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

Table of Contents

Table of Tables

Table of Figures

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.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.