CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201023

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	6/17/2010
From	Amna Ibrahim MD
Subject	Division Director Summary Review
NDA #	201023
Applicant Name	Sanofi aventis
Date of Submission	5/31/2010
PDUFA Goal Date	9/30/2010
Proprietary Name / Established (USAN) Name	Cabazitaxel (XRP6258)/ JEVTANA®
Dosage Forms / Strength	Intravenous formulation supplied as 60 mg/1.5 mL
Proposed Indication(s)	JEVTANA® is a microtubule inhibitor used in combination with prednisone indicated for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Amy McKee, MD (efficacy); Ian Waxman MD (safety)
Statistical Review	Chia-Wen Ko, PhD
Pharmacology Toxicology Review	Sachia Khasar, PhD; Whitney Helms, PhD
CMC Review/OBP Review	Xiao-Hong Chen, PhD
Microbiology Review	Steven E Fong, PhD
Clinical Pharmacology Review	Pengfei Song, PhD
DDMAC	Keith Olin
DSI	Robert Young, MD
CDTL Review	John R. Johnson, MD
OSE/DMEPA	Lubna Najam, MS, PharmD,
OSE/DRISK	Sharon Mills, BSN, RN, CCRP
Other (SEALD)	Ann Marie Trentacosti

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

1. Introduction

According to CDC, prostate cancer is the most common cancer in men. In 2005 (the most recent year for which statistics are available), 185,895 men were diagnosed with prostate cancer, and 28,905 men died from it. There is no drug approved for patients who require second-line treatment after Taxotere for metastatic, hormone-refractory prostate cancer. Cabazitaxel, a taxane, has been submitted for a New drug Application (NDA) for this patient population.

As per CDTL review by John Johnson MD, *"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."*

2. Background

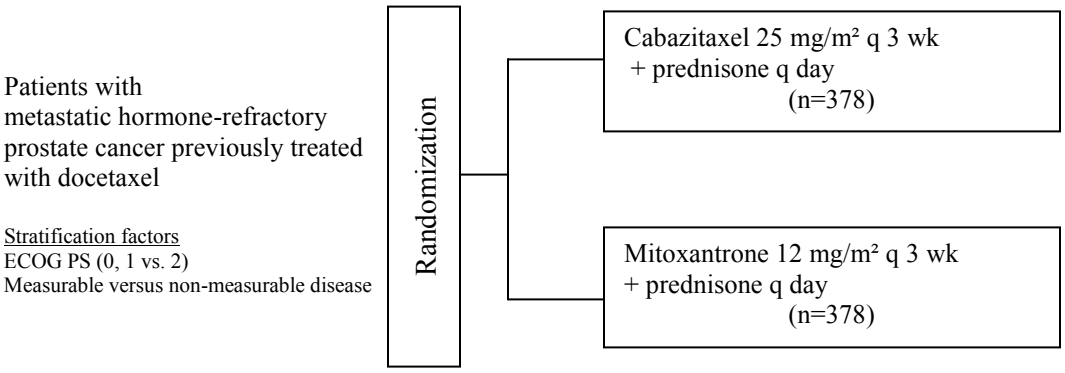
One international study, EFC6193 (TROPIC) has been submitted as the major trial to support the proposed indication. It is titled "A randomized, open label multi-center study of XRP6258 at 25 mg/m^2 in combination with Prednisone every 3 weeks compared to Mitoxantrone in combination with Prednisone for the treatment of hormone refractory metastatic prostate cancer previously treated with a Taxotere®-containing regimen". The protocol was granted a Special Protocol Assessment in September 2006. FDA granted a Fast Track designation on November 9, 2009 to cabazitaxel for metastatic prostate cancer which has progressed during or after a docetaxel-based therapy, and the NDA was submitted as a rolling review. The final section was submitted on 5/31/2010. A priority review was requested and granted.

Despite active research, it has been difficult to develop effective drugs to treat metastatic, hormone-refractory prostate cancer. In 2004, Taxotere® (docetaxel) was approved in combination with prednisone as a treatment for patients with androgen independent (hormone refractory) metastatic prostate cancer. Since that time, two drugs have been presented to the Oncology Drug Advisory Committee for an indication similar to the one proposed. These drugs were not approved. Given the expected impact on public health, the review of the Jevtana NDA was expedited. There are few drugs available for the advanced form of this common cancer and none for this indication. An improvement in overall survival, the prespecified primary endpoint, was demonstrated with the use of cabazitaxel. The expedited review was also made possible by the rapid responses by the applicant to FDA questions and concerns. The review of this NDA was completed in less than 3 months.

A total of 755 patients were randomized to receive either JEVTANA 25 mg/m^2 intravenously every 3 weeks for a maximum of 10 cycles with prednisone 10 mg orally daily (n=378), or to receive mitoxantrone 12 mg/m^2 intravenously every 3 weeks for 10 cycles with prednisone 10 mg orally daily (n=377) for a maximum of 10 cycles. A major issue observed during review

was the high rate of toxicity including toxic deaths on the investigational arm. Because an improvement in overall survival (OS) was demonstrated despite deaths due to adverse reactions, these toxicity issues will be addressed with post-marketing requirements (PMRs) as well as labeling. Other issues such as those including potential for precipitation of the drug, hepatic impairment trials, potential for QTc prolongation, drug-drug interaction studies will also be addressed by PMRs. Please see action letter for the description of the PMRs.

Figure 1: Study Schema



Jevtana has not been marketed anywhere in the world at this time.

3. CMC/Device

CMC review states that the NDA is approvable and was signed by Xiao-Hong Chen, PhD and cosigned by William Adams, PhD on 6/2/10.

There have been concerns regarding overfill in the cabazitaxel vial and the diluent. According to Dr. Chen, both the drug and diluent vials have overfill. If the entire content of the diluent vial is withdrawn and added into the drug vial, there may be greater than 10% variation in the concentration of the premix solution. Per Dr. Chen, the worst case scenario could be up to (b) (4) under dose and (b) (4) overdose. She also states in her review that *"Sanofi's justification for overfill is that the overage will ensure an extractable volume of* (b) (4) *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) *for the premix solution as demonstrated by the applicant), which could lead to inaccurate dosing (up to* (b) (4) *under dosing or up to* (b) (4) *overdosing). Note that the common pharmaceutical products allow ±10% assay variation."* Dr. Chen also states that *"Although it is not the preferred approach, it was found to be acceptable as it is the same approach used by Taxotere® Injection."* Particular attention was paid to labeling to make instructions for preparation of infusion solution clear.

Richard Lostritto, PhD (Division Director, ONDQA) expressed concern that the applicant has not adequately characterized a precipitation problem both in the first premix dilution and in the final infusion solution and it is not known whether a standard in-line filter has the capacity to not clog from precipitate. This was also discussed in an internal meeting. Because a survival advantage was observed, the team decided to implement PMRs to resolve the issue of possible precipitation. Please see the action letter for the description of PMRs. Dr. Lostritto states in his memo dated 6/8/2010 that the approved drug substance retest interval to be conveyed to the sponsor is eighteen (b) (4). He recommended approval in this memo.

The chemistry review finds the manufacturing of the drug product and drug substance acceptable. Manufacturing site inspections were acceptable.

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 5°C 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.

I concur with the conclusion that there are no other outstanding issues.

4. Nonclinical Pharmacology/Toxicology

Gabriel S. Khasar, PhD and Whitney Helms, PhD state that the non-clinical studies with cabazitaxel support the safety of its use in hormone-refractory metastatic prostate cancer. They recommend approval.

S. Leigh Verbois, PhD, provided concurrence to the conclusions of Drs. Helms and Khasar and stated, *"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"*

I concur with the conclusions reached by the pharmacology/toxicology reviewers that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

According to the review by Pengfei Song, PhD, co-signed by several people including Nam Atiqur Rahman PhD, the NDA is acceptable from clinical pharmacology perspective. Dr. Song states the following in his review:

"Following a one-hour intravenous infusion, plasma concentrations of cabazitaxel can be described by a three-compartment pharmacokinetic (PK) model with a-, ß-, and .- 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 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."

"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."

Four PMRs will be implemented. These will be to assess the potential for QTc prolongation, to determine the PK and safety of this drug in patients with hepatic impairment, and to assess drug interactions with strong CYP3A4 inducers and inhibitors. Please see the action letter for the description of the PMRs.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Steven Fong, PhD recommends approval from a microbiology quality standpoint in his review. I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

As in the label *"The efficacy and safety of JEVTANA in combination with prednisone were evaluated in a randomized, open-label, international, multi-center study in patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen."*

"A total of 755 patients were randomized to receive either JEVTANA 25 mg/m^2 intravenously every 3 weeks for a maximum of 10 cycles with prednisone 10 mg orally daily (n=378), or to receive mitoxantrone 12 mg/m^2 intravenously every 3 weeks for 10 cycles with prednisone 10 mg orally daily (n=377) for a maximum of 10 cycles."

"This study included patients over 18 years of age with hormone-refractory metastatic prostate cancer either measurable by RECIST criteria or non-measurable disease with rising PSA levels or appearance of new lesions, and ECOG (Eastern Cooperative Oncology Group) performance status 0-2. Patients had to have neutrophils >1,500 cells/mm^3, platelets > 100,000 cells/mm^3, hemoglobin > 10 g/dL, creatinine < 1.5 x upper limit of normal (ULN), total bilirubin < 1xULN, AST < 1.5 x ULN, and ALT < 1.5 x ULN. Patients with a history of congestive heart failure, or myocardial infarction within the last 6 months, or patients with uncontrolled cardiac arrhythmias, angina pectoris, and/or hypertension were not included in the study."

"Demographics, including age, race, and ECOG performance status (0-2) were balanced between the treatment arms. The median age was 68 years (range 46-92) and the racial distribution for all groups was 83.9% Caucasian, 6.9% Asian, 5.3% Black, and 4% Others in the JEVTANA group"

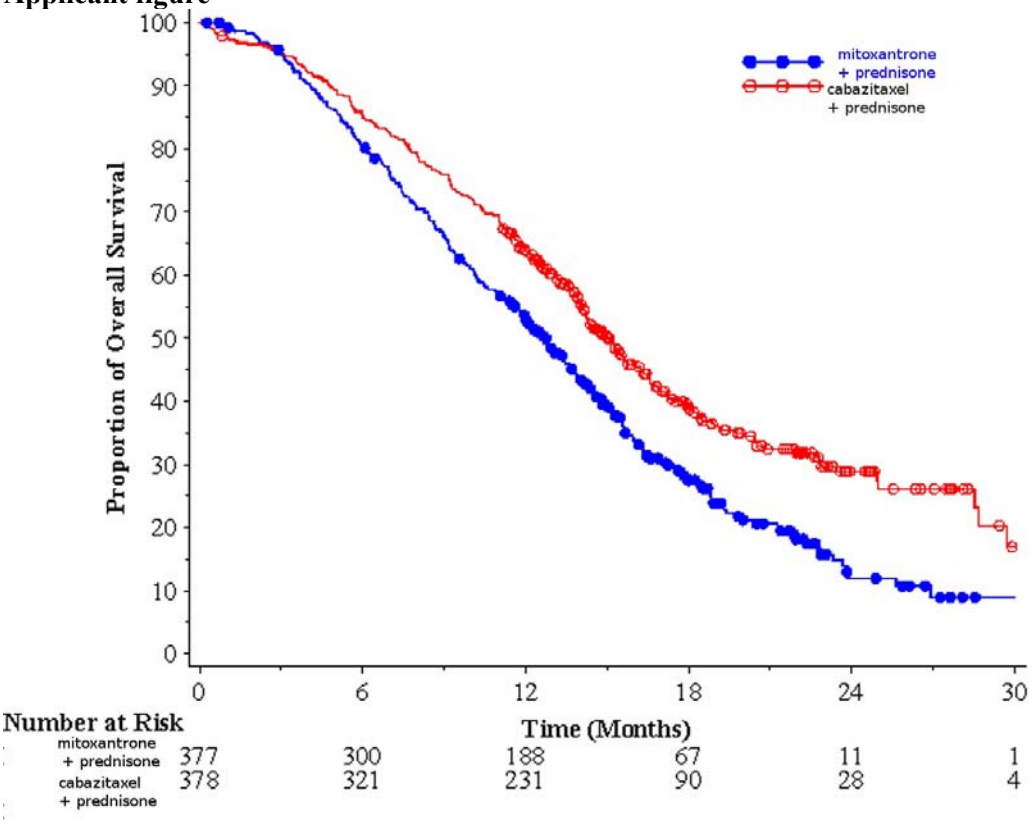
The median number of cycles was 4 in the Mitoxantrone/Prednisone arm and 6 in the Cabazitaxel/Prednisone arm.

Table 1: Efficacy of Cabazitaxel in the Treatment of Patients with Hormone Refractory Metastatic Prostate Cancer (Intent-to-Treat Analysis)

	Cabazitaxel + Prednisone n=378	**Mitoxantrone + Prednisone n=377**
Overall Survival		
Number of deaths (%)	234 (61.9 %)	279 (74%)
Median survival (month) (95% CI)	15.1 (14.1-16.3)	12.7 (11.6-13.7)
Hazard Ratio[1] (95% CI)	0.70 (0.59-0.83)	
p-value	<0.0001	

[1]Hazard ratio estimated using Cox model; a hazard ratio of less than 1 favors Cabazitaxel

Figure 2: Kaplan-Meier Overall Survival Curves
Applicant figure



The primary clinical review by Drs. McKee and Waxman recommends approval for this NDA. They state that *"The single clinical trial enrolled 755 men with mHRPC who had progressed on or after a docetaxel-containing regimen. The cabazitaxel arm had a median overall survival of 15.1 months compared to 12.7 months on the mitoxantrone arm. Although there were deaths due to toxicity on the cabazitaxel arm, an overall survival advantage was still demonstrated for cabazitaxel-treated patients. Furthermore, as some of the deaths were due to infectious complications during a period of neutropenia, infection-related deaths may be better prevented in the post-marketing setting with the use of prophylactic G-CSF in patients at high risk of neutropenic complications. The proposed patient population currently has no treatment options which offer a survival benefit, and the robust results in overall survival demonstrated by cabazitaxel would provide a new treatment option for these patients."*

In the statistical review, Chia-Wen Ko PhD., states that *"the pivotal trial met its study objective by showing a hazard ratio of 0.70 (95% confidence interval: 0.59-0.83, p<0.0001) for the experimental arm versus the control arm in overall survival. The median survival time was 15.1 months in the experimental arm compared to 12.7 months for patients in the control arm. Subgroup analyses showed consistent results in favor of cabazitaxel. There were no identified major statistical issues in efficacy analyses to prevent approval."*

The CDTL, Dr. John Johnson, also recommended 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".

8. Safety

According to the clinical review *"The safety of cabazitaxel was evaluated in 371 patients with hormone-refractory prostate cancer in the phase 3 trial EFC6193, in which patients were randomized to receive either cabazitaxel 25 mg/m^2 with prednisone every three weeks or mitoxantrone 12 mg/m^2 with prednisone every three weeks for up to ten cycles. A summary of important safety results is included below."*

- *"Deaths not directly attributed to disease progression and occurring within 30 days of the last dose of study drug were reported in 18 (5%) cabazitaxel-treated patients and three (<1%) mitoxantrone-treated patients. The most common fatal adverse reactions in cabazitaxel-treated patients were infections (n=5) and renal failure (n=4). The majority (80%) of fatal infection-related adverse reactions occurred after a single dose of cabazitaxel. Other fatal adverse reactions in cabazitaxel-treated patients included electrolyte imbalance in a patient with diarrhea, ventricular fibrillation, cerebral hemorrhage, and dyspnea."*
- *"The most common ($\geq$ 10%) grade 1-4 adverse reactions in cabazitaxel-treated patients were neutropenia, anemia, leukopenia, thrombocytopenia, diarrhea, fatigue, nausea, vomiting, constipation, asthenia, abdominal pain, hematuria, back pain, anorexia, peripheral neuropathy, pyrexia, dyspnea, dysgeusia, cough, arthralgia, and alopecia."*
- *"The most common ($\geq$ 5%) grade 3-4 adverse reactions in cabazitaxel-treated patients were neutropenia, leukopenia, anemia, febrile neutropenia, diarrhea, fatigue, and asthenia."*
- *"Adverse reactions of interest in cabazitaxel-treated patients included neutropenic complications (febrile neutropenia and infection), renal failure, hematuria, and cardiac toxicity."*
- *"Treatment discontinuations due to adverse drug reactions occurred in 18% of patients who received cabazitaxel and 8% of patients who received mitoxantrone. The most common adverse reactions leading to treatment discontinuation on the cabazitaxel arm were neutropenia and renal failure."*
- *"Dose reductions were reported in 12% of cabazitaxel-treated patients and 4% of mitoxantrone-treated patients. Dose delays were reported in 28% of cabazitaxel-treated patients and 15% of mitoxantrone-treated patients."*

Table 2: Dose modifications

	Cabazitaxel + Prednisone N = 371	Mitoxantrone + Prednisone 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%)

From CDTL Review by Dr Johnson

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

	Cabazitaxel + Prednisone N	Mitoxantrone + Prednisone %
Any TEAE	**18.3**	**8.4**
Neutropenia	2.4	0
Hematuria	1.3	0.3
Diarrhea	1.1	0.3
Fatigue	1.1	0.3
Acute renal failure	1.1	0
Abdominal pain	0.8	0
Febrile neutropenia	0.8	0
Renal failure	0.8	0
Sepsis	0.8	0

Applicant Table

A high degree of toxicity including toxic deaths was observed on trial, particularly in patients 65 years of age or older. More than a third of the patients required some dose modification (see table 2 above) and approximately 18% patients required treatment discontinuation because of treatment emergent adverse reactions (see table 3 above). According to Dr. Waxman, the most common fatal adverse reactions in cabazitaxel-treated patients were infections (n=5) and renal failure (n=4). Four of the five were infection-related deaths, 3 of 4 deaths were related to renal failure, and all 4 cardiac deaths occurred in patients ≥65 years of age. Among 18 cabazitaxel-treated patients with treatment-emergent deaths, only 3 were <65 years of age. The following wording was including in the Warning and Precaution section of the label: *"In the randomized clinical trial, 3 of 131 (2%) patients < 65 years of age and 15 of 240 (6%) ≥ 65 years of age died of causes other than disease progression within 30 days of the last cabazitaxel dose. Patients ≥ 65 years of age are more likely to experience certain adverse reactions, including neutropenia and febrile neutropenia."*

Table 4: Neutropenia and Associated Events

	Cabazitaxel + Prednisone N = 371		Mitoxantrone + Prednisone N=371	
	All grades	**Grade ≥3**	**All grades**	**Grade ≥3**
Neutropenia	347 (93.5)	303 (81.7)	325 (87.5)	215 (58)
Infections and infestations	126 (34)	38(10.2)	84 (22.6)	19 (5.1)
Sepsis	9 (2.4)	9(2.4)	6 (1.6)	5 (1.3)
Septic shock	4 (1.1)	4(1.1)	0	0
Neutropenic infections	2(0.5)	2(0.5)	0	0
Febrile neutropenia	28(7.5)	28(7.5)	5 (1.3)	5 (1.3)

Adapted from applicant's table

Neutropenia: According to the Clinical Review, 82% patients experienced grade 3 or greater neutropenia with five deaths related to neutropenia on the cabazitaxel arm compared to one death on the mitoxantrone arm. Approximately half of the patients received secondary prophylaxis with GCSF. However, most of the deaths related to neutropenia occurred in the first cycle and in patients older than 65 years in age. Consequently, consideration for primary prophylaxis for 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) adapted from ASCO guidelines has been included in the Warning and Precautions section of the label.

Renal Failure: According to the Clinical Review, 15 cabazitaxel-treated patients and no mitoxantrone-treated patients treated in the phase 3 trial EFC6193 experienced renal failure of any grade and among 12 patients with grade ≥3 renal failure, 7 (58.3%) did not recover. While the majority of these events were possibly attributed by the FDA clinical reviewer to other conditions such as infection, dehydration, and structural abnormalities, 3 of the 12 grade ≥3 renal failure events could not be readily attributed to other conditions. Four patients with treatment-emergent renal failure died within 30 days of last dose on the cabazitaxel-treated arm compared to none on the mitoxantrone-treated arm (see table 18 of clinical review). Some deaths due to renal failure did not have a clear etiology. There were patients who had hematuria. The clinical reviewer commented that "As all cabazitaxel-treated patients with grade ≥2 hematuria who delayed or discontinued therapy eventually recovered and only one 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."

PMRs will be instituted to understand the etiology of renal failure with cabazitaxel and to come up with mechanisms to mitigate this toxicity.

Gastrointestinal symptoms: A patient on the cabazitaxel-treated arm died from electrolyte imbalance after experiencing diarrhea.

> Cardiac events: Per clinical review "*Although there were more grade 5 cardiac adverse events on the cabazitaxel arm, three of the four patients had confounding factors including diabetes, hypertension, atrial fibrillation, prior warfarin use, and history of pulmonary embolism. The only patient without a past cardiac history was an 83 year-old male whose death appears to have been secondary to myocardial infarction. Hence, there is no clear relationship between cabazitaxel exposure and fatal cardiotoxicity."*

Other subsections included in the Warning and Precautions section include hypersensitivity, risk for toxicity from use in patients with hepatic impairment (the drug is excreted mostly from the hepatic route), and use in pregnancy. Boxed warning includes neutropenic complications including death and hypersensitivity. Although no grade 3-5 adverse reactions were noted for hypersensitivity on trial, this reaction was included in the boxed warning because of the potential for severe reactions including death particularly if premedication is not used.

I agree with the CDTL's conclusions and recommendation on safety. He says *"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 HRPC. There should be a PMR to study a lower dose in prostate cancer, probably in a different population such as initial chemotherapy of mHRPC. Two additional PMRs are required to assess renal toxicity."

DRISK agreed that no REMS were required.

9. Advisory Committee Meeting

Cabazitaxel is being recommended for approval based on a survival advantage, which is considered a gold standard in the field of oncology. The review was expedited with action being taken within 3 months in the interest of public health. These timelines also do not allow for an advisory committee meeting.

10. Pediatrics

Prostate cancer does not occur in pediatric patients and a waiver was granted.

11. Other Relevant Regulatory Issues

DSI Audits:
According to Dr. Robert Young's memo, co-signed by Dr. Tejashri Purohit- Sheth, *"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."*

Financial Disclosure:
According to the clinical 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."

DDMAC:
Suggestions made in the DDMAC consult by Keith Olin were used to amend the label if applicable and if in accordance with the PLR format.

There are no other unresolved relevant regulatory issues

12. Labeling

Proprietary name:
A letter dated 5/26/2010 from Carol Holquist RPh was sent to the applicant. Ms. Holquist stated that *"We have completed our review of the proposed proprietary name, Jevtana and have concluded that it is acceptable."*

Physician labeling
As per Dr Johnson's review, *"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 hypersensitivity have been included in the boxed warning. Hypersensitivity has also been included in the boxed warning even though only grade 1 and 2 adverse reactions were observed in the trial.

Because of the higher mortality in the first cycle from complications of neutropenia in patients 65 years of age and older, physicians are being asked to consider primary prophylaxis with GCSF in patients with high risk features. In the trial, only secondary prophylaxis with GCSF was proposed.

Premedication is required.

Attention was given the preparation of the dilution solution to avoid confusion and issue with over- or underdosing.

Carton and immediate container labels
No major revisions required

Patient labeling/Medication guide
No REMS or medication guide were recommended. The issues for cabazitaxel are similar to the Taxotere label, another drug in the same class. There are no REMS or medication guide in Taxotere.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

I recommend approval 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

As indicated by the CDTL, Dr. Johnson, *"(t)he 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 (≥ 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 a PMR. The cabazitaxel toxicity will be addressed in the label and with several PMRs."

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

Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

REMS are not required as agreed by DRISK.

Recommendation for other Postmarketing Requirements and Commitments

For the complete description of the PMRs, please see the approval letter.

There will be 10 PMRs in all and no PMCs. PMRs will evaluate the potential for intravenous infusion of particulate matter into the blood stream. PMRs will also be implemented to assess the unusually high incidence and severity of toxicity observed in the randomized trial in metastatic hormone refractory prostate cancer and the increased incidence of drug-related death. In addition, PMRs will be implemented to assess the signals of the serious risks of hepatic impairment, Q-T prolongation and drug-drug interaction with Jevtana® (cabazitaxel) Injection.

Amna Ibrahim MD
Deputy Division Director
Division of Drug Oncology Products

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMNA IBRAHIM
06/17/2010