

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**20-1023**

**OFFICE DIRECTOR MEMO**

## Office Director Summary Review for Regulatory Action

<b>Date</b>	June 17, 2010
<b>From</b>	Richard Pazdur, MD
<b>Subject</b>	Office Director Summary
<b>NDA/BLA #</b>	NDA 201023
<b>Supplement #</b>	
<b>Applicant</b>	Sanofi-Aventis
<b>Date of Submission</b>	March 31, 2010
<b>PDUFA Goal Date</b>	September 30, 2010
<b>Proprietary Name / Established (USAN) names</b>	Jevtana <sup>®</sup> (cabazitaxel) Injection Concentrate
<b>Dosage forms / Strength</b>	Jevtana (cabazitaxel) Injection Concentrate 60 mg/1.5 mL is supplied as a kit consisting of the following: <ul style="list-style-type: none"> <li>– Jevtana 60mg/1.5 mL concentrate: contains 60 mg cabazitaxel in 1.5 mL polysorbate 80</li> <li>– Diluent for Jevtana 60 mg/1.5 mL: contains (b) (4) of 13% (w/w) ethanol in water for injection</li> </ul>
<b>Proposed Indication</b>	Jevtana in combination with prednisone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen
<b>Recommended:</b>	<b>Approval</b>

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Division Director Review	Amna Ibrahim, MD
CDTL Review	John Johnson, MD
Medical Reviews	Amy McKee, MD (efficacy); Ian Waxman, MD (safety)
Statistical Review	Chia-Wen Ko, PhD; Shenghui Tang, PhD; Rajeshwari Sridhara, PhD
Pharmacology Toxicology Review	Sachia Khasar, PhD; Whitney Helms, PhD; S. Leigh Verbois, PhD; John Leighton, PhD
CMC Review/OBP Review	Xiao-Hong Chen, PhD; Sue Ching Lin, PhD; Brian D. Rogers, PhD; William M. Adams, PhD; Richard Lostritto, PhD
Microbiology Review	Steven E Fong, PhD; Bryan S. Riley, PhD
Clinical Pharmacology Review	Pengfei Song, PhD; Nitin Mehrotra, PhD; Qi Liu, PhD; Christine Garnett, PharmD; Nam Atiqur Rahman, PhD
DDMAC	Keith Olin, PharmD
DSI	Robert Young, MD; Tejashri Purohit-Sheth, MD
OSE/DMEPA	Lubna Najam, MS, PharmD
OSE/DDRE	N/A
OSE/DRISK	Sharon Mills BSN, RN, CCRP

OND = Office of New Drugs

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

## I. Introduction/Background

First-line therapy for patients with metastatic prostate cancer is medical or surgical castration (which includes gonadotropin-releasing hormone antagonists or surgery) where approximately 85% will respond and approximately 15% will not respond but will become refractory to hormonal intervention (i.e., resulting in metastatic hormone refractory prostate cancer (mHRPC)). For this refractory population, recommended first-line therapy is combination docetaxel and prednisone. For patients who have progressed on docetaxel/prednisone combination therapy, there is no approved therapy.

Jevtana (cabazitaxel) is a new molecular entity, similar to docetaxel and paclitaxel, and is currently not marketed anywhere in the world. The proposed indication is “Jevtana in combination with prednisone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen”—an indication for which there is no currently approved therapy. Review of this application was expedited due to anticipated impact on public health.

## II. Efficacy and Safety

This application is primarily supported by a single randomized, open label, multi-center, international study (EFC6193 (TROPIC)) entitled, “A randomized, open label multi-center study of XRP6258 at 25 mg/m<sup>2</sup> 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<sup>®</sup>-containing regimen”.

*As in Dr. Ibrahim's Division Director Review, “A total of 755 patients were randomized to receive either Jevtana 25 mg/m<sup>2</sup> 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<sup>2</sup> 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.”*

The primary clinical review by Drs. McKee and Waxman states *“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.”*

Statistical reviewer, Dr. Ko, recommends approval based on the following: *“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.”*

For safety as indicated in 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<sup>2</sup> with prednisone every three weeks or mitoxantrone 12 mg/m<sup>2</sup> 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 (= 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 (= 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.”*

The risk-benefit assessment by Dr. Johnson’s (CDTL), in which I agree, states *“(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/m<sup>2</sup> 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 (See below for a complete list of PMRs).”*

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

For the above safety findings, DRISK agreed that no REMS were required. However, to further characterize the safety of cabazitaxel, 10 PMRs will be conducted by the sponsor. As indicated in Dr. Ibrahim’s review, *“Two PMRs will evaluate the potential for a serious risk of intravenous infusion of particulate matter into the blood stream to understand and characterize the supersaturated pre-mix and in the infusion solution. PMRs will 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. A lower Jevtana<sup>®</sup> (cabazitaxel) Injection dose may be equally effective with less toxicity. PMRs will also be implemented to assess the signals of the serious risks of hepatic impairment, Q-T prolongation and drug-drug interaction with Jevtana<sup>®</sup> (cabazitaxel) Injection.”*

Please refer to the action letter for a description of these PMRs.

### **III. CMC**

For CMC, there were concerns regarding overfill of both the cabazitaxel vial and diluent. If the entire content of the diluent were added into the drug vial, there may be a greater than 10% concentration variation of the resulting premix solution. Dr. Chen, CMC reviewer, notes that *“Although it is not the preferred approach, it was found to be acceptable as it is the same approach used by Taxotere<sup>®</sup> Injection.”* As indicated

by Dr. Ibrahim's review, particular attention was given to instructions for preparation of the infusion solution in labeling.

Dr. Lostritto, Division Director, ONDQA, was concerned that precipitation problems were not fully characterized in both the premix solution and in the final infusion solution, and it was unknown whether a standard in-line filter would not clog due to the precipitation. However due to the observed survival advantage, this issue will be further characterized in a PMR. ONDQA recommends approval of this application. In addition, manufacturing site inspections were acceptable.

#### **IV. Nonclinical**

Drs. Khasar, Helms, Verbois and Leighton recommend approval of this application and state that nonclinical studies with cabazitaxel support the safety of its use in the proposed population. They concluded, *"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"*.

#### **V. Clinical Pharmacology**

Clinical Pharmacology recommends approval of this application; however, 4 PMRs will be implemented to assess the following: Potential for QTc prolongation, PK and safety in patients with hepatic impairment, drug interactions with strong CYP3A4 inducers and inhibitors. Please see the action letter for description of PMRs.

#### **VI. Clinical Microbiology**

Dr. Fong recommends approval from a microbiology quality standpoint.

#### **VII. Other Disciplinary Reviews**

This application was also reviewed by the Division of Scientific Investigations (DSI), DDMAC, DMEPA and DRISK. DSI supports approval of this application. Issues brought forth by the other disciplines have been addressed in labeling. There are no outstanding issues from these disciplines.

#### **VIII. Regulatory Action**

Approval based on a single, randomized clinical trial (N=755) in men with mHRPC who had progressed on or after a docetaxel-containing regimen, a population with no approved therapy, where a statistically significant improvement in median survival of 2.4 months was observed for combination cabazitaxel/prednisone compared to mitoxantrone/prednisone. Approval is contingent upon the conduct of 10 PMRs as described above and in the action letter.

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

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/s/

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TAMY E KIM

06/17/2010

T. Kim entered into DARRTS for Dr. Pazdur signature.

RICHARD PAZDUR

06/17/2010