and peripheral motor neuropathy have been observed in patients receiving cabazitaxel.
  - 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.
- Anaemia:
  - Anaemia has been observed in patients receiving cabazitaxel.
  - Haemoglobin and haematocrit should be checked before treatment with cabazitaxel and if patients exhibit signs or symptoms of anaemia or blood loss.
  - Caution is recommended in patients with haemoglobin <10 g/dl and appropriate measures should be taken as clinically indicated.
- 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.
- Appropriate measures should be taken to identify the cause and intensively treat the patients if this occurs.
- 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 any degradation of renal function to renal failure ≥ CTCAE 4.0 Grade 3.

❖ Respiratory disorders:
- Interstitial pneumonia/pneumonitis and interstitial lung disease have been reported and may be associated with fatal outcome.
- If new or worsening pulmonary symptoms develop, patients should be closely monitored, promptly investigated, and appropriately treated.
- Interruption of cabazitaxel therapy is recommended until diagnosis is available. Early use of supportive care measures may help improve the condition. The benefit of resuming cabazitaxel treatment must be carefully evaluated.

❖ Risk of cardiac arrhythmias:
- Cardiac arrhythmias have been reported, most commonly tachycardia and atrial fibrillation.

❖ Elderly :
- Elderly patients (≥ 65 years of age) may be more likely to experience certain adverse reactions including neutropenia and febrile neutropenia.

❖ Patients with liver impairment:
- Treatment with Cabazitaxel Accord is contraindicated in patients with moderate and severe hepatic impairment (total bilirubin > 1.5 x ULN).
- Dose should be reduced for patients with mild (total bilirubin >1 to ≤1.5 x ULN or AST >1.5 x ULN), hepatic impairment.

Study characteristics [5, 6]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
PROSELICA, EFC11785 NCT01308580	1,200	Cabazitaxel **20 mg/m²** intravenously (Day 1) every 3 weeks + **prednisone** 10 mg orally given daily	Cabazitaxel **25 mg/m²** intravenously (Day 1) every 3 weeks + **prednisone** 10 mg orally given daily	OS	phase III, randomized, open-label, noninferiority	-	Sanofi	Link

Efficacy (I vs. C)

Median OS: 13.4 vs. 14.5 months (HR, 1.024)
Median OS in a secondary analysis of the **per-protocol population** (including only patients who had received at least three doses of cabazitaxel): 15.1 vs. 15.9 months (HR, 1.042)
Median PFS: 2.9 vs. 3.5 months (HR, 1.099; 95% CI, 0.974-1.240)
Tumour response rate: no significant difference between both groups (18.5% vs. 23.4%, p=.1924)
Median time to tumor progression: was 9.0 months vs. 9.3 months (HR, 1.096; 95% CI, 0.902-1.33)
PSA response rates: were significantly higher in C n=231/538 (42.9%) vs. I n=160/543 (29.5%), p<0.001
Median time to PSA progression: 6.8 v 5.7 months (HR for I vs. C, 1.195; 95% CI, 1.025-1.393)
The rate of pain progression: 39.8% vs. 40.9%
The median time to pain progression: 6.2 vs. 6.4 months
HRQoL: the median time to definitive deterioration did not differ between the two doses of cabazitaxel for any of the well-being subscales or for prostate-specific concerns.

Safety (I vs. C)

Any TEAE of grade ≥3: n=230/580 (39.7%) vs. n=324/595 (54.5%)
Serious TEAEs: n=177/580 (30.5%) vs. n=257/595 (43.2%)
Death[1]: 2.1% vs. 3.2%
Discontinuation[2]: n=95/580 (16.4%) vs. n=116/595 (19.5%)

ESMO-MCBS version 1.1

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM

1 Death a result of AEs within 30 days of last treatment dose
2 TEAEs possibly related to study treatment leading to permanent treatment discontinuation

Original	noninferiority	2c	x	x	x	Reduced toxicity or improved QoL (using a validated scale) with evidence for statistical non-inferiority or superiority in PFS/OS	4	-12.7% serious treatment-emergent AE	ND	x	4
Adapted	noninferiority	2c	x	x	x	Reduced toxicity or improved QoL (using a validated scale) with evidence for statistical non-inferiority or superiority in PFS/OS	4	-12.7% serious treatment-emergent AE	ND	x	4

Risk of bias (study level)				
Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	-	open-label	yes	yes	high risk

First published: 04/2020
Last updated: 12/2020

Abbreviations: AE=adverse event, ASCO=American Society of Clinical Oncology, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CTCAE= Common Terminology Criteria for Adverse Events, ECOG= Eastern Cooperative Oncology Group, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FACT-P=Functional Assessment of Cancer Therapy–Prostate Cancer, G-CSF=granulocyte-colony stimulating factor, GI=gastrointestinal, HR=hazard ratio, HRQoL=health-related quality of life, mCRPC=castration-resistant prostate cancer, n=number, ND=no difference, NSAIDs=nonsteroidal anti-inflammatory drugs, SAE=serious adverse event, TEAE=treatment-emergent adverse event, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PSA=prostate-specific antigen, QoL=quality of life

References:

1. European Medicines Agency (EMA). Medicines. Docetaxel Accord. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/cabazitaxel-accord.
2. National Institute for Health Research (NIHR). Niraparib for metastatic castration-resistant prostate cancer with DNA-repair anomalies [Available from: http://www.io.nihr.ac.uk/wp-content/uploads/2020/03/13159-Niraparib-for-Prostate-Cancer-V1.0-FEB2020-NON-CONF.pdf.
3. U.S Food and Drug Administration (FDA). Drugs@FDA. Jevtana. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/201023s023lbl.pdf.
4. European Medicines Agency (EMA). Cabazitaxel Accord: EPAR - Product Information [Available from: https://www.ema.europa.eu/en/documents/product-information/cabazitaxel-accord-epar-product-information_en.pdf.
5. Eisenberger M, et al. A Phase III study comparing a reduced dose of cabazitaxel (20 mg/m2) and the currently approved dose (25 mg/m2) in post-docetaxel patients with metastatic castration-resistant prostate cancer (PROSELICA). Trial protocol. [Available from: https://ascopubs.org/doi/suppl/10.1200/JCO.2016.72.1076.
6. Eisenberger M, Hardy-Bessard A, Soo Kim C, G´eczi L, Ford D, Mourey L, et al. Phase III Study Comparing a Reduced Dose of Cabazitaxel (20 mg/m2) and the Currently Approved Dose (25 mg/m2) in Postdocetaxel Patients With Metastatic Castration-Resistant Prostate Cancer—PROSELICA. J Clin Oncol 35:3198-3206.