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Regulatory Issues: EMA

The European Medicines Agency Review of Cabazitaxel (Jevtana®) for the Treatment of Hormone-Refractory Metastatic Prostate Cancer: Summary of the Scientific Assessment of the Committee for Medicinal Products for Human Use

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Summarize the efficacy outcomes of cabazitaxel pivotal trials in the treatment of hormone-refractory metastatic prostate cancer.
2. Describe the safety profile and most common adverse effects of cabazitaxel in patients with hormone-refractory metastatic prostate cancer.

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ABSTRACT

On March 17, 2011 the European Commission issued a marketing authorization valid throughout the European Union for Jevtana® (Sanofi-Aventis, Paris, France) for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.

The active substance of Jevtana® is cabazitaxel acetone solvate, an antineoplastic agent that acts by disrupting the microtubular network in cells. The recommended dose of cabazitaxel is 25 mg/m^2 administered as a 1-hour i.v. infusion every 3 weeks in combination with oral prednisone or prednisolone, 10 mg, administered daily throughout treatment.

In the main study submitted for this application, a 2.4-month longer median overall survival time and a 30% lower risk for death were observed for cabazitaxel, compared with mitoxantrone. The most common side effects with cabazitaxel were anemia, leukopenia, neutropenia, thrombocytopenia, and diarrhea.

This paper summarizes the scientific review of the application leading to approval in the European Union. The detailed scientific assessment report and product informa-

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tion, including the summary of product characteristics, are available on the European Medicines Agency Web site (http://www.ema.europa.eu). ***The Oncologist*** 2012;17: 543–549

Introduction

Treatment of patients with metastatic hormone-refractory prostate cancer (mHRPC) who progress following docetaxel as first-line therapy has included low-dose prednisone and mitoxantrone administered with either prednisone or hydrocortisone [1–3]. Supportive care, with various nonapproved agents with limited activity, is currently used in this setting, with palliation being the main goal of therapy [4].

The applicant, Sanofi-Aventis (Paris, France), submitted, on April 20, 2010, an application for marketing authorization to the European Medicines Agency (EMA) for cabazitaxel (Jevtana®).

Cabazitaxel is a semisynthetic derivative of 10-deacetyl baccatin III, which is extracted from European yew needles. Cabazitaxel is the 7,10-dimethoxy analog of docetaxel (Fig. 1). It acts by disrupting the microtubular network in cells. Cabazitaxel binds to tubulin and promotes the assembly of tubulin into microtubules while simultaneously inhibiting their disassembly. This leads to the stabilization of microtubules, which results in the inhibition of mitotic and interphase cellular functions.

Cabazitaxel has a broad spectrum of antitumor activity in murine tumors, including prostate, colon, and mammary adenocarcinomas. It has shown cytotoxic activity in vitro similar to that of docetaxel, and its toxicity profile is similar to those of other taxanes. Clinical activity has been reported in prostate and taxane-resistant metastatic breast cancer patients [5, 6].

The review of this drug application was conducted by the Committee of Human Medicinal Products (CHMP). The CHMP recommended the granting of a marketing authorization for Jevtana based on a positive benefit-risk balance. Following this review the European Commission issued a marketing authorization for cabazitaxel on March 17, 2011. Cabazitaxel in combination with prednisone or prednisolone is indicated for the treatment of patients with mHRPC previously treated with a docetaxel-containing regimen.

This paper summarizes the scientific review of the application leading to approval of cabazitaxel in the European Union. Another recent addition to the approved drug list for docetaxel-resistant tumors is abiraterone (Zytiga®; Centocor Ortho Biotech, Inc., Horsham, PA). The detailed scientific assessment reports and product information for these products are available on the EMA Web site (http://www.ema.europa.eu).

Nonclinical aspects

In vitro, cabazitaxel has demonstrated antitumor activity in sensitive murine and human cell lines. Cabazitaxel showed cytotoxic activity similar to that of docetaxel. In vitro, cabazitaxel has demonstrated activity in several docetaxel-resistant cell lines, including cell lines expressing the multidrug resistance gene (*mdr-1*) and tumor cell lines resistant to selected chemotherapeutic agents. However, no studies were presented with docetaxel-resistant prostate tumor cell lines.

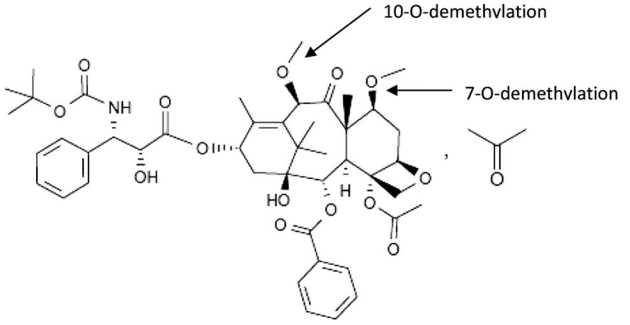

Figure 1. Structural formula of cabazitaxel.

There were similarities in the toxicological profile of cabazitaxel between preclinical and clinical studies, and the major expected effects observed in the clinic are hematological findings (mainly neutropenia and its complications) and gastrointestinal disorders (mainly diarrhea, nausea, and vomiting).

Clinical Pharmacology

Pharmacokinetics

In clinical trials, cabazitaxel exhibited a long terminal half-life of 95 hours. Cabazitaxel was extensively metabolized in the liver (>95%). Cabazitaxel was mainly metabolized by cytochrome P450 (CYP)3A4 and CYP3A5 (the contribution of CYP3A estimated to be in the range of 80%–90%) and to a lesser extent by CYP2C8. The metabolism of cabazitaxel may be modified by the concomitant administration of compounds that are known to be potent inhibitors (e.g., ketoconazole) or inducers (e.g., rifampicin, carbamazepine, phenobarbital, and phenytoin) of CYP3A. Likewise, coadministration of cabazitaxel with medicinal products that are known to be primarily metabolized through CYP3A may increase the exposure of these medicinal products. Cabazitaxel is also a substrate of P-glycoprotein (P-gp). CYP3A4, CYP3A5, and P-gp are subject to genetic polymorphism. In a population pharmacokinetic analysis in 70 patients aged ≥65 years (57 were aged 65–75 years and 13 were aged >75 years), no age effect on the pharmacokinetics of cabazitaxel was observed. The safety and efficacy of cabazitaxel have not been established in children and adolescents aged <18 years, and cabazitaxel is not indicated for use in these age groups. Interindividual variability in cabazitaxel clearance was significantly related to body surface area.

Cabazitaxel is contraindicated in patients with hepatic impairment (bilirubin ≥1× the upper limit of normal [ULN] or aspartate aminotransferase and/or alanine aminotransferase ≥1.5× ULN). Mild to moderate renal impairment did not have meaningful effects on the pharmacokinetics of cabazitaxel. No data are available for patients with severe renal impairment (creatinine clearance <30 mL/minute) or end-stage renal dis-

ease; therefore, these patients should be treated with caution and monitored carefully during treatment.

Dose Finding

Initially, a dose of 20 mg/m^2 administered every 3 weeks as a 1-hour i.v. infusion was determined in a phase I study in patients with advanced solid tumors and was recommended for further clinical development [7]. The dose-limiting toxicity of cabazitaxel was neutropenia and its infectious complications at the highest dose tested.

In a phase II study with metastatic breast cancer patients (Study ARD6191), the safety and antitumor activity were assessed at a dose of 20 mg/m^2 every 3 weeks for the first cycle, with possible intrapatient escalation to 25 mg/m^2 for cycle 2 allowed in the absence of any toxicity of grade >2 during cycle 1. In 21 of 71 patients, the dose of cabazitaxel could be escalated to 25 mg/m^2 i.v. after the first cycle [8]. Thus, the 25-mg/m^2 dose was selected for the pivotal phase III study (EFC6193).

The optimal dose of cabazitaxel is still to be further explored. A phase III study (EFC11785) is under preparation with the primary objective of demonstrating noninferiority in terms of overall survival (OS) for cabazitaxel at a dose of 20 mg/m^2 (arm A) versus a dose of 25 mg/m^2 (arm B) in combination with prednisone in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel. Approximately 1,200 patients are planned to be enrolled.

Clinical Efficacy and Safety

Clinical Efficacy

The pivotal study for this application was trial EFC6193 (TROPIC; ClinicalTrials.gov identifier, NCT00417079) [5]. The TROPIC study was a multicenter, multinational, randomized, open-label phase III study comparing the efficacy and safety of cabazitaxel plus prednisone or prednisolone with those of mitoxantrone plus prednisone or prednisolone in patients with mHRPC previously treated with a docetaxel-containing regimen.

The trial included patients with histologically or cytologically proven prostate adenocarcinoma refractory to hormone therapy and previously treated with a docetaxel-containing regimen. Patients needed to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0–2 and documented progression according to the Response Evaluation Criteria in Solid Tumors (measurable disease) or based on a rising prostate-specific antigen (PSA) level or the appearance of new lesions (nonmeasurable disease). Patients with previous treatment with a <225 mg/m^2 cumulative dose of docetaxel were not eligible (following protocol amendment).

Cabazitaxel was administered i.v., over 1 hour every 3 weeks, at a starting dose of 25 mg/m^2. Mitoxantrone was administered i.v., over 15–30 minutes every 3 weeks, at a starting dose of 12 mg/m^2. Prednisone, 10 mg, was administered orally, daily, to all patients.

The primary efficacy endpoint was the OS duration, defined as the time interval from the date of randomization to the date of death resulting from any cause. The primary analysis of the primary efficacy endpoint was performed using the intent-to-treat population. Randomization was stratified according to

Table 1. Summary of baseline and demographic characteristics: intent-to-treat population

Characteristic	MTX + PRED (n = 377)	CBZ + PRED (n = 378)
Age, yrs		
Median	67.0	68.0
Minimum	47	46
Maximum	89	92
ECOG PS score		
0	120 (31.8%)	141 (37.3%)
1	224 (59.4%)	209 (55.3%)
2	33 (8.8%)	28 (7.4%)
ECG		
Normal	251 (66.6%)	268 (70.9%)
Abnormal	98 (26.0%)	86 (22.8%)
Missing	28 (7.4%)	24 (6.3%)
Echocardiography LVEF, %		
n of patients	243	235
Median	64.00	63.00
Minimum	42.0	38.0
Maximum	80.0	86.0
Radionuclide ventriculography LVEF, %		
n of patients	129	140
Median	63.00	62.00
Minimum	50.0	50.2
Maximum	80.0	81.0
PSA, ng/mL		
n of patients	370	371
Median	127.5	143.9
Minimum	2	2
Maximum	11220	7842
Measurable disease		
Yes	204 (54.1%)	201 (53.2%)
No	173 (45.9%)	177 (46.8%)
Extent of disease		
Metastatic	356 (94.4%)	364 (96.3%)
Locoregional recurrence	20 (5.3%)	14 (3.7%)
Missing	1 (0.3%)	0

Abbreviations: CBZ, cabazitaxel; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; LVEF, left ventricular ejection fraction; MTX, mitoxantrone; PRED, prednisone or prednisolone; PSA, prostate-specific antigen.

Table 2. Summary of efficacy results: phase III EFC6193 study

Measure	MTX + PRED (n = 377)	CBZ + PRED (n = 378)	HR[a] (95% CI)	p-value[b]
Median (95% CI) survival, mos	12.7 (11.6–13.7)	15.1 (14.1–16.3)	0.70 (0.59–0.83)	<.0001
Median (95% CI) PFS, mos	1.4 (1.4–1.7)	2.8 (2.4–3.0)	0.74 (0.64–0.86)	<.0001
Median (95% CI) tumor progression free, mos	5.4 (4.7–6.5)	8.8 (7.4–9.6)	0.61 (0.49–0.76)	<.0001
Median (95% CI) PSA progression free, mos	3.1 (2.2–4.4)	6.4 (5.1–7.3)	0.75 (0.63–0.90)	.001
Median (95% CI) pain progression free, mos	–	11.1 (8.0-.)	0.91 (0.69–1.19)	.52

[a]The HR was estimated using a Cox proportional hazards regression model. An HR <1 indicates a lower risk with CBZ + PRED than with MTX + PRED.
[b]p-value from stratified log-rank test, stratifying by Eastern Cooperative Oncology Group performance status and measurable disease at baseline.
Abbreviations: CBZ, cabazitaxel; HR, hazard ratio; MTX, mitoxantrone; PRED, prednisone or prednisolone; PFS, progression-free survival; PSA, prostate-specific antigen.

measurable versus nonmeasurable disease and ECOG PS score (0 or 1 versus 2), and used a dynamic allocation method.

In total, 755 patients were randomized into the study. The baseline characteristics were well balanced between the treatment groups (Table 1). Almost all patients (99.3%) had received hormonal therapy for their prostate cancer, 60.1% of the patients had received radiotherapy, 53.3% of the patients had prior surgery, and 14.9% of the patients had received two or more regimens of prior docetaxel-based chemotherapy. Most of the patients (72%) had progressed during or within 3 months since their last docetaxel dose.

The main efficacy results are summarized in Table 2. In the primary analysis, the superiority of cabazitaxel over mitoxantrone was observed, with a 2.4-month longer median OS time and a 30% lower risk for death (Fig. 2).

Clinical Safety

In the EFC6193 pivotal study, grade ≥3 treatment-emergent adverse events occurred in 57.4% of patients in the cabazitaxel group and 39.4% of patients in the mitoxantrone group (Table 3). The most commonly reported treatment-emergent adverse events of all grades were diarrhea (46.6%), fatigue (36.7%), nausea (34.2%), vomiting (22.6%), and neutropenia (21.8%). The most commonly (≥3%) reported grade ≥3 treatment-emergent adverse events were neutropenia (21.3%), febrile neutropenia (7.5%), diarrhea (6.2%), fatigue (4.9%), asthenia (4.6%), back pain (3.8%), leukopenia (3.8%), and anemia (3.5%).

Neutropenia was the most common adverse reaction leading to treatment discontinuation (2.4%). Neutropenic complications included neutropenic infections (0.5%), neutropenic sepsis (0.8%), and septic shock (1.1%), which in some cases resulted in a fatal outcome. The dose should be reduced in cases of febrile neutropenia or prolonged neutropenia despite appropriate treatment. Patients should be retreated only when neutrophils recover to a level ≥1,500/mm^3.

The use of G-CSF has been shown to limit the incidence and severity of neutropenia. Primary prophylaxis with G-CSF should be considered in patients with high-risk clinical features (age >65 years, poor PS, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, and other serious comorbidities) that predispose them to greater complications from prolonged neutropenia.

Hypersensitivity reactions have been reported in patients treated with cabazitaxel. A causal association with any of the excipients or the active substance has not been established. Premedication including an antihistamine, a corticosteroid, and an H_2 antagonist should be performed to mitigate the risk for and severity of hypersensitivity. Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions.

Among the 371 patients treated with cabazitaxel in the prostate cancer study, 240 patients were aged ≥65 years, including 70 patients aged >75 years. The following adverse reactions were reported at rates ≥5% higher in patients aged ≥65 years than in younger patients: fatigue (40.4% versus 29.8%), clinical neutropenia (24.2% versus 17.6%), asthenia (23.8% versus 14.5%), pyrexia (14.6% versus 7.6%), dizziness (10.0% versus 4.6%), urinary tract infection (9.6% versus 3.1%), and dehydration (6.7% versus 1.5%). The incidences of the following grade ≥3 adverse reactions were higher in patients aged ≥65 years than in younger patients: neutropenia based on laboratory abnormalities (86.3% versus 73.3%), clinical neutropenia (23.8% versus 16.8%), and febrile neutropenia (8.3% versus 6.1%).

In study EFC6193, the percentage of patients who died from treatment-emergent adverse events (other than progressive disease) within 30 days of their last infusion was 4.9% in the cabazitaxel group, compared with 1.9% in the mitoxantrone group. Of the 18 patients who died in the cabazitaxel group, seven of these deaths were attributed to neutropenia and its consequences and five deaths were a result of cardiac events.

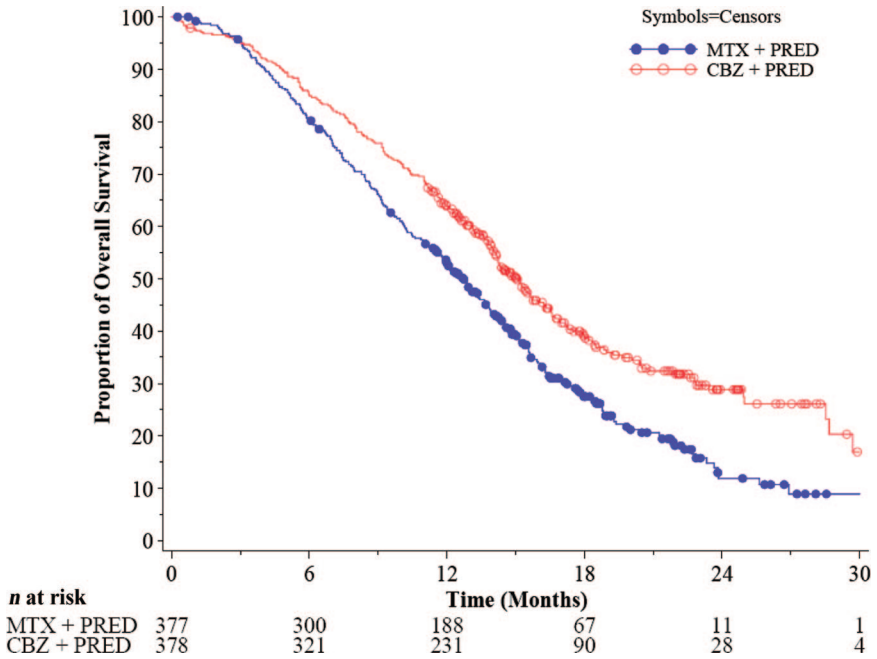

Figure 2. Kaplan–Meier curves of overall survival by treatment group (TROPIC trial, intent-to-treat population).
Abbreviations: CBZ, cabazitaxel; MTX, mitoxantrone; PRED, prednisone or prednisolone.

Benefit–Risk Assessment

Cabazitaxel plus prednisone was associated with a 2.4-month longer median OS duration than with mitoxantrone plus prednisone. Secondary endpoints, such as the progression-free survival (PFS) interval, tumor response rate, and tumor progression were consistent with the primary endpoint. In secondary analyses, a median PFS difference of 1.4 months in favor of cabazitaxel plus prednisone was also observed. Cabazitaxel plus prednisone was also associated with a higher response rate and longer time to PSA progression. However, these parameters have inherent limitations as a result of, among other things, ascertainment bias, interobserver variability, and the fact that no independent review of the PFS assessment was carried out.

There was some uncertainty over the efficacy in patients who had received <225 mg/m^2 of docetaxel. Previous treatment with a <225 mg/m^2 cumulative dose of docetaxel was introduced as an exclusion criterion after protocol amendment. A subgroup of 59 patients had received a prior cumulative dose of docetaxel <225 mg/m^2 (29 patients in the cabazitaxel arm and 30 patients in the mitoxantrone arm). There was no significant difference in the OS time between study arms in this subgroup of patients (hazard ratio, 0.96; 95% confidence interval, 0.49–1.86). This observation may be a result of lower efficacy in this subgroup because of different patient or disease characteristics. However, the low number of patients in this subgroup analysis may also explain the lack of a clear effect.

Neutropenia was the most common adverse reaction with cabazitaxel. In the pivotal trial, cabazitaxel at the dose tested caused life-threatening neutropenia. Investigators were advised to strictly follow the protocol regarding dose delays and modifications and to treat neutropenia in accordance with the American Society of Clinical Oncology guidelines. This appeared to limit the incidence and severity of neutropenia. Monitoring of CBCs is essential on a weekly basis during cycle 1 and before each treatment cycle thereafter so that the dose can be adjusted if needed. No specific dose adjustment recommendation was considered in elderly patients because no age effect on the pharmacokinetics of cabazitaxel was observed, although these patients may be more likely to experience certain adverse reactions.

The numbers of patients with any treatment-emergent adverse event, serious treatment-emergent adverse event, or grade ≥ 3 treatment-emergent adverse event and withdrawals resulting from any treatment-emergent adverse event were significantly higher in the cabazitaxel group than in the mitoxantrone group. In study EFC6193, the percentages of patients who died from treatment-emergent adverse events (other than progressive disease) within 30 days of their last infusion were 4.9% in the cabazitaxel group and 1.9% in the mitoxantrone group. The hematological toxicity was also higher with cabazitaxel plus prednisone than with mitoxantrone plus prednisone. Even with prophylactic or therapeutic G-CSF, cabazitaxel was associated with a higher rate of neutropenia leading to infections and sepsis.

Fatigue, clinical neutropenia, asthenia, pyrexia, dizziness, urinary tract infection, and dehydration were reported at rates $\geq 5\%$ higher in patients aged ≥ 65 years than in younger patients. Currently, there are no specific dose recommendations for elderly patients. It is unclear whether or not the <25-mg/m^2 dose would have activity similar to that of the ≥ 25-mg/m^2 dose but with a more acceptable side-effect profile. The company has submitted the synopsis of a randomized, open-label study comparing a 20-mg/m^2 dose of cabazitaxel with a 25-mg/m^2 dose in second-line mHRPC patients.

Table 3. Treatment-emergent adverse events (all grades and grade ≥3) regardless of relationship to study drug by preferred term (≥5% incidence in any treatment group): phase 3 EFC6193 study

	MTX + PRED (*n* = 371)		CBZ + PRED (*n* = 371)	
Preferred term	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Any event	328 (88.4%)	146 (39.4%)	355 (95.7%)	213 (57.4%)
Diarrhea	39 (10.5%)	1 (0.3%)	173 (46.6%)	23 (6.2%)
Fatigue	102 (27.5%)	11 (3.0%)	136 (36.7%)	18 (4.9%)
Nausea	85 (22.9%)	1 (0.3%)	127 (34.2%)	7 (1.9%)
Vomiting	38 (10.2%)	0	84 (22.6%)	7 (1.9%)
Clinical neutropenia[a]	40 (10.8%)	26 (7.0%)	81 (21.8%)	79 (21.3%)
Asthenia	46 (12.4%)	9 (2.4%)	76 (20.5%)	17 (4.6%)
Constipation	57 (15.4%)	2 (0.5%)	76 (20.5%)	4 (1.1%)
Hematuria	14 (3.8%)	2 (0.5%)	62 (16.7%)	7 (1.9%)
Back pain	45 (12.1%)	11 (3.0%)	60 (16.2%)	14 (3.8%)
Anorexia	39 (10.5%)	3 (0.8%)	59 (15.9%)	3 (0.8%)
Pyrexia	23 (6.2%)	1 (0.3%)	45 (12.1%)	4 (1.1%)
Dyspnea	17 (4.6%)	3 (0.8%)	44 (11.9%)	5 (1.3%)
Abdominal pain	13 (3.5%)	0	43 (11.6%)	7 (1.9%)
Dysgeusia	15 (4.0%)	0	41 (11.1%)	0
Anemia	20 (5.4%)	5 (1.3%)	40 (10.8%)	13 (3.5%)
Cough	22 (5.9%)	0	40 (10.8%)	0
Arthralgia	31 (8.4%)	4 (1.1%)	39 (10.5%)	4 (1.1%)
Alopecia	18 (4.9%)	0	37 (10.0%)	0
Edema, peripheral	34 (9.2%)	1 (0.3%)	34 (9.2%)	2 (0.5%)
Weight decreased	28 (7.5%)	1 (0.3%)	32 (8.6%)	0
Pain in extremity	27 (7.3%)	4 (1.1%)	30 (8.1%)	6 (1.6%)
Neuropathy, peripheral	4 (1.1%)	1 (0.3%)	30 (8.1%)	2 (0.5%)
Dizziness	21 (5.7%)	2 (0.5%)	30 (8.1%)	0
Febrile neutropenia	5 (1.3%)	5 (1.3%)	28 (7.5%)	28 (7.5%)
Headache	19 (5.1%)	0	28 (7.5%)	0
Urinary tract infection	11 (3.0%)	3 (0.8%)	27 (7.3%)	4 (1.1%)
Muscle spasms	10 (2.7%)	0	27 (7.3%)	0
Dyspepsia	6 (1.6%)	0	25 (6.7%)	0
Dysuria	5 (1.3%)	0	25 (6.7%)	0
Mucosal inflammation	10 (2.7%)	1 (0.3%)	22 (5.9%)	1 (0.3%)
Leukopenia	11 (3.0%)	5 (1.3%)	20 (5.4%)	14 (3.8%)
Thrombocytopenia	10 (2.7%)	1 (0.3%)	20 (5.4%)	9 (2.4%)
Pain	18 (4.9%)	7 (1.9%)	20 (5.4%)	4 (1.1%)
Hypotension	9 (2.4%)	1 (0.3%)	20 (5.4%)	2 (0.5%)
Peripheral sensory neuropathy	5 (1.3%)	0	20 (5.4%)	1 (0.3%)
Abdominal pain, upper	5 (1.3%)	0	20 (5.4%)	0
Bone pain	19 (5.1%)	9 (2.4%)	19 (5.1%)	3 (0.8%)
Musculoskeletal pain	20 (5.4%)	3 (0.8%)	18 (4.9%)	2 (0.5%)

[a]Clinical neutropenia defined as grade ≥3 requiring intervention.
Abbreviations: CBZ, cabazitaxel; MTX, mitoxantrone; PRED, prednisone or prednisolone.

The use of cabazitaxel should be confined to units specialized in the administration of cytotoxics, and it should only be administered under the supervision of a physician experienced in the use of anticancer chemotherapy.

The CHMP concluded that there was a clear benefit in terms of the OS time associated with cabazitaxel and prednisone. The effect in terms of the OS duration is similar to what has been observed with other late-line cancer therapies, for which dramatic effects in terms of OS times are rare because of the advanced stage of the disease. Because of the poor prognosis, high unmet clinical need, and lack of alternative therapies, the observed OS benefit was considered to outweigh the risks. Therefore, on March 14, 2011 the European Commission granted marketing authorization valid throughout the European Union for cabazitaxel. The EMA will review new information about cabazitaxel on a regular basis. Up-to-date information on this medicinal product is available on the EMA Web site (http://www.ema.europa.eu).

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The scientific assessment as summarized in this report is based on the marketing authorization application submitted by the applicant company and on important contributions from, among others, the rapporteur and corapporteur assessment teams, CHMP members, and additional experts.

This publication is a summary of the European Public Assessment Report (EPAR) available in the public domain, together with the summary of product characteristics (SmPC), and other product information on the EMA website (http://www.ema.europa.eu). The authors remain solely responsible for the opinions expressed therein.

AUTHOR CONTRIBUTIONS

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