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

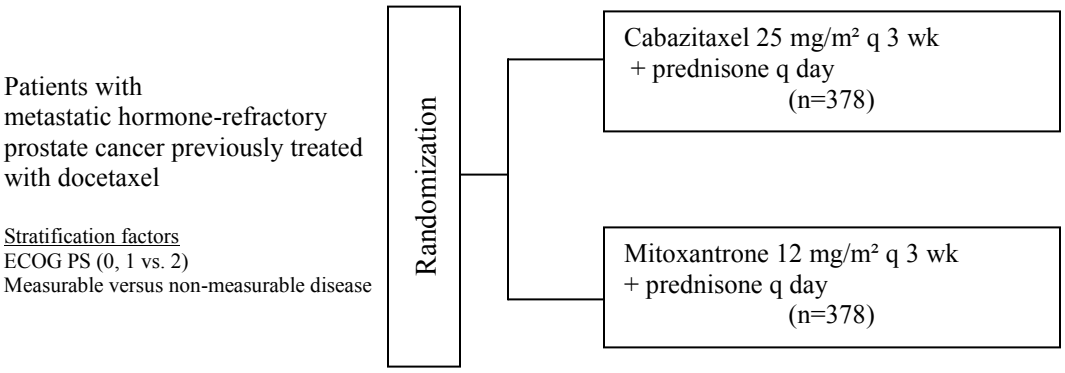
One international study, EFC6193 (TROPIC) has been submitted as the major trial to support the proposed indication. It is titled "A randomized, open label multi-center study of XRP6258 at 25 mg/m^2 in combination with Prednisone every 3 weeks compared to Mitoxantrone in combination with Prednisone for 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.

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