CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for: Jevtana

APPLICATION NUMBER:

NDA 20-1023

Trade Name: **Jevtana**

Generic Name: **Cabazitaxel**

Sponsor: **Sanofi-aventis U.S., LLC**

Approval Date**: June 17, 2010**

Indications: **For for the treatment of patients with hormone-refractory metastaticprostate cancer previously treated with a docetaxel-containing treatment regimen.**

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CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	**X**
Officer/Employee List	**X**
Office Director Memo	**X**
Cross Discipline Team Leader Review	
Medical Review(s)	**X**
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology Review(s)	**X**
Statistical Review(s)	**X**
Microbiology Review(s)	**X**
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	**X**
Administrative/Correspondence Document(s)	x

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201023 **NDA APPROVAL**

sanofi-aventis U.S., LLC
c/o sanofi-aventis U.S., Inc.
200 Crossing Boulevard, Mailstop: BX2-712B
Bridgewater, NJ 08807

Attention: Linda M. Gustavson
Director, U.S., Associate Therapeutics Head, Oncology

Dear Ms. Gustavson:

Please refer to your New Drug Application (NDA) dated March 31, 2010, received March 31, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Jevtana® (cabazitaxel) Injection, 60 mg/1.5 mL.

We acknowledge receipt of your submissions dated April 16 (2), May 5, 7, 10, 18, 21, 24, 25 (2), 28, June 1, 4 (2), 8, 14, 16, and 17, 2010.

This new drug application provides for the use of Jevtana® (cabazitaxel) Injection in combination with prednisone for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 201023**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for Jevtana® (cabazitaxel) Injection was not referred to an FDA advisory committee because taking this NDA to an advisory committee would result in a several month delay in making this advance in prostate cancer therapy available to patients for whom there is currently no available therapy.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable since prostate cancer does not occur in children.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of intravenous infusion of particulate matter into the blood stream.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risk(s).

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

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, in the final report.

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

The timetable you submitted on June 16, 2010, states that you will conduct this study according to the following schedule:

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

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.), in the final report.

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

The timetable you submitted on June 16, 2010, states that you will conduct this study according to the following schedule:

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

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

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

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

The timetable you submitted on June 16, 2010, states that you will conduct this trial according to the following schedule:

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

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

The timetable you submitted on June 16, 2010, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	November 2010
Trial Completion Date:	September 2017
Final Report Submission:	June 2018

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 to cause QTc interval prolongation in patients.

The timetable you submitted on June 16, 2010, states that you will conduct this trial according to the following schedule:

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

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

The timetable you submitted on June 16, 2010, states that you will conduct this trial according to the following schedule:

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

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.

The timetable you submitted on June 16, 2010, states that you will conduct this trial according to the following schedule:

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

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.

The timetable you submitted on June 16, 2010, states that you will conduct this trial according to the following schedule:

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

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

Final Report Submission Date: March 2011

PMR 1649-10:
Submit integrated analyses of renal toxicity from two randomized trials in patients with metastatic hormone refractory prostate cancer every 6 months for 3 years from the initiation of the clinical trial. These trials have been described in PMR 1649-3 and PMR 1649-4.

The timetable you submitted on June 16, 2010, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	November 2010
Interim Report Submission:	May 2011
	November 2011
	May 2012
	November 2012
	May 2013
Final Report Submission:	November 2013

Submit the protocols to your IND, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

CHEMISTRY, MANUFACTURING, AND CONTROLS

Based on the available primary and supportive drug substance stability data, an (b) (4) retest date for the drug substance is granted when stored under the long term storage conditions of 5º C.

Based on the provided stability data, an 18-month expiration dating period for the drug product is granted when stored under the following long term storage conditions:

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

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

Please submit one market package of the drug product when it is available.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Christy Cottrell, Regulatory Project Manager, at (301) 796-4256.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

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/

RICHARD PAZDUR
06/17/2010