CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201023s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 16, 2010
From	John R. Johnson, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	201023
Applicant	Sanofi-Aventis
Date of Submission	3/31/10
PDUFA Goal Date	9/30/10
Proprietary Name / Established (USAN) names	Jevtana® Cabazitaxel Injection Concentrate
Dosage forms / Strength	Jetvana (cabazitaxel) Injection concentrate 60 mg/1.5 mL is supplied as a kit consisting of the following: – Jetvana 60mg/1.5 mL concentrate: contains 60 mg cabazitaxel in 1.5 mL polysorbate 80, Diluent for JEVTANA 60 mg/1.5 mL: contains (b) (4) of 13% (w/w) ethanol in water for injection.
Proposed Indication(s)	Jetvana in combination with prednisone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.
Recommended:	Approval

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1. Introduction

Jevtana® (cabazitaxel injection) is a new molecular entity and is a novel taxane, similar to the taxanes docetaxel and paclitaxel. Like the taxanes docetaxel and paclitaxel, cabazitaxel acts by targeting tubulin, the protein component of microtubules, to stabilize microtubules and prevent progression of mitosis in the cell cycle.

Cabazitaxel is not marketed anywhere in the world. The proposed indication is "Jetvana in combination with prednisone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen." There is currently no effective therapy for patients with this condition.

The application is supported primarily by one randomized controlled trial (RCT) conducted under an SPA agreement. The primary endpoint of the RCT showed a statistically significant improvement in median survival of 2.4 months for cabazitaxel in combination with prednisone compared to mitoxantrone in combination with prednisone. The mitoxantrone/prednisone combination has not been shown to improve survival. The cabazitaxel 25 mg/m2 dose every 3 weeks causes considerable toxicity and may be unnecessarily high. However, we have no information from RCTs on any other cabazitaxel dose and do not know if a lower dose would be effective. Despite the increased toxicity and increase in deaths due to toxicity in the cabazitaxel arm relative to the control arm, there is still a survival advantage for the cabazitaxel treatment group. The cabazitaxel dose will be addressed with a PMR. The cabazitaxel toxicity will be addressed in the label and with several post marketing required trials and studies (PMRs).

Chemistry has identified a concern with the supersaturated pre-mix and infusion solutions with the risk of introducing particulate matter intravenously. Clinical Pharmacology has concerns about use in patients with hepatic impairment, use with strong CPY3A4 inhibitors, use with strong CYP3A4 inducers and lack of adequate assessment of risk of QTc interval prolongation. These concerns will be addressed by PMRs

2. Background

Cabazitaxel is a new molecular entity and is a novel taxane, similar to the taxanes docetaxel and paclitaxel. Like the taxanes docetaxel and paclitaxel, cabazitaxel acts by targeting tubulin, the protein component of microtubules, to stabilize microtubules and prevent progression of mitosis in the cell cycle.

Cabazitaxel is a semi-synthetic product derived from 10-deacetyl Baccatin III, which is extracted from European yew needles.

First-line therapy for patients with metastatic prostate cancer is medical or surgical castration. Approximately 85% of patients will respond to this therapy, which includes gonadotropin-releasing hormone antagonists or surgery. However, approximately 15% of patients will not

respond to hormonal intervention and responders will eventually become refractory to hormonal intervention. For this metastatic hormone refractory (mHRPC) population, recommended first-line therapy is the combination of docetaxel and prednisone, which showed a survival advantage compared to the combination of mitoxantrone and prednisone in the randomized Phase 3 TAX327 trial.[i]

There is no available therapy for patients with mHRPC who have already progressed on or after a docetaxel regimen. This is the population studied in the submitted cabazitaxel RCT.

This NDA is supported mainly by a single RCT conducted under an SPA. At end of Phase 2 meeting and at the SPA FDA emphasized that a Phase 3 trial in mHRPC must win on its primary endpoint of overall survival before any analysis of secondary endpoints could be undertaken and that as the trial was unblinded. (b) (4) Furthermore, the FDA stressed that the composite secondary endpoint of PFS as defined by PSA progression, tumor progression by RECIST criteria or death would be considered an exploratory analysis (b) (4)

The primary endpoint of the RCT showed a statistically significant improvement in median survival of 2.4 months for cabazitaxel in combination with prednisone compared to mitoxantrone in combination with prednisone. The mitoxantrone/prednisone combination has not been shown to improve survival. The cabazitaxel 25 mg/m2 dose every 3 weeks causes considerable toxicity and may be unnecessarily high. However, we have no information from RCTs on any other cabazitaxel dose and do not know if a lower dose would be effective. Despite the increased toxicity and increase in deaths due to toxicity in the cabazitaxel arm relative to the control arm, there is still a survival advantage for the cabazitaxel treatment group. The cabazitaxel dose will be addressed with a PMR. The cabazitaxel toxicity will be addressed in the label and with several PMRs.

3. CMC/Device

Recommendation abstracted from the Chemistry Review.

This NDA is recommended for Approval from a Chemistry, Manufacturing, and Controls standpoint. There are no outstanding Chemistry, Manufacturing, and Controls issues.

The following 2 PMRs are required.

PMR 1649-1
To evaluate the potential for a serious risk of intravenous infusion of particulate matter into the blood stream, it is necessary to better understand and characterize the supersaturated pre-mix. Conduct a study to provide data which address particulate nucleation and kinetic factors of precipitation in the pre-mix. Conduct this study using multiple samples drawn from multiple batches so as to more fully support an in-use life of the pre-mix.

Study considerations include (but are not necessarily limited to); interior surface properties of the container closure (e.g., treatments, roughness, scratches, etc.), initial mixing agitation force (vigorous shaking), physical shock on standing (e.g., vigorous shaking during in-use storage), needle sticks, syringe use, temperature (and temperature changes during in-use storage), and additional time point sampling beyond the proposed duration of in-use storage of the pre-mix solution (e.g., 1 to 4 hours).

Collect and provide photographs of the precipitate as it appears in the container and isolated photomicrographs of the particles, as feasible.

Provide by mass balance, the mass of precipitated drug as precipitated mass and as mass percent of the total cabazitaxel content.

PMR 1649-2
To evaluate the potential for a serious risk of intravenous infusion of particulate matter into the blood stream, it is necessary to better understand and characterize the supersaturated infusion solution. Conduct a study which addresses particulate nucleation and kinetic factors of precipitation from the infusion solution. Conduct this study using multiple samples drawn for at least three additional batches in the containers (bags and sets) which you propose to label for this use so as to more fully support an in-use life of the infusion solution..

Study factors include (but are not necessarily limited to); interior surface properties of the container (e.g.., treatments, roughness, plasticizers, etc.), initial mixing agitation force (vigorous shaking), physical shock on standing (e.g., vigorous shaking during in-use storage), needle sticks, temperature (and temperature changes during in-use storage), and additional time point sampling beyond the proposed duration of in-use storage of the infusion solution.

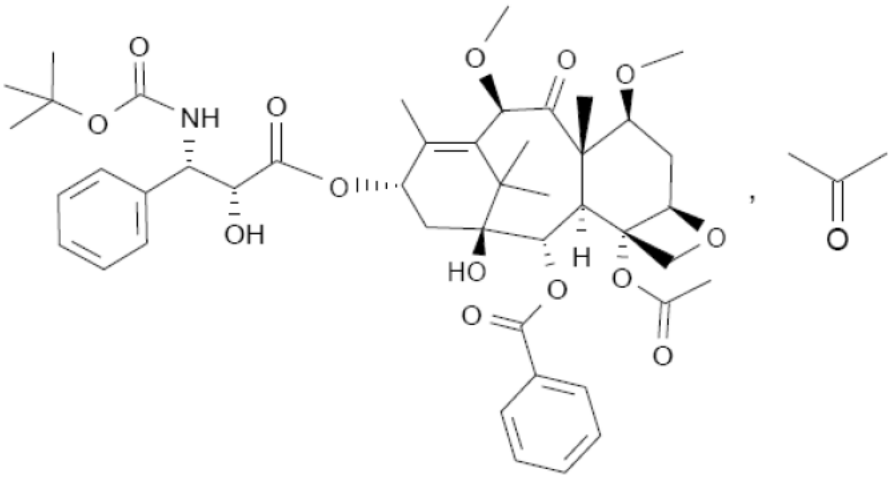
Collect and provide photographs of the precipitate as it appears in the container and isolated photomicrographs of the particles, as feasible, for each observed precipitation or evidence of precipitation (e.g., clogged filters, impeded infusion flow, etc.).

Provide by mass balance, the mass of precipitated drug as precipitated mass and as mass percent of the total cabazitaxel content.

Review

The cabazitaxel structural formula is shown in Figure 1.

Figure 1 Cabazitaxel Structural Formula



- General product quality considerations

The following is abstracted from the Chemistry Review.

Drug Substance

Cabazitaxel (also referred as RPR116258 / XRP6258) is an antineoplastic agent belonging to the taxane class. It is a diether derivative of docetaxel with the C-7 and C-10 hydroxy groups alkylated into methyl ethers. Cabazitaxel contains 11 asymmetric centers. Cabazitaxel acetone solvate is a rod-like crystalline powder which is practically insoluble in water (8 µg/mL); freely soluble in acetone and dichloromethane; and soluble in ethanol. Due to its extreme low solubility in aqueous solution, the cabazitaxel drug product is formulated in the surfactant, polysorbate 80.

Drug substance is manufactured (b) (4)

A genotoxic impurity, (b) (4) *, was identified in the Ames test. Test results for* (b) (4)

(b) (4) in the 3 primary stability batches and the 3 production batches show less than (b) (4). Safety evaluation of the observed levels of (b) (4) in the drug substance batches has been consulted to the pharm/tox reviewer. Up to (b) (4) of (b) (4) in the drug substance is acceptable considering the patient population.

Drug Product

The drug product, JEVTANA (cabazitaxel) Injection, 60 mg/1.5 mL, is supplied as a nonaqueous concentrated solution for infusion co-packaged with a diluent vial containing 5.7 mL of a 13% w/w aqueous solution of alcohol (USP). The diluent is to be used for preparation of a premix solution of 10 mg/mL of cabazitaxel, followed by a second dilution of the appropriate dose in 0.9% sodium chloride solution or 5% dextrose solution in an infusion bag.

The entire content of the diluent vial is to be withdrawn and added to the concentrated drug vial to obtain a premix solution containing approximately 10 mg/mL of cabazitaxel. Premix solution is prepared by repeated inversions for at least 45 seconds to assure complete mixing of the concentrated drug solution and the diluent. Immediately following preparation, a volume of premix solution (calculated based on a dose of 25 mg/m2) is withdrawn and to be injected into a PVC-free container of either 0.9% sodium chloride solution or 5% dextrose solution for infusion. Concentration of the infusion solution should be between 0.10 mg/mL and 0.26 mg/mL. Diluted infusion solution should be used for intravenous administration immediately, or within 8 hours if stored at room temperature or within 24 hours if stored at refrigerated conditions (including the 1-hour infusion).

Based on the 12 months primary stability data, 6 month of accelerated data, and 36 months of the supportive stability data for drug substance and per ICH Q1E guidelines, an initial retest date of (b) (4) with storage at 5oC can be granted.

Based on the 12 months primary stability data, 6 month of accelerated data for drug product and diluent, and per ICH Q1E guidelines, an initial expiration dating period of 18-months for the drug product stored under the following conditions can be granted.

- Store at 25°C (77°F); excursion permitted between 15°C – 30°C (59°F – 86°F)
- Do not refrigerate

Super saturation of Pre-mix and Infusion Solutions

Both the pre-mix and infusion solution are supersaturated. To evaluate the potential for a serious risk of intravenous infusion of particulate matter into the blood stream two PMRs are required (See above under Recommendations).

Cabazitaxel Vial and Diluent Vial Overfill

The reviewing chemist expressed concern about the cabazitaxel vial and Diluent vial overfill. **The following is abstracted from the chemistry review.**

The cabazitaxel vial is manufactured with a (b) (4) overfill and the diluent vial is manufactured with a (b) (4) overfill. Data provided in tables 6, 7 and 8 (NDA section 3.2.P.2.3 Manufacturing Process Development) describes the variations in concentrations of the premix solutions (from (b) (4) mg/mL) obtained by three operators. We feel that the presence of the excess diluent and cabazitaxel could result in inaccurate dosing.

The following Table abstracted from the Chemistry review compares the overfill for Taxotere and cabazitaxel concentrates and solvents.

Table 2 – Comparison of fill volumes for Taxotere® and Cabazitaxel concentrates and solvents

	Concentrate for solution for infusion		Solvent for dilution	
	Taxotere® (80 mg/2 mL)	Cabazitaxel (60mg/1.5 mL)	Taxotere® (8 mL)	Cabazitaxel (4.5 mL)
Nominal volume	2 mL	1.5 mL	8 mL	4.5 mL
Overfill	(b) (4)			
Total fill volume	(b) (4)			

The following abstract from the chemistry review shows the recommended resolution of this issue.

Final Evaluation: Acceptable. *Sanofi's justification for overfill is that the overage will ensure an extractable volume of 6 mL, and this practice has been used for Taxotere and other drugs that require dilutions. However, Sanofi did not address the following concerns: Due to the fact that both vials are overfilled (the diluent vial has a slight more overfill than the drug vial), the entire content of the diluent vial is withdrawn and added into the drug vial. This practice may cause variations of the concentrations for the premix solution (from (b) (4) mg/mL for the premix solution as demonstrated by the applicant), which could lead to inaccurate dosing (up to (b) (4) overdosing). Note that the common pharmaceutical products allow ±10% assay variation. If considering the allowable assay variation of ±10%, the worst case scenario could be up to (b) (4) overdose. These concerns have been conveyed to the applicant as well as to the review team in the internal labeling meeting. Due to the time constrain of reviewing this NDA, it was decided at the May 25, 2010 meeting that the current approach is acceptable considering that both clinical trial and Taxotere used this approach, and no significant risk has been shown to be associated with it. Furthermore, changing to the new approach may also introduce other errors.*

- Facilities review/inspection

The facilities inspection was judged satisfactory by the Offices of Compliance and New Drug Quality Assessment. Report received May 3, 2010.

- Other notable issues (resolved or outstanding)

None.

4. Nonclinical Pharmacology/Toxicology

Recommendation abstracted from the Supervisory Pharmacology Memorandum

I concur with Drs. Helms's and Khasar's conclusion that pharmacology and toxicology data support the approval of NDA 201,023 for JEVTANA. There are no outstanding nonclinical issues related to the approval of JEVTANA for the proposed indication.

Review abstracted from the Supervisory Pharmacology Memorandum

The supporting information included studies of intravenously administered cabazitaxel that investigated the drug's pharmacology, pharmacokinetics and ADME, safety pharmacology, general toxicology (rat and dog), genetic toxicity (in vivo and in vitro), and reproductive toxicity in both rats and rabbits. The studies cited in the review consist primarily of original research conducted by the applicant.

The pharmacology studies submitted to the NDA demonstrate that cabazitaxel is a taxane which binds tubulin, promotes microtubule polymerization and prevents disassembly. Based on this, the pharmacological classification of cabazitaxel is a microtubule inhibitor, like other taxanes which have similar mechanisms of action.

Drug induced toxicity, including gastrointestinal toxicity, bone marrow toxicity, and neuronal toxicity were observed non-clinically. These findings are not unexpected and were well characterized.

Cabazitaxel increased micronuclei in rats, and increased numerical aberrations with or without metabolic activation in an in vitro test in human lymphocytes. No induction of structural aberrations was observed in human lymphocytes. Additionally cabazitaxel was negative in the Ames test. The positive in vivo genotoxicity findings are consistent with the pharmacological activity of the compound (inhibition of tubulin depolymerization).

Like other taxanes, cabazitaxel is a highly toxic to the developing embryo or fetus causing embryolethality, pre and post implantation loss, fetal death and decreased fetal weight at a doses approximately 0.02-0.06 times the Cmax in cancer patients at the recommended human dose of 25 mg/m2. Teratogenesis was not detected however minor

variations, (i.e. delays in skeletal ossifications) at doses 0.02x the maximum recommended human dose were observed. In the rabbit study abject maternal toxicity without fetal or embryonic toxicity was observed. Although these studies utilized doses that there far below the clinical dose maternal toxicity or development toxicity was observed in each study. Because the potential benefit from the use of the JEVTANA in pregnant women in this patient population may outweigh the potential risk to the developing fetus, Pregnancy Category D is recommended for this patient population.

Numerous issues chemistry and manufacturing issues were identified during the review of JEVTANA which impacted the pharmacology and toxicology review of JEVTANA. These are discussed in detail in the primary review and include the potential propensity of the drug product to form a precipitate, and impurity and residual solvent qualification. The sponsor has adequately qualified impurities either through non-clinical studies or through provided information.

With regard to precipitate formation, although the lung is the most sensitive organ for precipitate induced toxicity and wheezing was noted in the rat in chronic study, precipitate was not noted in the study and nor was there histopathological evidence of pulmonary toxicity associated with wheezing. Although this is a theoretical concern there is not data to indicate that precipitation occurred in the drug product in non-clinical studies.

5. Clinical Pharmacology/Biopharmaceutics

Recommendation abstracted from the Clinical Pharmacology review.

The Office of Clinical Pharmacology has reviewed NDA 20-1023. This NDA is acceptable from a clinical pharmacology perspective provided that the applicant agrees to the labeling language and the post-marketing requirements listed below.

1. Complete and submit the final report of trial TES10884, along with a thorough review of cardiac safety data, for the potential of cabazitaxel on QTc interval prolongation in patients.
2. Conduct and submit the final report of trial POP6972 to determine the pharmacokinetics and safety of cabazitaxel in patients with hepatic impairment.
3. Conduct a drug interaction trial to evaluate the effect of a strong CYP3A4 inducer (e.g., rifampin) on the pharmacokinetics of cabazitaxel in humans.
4. Conduct a drug interaction trial to evaluate the effect of a strong CYP3A4 inhibitor (e.g., ketoconazole) on the pharmacokinetics of cabazitaxel in humans.

Review abstracted from the Clinical Pharmacology review.

Following a one-hour intravenous infusion, plasma concentrations of cabazitaxel can be described by a three-compartment pharmacokinetic (PK) model with α-, β-, and γ- half-lives of 4 minutes, 2 hours, and 95 hours, respectively. Cabazitaxel demonstrates no major deviation

from dose proportionality between 10 mg/m² and 30 mg/m². No accumulation or changes in the pharmacokinetics were observed for up to three treatment cycles. Mean human plasma protein binding was 92%. Based on the population PK analysis, steady-state volume of distribution and plasma clearance of cabazitaxel were 4,864 L and 48.5 L/h (i.e., 2,643 L/m² and 26.4 L/h/m² for a patient with a median BSA of 1.84 m²), respectively.

Cabazitaxel is the major circulating compound in plasma (70%) with no other relevant circulating metabolites. In addition, cabazitaxel was equally distributed between plasma and blood cells, with a blood to plasma ratio of 0.90 to 0.99 (Studies PKFAC 9901 and DMPK/FR 2238). Therefore, plasma was an appropriate matrix for monitoring the PK of cabazitaxel. In plasma, the parent drug was the main circulating compound, representing an average 70.2% (range: 49.8% to 89.9%) of radioactivity AUC. Seven metabolites were detected in plasma, each accounting for less than 10% of parent drug AUC. The main metabolite was RPR123142, the 10- O-demethylated derivative on the taxane ring, accounting for 3.6% of radioactivity AUC and 5.1% of parent drug AUC. All the other circulating metabolites (docetaxel, RPR111026, RPR111059, M09b, RPR130523, and RPR112698) represented on average less than 2.3% of the radioactivity AUC. Cabazitaxel and RPR123142 were the only compounds quantifiable 6 to 24 hours after the end of infusion.

Cabazitaxel was extensively metabolized by hepatic cytochrome P450 (CYP) 3A4/5 (80% to 90%) and to a lesser extent by CYP2C8. Cabazitaxel is primarily excreted into feces as metabolites (76% of the administered dose), with a low urinary excretion (3.7% of the administered dose, with 2.3% excreted as unchanged drug). At clinically relevant concentrations in vitro, cabazitaxel does not inhibit CYPs or transporters including P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug-resistance protein (MRP). Based on in vitro studies, the potential for cabazitaxel to inhibit or induce major CYPs is low. Furthermore, cabazitaxel is a substrate of P-gp, but not a substrate of MRP1, MRP2, or BCRP. Body surface area (BSA) and tumor type were identified as significant covariates on the plasma clearance of cabazitaxel. The BSA effect was accounted for by a BSA-based dosing regimen. Plasma clearance of cabazitaxel is 60% lower in patients with breast cancer compared to other tumor types. However, as 34 out of 37 breast cancer patients came from a single trial (ARD6191), it is difficult to distinguish if this is a trial effect or true tumor type effect.

No formal studies have been conducted to assess the effect of age, gender, race, BSA, renal or hepatic function on cabazitaxel PK. No impact of intrinsic factors (age, race, renal function, or hepatic function) on the PK of cabazitaxel was identified by the population PK analysis. No dosage regimen adjustments were proposed for the special populations. The impact of BSA on the clearance has already been accounted for by the BSA-based dosing regimen. The dose adjustments were mainly based on the safety endpoints (b) (4)

No formal hepatic impairment trials have been conducted. As cabazitaxel is extensively metabolized by CYP 3A in liver, liver dysfunction is expected to increase the plasma concentrations of cabazitaxel. Patients with impaired hepatic function (total bilirubin ≥ ULN, or AST and/or ALT ≥1.5 × ULN) were excluded from the randomized clinical trial.

Conducting a hepatic impairment trial will be a PMR to determine the dose regimen in patients with hepatic impairment. Population PK analysis did not determine transaminases as significant covariates influencing cabazitaxel PK, possibly due to the fact that only a small number of patients had elevated transaminases, bilirubin, or alkaline phosphatase levels (e.g., one patient with a bilirubin ratio > ULN, four and 19 patients with ALT and AST ratios > 1.5 x ULN, respectively, and 18 patients with ALP ratio >2.5 x ULN). Based on the limited number of patients with abnormal liver function at baseline, no dose adjustment can be recommended.

No formal trial has been conducted in patients with renal impairment. Population PK analysis suggested renal function measured by creatinine clearance has no significant correlation with the cabazitaxel clearance. As only 2.3% of the administered dose of cabazitaxel is eliminated renally, cabazitaxel PK was not changed in patients with mild renal impairment (50mL/min ≤CLCR≤80 mL/min) and moderate (30 mL/min≤CLCR≤50 mL/min). Patients with severe renal impairment (CLCR<30 mL/min) and end stage renal disease should be treated with caution and monitored carefully during treatment. Dose delay or reduction should be considered in the event of adverse drug reactions.

The potential effects of race/ethnicity on cabazitaxel PK were not formally investigated. Population PK analysis did not identify race (non-Caucasian versus Caucasian) as a significant covariate influencing cabazitaxel pharmacokinetics. The model predicted a similar plasma CL value of cabazitaxel in Caucasian patients (24.2 L/h/m², N=144) and in non-Caucasian patients (24.3 L/h/m², N=26) (Table 8). Small changes in predicted CL in different races were observed: the predictive plasma CL values in non-Caucasian patients were 29.6 L/ h/m² in oriental patients (N=9), 22.9 L/h/m² in black patients (N N=4), 22.0 L/h/m² in Hispanic patients (N=7), and 19.8 L/h/m² in "other" patients (N=6).

A conclusive exposure-response relationship could not be identified for overall survival possibly due to limited PK data (N=67) at one dose level (25 mg/m2) collected in the pivotal trial. The shallow slope of the exposure–response relationship for ≥ Grade 3 neutropenia suggested that dose reduction from 25 to 20 mg/m2 will reduce the risk of having ≥ grade 3 neutropenia by 5% when no prophylactic G-CSF was used.

The effect of cabazitaxel on cardiac repolarization has not been evaluated. A PMR will be issued to require the applicant to complete and submit the final report of ongoing trial TES10884, along with a thorough review of all available cardiac safety data, for the potential of cabazitaxel on QTc interval prolongation in patients.

6. Clinical Microbiology

Recommendations abstracted from the microbiologist review.

A. Recommendation on Approvability – *Recommended for approval from a microbiology quality standpoint.*

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – *N/A*

Review abstracted from the microbiologist review.

Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology *- CCSI is (b) (4) and filled into sterile, (b) (4) 15 mL glass vials that are sealed with 13 mm grey (b) (4) rubber stoppers and aluminum overseals. CS is (b) (4) and filled into the same container-closure system used for CCSI: 15 mL glass vials sealed with 13 mm grey (b) (4) rubber stoppers and aluminum overseals. The CS vials are (b) (4)*

B. Brief Description of Microbiology Deficiencies – *No deficiencies identified.*

C. Assessment of Risk Due to Microbiology Deficiencies – *Minimal risk.*

7. Clinical/Statistical- Efficacy

Clinical/Statistical Recommendation

Recommend approval. See PMRs and labeling revisions in section 12 below.

Clinical/Statistical Review

During clinical development, a total of 565 patients were enrolled and/or randomized to receive cabazitaxel in 3 Phase 1 trials (TED6188, TED6189, and TED6190), 1 trial investigating the disposition of radio labeled cabazitaxel (BEX6702), 1 Phase 2 trial with single agent cabazitaxel in patients with breast cancer (ARD6191) and the Phase 3 pivotal trial in patients with mHRPC (EFC6193). In addition, there were 33 patients enrolled into a Phase 2

combination therapy trial (TCD6945). Only efficacy data from the pivotal Phase 3 trial EFC6193/TROPIC will be used to support the efficacy of cabazitaxel in combination with prednisone in the treatment of mHRPC in patients previously treated with a docetaxel-containing regimen, the indication for which the Sponsor is seeking approval.

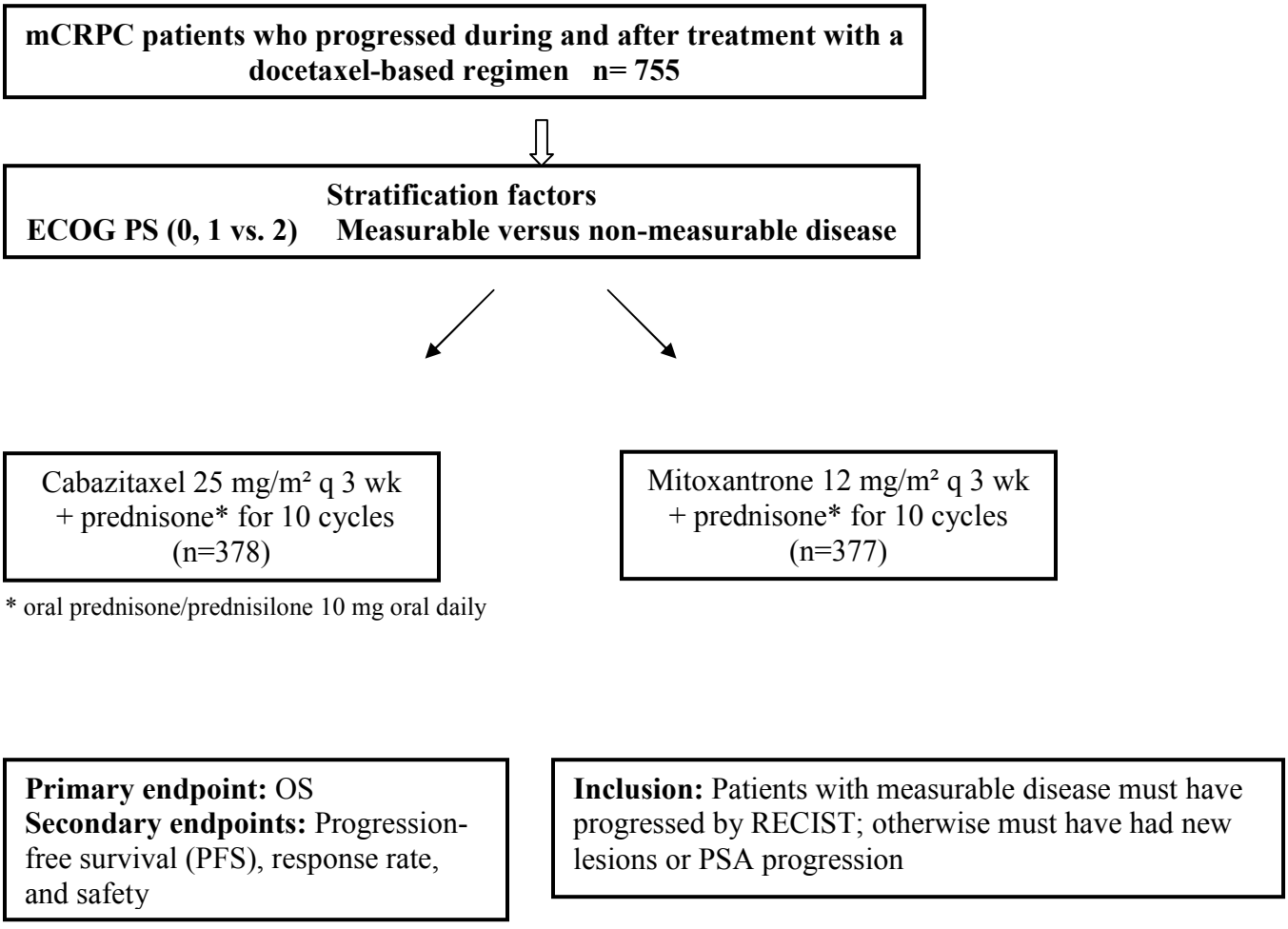
EFC6193 (TROPIC), the pivotal trial was a multicenter, multinational, randomized, open-label, comparative Phase 3 trial in mHRPC patients previously treated with a docetaxel containing regimen. Patients were randomly assigned (1:1) to receive cabazitaxel or mitoxantrone plus prednisone. Each patient was treated until disease progression, death, unacceptable toxicity, or a maximum of 10 cycles.

The 2 trial treatment arms were stratified for measurability of disease per RECIST criteria (measurable versus nonmeasurable disease) and ECOG performance status (0 or 1 versus 2). Antitumor activity was assessed by computerized tomography (CT) or magnetic resonance imaging (MRI) of the whole body (chest, abdomen, and pelvis) and by bone scan at baseline, and except for bone scans which were only performed if clinically indicated, these assessments were repeated at the end of each even-numbered treatment cycle, whenever disease progression was suspected, and at the end of treatment/withdrawal visit, using the same method for each assessment.

EFC6193 was a worldwide trial conducted in 146 centers in 26 countries. The trial schema is shown in Figure 2.

Figure 2 TROPIC: Phase 3 Registration Trial Schema

146 Sites in 26 Countries



Demography and patients characteristics are shown in Table 1.

Table 1 Demography and Patient Characteristics

	MTX+PRED (N=377)	CBZ+PRED (N=378)
Age, in years		
Median	67.0	68.0
Minimum	47	46
Maximum	89	92
Age		
18 to 64	162 (43.0%)	133 (35.2%)
65 to 74	145 (38.5%)	176 (46.6%)
75 and above	70 (18.6%)	69 (18.3%)
Race		
Caucasian/White	314 (83.3%)	317 (83.9%)
Black	20 (5.3%)	20 (5.3%)
Asian/Oriental	32 (8.5%)	26 (6.9%)
Other	11 (2.9%)	15 (4.0%)
ECOG PS[a]		
0 or 1	344 (91.2%)	350 (92.6%)
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 (Left ventricular ejection fraction) %		
Number of patients	243	235
Median	64.00	63.00
Minimum	42.0	38.0
Maximum	80.0	86.0
Radionuclide Ventriculography (LVEF) %		
Number of patients	129	140
Median	63.00	62.00
Minimum	50.0	50.2
Maximum	80.0	81.0

(continued)

Demography and Patient Characteristics (Continued)

	MTX+PRED (N=377)	CBZ+PRED (N=378)
PSA (in ng/mL)		
Number of patients	370	371
Median	127.5	143.9
Minimum	2	2
Maximum	11220	7842
Measurable Disease		
Measurable Disease	204 (54.1%)	201 (53.2%)
Not Measurable Disease	173 (45.9%)	177 (46.8%)
Extent of disease		
Metastatic	356 (94.4%)	364 (96.3%)
Loco Regional Recurrence	20 (5.3%)	14 (3.7%)
Missing	1 (0.3%)	0

MTX+PRED: Mitoxantrone + Prednisone/Prednisolone

CBZ+PRED: Cabazitaxel + Prednisone/Prednisolone

[a]According to the protocol, patients were stratified according to ECOG PS 0 1, versus 2.

Applicant Table

Table 2 Prior Docetaxel-Containing Regimens

		MTX+PRED (N=377)	CBZ+PRED (N=378)
Months from last Taxotere dose to randomization of this trial	Median	3.7	4.1
	Mean (SD)	5.7 (6.8)	6.2 (6.7)
Number of patients randomized	Within 6 months since last Taxotere dose	270 (71.6%)	234 (61.9%)
	More than 6 months since last Taxotere dose	107 (28.4%)	143 (37.8%)
	Missing	0	1 (0.3%)
Months from last Taxotere dose to progression	Median	0.7	0.8
	Mean (SD)	2.2 (4.4)	2.1 (4.4)
Number of patients progressed	During last Taxotere treatment	104 (27.6%)	115 (30.4%)
	<3 months since last Taxotere dose	181 (48.0%)	158 (41.8%)
	3 months to < 6 months after last Taxotere dose	50 (13.3%)	58 (15.3%)
	≥6 months since last Taxotere dose	40 (10.6%)	44 (11.6%)
	Missing	2 (0.5%)	3 (0.8%)
Number of regimen containing Taxotere	1	327 (86.7%)	316 (83.6%)
	2	43 (11.4%)	53 (14.0%)
	3 or more	7 (1.9%)	9 (2.4%)
Total prior Taxotere (mg/m^2)	Median	529.2	576.6
	Min	0	22
	Max	2999	3089
Number of patients received total Taxotere	<225 mg/m^2	30 (8.0%)	29 (7.7%)
	>=225 to 450 mg/m^2	112 (29.7%)	94 (24.9%)
	>=450 to 675 mg/m^2	105 (27.9%)	112 (29.6%)
	>=675 to 900 mg/m^2	57 (15.1%)	74 (19.6%)
	>=900 mg/m^2	68 (18.0%)	66 (17.5%)
	Missing	5 (1.3%)	3 (0.8%)

MTX+PRED: Mitoxantrone + Prednisone/Prednisolone
CBZ+PRED: Cabazitaxel + Prednisone/Prednisolone
Applicant Table

Median survival was 15.1 months in the cabazitaxel group and 12.7 months in the mitoxantrone group. The hazard ratio was 0.70 (95% CI: 0.59, 0.83) in favor of cabazitaxel corresponding to a 30% reduction in risk of death (Table 3). The difference was statistically significant in favor of the cabazitaxel group ($p<0.0001$). Patients were censored in both arms due to the trial cut-off of September 25, 2009. The Kaplan-Meier plots of OS are shown in Figure 3.

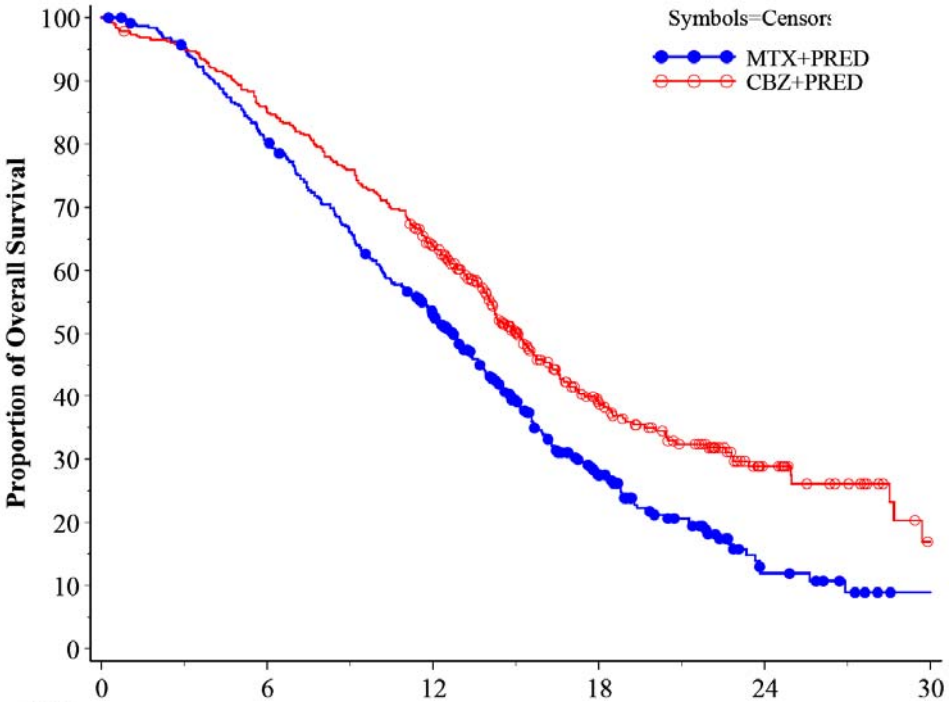
Table 3 Overall Survival by Treatment (ITT)

	MTX+PRED (N=377)	CBZ+PRED (N=378)
Overall survival		
Number of patients with deaths (%)	279 (74.0%)	234 (61.9%)
Median survival in months (95% CI)	12.7 (11.6-13.7)	15.1 (14.1-16.3)
Hazard ratio (95% CI)	0.70 (0.59-0.83)	
p-value	<0.0001	

Note: A hazard ratio <1 favors cabazitaxel.

Applicant Table

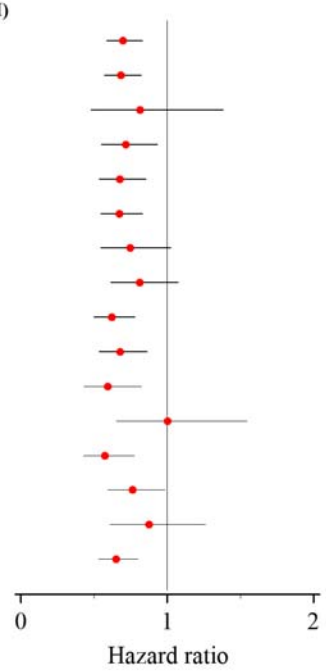
Figure 3 Kaplan-Meier Curves Overall Survival by Treatment (ITT)



Applicant Figure

Figure 4 Hazard Ratios Overall Survival by Treatment for Baseline Factors

Factor	Subgroup	Number	Hazard ratio(95% CI)
ITT population	All patients	755	0.70 (0.59 - 0.83)
ECOG Status	0,1	694	0.68 (0.57 - 0.82)
ECOG Status	2	61	0.81 (0.48 - 1.38)
Measurable disease	No	350	0.72 (0.55 - 0.93)
Measurable disease	Yes	405	0.68 (0.54 - 0.85)
No. of prior chemo	1	528	0.67 (0.55 - 0.83)
No. of prior chemo	>=2	227	0.75 (0.55 - 1.02)
Age	< 65	295	0.81 (0.61 - 1.08)
Age	>= 65	460	0.62 (0.50 - 0.78)
Country	Europe countries	402	0.68 (0.53 - 0.86)
Country	North America countries	235	0.59 (0.43 - 0.82)
Country	Other countries	118	1.00 (0.65 - 1.54)
Pain at baseline	No	314	0.57 (0.43 - 0.77)
Pain at baseline	Yes	310	0.76 (0.59 - 0.98)
Rising PSA at baseline	No	159	0.88 (0.61 - 1.26)
Rising PSA at baseline	Yes	583	0.65 (0.53 - 0.80)



Applicant Figure

In addition to the primary efficacy endpoint of overall survival, the Cabazitaxel/Prednisone treatment group was also statistically significantly superior to the Mitoxantrone/Prednisone treatment group for the following secondary endpoints.

1) Progression-free survival. Criteria for this endpoint were not standard. (b) (4) . In addition to the standard RECIST criteria, it was a composite endpoint also consisting of PSA progression and pain progression.
2) Time to Progression by RECIST criteria. This secondary endpoint was not protocol-specified, but added post hoc.
3) Tumor response by RECIST criteria.
4) PSA Response
5) Time to PSA Progression

Secondary endpoints that the Cabazitaxel/Prednisone treatment group was not statistically superior on were Pain Response and Time to Pain Progression. However,

Mitoxantrone/Prednisone is approved based on pain response and pain progression. So this does not mean that Cabazitaxel/Prednisone does favorably impact pain. (b) (4)

8. Safety

Two Phase 1 trials were conducted using the every 3 week schedule of administration of cabazitaxel. In one trial (TED6188) the dose of 20 mg/m² administered every 3 weeks as a 1-hour intravenous (IV) infusion was established as the recommended dose while in the second trial (TED6190), 25 mg/m² administered every 3 weeks as a 1-hour IV infusion was established as the recommended dose. Consequently, the dose of 20 mg/m² administered every 3 weeks as a 1-hour IV infusion was selected initially for further clinical development. In a Phase 2 study with metastatic breast cancer patients (ARD6191), the safety and anti-tumor activity was assessed at the dose of 20 mg/m² every 3 weeks at the first cycle, with possible intra-patient escalation to 25 mg/m2 at Cycle 2 allowed in the absence of any toxicity Grade >2 at Cycle 1. In 21 patients out of 71 patients, the dose of cabazitaxel could be escalated to 25 mg/m2 IV after the first cycle. The 25 mg/m² dose was chosen for the Phase 3 trial because this dose was expected to provide optimal dose intensity and potentially increase clinical benefit. The Phase 3 trial (EFC6193) used a 25 mg/m2 Cabazitaxel dose every 3 weeks for a maximum of 10 cycles, The were 371 patients in the safety population in each trial arm (See Table 4).

Table 4 Clinical Trials

Study	Study description	Indication	Design and Regimen	Treatment	Cabazitaxel dose level	Number treated
PHASE 3 STUDY EFC6193 STUDY						
EFC6193 (Phase 3)	A randomized, open label multi-center study of XRP6258 at 25 mg/m^2 in combination with prednisone every 3 weeks compared to mitoxantrone in combination with prednisone for the treatment of hormone refractory metastatic prostate cancer previously treated with a Taxotere®-containing regimen	2nd line prostate cancer	Cabazitaxel (25 mg/m^2) versus mitoxantrone (12 mg/m^2) (Day 1) every 3 weeks, plus prednisone (10 mg) orally given daily	Mitoxantrone + prednisone Cabazitaxel + prednisone	NA 25 mg/m^2	371 371
PHASE 1/PHASE 2 STUDIES						
Phase 1						
TED6188 (Phase 1)	A Phase 1 dose finding study of XRP6258 administered as a one hour intravenous infusion to patients with advanced solid tumors.	Advanced solid tumors	Cabazitaxel (10, 20, 25, and 30 mg/m^2) every 3 weeks	Cabazitaxel alone	10 mg/m^2 20 mg/m^2 25 mg/m^2 30 mg/m^2	3 7 6 5
TED6189 (Phase 1)	A Phase 1 dose finding study of XRP6258administered as a weekly one hour intravenous infusion to patients with advanced solid tumors	Advanced solid tumors	Cabazitaxel (1.5, 3, 6, 8.4, 10, and 12 mg/m^2) weekly	Cabazitaxel alone	1.5 mg/m^2 3 mg/m^2 6 mg/m^2 8.4 mg/m^2 10 mg/m^2 12 mg/m^2	1 1 4 23 7 6
TED6190 (Phase 1)	A Phase 1 dose finding study of cabazitaxel administered as a one hour intravenous infusion to patients with advanced solid tumors	Advanced solid tumors	Cabazitaxel (10, 15, 20, and 25 mg/m^2) every 3 weeks	Cabazitaxel alone	10 mg/m^2 15 mg/m^2 20 mg/m^2 25 mg/m^2	3 6 20 7

(continued)

Clinical Trials (Continued)

Study	Study description	Indication	Design and Regimen	Treatment	Cabazitaxel dose level	Number treated
			Phase 1 PK			
BEX6702 (open/disposition of cabazitaxel study)	A Phase 1, open study investigating the disposition of 25 mg/m² [^{14}C]-XRP6258 (50 µCi) administered as a 1-hour intravenous infusion to patients with advanced solid tumors	Advanced solid tumors	[^{14}C]-cabazitaxel as a 1-hour IV infusion (25 mg/m²) at Cycle 1 (3 weeks).	Cabazitaxel alone	25 mg/m²	4
			Phase 2			
ARD6191 (Phase 2)	A multicenter Phase 2 study of XRP6258 administered as a 1-hour intravenous infusion every three weeks in taxoid-resistant metastatic breast cancer patients	Taxoid-resistant metastatic breast cancer	Cabazitaxel 20, 25 mg/m² every 3 weeks (Arm A)	Cabazitaxel alone (Arm A)	20 mg/m² 25 mg/m²	50 21
			Cabazitaxel 10 mg/m² weekly (Arm B)	Cabazitaxel alone (Arm B)	10 mg/m²	13 [a]
				Larotaxel alone (Arm C)	NA	12 [b]
			Combination study			
TCD6945 (Phase 2)	A dose-escalating, multicenter, single arm, open-label study of XRP6258 in combination with capecitabine (Xeloda®), in patients with metastatic breast cancer with disease progressing after anthracycline and taxane therapy	Metastatic breast cancer with disease progressing after anthracycline and taxane therapy	Cabazitaxel (20 mg/m² and 25 mg/m²) in combination with capecitabine (825 mg/m² and 1000 mg/m²) every 3 weeks	Cabazitaxel + capecitabine 825 mg/m² every 3 weeks (Dose level I, Part 1)	20 mg/m²	6
				Cabazitaxel + capecitabine 1000 mg/m² every 3 weeks (Dose level II, Part 1 and Part 2)	20 mg/m²	21
				Cabazitaxel + capecitabine 1000 mg/m² every 3 weeks (Dose level III, Part 1)	25 mg/m²	6
			ONGOING STUDY [c]			
TCD10870 (Phase 1/2)	A dose-escalation study of the safety, tolerability, and pharmacokinetics of XRP6258 in combination with cisplatin administered every 3 weeks in patients with advanced solid malignancies	Advanced solid tumors	Cabazitaxel (20 mg/m² and 25 mg/m²) in combination with cisplatin (75 mg/m²) every 3 weeks	Cabazitaxel in combination with cisplatin every 3 weeks	20 and 25 mg/m² (could be reduced to 15 mg/m²)	4 [c]

I.V: intravenous; NA: not applicable

[a] ARD6191 Arm B patients (10 mg/m² weekly) were included in the analysis for the SCS but not included in the safety analysis for the CSR

[b] ARD6191 Arm C patients (larotaxel only) were included in the analysis for CSR but not SCS

[c] TCD10870 study was ongoing as of cut-off date

Applicant Table

Safety Results in Phase 3 Clinical Trial

The median number of cycles was 4 in the Mitoxantrone/Prednisone arm and 6 in the Cabazitaxel/Prednisone arm. The median relative dose intensity was 97% for Mitoxantrone and 96% for Cabazitaxel (See Table 5).

Table 5 Exposure

	MTX+PRED (N=371)	CBZ+PRED (N=371)
Number of cycles Median Min Max	4.00 1.0 10.0	6.00 1.0 10.0
Cumulative total dose (mg/m²) Median Min Max	46.40 10.9 23.3	148.50 22.5 258.4
Dose intensity (mg/m²/week) Median Min Max	3.89 1.7 4.2	8.01 4.1 9.0
Relative dose intensity (%) Median Min Max	97.25 42.5 1 06.0	96.12 49.0 108.2

Applicant Table

Deaths

Deaths due to AEs within 30 days of the last dose were 18 (4.9%) in the cabazitaxel group and (2.4%) in the mitoxantrone group and 3 (0.8%) patients in the mitoxantrone group.

Table 6 abstracted from the medical officer review shows the deaths due to AEs occurring within 30 days of last dose in the cabazitaxel and mitoxantrone groups.

Note that some deaths were attributed to more than one AE, so the total in the cabazitaxel column is 20.

Table 6 ***Deaths due to Treatment-Emergent Adverse Events Excluding Disease Progression and Occurring Within 30 Days of Last Dose on the Cabazitaxel Arm***

Grade 5 AE	*Cabazitaxel N = 18*	*Mitoxantrone N = 3*
Infection[1]	*5*	*1*
Cardiac Disorders[2]	*4*	*0*
Renal Failure[3]	*4*	*0*
Respiratory Disorders[4]	*2*	*1*
Other Neutropenia-Associated[5]	*2*	*0*
Other Not Neutropenia-Associated[6]	*3*	*1*

[1]Includes 158-003-003/fungal sepsis, 208-003-005/sepsis, 528-001-002/neutropenic sepsis, 724-003-002/septic shock (also renal failure), and 826-007-003/neutropenic sepsis on the cabazitaxel arm, and 250-001-027/pneumococcal sepsis on the mitoxantrone arm.
[2]Includes 056-003-001/ventricular fibrillation, 208-001-014/cardiac arrest, 250-001-023/cardiac failure, and 356-007-003/cardiac arrest on the cabazitaxel arm.
[3]Includes 710-005-005/renal failure, 724-003-002/renal failure, 752-001-008/renal failure, and 792-001-006/acute renal failure on the cabazitaxel arm. Note that 724-003-002 is also included under infections (septic shock) and 792-001-006 is also included under respiratory disorders (respiratory failure).
[4]Includes 356-001-007/dyspnea and 792-001-006/respiratory failure (also with acute renal failure) on the cabazitaxel arm, and 724-004-005/pleural effusion on the mitoxantrone arm.
[5]Includes 356-001-004/pancytopenia and 356-001-010/aspiration.
[6]Includes 276-008-003/cerebral hemorrhage, 484-001-006/electrolyte imbalance, and 840-073-001/sudden death on the cabazitaxel arm, and 380-003-014/multiple fracture on the mitoxantrone arm.
This above information was verified using the ADAE (Adverse Events) dataset.

A disparity in excess of TEAE deaths on cabazitaxel was noted in early 2008 as part of the Sponsor's ongoing pharmacovigilance review of SAEs and deaths. The IDMC, in an ad-hoc IDMC meeting, reviewed these deaths and was of the opinion that in the cabazitaxel group, 7 deaths were due to neutropenic complications most of them during Cycle 1 of study treatment; and 2 were due to renal failure secondary to dehydration. Based on IDMC recommendations the Investigators were advised to strictly follow the protocol regarding dose delay and modifications and to treat neutropenia per ASCO guidelines. These recommendations were instituted and no new neutropenic deaths were reported.

Dose Reductions, Delays and Discontinuance

In the cabazitaxel group, 9.8% of cycles were administered with a dose reduction of ≥20% and 9.3% of cycles were delayed by ≥4 days compared with 5.1% of cycles dose reduced and 7.9% cycles delayed in the mitoxantrone group.

Dose reductions, delays and interruptions are shown in Table 7 abstracted from the medical officer review.

Table 7 Dose modifications

	Cabazitaxel N = 371	*Mitoxantrone N =371*
Any Modification	*138 (37.2%)*	*68 (18.3%)*
Delay	*95 (25.6%)*	*52 (14.0%)*
Reduction	*35 (9.4%)*	*9 (2.4%)*
Delay and Reduction	*11 (3.0%)*	*4 (1.1%)*
Interruption	*18 (4.9%)*	*4 (1.1%)*

Study treatment discontinuation due to a TEAE (including disease progression that was reported as a TEAE) was reported in 18.3% of patients in the cabazitaxel group and 8.4% of patients in the mitoxantrone group.

Table 8 Most Frequent TEAE (All Grades) Leading to Discontinuation (≥3 Patients)

	MP (n=371) %	**CBZP (n=371) %**
Any TEAE	**8.4**	**18.3**
Neutropenia	**0**	**2.4**
Hematuria	**0.3**	**1.3**
Diarrhea	**0.3**	**1.1**
Fatigue	**0.3**	**1.1**
Acute renal failure	**0**	**1.1**
Abdominal pain	**0**	**0.8**
Febrile neutropenia	**0**	**0.8**
Renal failure	**0**	**0.8**
Sepsis	**0**	**0.8**

Applicant Table

Adverse Events

Table 9 Summary of Safety

% of patients	MP (n=371)	CBZP (n=371)
Any TEAE	88.4	95.7
Grade ≥3 TEAEs	39.4	57.4
Serious TEAEs	20.8	39.1
Leading to discontinuation	8.4	18.3

Applicant Table

Table 10 Most Frequent Treatment-Emergent AEs Safety Population

	MP (n=371)		CBZP (n=371)	
	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Any adverse event	88.4	39.4	95.7	57.4
Febrile neutropenia	1.3	1.3	7.5	7.5
Diarrhea	10.5	0.3	46.6	6.2
Fatigue	27.5	3.0	36.7	4.9
Asthenia	12.4	2.4	20.5	4.6
Back pain	12.1	3.0	16.2	3.8
Nausea	22.9	0.3	34.2	1.9
Vomiting	10.2	0	22.6	1.6
Hematuria	3.8	0.5	16.7	1.9
Abdominal pain	3.5	0	11.6	1.9

Applicant Table

The most frequent **hematological AEs** in the cabazitaxel group (Grade ≥3) were neutropenia and its clinical associated consequences of febrile neutropenia and infections. Based on laboratory assessments, 81.7% of patients in the cabazitaxel group and 58.0% of patients in the mitoxantrone group had neutropenia, of which clinical neutropenia (Grade ≥3) requiring intervention was reported in 21.3% of patients treated with cabazitaxel and 7.0% of patients

treated with mitoxantrone. Patients treated with cabazitaxel also had higher rates of infections Grade ≥3 (10.2% cabazitaxel, 5.1% mitoxantrone) and febrile neutropenia (7.5% cabazitaxel, 1.3% mitoxantrone). Based on laboratory data, in patients who developed neutropenia, the time to first occurrence of neutropenia in the cabazitaxel group was within the first 2 cycles in 70 to 80% of patients. Primary prophylaxis with G-CSF was not permitted at Cycle 1; however, per protocol, G-CSF use was permitted for prophylaxis following the first occurrence of either neutropenia lasting for ≥7 days or if complicated by temperature > 38.5°C, or a temperature >38.1°C x 3 observations during a 24 hour period, or infection. G-CSF was used to decrease the incidence of neutropenia Grade ≥3. Anemia was more frequent in the cabazitaxel group (10.5%) compared with the mitoxantrone group (4.9%) as well.

Table 11 Neutropenia and Associated Events

	MTX+PRED (N=371)		CBZ+PRED (N=371)	
Neutropenia	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Laboratory neutropenia	325 (87.6%)	215 (58.0%)	347 (93.5%)	303 (81.7%)
Clinical neutropenia	40 (10.8%)	26 (7.0%)	81 (21.8%)	79 (21.3%)
Associated events				
Infections and Infestations	84 (22.6%)	19 (5.1%)	126 (34.0%)	38 (10.2%)
Sepsis	6 (1.6%)	5 (1.3%)	9 (2.4%)	9 (2.4%)
Septic shock	0	0	4 (1.1%)	4 (1.1%)
Neutropenic infection	0	0	2 (0.5%)	2 (0.5%)
Febrile neutropenia	5 (1.3%)	5 (1.3%)	28 (7.5%)	28 (7.5%)

Note: Sepsis includes the preferred terms of bacterial sepsis, fungal sepsis, neutropenic sepsis, pneumococcal sepsis, sepsis, and urosepsis.
Applicant Table

The **prophylactic or therapeutic use of G-CSF** was evaluated relative to the occurrence of neutropenia Grade ≥3. For this analysis, the use of G-CSF was defined as prophylactic use if it was administered within 3 days of dosing or was defined as therapeutic if G-CSF was administered after 3 days of dosing. During Cycle 1, the incidence of neutropenia was high (91.7%) in patients in the cabazitaxel group who received G-CSF after 3 days of dosing. After Cycle 1, more patients in the cabazitaxel group received prophylactic G-CSF and the neutropenia rate (Grade ≥3) rate decreased to approximately 25% compared to 44.6% in patients who did not receive G-CSF showing that G-CSF use could reduce neutropenia occurrence in the cabazitaxel group.

Table 12 Neutropenia and G-CSF Use

Neutropenia grade	MP n=371 G-CSF user N=65 (17.5%)	MP n=371 No G-CSF user N=306 (82.5%)	CBZP n=371 G-CSF user N=168 (45.3%)	CBZP n=371 No G-CSF user N=203 (54.7%)
All Grade	62 (95.4%)	264 (86.6%)	167 (99.4%)	181 (89.6%)
Grade ≥ 3	51 (78.5%)	165 (54.1%)	163 (97.0%)	142 (70.3%)

Applicant Table

The following dose dependency information is abstracted from the medical officer review.

Grade 1-4 neutropenia and grade 3-4 neutropenia occurred more frequently in ISS database patients who received ≥25 mg/m^2 q3 weekly cabazitaxel dosing than in patients who received lower doses.

Table 13: Neutropenia in Cabazitaxel-Treated Patients Receiving <25 mg/m^2 q3 Weekly Dosing vs. ≥25 mg/m^2 q3 Weekly Dosing in ISS Database

	<25 mg/m^2 q3 week N = 89	*≥25 mg/m^2 q3 week N = 412*
Grade 1-4 Neutropenia	*72 (80.9%)*	*387 (93.9%)*
Grade 3-4 Neutropenia	*54 (60.7%)*	*335 (81.3%)*

The above information was verified using the ISS ADAE (Adverse Events) dataset.

The applicant performed an analysis of the rates of grade 1-4 and grade 3-4 neutropenia in patients who received 20 mg/m^2 q3 weekly dosing in supportive studies, including a total of 77 patients. A comparison of neutropenia rates in these 77 patients is compared to cabazitaxel-treated patients on EFC6193 in table 38 below.

Table 14: Neutropenia in Cabazitaxel-Treated Patients Receiving 20 mg/m^2 q3 Weekly Dosing in ISS Database

	EFC6193 25 mg/m^2 Dosing N = 369	TED6188, TED6190, ARD6191 20 mg/m^2 Dosing N = 77
Neutropenia		
All Grades	347 (94.0%)	62 (80.5%)
Grade 3-4	303 (82.1%)	44 (57.1%)

Applicant's Analysis

Reviewer Comment: *The rate of grade 3-4 neutropenia was lower among patients who received 20 mg/m^2 dosing. Of note, fifty of the 77 patients who received 20 mg/m^2 dosing were breast cancer patients treated on ARD6191. Despite the lower rate of grade 3-4 neutropenia, patients on ARD6191 were found to have a higher overall exposure to cabazitaxel.*

Infections and infestations were more common in the cabazitaxel group (34.0% all grades, 10.2% Grade ≥3) than in the mitoxantrone group (22.6% all grades, 5.1% Grade ≥3), accounted for primarily by infections – pathogen unspecified (cabazitaxel 27.0% all grades, 7.8% Grade ≥3 versus mitoxantrone 16.2% all grades, 3.2% Grade ≥3. Serious adverse events within the infections –pathogen unspecified HLGT were reported in 7.8% of the patients in the cabazitaxel group and 3.2% of patients in the mitoxantrone group. Sepsis, bacteremia, viremia, and fungemia were more common in cabazitaxel patients (3.5%) than in mitoxantrone patients (1.3%). Serious TEAEs within this HLT were reported in 3.5% of patients in the cabazitaxel group and 1.1% of patients in the mitoxantrone group

Gastrointestinal disorders of all types (Grade ≥3) were more common in the cabazitaxel group (12.4% cabazitaxel, 1.6% mitoxantrone). Notably, Grade ≥3 diarrhea was more common on cabazitaxel (6.2%) compared with mitoxantrone (0.3%). Grade ≥3 nausea and vomiting was 3% on cabazitaxel and 0.3% on mitoxantrone while the incidence of Grade ≥3 stomatitis (0% in both groups) and mucositis (0.3% in both groups) were similar in both treatment groups.

Amongst the system organ class (SOC) of **general disorders and site conditions** (Grade ≥3) asthenic conditions (asthenia and fatigue) were more common with cabazitaxel (9.2%) compared to mitoxantrone (5.4%).

Adverse events in the **renal and urinary disorders** SOC (Grade ≥3) also were more common in the cabazitaxel group (8.6% cabazitaxel, 2.4% mitoxantrone). These events consisted of renal failure and impairment (3.2% cabazitaxel, 0.3% mitoxantrone) as well as renal obstructive disorders (0.8% cabazitaxel, 0.5% mitoxantrone). In the cabazitaxel group, 15 patients were reported to have acute renal AEs Grade ≥3, the etiology of which was multifactorial consisting of pre-renal, renal, or obstructive causes. A review of patient narratives demonstrated that based either on serum creatinine and BUN or physician assessment, 8 patients
recovered, and 7 patients did not recover including 1 patient who received hemodialysis. There were 4 deaths due to renal failure on the cabazitaxel arm.

There were more **hematuria** cases on the cabazitaxel arm than the mitoxantrone arm.
The following analysis of hematuria is abstracted from the medical officer review.

Hematuria of all grades was increased on the cabazitaxel arm, as shown in the table below. Note that total numbers of hematuria events in this section differ slightly from those presented in other sections, as the following analyses include all hematuria-associated events (blood urine present, urinary tract hemorrhage, and urinary bladder hemorrhage), rather than strictly events with the preferred term hematuria.

Table 15: Hematuria Adverse Events[1]

Adverse Event	*Cabazitaxel N = 371*	*Mitoxantrone N = 371*
All Grades	*67 (18.1%)*	*15 (4.0%)*
Grade ≥2	*24 (6.5%)*	*9 (2.4%)*
Grade 1	*43 (11.6%)*	*6 (1.6%)*
Grade 2	*16 (4.3%)*	*6 (1.6%)*
Grade 3	*7 (1.9%)*	*2 (<1%)*
Grade 4	*1 (<1%)*	*0*
Grade 5	*0*	*1 (<1%)*

[1]*Includes blood urine present, urinary tract hemorrhage, and urinary bladder hemorrhage.*
The above information was verified using the ADAE (Adverse Events) dataset.

Reviewer Comment: *As all cabazitaxel-treated patients with grade ≥2 hematuria who delayed or discontinued therapy eventually recovered and only 1 case of irreversible renal failure occurred among all cabazitaxel-treated patients with hematuria, the occurrence of hematuria appears to be manageable and not closely correlated with irreversible renal failure.*

All Grade events in the **cardiac disorders** SOC were more common on cabazitaxel compared with mitoxantrone of which 6 patients (1.6%) had Grade ≥3 cardiac arrhythmias on cabazitaxel compared with 1 patient (0.3%) on mitoxantrone. The incidence of tachycardia on cabazitaxel was 1.6%, none of which were Grade ≥3. Cardiac failure events were more common on cabazitaxel (2 patients [0.5%] versus none on mitoxantrone). One patient in the cabazitaxel group died from cardiac failure. As expected, left ventricular dysfunction (all grades) (3 patients [1.6%] versus 1 patient [0.3%]) was more common with mitoxantrone.

The TEAEs (Grade ≥3) with a higher incidence in patients ≥65 years old in the cabazitaxel group were blood and lymphatic disorders (including neutropenia and febrile neutropenia), cardiac disorders, and infections and infestations. All grade asthenia and dehydration were also more common in patients ≥65 years old treated with cabazitaxel than mitoxantrone.

The following is abstracted from the medical officer review regarding the relationship of age and adverse reactions.

Overall, grade 1-4 adverse event rates were similar in patients <65 years old and ≥65 years old. However, among the most common (>15%) grade 1-4 adverse events, several occurred more frequently (≥5% difference) in older patients. The common grade 1-4 events that occurred more frequently in patients ≥65 years old were: neutropenia (89.2% in <65 yrs vs. 96.7% in ≥65 yrs), thrombocytopenia (39.2% in <65 yrs vs. 52.3% in ≥65 yrs), fatigue (29.8% in <65 yrs vs. 40.4% in ≥65 yrs), and asthenia (14.5% in <65 yrs vs. 23.8% in ≥65 yrs).

Several less common grade 1-4 adverse events also occurred more commonly in older patients, including pyrexia in 7.6% <65 yrs vs. 14.6% ≥65 yrs, dizziness 4.6% <65 yrs vs. 10.0% ≥65 yrs, urinary tract infection in 3.1% <65 yrs vs. 10.4% ≥65 yrs, and dehydration in 1.5% <65 yrs vs. 6.7% ≥65 yrs.

Overall, grade 3-4 adverse event rates were higher in patients ≥65 years old. Among the most common (>2%) grade 3-4 adverse events, several occurred more frequently (≥5% difference) in older patients. The common grade 3-4 events that occurred more frequently in patients ≥65 years old were: neutropenia (73.8% in <65 yrs vs. 86.6% in ≥65 yrs) and leukopenia (57.7% in <65 yrs vs. 74.5% in ≥65 yrs). Grade 3-4 febrile neutropenia, anemia, asthenia, thrombocytopenia, pneumonia, and dehydration were also more common in older patients.

Among 18 cabazitaxel-treated patients with treatment-emergent grade 5 adverse events other than disease progression, only 3 were <65 years of age: 484-001-006/electrolyte imbalance, 752-001-008/renal failure, and 826-007-003/neutropenic sepsis. Four of 5 infection-related grade 5 events occurred in patients ≥65 years of age, 3 of 4 grade 5 renal failure adverse events occurred in patients ≥65 years of age, and all 4 grade 5 cardiac events occurred in patients ≥65 years of age.

Cabazitaxel-treated patients ≥75 years had a higher incidence of Grade ≥3 neutropenia, infections and infestations, fatigue, and asthenia. These results should be interpreted with caution because there were approximately 70 patients in each group who were over 75 years compared with approximately 300 patients who were under age 75 years.

Conclusions and Recommendations on Safety

The 25 mg/m2 cabazitaxel dose in this trial may be too high. In one Phase 1 trial the MTD was 20 mg/m2 and in the other Phase 1 trial the MTD was 25 mg/m2. In the Phase 2 breast cancer trial the dose was 20 mg/m2 with the plan to escalate in the 2nd cycle to 25 mg/m2 in patients who did not have serious toxicity on the first cycle. They were able to increase the dose to 25 mg/m2 in only 21 of 71 patients.

The risk/ benefit ratio in the Phase 3 trial is favorable, but suboptimal. The severity of toxicity would be more acceptable in a setting where cure is the objective. But the severity of toxicity is suboptimal where the objective is palliation in a group of elderly men. The necessity for almost 50% of patients to be supported with G-CSF is not what we would desire for this setting.

Prophylactic G-CSF was not permitted in the first cycle of the RCT. The FDA review team has revised the package insert to indicate that "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. Therapeutic use of G-CSF and secondary prophylaxis should be considered in all patients considered to be at increased risk for neutropenia complications".

Because the risk/benefit ratio is favorable and 25 mg/m2 is the only dose we have data on, we are stuck with this dose. Unfortunately so are elderly men with mHRPC. There should be a PMR to study a lower dose in mHRPC, probably in a different population such as initial chemotherapy of mHRPC. Another RCT in mHRPC in patients progressing on or after

docetaxel comparing cabazitaxel 20 mg/m2 with cabazitaxel 25 mg/m2 shold also be considered for a PMR. Two additional PMRs are required to assess renal toxicity (See Section 12 below for a complete list of PMRs).

Advisory Committee Meeting

No Advisory Committee Meeting was held.

9. Pediatrics

Cabazitaxel has been granted a waiver by PERC because prostate cancer does not occur in children.

10. Other Relevant Regulatory Issues

- Financial Disclosures

The following information on Financial Disclosures is abstracted from the Medical Officer Review.

Eight investigators in the key study supporting this NDA were found to have financial conflict of interest, either a proprietary interest or significant payments from or equity interest in the applicant. These investigators received payments as honoraria for speaking events, professional fees and consulting fees ranging from totals of $29,550 to $94,000. Amount of honoraria was not provided for three investigators.

There were 142 sites where patients were enrolled on the pivotal, Phase 3 trial. The number of patients enrolled at each of the sites for the investigators with a financial disclosure was not found to drive the efficacy or safety data.

- DSI Audits

The following is abstracted from the DSI Clinical Inspection Summary.

OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS
Four clinical investigators were inspected in support of this application, two domestic and two foreign. Although regulatory violations were noted for three of the four clinical investigators, the findings are considered isolated in nature and unlikely to significantly impact data integrity. The data from these investigators are considered reliable and may be used to support approval of the application.

***Note**: Observations noted above are based on the Form FDA 483 and/or oral and written*

communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

11. Labeling

Much labeling discussion focused on proper format and editing to improve clarity. Special attention was directed to clarity and content of the Boxed Warning, Contraindications, Warnings and Precautions sections. Emphasis was on neutropenia, febrile neutropenia, infection, diarrhea, hypersensitivity reactions and renal failure.

Neutropenia and related complications were the main safety issue in the RCT. Prophylactic G-CSF was not permitted for the first cycle in the RCT. Most neutropenic deaths occurred on the first cycle. Accordingly the FDA review team revised the package insert to indicate that, "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. Therapeutic use of G-CSF and secondary prophylaxis should be considered in all patients considered to be at increased risk for neutropenia complications". The package insert already indicated that "JEVTANA should not be administered to patients with neutrophils ≤ 1,500/mm^3."

The following was also added to the package insert. "JEVTANA should not be given to patients with hepatic impairment (total bilirubin ≥ ULN, or AST and/or ALT ≥ 1.5 × ULN)."

- Proprietary name

The Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis has approved Jevtana as the proprietary name.

- Important issues raised by DDMAC and OSE .

The Office of Safety agreed that a REMS is not needed. A Patient Package Insert is adequate.
The Office of Safety also agreed with the nine required PMRs.
The Office of Safety agreed with the labeling as revised by the cabazitaxel review team.
DDMAC review is not yet received.

- Physician labeling

Labeling is submitted in Physician Labeling Format and is revised by the cabazitaxel review team.

- Highlight major issues that were discussed, resolved, or not resolved at the time of completion of the CDTL review.

Major issues are reflected in the PMRs (See section 12 below).

- Carton and immediate container labels (if problems are noted)

Only minor revisions were needed.

- Patient labeling/Medication guide (if considered or required)

The Office of Safety does not recommend a REMS. Other similar oncology products do not have a REMS. Cabazitaxel is labeled for use only by experts in the use of oncology products and we know that non-experts seldom if ever use this type of drug. A patient package insert is included.

12. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The CDTL recommends approval of cabazitaxel for the following indication. "Jetvana in combination with prednisone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen".

- Risk Benefit Assessment

The single RCT showed a statistically significant improvement in median survival of 2.4 months for cabazitaxel in combination with prednisone compared to mitoxantrone in combination with prednisone. The mitoxantrone/prednisone combination has not been shown to improve survival. The cabazitaxel 25 mg/m2 dose every 3 weeks causes considerable toxicity and may be unnecessarily high. However, we have no information from RCTs on any other cabazitaxel dose and do not know if a lower dose would be effective. Despite the increased toxicity and increase in deaths due to toxicity in the cabazitaxel arm relative to the control arm, there is still a survival advantage for the cabazitaxel treatment group. The most common ($\geq$ 5%) grade 3-4 adverse reactions in cabazitaxel-treated patients were neutropenia, leukopenia, anemia, febrile neutropenia, diarrhea, fatigue, and asthenia. The cabazitaxel dose will be addressed in two PMRs. The cabazitaxel toxicity will be addressed in the label and with several PMRs (See below for a complete list of PMRs).

There were no disagreements among review team members regarding Risk Benefit Assessment.

- Recommendation for Post marketing Risk Evaluation and Management Strategies

See the ten PMRs in the next section.

The Office of Safety does not recommend a REMS. Other similar oncology products do not have a REMS. Cabazitaxel is labeled for use only by experts in the use of oncology products and we know that non-experts seldom if ever use this type of drug.

- Recommendation for other Post marketing Requirements and Commitments

The following ten PMRs are required.

PMR 1649-1:
To evaluate the potential for a serious risk of intravenous infusion of particulate matter into the blood stream, it is necessary to better understand and characterize the supersaturated pre-mix. Conduct a study to provide data which address particulate nucleation and kinetic factors of precipitation in the pre-mix. Conduct this study using multiple samples drawn from multiple batches so as to more fully support an in-use life of the pre-mix.

Study considerations include (but are not necessarily limited to); interior surface properties of the container closure (e.g., treatments, roughness, scratches, etc.), initial mixing agitation force (vigorous shaking), physical shock on standing (e.g., vigorous shaking during in-use storage), needle sticks, syringe use, temperature (and temperature changes during in-use storage), and additional time point sampling beyond the proposed duration of in-use storage of the pre-mix solution (e.g., 1 to 4 hours).

Collect and provide photographs of the precipitate as it appears in the container and isolated photomicrographs of the particles, as feasible.

Provide by mass balance, the mass of precipitated drug as precipitated mass and as mass percent of the total cabazitaxel content.

Final Protocol Submission:	September 30, 2010
Study Completion Date:	March 31, 2011
Final Report Submission:	June 30, 2011

The rationale for this PMR is to evaluate the risk of infusion of particulate matter into the blood stream because the pre-mix solution is supersaturated.

PMR 1649-2:
To evaluate the potential for a serious risk of intravenous infusion of particulate matter into the blood stream, it is necessary to better understand and characterize the supersaturated infusion solution. Conduct a study which addresses particulate nucleation and kinetic factors of precipitation from the infusion solution. Conduct this study using multiple samples drawn for at least three additional batches in the containers (bags and sets) which you propose to label for this use so as to more fully support an in-use life of the infusion solution.

Study factors include (but are not necessarily limited to); interior surface properties of the container (e.g.., treatments, roughness, plasticizers, etc.), initial mixing agitation force (vigorous shaking), physical shock on standing (e.g., vigorous shaking during in-use storage), needle sticks, temperature (and temperature changes during in-use storage), and additional time point sampling beyond the proposed duration of in-use storage of the infusion solution.

Collect and provide photographs of the precipitate as it appears in the container and isolated photomicrographs of the particles, as feasible, for each observed precipitation or evidence of precipitation (e.g., clogged filters, impeded infusion flow, etc.).

Provide by mass balance, the mass of precipitated drug as precipitated mass and as mass percent of the total cabazitaxel content.

Final Protocol Submission:	September 30, 2010
Study Completion Date:	March 31, 2011
Final Report Submission:	June 30, 2011

The rationale for this PMR is to evaluate the risk of infusion of particulate matter into the blood stream because the infusion solution is supersaturated.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the unusually high incidence and severity of toxicity in your Phase 3 cabazitaxel trial in metastatic hormone refractory prostate cancer. We are concerned about the entire toxicity spectrum with special concern for neutropenia, febrile neutropenia, infection, diarrhea, renal and cardiac toxicities and the increased incidence of drug-related death. A lower cabazitaxel dose may be equally effective with less toxicity. We have also determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of hepatic impairment, Q-T prolongation and drug-drug interaction with Jevtana®.

PMR 1649-3:
Conduct a Phase 3 randomized controlled trial with adaptive design in patients with hormone refractory metastatic prostate cancer comparing 75 mg/m^2 docetaxel/prednisone with cabazitaxel 25 mg/m^2/prednisone and cabazitaxel 20 mg/m^2/prednisone as first line therapy. The primary endpoint should be overall survival. The trial should be powered to detect a 25% difference in overall survival. The study will include interim analyses for evaluation of efficacy based on overall survival and safety of the 25 mg/m^2/prednisone arm versus the 20 mg/m^2/prednisone arm to potentially drop one of the cabazitaxel arms. Submit the protocol for agency review prior to commencing the trial.

Final Protocol Submission:	November 30, 2010
Trial Completion Date:	December 31, 2017
Final Report Submission:	June 30, 2018

The rationale for this PMR is that the toxicity of the cabazitaxel 25 mg/m2 dose is relatively high. A lower dose may be equally effective and less toxic.

PMR 1649-4:
Conduct a Phase 3 randomized controlled trial in 1222 patients with hormone refractory metastatic prostate cancer **previously treated** with docetaxel: cabazitaxel 20 mg/m2/prednisone versus cabazitaxel 25 mg/m2/prednisone powered to preserve 50% of the treatment effect of cabazitaxel 25mg/m2. The study will include interim analyses for evaluation of efficacy based on overall survival and safety of the 25 mg/m^2/prednisone arm versus the 20 mg/m^2/prednisone arm to potentially discontinue the study. The sponsor will submit the protocol for agency review prior to commencing the trial.

Final Protocol Submission:	November 30, 2010
Trial Completion Date:	December 31, 2017
Final Report Submission:	June 30, 2018

The rationale for this PMR is that the toxicity of the cabazitaxel 25 mg/m2 dose is relatively high. A lower dose may be equally effective and less toxic.

PMR 1649-5:
Complete and submit the final report of trial TES10884, along with a thorough review of cardiac safety data, for the potential of cabazitaxel on QTc interval prolongation in patients.

Final Protocol Submission:	January 31, 2010
Trial Completion Date:	December 31, 2011
Final Report Submission:	June 30, 2012

The rationale for this PMR is that the required assessment of cabazitaxel potential to prolong the QTc interval has not been completed.

PMR 1649-6:
Conduct the trial POP6972 to determine the pharmacokinetics and safety of cabazitaxel in patients with hepatic impairment.

Final Protocol Submission:	March 31, 2010
Trial Completion Date:	May 31, 2012
Final Report Submission:	November 30, 2012

The rationale for this PMR is that cabazitaxel is eliminated primarily by the liver and patients with liver impairment may be exposed to increased cabazitaxel levels.

PMR 1649-7:
Conduct a drug interaction trial to evaluate the effect of a strong CYP3A4 inhibitor (e.g., ketoconazole) on the pharmacokinetics of cabazitaxel in cancer patients.

Final Protocol Submission:	October 31, 2010
Trial Completion Date:	April 30, 2012
Final Report Submission:	December 31, 2012

The rationale for this PMR is to determine whether and to what extent patients may be exposed to increased cabazitaxel levels in the presence of a strong CYP3A4 inhibitor.

PMR 1649-8:
Conduct a drug interaction trial to evaluate the effect of a strong CYP3A inducer (e.g., rifampin) on the pharmacokinetics of cabazitaxel in cancer patients.

Final Protocol Submission:	October 31, 2010
Trial Completion Date:	April 30, 2012
Final Report Submission:	December 31, 2012

The rationale for this PMR is to determine whether and to what extent patients may be exposed to decreased cabazitaxel levels in the presence of a strong CYP3A inducer.

PMR 1649-9:
Organize a group of renal experts to review and analyze renal toxicity from all currently available cabazitaxel trials to identify etiologies and to provide recommendations for toxicity mitigation by patient selection or other measures. This group's findings and recommendations should be submitted within 9 months of the cabazitaxel approval date.

Final Report Submission Date: March 31, 2011

The rationale for this PMR is that there were more patients with renal failure and clinically significant hematuia on the cabazitaxel arm than the control arm. The etiology of the renal toxicity is unknown. We need to know whether the renal toxicity can be mitigated by patient selection or other measures.

PMR 1649-10:
Submit updates on renal toxicity from the next randomized trial every 6 months for 3 years from the initiation of the clinical trial.

Final Protocol Submission:	December 31, 2010

The rationale for this PMR is that there were more patients with renal failure and clinically significant hematuia on the cabazitaxel arm than the control arm. The etiology of the renal toxicity is unknown. We need to know whether the renal toxicity can be mitigated by patient selection or other measures.

All of these PMRs involve potential safety issues and any of them could be the basis for not approving the NDA. However, even without resolution of these potential safety issues, the risk/benefit ratio is favorable because patients who take cabazitaxel live longer than patients who do not take it. These PMRs hopefully will make cabazitaxel even more safe and effective, but the risk/benefit ratio is already favorable. Thus delaying cabazitaxel approval until after resolution of all or some of these potential safety issues is not appropriate.

- Recommended Comments to Applicant

1) The ten above PMRs must be completed as indicated.

2) Based on the 12 months primary stability data, 6 month of accelerated data, and 36 months of the supportive stability data for drug substance and per ICH Q1E guidelines, an initial retest date of (b) (4) with storage at 5oC is granted.

   Based on the 12 months primary stability data, 6 month of accelerated data for drug product and diluent, and per ICH Q1E guidelines, an initial expiration dating period of 18-months for the drug product stored under the following conditions is granted.

   - Store at 25°C (77°F); excursion permitted between 15°C – 30°C (59°F – 86°F).
   - Do not refrigerate.

3) Please revise the package insert, patient package insert, carton and container label as revised by the cabazitaxel review team.

[i] Tannock IF, de Wit R, Berry WR, et al: Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004; 351:1502-1512.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

JOHN R JOHNSON
06/16/2010