

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**201023**

**OTHER REVIEW(S)**

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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PMR/PMC Description: 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.

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PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>September 2010</u>
	Study/Clinical trial Completion Date:	<u>March 2011</u>
	Final Report Submission Date:	<u>June 2011</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The concentration of cabazitaxel in the first dilution pre-mix solution (e.g., 10 mg/mL) is super saturated (b) (4) exceeding the solubility in the pre-mix vehicle by (b) (4). Nucleation and kinetic factors are critical in that they will largely determine the duration that this desired but thermodynamically unstable pre-mix solution will persist. The database you have provided to support the one-hour physical in-use stability (i.e., no precipitation) is inadequate.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.  
*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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PMR/PMC Description: 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.

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PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>September 2010</u>
	Study/Clinical trial Completion Date:	<u>March 2011</u>
	Final Report Submission Date:	<u>June 2011</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The concentration of cabazitaxel in the infusion solution (0.10 mg/mL to 0.26 mg/mL) is also super saturated (b) (4) exceeding the solubility by up to (b) (4). Nucleation and kinetic factors are critical in that they will largely determine the duration that the desired but thermodynamically unstable infusion solution will persist. The database you have provided to support the in-use shelf life is inadequate.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study  
 Registry studies

Continuation of Question 4

- Primary safety study or clinical trial  
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety  
 Thorough Q-T clinical trial  
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)  
 Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)  
 Pharmacokinetic studies or clinical trials  
 Drug interaction or bioavailability studies or clinical trials  
 Dosing trials  
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials  
 Immunogenicity as a marker of safety  
 Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)  
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)  
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E  
 Dose-response study or clinical trial performed for effectiveness  
 Nonclinical study, not safety-related (specify)

- 
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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PMR/PMC Description: PMR 1649-3: Conduct a Phase 3 randomized controlled trial in patients with hormone-refractory metastatic prostate cancer comparing 75 mg/m<sup>2</sup> docetaxel with prednisone with cabazitaxel 25 mg/m<sup>2</sup> with prednisone and cabazitaxel 20 mg/m<sup>2</sup> 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<sup>2</sup> with prednisone arm versus the 20 mg/m<sup>2</sup> with prednisone arm to potentially drop one of the cabazitaxel arms. Submit the protocol for agency review prior to commencing the trial.

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PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>November 2010</u>
	Study/Clinical trial Completion Date:	<u>December 2017</u>
	Final Report Submission Date:	<u>June 2018</u>
	Other: _____	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Cabazitaxel has demonstrated a survival advantage for patients with metastatic hormone-refractory prostate cancer (mHRPC) who already have received docetaxel. Although the dose studied in the Phase 3 trial demonstrated a survival advantage, there was significant toxicity, and some Phase 1 data indicates that a lower dose could have been studied. Therefore, we are asking the applicant to study a lower dose; however, we do not want deny patients the potential benefit of this treatment while the study is ongoing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The dose of cabazitaxel studied in the Phase 3 trial as a second-line therapy for patients with mHRPC demonstrated a survival advantage but also had an extensive adverse event profile. The goal of the trial in this PMR is to determine whether a lower dose will increase the safety but preserve the efficacy of the dose that will be in the labeling.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.  
*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A Phase 3 randomized controlled trial in patients with hormone-refractory metastatic prostate cancer comparing 75 mg/m<sup>2</sup> docetaxel with prednisone with cabazitaxel 25 mg/m<sup>2</sup> with prednisone and cabazitaxel 20 mg/m<sup>2</sup> 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<sup>2</sup> with prednisone arm versus the 20 mg/m<sup>2</sup> with prednisone arm to potentially drop one of the cabazitaxel arms. Submit the protocol for agency review prior to commencing the trial.

Required

- Observational pharmacoepidemiologic study
- Registry studies

*Continuation of Question 4*

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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PMR/PMC Description: 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<sup>2</sup> with prednisone versus cabazitaxel 25 mg/m<sup>2</sup> with prednisone and powered to preserve 50% of the treatment effect of cabazitaxel 25 mg/m<sup>2</sup>. The study will include interim analyses for evaluation of drug-related deaths as well as efficacy based on the safety and overall survival of the cabazitaxel 25 mg/m<sup>2</sup> with prednisone arm versus the cabazitaxel 20 mg/m<sup>2</sup> with prednisone arm to potentially discontinue the trial. Submit the protocol for agency review prior to commencing the trial.

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PMR/PMC Schedule Milestones:	Final protocol Submission Date:	November 2010
	Study/Clinical trial Completion Date:	(b) (4) 2017
	Final Report Submission Date:	June 2018
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Cabazitaxel has demonstrated a survival advantage for patients with metastatic hormone-refractory prostate cancer (mHRPC) who already have received docetaxel. Although the dose studied in the Phase 3 trial demonstrated a survival advantage, there was significant toxicity, and some Phase 1 data indicates that a lower dose could have been studied. Therefore, we are asking the applicant to study a lower dose; however, we do not want deny patients the potential benefit of this treatment while the study is ongoing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The dose of cabazitaxel studied in the Phase 3 trial as a second-line therapy for patients with mHRPC demonstrated a survival advantage but also had an extensive adverse event profile. The goal of the trial in this PMR is to determine whether a lower dose will increase the safety but preserve the efficacy of the dose that will be in the labeling.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.  
*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A Phase 3 randomized controlled trial in 1222 patients with hormone-refractory metastatic prostate cancer previously treated with docetaxel comparing cabazitaxel 20 mg/m<sup>2</sup> with prednisone versus cabazitaxel 25 mg/m<sup>2</sup> with prednisone and powered to preserve 50% of the treatment effect of cabazitaxel 25mg/m<sup>2</sup>. 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<sup>2</sup> with prednisone arm versus the cabazitaxel 20 mg/m<sup>2</sup> with prednisone arm to potentially discontinue the trial. The sponsor will submit the protocol for agency review prior to commencing the trial.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)



3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

TES10884 is a prospective, multicenter, multinational, open-label clinical trial in patients with advanced solid tumors. The response of applicant to QT-IRT comments regarding the study design of TES10884 is under Agency's review. Intensive PK sample and ECG measurements will be collected to evaluated the effect of cabazitaxel on QT prolongation.

Required

- Observational pharmacoepidemiologic study
- Registry studies

*Continuation of Question 4*

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety

- Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)  
QT prolongation assessment using open-label, non-thorough QT study design.

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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PMR/PMC Description: PMR 1649-6: Conduct the trial POP6792 to determine the pharmacokinetics and safety of cabazitaxel in patients with hepatic impairment.

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PMR/PMC Schedule Milestones: Final protocol Submission Date: March 2010  
Study/Clinical trial Completion Date: May 2012  
Final Report Submission Date: November 2012  
Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

As cabazitaxel is extensively metabolized by CYP 3A in liver, hepatic impairment is expected to affect the pharmacokinetics of cabazitaxel. However, in the NDA submission, no formal hepatic impairment trial has been conducted. Possibly due to a small number of patients with abnormal liver function, population PK analysis did not determine transaminases as significant covariates influencing cabazitaxel PK. Based on the limited number of patients with abnormal liver function at baseline, no dose adjustment can be recommended.

Therefore, a clinical trial in patients with mild, moderate and severe hepatic impairment is required to identify safe doses for patients with various levels of hepatic impairment.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Due to the fact that cabazitaxel is excreted primarily via hepatic route and extensively metabolized by hepatic CYP3A4/5. Hepatic impairment may cause increase in the cabazitaxel concentrations and lead to serious risk. A trial in patients with mild, moderate and severe hepatic impairment is therefore required to identify safe doses for patients with hepatic impairment.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The required clinical trial will be a phase 1 trial designed to assess the PK of cabazitaxel in advanced cancer patients with mild, moderate and severe hepatic impairment. The Applicant's proposed protocol POP6792 is currently under agency's review.

Required

- Observational pharmacoepidemiologic study
- Registry studies

*Continuation of Question 4*

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety

- Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

---

**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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PMR/PMC Description: 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.

---

PMR/PMC Schedule Milestones: Final protocol Submission Date: October 2010  
Study/Clinical trial Completion Date: April 2012  
Final Report Submission Date: December 2012  
Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

NDA review indicated the need for an *in vivo* study. Cabazitaxel is extensively metabolized by CYP3A in human liver microsomes *in vitro*. Thus, co-administration of cabazitaxel with strong CYP3A inhibitors can lead to increase in cabazitaxel concentrations and risk of toxicity. However, no clinical drug-drug interaction trial has been conducted to address this issue. Therefore, a drug interaction trial with a strong CYP3A inhibitor, such as ketoconazole, is required.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Cabazitaxel is extensively metabolized by CYP3A. Therefore, co-administration of cabazitaxel with strong CYP3A inhibitors can lead to increase in cabazitaxel concentrations and risk of toxicity. A clinical trial with a strong CYP3A inhibitor, such as ketoconazole, is needed to accurately determine the magnitude of cabazitaxel exposure changes when they are co-administered. Depending on the results, a safe dose of cabazitaxel will be identified when co-administered with strong CYP3A inhibitors.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The required drug-drug interaction trial will be a phase 1, crossover design to evaluate the effect of a CYP3A4 inhibitor, ketoconazole, on the pharmacokinetics of cabazitaxel.

Required

- Observational pharmacoepidemiologic study
- Registry studies

*Continuation of Question 4*

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial

- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

---

**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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PMR/PMC Description: 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.

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PMR/PMC Schedule Milestones: Final protocol Submission Date: October 2010  
Study/Clinical trial Completion Date: April 2012  
Final Report Submission Date: December 2012  
Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

NDA review indicated the need for a clinical trial to evaluate the effect of a strong CYP3A inducer on the pharmacokinetics of cabazitaxel. Cabazitaxel is extensively metabolized by CYP3A in human liver microsomes *in vitro*. Thus, co-administration of cabazitaxel with potent CYP3A inducers can decrease cabazitaxel concentrations and lead to efficacy and safety concern. However, no clinical drug-drug interaction trial has been conducted to address this issue. Therefore, a clinical trial of cabazitaxel with a strong CYP3A inducer, such as rifampin, is required to identify a safe dose when cabazitaxel is coadministered with CYP3A inducer.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Cabazitaxel is extensively metabolized by CYP3A. Thus, co-administration of cabazitaxel with potent CYP3A inducers can decrease cabazitaxel concentrations and lead to safety concern. A clinical trial with a potent CYP3A inducer, such as rifampin, is needed to accurately determine the magnitude of cabazitaxel exposure changes when they are co-administered. Depending on the results, a safe dose of cabazitaxel will be identified when cabazitaxel is co-administered with potent CYP3A inducers.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This required drug-drug interaction clinical trial will be a phase 1, crossover design to evaluate the effects of a strong CYP3A inducer (e.g., rifampin) on the pharmacokinetics of cabazitaxel.

Required

- Observational pharmacoepidemiologic study
- Registry studies

*Continuation of Question 4*

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial

- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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PMR/PMC Description: 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.

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PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>N/A</u>
	Study/Clinical trial Completion Date:	<u>N/A</u>
	Final Report Submission Date:	<u>March 2011</u>
	Other:	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

An overall survival advantage has been demonstrated despite the occurrence renal toxicity. For this reason, the benefits of treatment with cabazitaxel in patients with hormone-refractory metastatic prostate cancer who have received docetaxel outweigh the risks of renal toxicity in this patient population.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Four renal failure deaths occurred in cabazitaxel-treated patients enrolled on the phase 3 trial. Although two of these cases of fatal renal failure had clear etiologies (dehydration and infection), an additional two cases did not have clear etiologies. In addition, there were more cases of any grade renal failure and more cases of clinically significant hematuria (grade 2 or higher) on the cabazitaxel-treated arm despite a balance of predisposing conditions for hematuria between arms. The goal of this PMR is to determine the mechanism of renal toxicity so that the risk can be mitigated.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A panel of experts will review all currently available renal toxicity data from all studies of cabazitaxel.
---

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

---

**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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PMR/PMC Description: 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.

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PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>November 2010</u>
	Study/Clinical trial Completion Date:	<u>N/A</u>
	Final Report Submission Date:	<u>November 2013</u>
	Other: Interim reports	<u>May 2011</u>
		<u>November 2011</u>
		<u>May 2012</u>
		<u>November 2012</u>
		<u>May 2013</u>

---

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

An overall survival advantage has been demonstrated despite the occurrence renal toxicity. For this reason, the benefits of treatment with cabazitaxel in patients with hormone-refractory metastatic prostate cancer who have received docetaxel outweigh the risks of renal toxicity in this patient population.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Four renal failure deaths occurred in cabazitaxel-treated patients enrolled on the phase 3 trial. Although two of these cases of fatal renal failure had clear etiologies (dehydration and infection), an additional two cases did not have clear etiologies. In addition, there were more cases of any grade renal failure and more cases of clinically significant hematuria (grade 2 or higher) on the cabazitaxel-treated arm, despite a balance of predisposing conditions for hematuria between arms. The goal of this PMR is to determine the mechanism of renal toxicity so that the risk can be mitigated.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.  
*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Two randomized clinical trials are being conducted as PMRs, one in the first-line setting and one in the second-line setting. Integrated analyses of renal toxicity from these two trials will be submitted every six months for three years from initiation of the trials.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)  
Integrated analyses of renal toxicity will be provided every six months for three years for the two required clinical studies (first-line setting and second-line setting).

---

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

---

- Other

---

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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

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

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/s/

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CHRISTY L COTTRELL  
06/17/2010

JOHN R JOHNSON  
06/17/2010

## Memorandum: Internal Labeling Consult

**Date:** June 15, 2010

**To:** Christy Cotrell, Project Manager, DDOP  
Amna Ibrahim MD, Deputy Division Director

**From:** Keith Olin, Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications (DDMAC)

**Subject:** NDA 201023  
DDMAC PI labeling comments for JEVTANA (cabazitaxel) Injection,  
60mg/1.5 mL

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DDMAC has reviewed the proposed PI for JEVTANA (cabazitaxel) Injection submitted for consult from DDOP and offers the following comments. The version of the draft PI used in this review was sent on June 14, 2010, via email.

### 5.4 Renal Failure

Renal failure, including cases with fatal outcome, was reported in the randomized clinical trial. Most cases occurred in association with sepsis, dehydration, or obstructive uropathy [see *Adverse Reactions (6.1)*]. Some deaths due to renal failure did not have a clear etiology. Appropriate measures should be taken to identify causes of renal failure and treat aggressively.

(b) (4)

### 8.1 Pregnancy

Pregnancy category D. See 'Warnings and Precautions' section.

(b) (4)

### 8.6 Renal Impairment

No dedicated renal impairment trial for JEVTANA has been conducted. Based on the population pharmacokinetic analysis, no significant difference in clearance was observed in patients with mild ( $50 \text{ mL/min} \leq \text{creatinine clearance (CLcr)} < 80 \text{ mL/min}$ ) and moderate renal impairment ( $30 \text{ mL/min} \leq \text{CLcr} < 50 \text{ mL/min}$ ). No data are available for patients with severe renal impairment or end-stage renal disease [see *Clinical Pharmacology (12.3)*]. Caution should be used in patients with severe renal impairment ( $\text{CLcr} < 30 \text{ mL/min}$ ) and patients with end-stage renal diseases.

(b) (4)

**14. CLINICAL STUDIES**

The efficacy and safety of JEV TANA 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.

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/  
-----

KEITH J OLIN  
06/15/2010

**RPM FILING REVIEW**  
**(Including Memo of Filing Meeting)**

**To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)**

<b>Application Information</b>		
NDA # 201023 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Jevtana Established/Proper Name: cabazitaxel Dosage Form: Injection (intravenous) Strengths: 60 mg/1.5 mL		
Applicant: sanofi-aventis Agent for Applicant (if applicable):		
Date of Application: March 31, 2010 Date of Receipt: March 31, 2010 Date clock started after UN:		
PDUFA Goal Date: September 30, 2010	Action Goal Date (if different): June 18, 2010	
Filing Date: May 30, 2010	Date of Filing Meeting: April 9, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Treatment of hormone refractory metastatic prostate cancer in patients previously treated with a docetaxel containing regimen		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<b><i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:</i></b> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html</a> <b><i>and refer to Appendix A for further information.</i></b>		
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<b><i>If the application includes a complete response to pediatric WR, review classification is Priority.</i></b>  <b><i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i></b>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <b><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i></b>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input checked="" type="checkbox"/> Fast Track <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical	

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 056999				
<b>Goal Dates/Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<b>If yes, explain in comment column.</b>				
<b>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</b>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</i>				

<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>																
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?																				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).																				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?  <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>																				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <b>Check the Electronic Orange Book at:</b> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>  <b>If yes, please list below:</b>																				
<table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>																				
<b>Exclusivity</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>																
Does another product have orphan exclusivity for the same indication? <b>Check the Electronic Orange Book at:</b> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>		X																		
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>			X																	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only)  <b>If yes, # years requested:</b> 5 years  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X																			

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDA</i> s only)?		X		
<b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission</b> , which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission</b> , does it follow the eCTD guidance <sup>1</sup> ? <b>If not</b> , explain (e.g., waiver granted).	X			
<b>Index:</b> Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 ( <i>NDA</i> s/ <i>NDA efficacy supplements</i> ) or under 21 CFR 601.2 ( <i>BLA</i> s/ <i>BLA efficacy supplements</i> ) including:  <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)  <b>If no</b> , explain.	X			
<b>Controlled substance/Product with abuse potential:</b> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>			X	
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?  <b>If yes</b> , BLA #			X	

<b>Forms and Certifications</b>				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is form FDA 356h included with authorized signature?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. agent must sign the form.</i></p>	X			
<p>Are all establishments and their registration numbers listed on the form/attached to the form?</p>	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is patent information submitted on form FDA 3542a?</p>	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>	X			
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is form FDA 3674 included with authorized signature?</p>	X			
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>)</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification.</i></p> <p><i>Note: Debarment Certification should use wording in FD&amp;C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>	X			

<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p><b>If the application triggers PREA</b>, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		X		
<p><b>If studies or full waiver not included</b>, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p><b>If a request for full waiver/partial waiver/deferral is included</b>, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p><b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>		X		

<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	X			
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input checked="" type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format?	X			
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? <i>(send WORD version if available)</i>	X			
REMS consulted to OSE/DRISK?			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>				

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		X		Consult sent to QT IRT- subsequently cancelled

<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> 6/28/06 <i>If yes, distribute minutes before filing meeting</i>	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> 2/23/10 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> 9/11/08 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** April 9, 2010

**BLA/NDA/Supp #:** NDA 201023

**PROPRIETARY NAME:** Jevtana

**ESTABLISHED/PROPER NAME:** cabazitaxel

**DOSAGE FORM/STRENGTH:** Injection (60 mg/ 1.5 mL)

**APPLICANT:** sanofi-aventis

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** Treatment of hormone refractory metastatic prostate cancer in patients previously treated with a docetaxel containing regimen

**BACKGROUND:** NDA submitted on March 31, 2010. Expedited review planned (action goal date of June 18, 2010).

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Christy Cottrell	Y
	CPMS/TL:	Alice Kacuba	N
Cross-Discipline Team Leader (CDTL)	John Johnson		N
Clinical	Reviewer:	Ian Waxman/Amy McKee	Y
	TL:	John Johnson	N
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Pengfei Song	Y
	TL:	Qi Liu	Y
Biostatistics	Reviewer:	Kiki Ko	N
	TL:	Shenghui Tang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Whitney Helms/Sachia Khasar	Y
	TL:	Leigh Verbois	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Xiao Hong Chen/Sue Ching Lin	Y
	TL:	Sarah Pope	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	Steven Fong	Y
	TL:	David Hussong	N
CMC Labeling Review ( <i>for BLAs/BLA supplements</i> )	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Colleen Hoyt/Marisa Stock/Barry Rothmann	N
	TL:	Rick Friedman	N
OSE/DMEPA (proprietary name)	Reviewer:	Lubna Najam	Y
	TL:	Melina Griffis	N
OSE/DRISK (REMS)	Reviewer:	Sharon Mills	N
	TL:	Robert Pratt	N
Bioresearch Monitoring (DSI)	Reviewer:	Robert Young	N
	TL:		

Other reviewers	Hari Sarker, Nitin Mehrotra, Debbie Mesmer, Sarah Simon, Laura Pincock, Anwar Goheer	Y
Other attendees	Robert Justice, Amna Ibrahim, Tony Murgo	

**FILING MEETING DISCUSSION:**

<b>GENERAL</b>	
<ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b> None</p>	<input type="checkbox"/> Not Applicable
<b>CLINICAL</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason: Expedited review; no contentious issues for AC review

<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>CMC Labeling Review (BLAs/BLA supplements only)</u></b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>

<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Richard Pazdur, M.D.	
<b>21<sup>st</sup> Century Review Milestones (see attached)</b> (optional): Mid-cycle meeting on 5/7/10	
<b>Comments:</b>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>
<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify DMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-201023

-----  
ORIG-1

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SANOFI AVENTIS  
SPA

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CABAZITAXEL (XRP6258)

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/s/  
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CHRISTY L COTTRELL

06/09/2010

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**CLINICAL INSPECTION SUMMARY**

**DATE:**

**TO:** Christy Cottrell, Regulatory Project Manager  
Amy McKee, Medical Officer  
Ian Waxman, Medical Officer  
Division of Drug Oncology Products

**FROM:** Robert Young  
Good Clinical Practice Branch 2  
Division of Scientific Investigations

**THROUGH:** Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch 2  
Division of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** 201 023

**APPLICANT:** Sanofi-aventis U.S. Inc.

**DRUG:** Cabazitaxel (SRP6258)

**NME:** Yes

**THERAPEUTIC CLASSIFICATION:** Priority Review

**INDICATION:** Metastatic prostate cancer which has progressed during or after docetaxel-based therapy

**CONSULTATION REQUEST DATE:** 8 April 2010

**DIVISION ACTION GOAL DATE:** 11 June 2010

**PDUFA DATE:** 1 October 2010

**I. BACKGROUND:** Cabazitaxel is a semi-synthetic derivative of the naturally occurring taxoid 10-deacetylbaaccatin III, a member of the taxane family of cell cycle specific cytotoxic agents. These agents bind to tubulin and thereby inhibit microtubule depolymerization arresting cells in the G2/M phase of the cell cycle. Cells, including cancer cells, may become resistant to a drug by transporting the drug out of the cell. This lowers the number of drug-receptor complexes. This mechanism of resistance has been found in members of the taxane family of drugs, but not cabazitaxel.

The sponsor submitted this application for the use of cabazitaxel in metastatic prostate cancer which has progressed during or after docetaxel-based therapy. One pivotal study was submitted in support of the application, Protocol EFC6193: “A Randomized, Open Label Multicenter Study of XRP6258 at 25 mg/m<sup>2</sup> in Combination With Prednisone Every 3 weeks Compared to Mitoxanthrone in Combination With Prednisone For the Treatment of Hormone Refractory Metastatic Prostate Cancer Previously Treated With a Taxotere®-Containing Regimen.” Seven hundred fifty-five subjects at 146 sites in 26 countries were randomized in Study EFC6193. Overall survival was the primary end point.

The conduct of Study EFC6193 by four clinical sites was inspected in support of the application. Sites with larger number of subjects and/or identified protocol deviations were selected for inspection.

## II. RESULTS (by Site):

Clinical Investigator	# of Subjects	Inspection Date	Final Classification
Mario Eisenberger Sydney Kimmel Cancer Center 1650 Orleans Street, Suite 1 Rm 51 Baltimore, MD 21230	7	April 14-29, 2010	Pending  Preliminary: VAI
Shaker Dakhil Cancer Center of Kansas 818 N Emporia S-403 Wichita, KS 67214	11	May 10-14, 2010	Pending  Preliminary: NAI

Stephane Oudard Hopital Europeen Georges Pompidou 20 Rue Leblanc Paris Cedex 15, 75008	52	May 17-20, 2010	Pending  Preliminary: VAI
Mustafa Ozguroglu Istanbul University Cerrahpasa Medical Faculty Ic Hastaliklari Tibbi Onkoloji A.D. Cerrahpasa Tip Fac. Ic Hast.B.D. Aksaray Istanbul 34303 TURKEY	33	May 10-14, 2010	Pending  Preliminary: VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;  
EIR has not been received from the field and/or complete review of EIR is pending.**1. Mario Eisenberger**

- a. **What was inspected:** Seven subjects were enrolled and the records of all of these subjects were audited. Three subjects completed the study and four subjects were withdrawn upon their death. Informed consent, eligibility criteria, study procedures, drug accountability, adverse events, and source documents were examined. There were no limitations to the inspection.
- b. **General observations/commentary:** The inspection documented instances of failure to adhere to the protocol and inaccurate recordkeeping:

Examples of Adherence to protocol issues:

- i. a single failure to delay dosing because of elevated liver function tests, as required by the protocol
- ii. failure to obtain a SGOT before one dosing
- iii. failure to obtain PSA tests in three subjects at the beginning of one cycle each
- i.v. dosing of a subject on 20 mg daily of prednisone rather than the 10 mg daily protocol dose for two months.

Recordkeeping issues:

- i. The misdosing of 20 mg daily of prednisone above was reported on the CRF as 10 mg daily of prednisone for one subject
- ii. Subject 001 was reported on the CRF to have received Mitoxantrone from 6 – 17 August 2008 when in fact the drug was received on 16 July 2008.

These observations were included on an issued Form FDA 483 and agreed to by the clinical investigator in his 25 May 2010 letter to the FDA, which was considered an adequate response.

- c. **Assessment of data integrity:** Although regulatory violations were noted, these do not impact the overall usefulness of the study because they are limited in number, random in occurrence and do not involve the main variables of the study. The data are acceptable in support of the pending application.

## 2. **Shaker Dakhil**

**Note:** The following comments are based on written communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR

- a. **What was inspected:** Eleven subjects were enrolled into the study. Three subjects completed the study and eight withdrew. The records of seven subjects were audited. Included in the inspection were review of consent, reporting of adverse events, and efficacy variables. There was no evidence of under reporting of adverse events. No limitations to the inspection were reported.
- b. **General observations/commentary:** No significant deviations were identified and no Form FDA 483 was issued.
- c. **Assessment of data integrity:** The data are acceptable in support of the pending application.

## 3. **Stephane Oudard**

**Note:** Observations below based on the Form FDA 483 and oral and written communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR

- a. **What was inspected:** The records of 18 subjects were audited. Further information was not available at the time this report was prepared.
- b. **General observations/commentary:** In general, the study appears to have been conducted adequately; however, a few isolated regulatory violations were noted. There were a few random instances of failure to document in the source materials information reported on the CRF such as Present Pain Intensity, misreporting of information such as the use of two tablets of Dafalcan when in fact the use was one tablet, and the incorrect calculation of an analgesia score. These were noted on the Form FDA 483 given to the clinical investigator.
- c. **Assessment of data integrity:** The regulatory violations identified were few in number, random in occurrence and not related to the principal variables in the study.

The data are considered acceptable in support of the pending application.

#### 4. Mustafa Ozguroglu

**Note:** Observations noted below are based on the Form FDA 483 and oral and written communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

- a. **What was inspected:** The records of 17 subjects were audited. Further information was not available at the time this report was prepared.
- b. **General observations/commentary:** In general, the study appears to have been conducted appropriately; however, some isolated regulatory violations were noted. For example, there were three instances where medications being taken before entry into the study were continued during the study, but not reported as concomitant medications. There were four instances where Present Pain Intensity scores were mistranscribed and a single instance where the score was miscalculated. These observations were noted on Form FDA 483 given to the clinical investigator. The clinical investigator acknowledged these lapses in his 28 May 2010 response letter to the FDA, which was considered adequate.
- c. **Assessment of data integrity:** Although regulatory violations were noted, the data from this site are considered acceptable in support of the pending application as the regulatory violations were few in number, random in nature and did not involve the principal variables of the study.

#### IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

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.

**Note:** Observations noted above are based on the Form FDA 483 and/or oral and written communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

*{See appended electronic signature page}*

Robert Young  
Good Clinical Practice Branch II  
Division of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

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

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ROBERT S K YOUNG  
06/08/2010

TEJASHRI S PUROHIT-SHETH  
06/08/2010



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: June 4, 2010

To: Robert Justice, MD, Director  
**Division of Drug Oncology Products (DDOP)**

Through: Mary Willy, PhD, Deputy Director  
**Division of Risk Management (DRISK)**

LaShawn Griffiths, MSHS-PH, BSN, RN  
Patient Labeling Reviewer, Acting Team Leader  
**Division of Risk Management**

From: Sharon R. Mills, BSN, RN, CCRP  
Senior Patient Labeling Reviewer, Acting Team Leader  
**Division of Risk Management**

Subject: DRISK Review of Patient Labeling (Patient Package Insert)

Drug Name(s): JEVTANA (cabazitaxel) Injection

Application Type/Number: NDA 201-023

Applicant/sponsor: Sanofi-Aventis U.S., LLC

OSE RCM #: 2010-740

## 1 INTRODUCTION

On December 18, 2009 Sanofi-Aventis U.S., LLC submitted a an original New Drug Application, NDA 201-023 for JEVTANA (cabazitaxel) Injection. The proposed indication for JEVTANA (cabazitaxel) Injection, used in combination with prednisone, is for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen. This application was submitted as a rolling review and was granted priority review status by DDOP.

This review is written in response to a request by the Division of Drug Oncology Products (DDOP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for JEVTANA (cabazitaxel) Injection. Please let us know if DDOP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

## 2 MATERIAL REVIEWED

- Draft JEVTANA (cabazitaxel) Injection Prescribing Information (PI) submitted on March 31, 2010, revised by the Review Division throughout the current review cycle and provided to DRISK on May 26, 2010, June 1, 2010, and June 2, 2010.
- Draft JEVTANA (cabazitaxel) Injection Patient Package Insert (PPI) submitted on March 31, 2010, and provided to DRISK on May 5, 2010.

## 3 RESULTS OF REVIEW

In our review of the PPI, we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- rearranged information due to conversion of the PI to PLR format
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated PPI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.

This DRISK PPI reviewer noted that the Amendment dated March 31, 2010, included a brief description of proposed Pharmacovigilance activities and voluntary risk mitigation measures. This DRISK PPI reviewer did not conduct a review of the proposal. If the review division feels that there are risks that warrant a Risk Evaluation and Mitigation Strategy (REMS) for JEVTANA (cabazitaxel) Injection, please re-consult DRISK.

Please let us know if you have any questions.

12 pages of draft labeling has been withheld in full immediately following this page as B4 CCI/TS

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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SHARON R MILLS  
06/04/2010

MARY E WILLY  
06/04/2010  
I concur



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: May 26, 2010

To: Robert Justice, MD, Division Director  
Division of Drug Oncology Products

Through: Melina Griffis, RPh, Team Leader  
Kellie Taylor, PharmD, MPH, Associate Director  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Lubna Najam, M.S., Pharm.D, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Jevtana (Cabazitaxel) Injection, 60 mg/1.5 mL

Application Type/Number: NDA 201023

Applicant/sponsor: Sanofi Aventis

OSE RCM #: 2010-714

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## 1. INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis evaluation of the proposed labels and labeling for Jevtana (Cabazitaxel) Injection, 60 mg/1.5 mL (NDA 201023) for areas of vulnerabilities that could lead to medication errors. The proposed proprietary name is evaluated under separate review (OSE # 2010-695)

## 2. METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis (FMEA),<sup>1</sup> the Division of Medication Error Prevention and Analysis (DMEPA) evaluates the container labels, carton and insert labeling. This review focuses on labels and labeling submitted as part of the April 01, 2010 original NDA submission. See Appendices A-C for images of the proposed container labels and carton labeling.

## 3. CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed labels and labeling noted areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations to the insert labeling in Section 3.1 Comments to the Division for discussion during the labeling meetings. Section 3.2 Comments to the Applicant contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Sarah Simon at 301-796-5205

### 3.1 COMMENTS TO THE DIVISION:

#### A. General Comment

Based on USP recommendations the labels and labeling for injectable drug products should state the total drug content as the primary strength expression on the labels, followed by the strength per mL. However, Jevtana requires a two-step dilution for preparation. Thus, a statement expressing the strength after first dilution of 10 mg/mL will be required on the label. Due to the two-step dilution, we recommend that the labels and labeling only contain the total drug content expression of strength of 60 mg/1.5 mL and not include the secondary concentration to avoid introduction of another concentration per mL on the label. DMEPA is concerned that the addition of the strength expression of 40 mg/mL on labels which already contains two expressions of strength could lead to confusion and result in dosing errors. Therefore, we request the strength be expressed as 60 mg/1.5 mL Before First Dilution\*. Then follow this with the statement: Reconstitute this vial using the entire contents of diluent (approximately 5.8 mL). The resultant solution contains a concentration of 10 mg/mL (see comment 3.2 B1).

#### B. Full Prescribing Information

##### 1. Dosage and administration- Section 2

The recommended dosage for this product is 25 mg/m<sup>2</sup> (based on body surface area) however, a maximum recommended dose is not provided in labeling. We recommend this section list the maximum recommended dosage of Jevtana to avoid potential overdoses.

---

<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2. In addition to the above recommendations, DMEPA has also provided recommended changes to the proposed package insert labeling (see attached track change document). These changes are consistent with the approved labeling for similar products, which require a two-step dilution.

### 3.2 COMMENTS TO THE APPLICANT:

#### A. General Comments

1. The instructions for second dilution under Step 2 state that the required amount of Jevtana 10 mg/mL solution should be mixed with 0.9% sodium chloride solution or 5% dextrose solution for infusion to obtain a final concentration between 0.10 mg/mL and 0.26 mg/mL. This step would require additional calculations, which have the potential to lead to dosing errors. We question the rationale for requiring a range of concentration for the final infusion solution and why a fixed volume of infusion solution cannot be recommended in labeling. We request that a specific volume of 0.9% sodium chloride solution or 5% dextrose solution required for second dilution be provided in section 2.5 of the package insert.
2. Delete the term “ (b) (4) ” from all container labels and carton labeling.
3. As currently presented, the color scheme utilized in the proposed Jevtana container label and carton labeling is identical to the color scheme utilized for your proposed Taxotere label and labeling. We recommend you revise the colors utilized for the Jevtana labels and labeling to allow for more adequate visual differentiation from the Taxotere labels and labeling.

#### B. Container Label for Jevtana (60 mg/1.5 mL)

1. The container label should provide the following directions for dilution in the event the drug vial is stored out of the carton.  
**CAUTION: Reconstitute this vial using the entire contents of the diluent vial (approximately 5.8 mL). Following this first dilution, the resultant solution contains a concentration of 10 mg/mL. Withdraw only the required amount of the first dilution to prepare the final infusion solution prior to administration. See package insert for full dilution information.**  
The directions should be prominently displayed and adequately differentiated from all other information on the vial. Please refer to the Taxotere container label for details on the presentation of the dilution directions.
2. The strength expression (b) (4) is currently in a colored box. Revise the label to state “60 mg/1.5 mL Before First Dilution\*” such that Before First Dilution has the same prominence as the strength expression and is located inside the box.
3. Revise the route of administration to read “\*FOR INTRAVENOUS INFUSION ONLY AFTER SECOND DILUTION.”
4. In accordance with 21 CFR 201.100(b)(iii), the container label requires the inactive ingredients be listed on the vial. Please include the Statement “Contains 60 mg cabazitaxel and 1.56 mg polysorbate 80” as appears under the description section of the insert labeling. However if inclusion of this statement prohibits the required caution statement then the inactive ingredient statement may be omitted.

**C. Container Label for Diluent (5.8 mL)**

1. In order to clarify that the vial only contains diluent, we request you revise the label as follows :

**DILUENT**

5.8 mL of 13 % (w/w) ethanol in water injection.

Use ONLY for dilution of Jevtana.

2. Delete the following statement from the label: [REDACTED] (b) (4)
4. We recommend that the drug vial and diluent vial be physically linked to lessen the likelihood that they will become separated. If separated, we are concerned that Jevtana could be administered without dilution or the diluent of Jevtana could be inadvertently administered instead of Jevtana.
4. The storage conditions should be specified on the Diluent label.

**D. Carton Labeling**

1. As currently presented the carton labeling states Jevtana on the principal display panel and the side panels. This may mislead practitioners to believe the package only contains the drug and no diluent. The carton contains both the drug and diluent. Revise the carton label to read as follows:

JEVTANA

(Cabazitaxel) Injection

60 mg/1.5 mL Before First Dilution\*

This carton contains: 1 Jevtana vial and 1 Diluent vial

Please note “60 mg/1.5 mL Before First Dilution\*” should have the same prominence as the strength expression.

2. Add a statement: \*Requires two dilutions before administration-See back panel for details before the “FOR INTRAVENOUS INFUSION...” statement.
3. Revise the statement [REDACTED] (b) (4) ...” to state “FOR INTRAVENOUS INFUSION ONLY AFTER SECOND DILUTION”
4. Revise the directions of dilution on the back panel to state the following:

Two-step dilution required

**First Dilution:** Add **entire** contents of the diluent (approximately 5.8 mL) to Jevtana injection to obtain a concentration of **10 mg/mL**.

**Second Dilution:** Withdraw the exact volume required from the 10 mg/mL solution and add to XX mL (Note to Applicant- please fill in specific volume) of 0.9% sodium chloride or 5% dextrose solution.

For intravenous infusion only after second dilution.

See package insert.....

5. Revise the side panel to state  
JEVTANA  
(Cabazitaxel) Injection  
60 mg/1.5 mL Before First Dilution\*  
\* Requires two dilutions before administration  
Contains: 1 Jevtana vial  
1 Diluent vial

25 pages of draft labeling has been withheld in full immediately following this page as B4 CCI/TS

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

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MELINA N GRIFFIS  
05/28/2010

KELLIE A TAYLOR  
05/28/2010

KELLIE A TAYLOR on behalf of CAROL A HOLQUIST  
05/28/2010

## STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	2010-42
APPLICATION NUMBER	NDA 20-1023
LETTER DATE/SUBMISSION NUMBER	March 31, 2010
REQUESTED COMPLETION DATE	May 21, 2010
DATE OF CONSULT REQUEST	April 22, 2010
REVIEW DIVISION	Division of Drug Oncology Products (DDOP)
MEDICAL REVIEWER	Amy McKee
REVIEW DIVISION PM	Christy Cottrell
SEALD REVIEWER(S)	Ann Marie Trentacosti
REVIEW COMPLETION DATE	May 10, 2010
ESTABLISHED NAME	Cabazitaxel
TRADE NAME	Jevtana
APPLICANT	Sanofi-Aventis
ENDPOINT(S) CONCEPT(S)	Pain Intensity (Component of Progression Free Survival; Pain Progression; Pain Response)
INSTRUMENT(S)	McGill-Melzack Pain Questionnaire-Present Pain Intensity (PPI)
INDICATION	In combination with prednisone or prednisolone for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.

## STUDY ENDPOINT REVIEW

### 1 EXECUTIVE SUMMARY

This Study Endpoints and Labeling Development (SEALD) review is provided as a response to a request for consultation by the Division of Drug Oncology Products (DDOP) regarding NDA 20-1023 which provides the efficacy and safety information to support the proposed indication of cabazitaxel in combination with prednisone or prednisolone for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen. DDOP has requested SEALD evaluate the patient-reported outcome (PRO) measure of pain intensity, which was used to define several secondary endpoints in pivotal trial EFC6193 (component of progression free survival; pain progression; and pain response).

The review concludes that open-label trials, such as EFC6193, in which patients and investigators are aware of assigned therapy, are not adequately designed to support efficacy conclusions, based on subjective PRO measures, such as pain intensity. Patients who know they are in active treatment group may overestimate benefit whereas patients who know they are not receiving active treatment may underreport any improvement actually experienced. Therefore, the validity of the data is questionable.

In addition, to the open-label study design, several other deficiencies were identified in the review which suggests that pain intensity was not adequately measured and therefore changes in pain intensity with treatment cannot be effectively interpreted.

The content validity of the pain intensity measure, the McGill-Melzack Pain Questionnaire present pain intensity (PPI), has not been adequately established and cannot effectively support efficacy claims. The response options (i.e. discomforting, distressing, horrible, and excruciating) are ambiguous and have not been shown to be interpretable and appropriate measures of pain intensity. In addition, the sponsor has not provided any information to justify that the pain progression and pain response definitions included in the trial are clinically meaningful.

An effective assessment of pain progression and response must include an adequate measure of the patient's analgesic use. The sponsor has not provided a copy of the analgesic log. Similar to other PRO instruments, it would be important to establish that the analgesic measure, including recall period, was appropriate and interpretable for patients. In addition it is unclear that the morphinic equivalent table used to define a change in analgesic use is clinically meaningful.

Trial EFC6193 was not adequately designed to measure pain progression or pain response. The trial inclusion criteria did not require specific baseline pain intensity criteria for enrollment. In order to adequately evaluate a pain palliation response to treatment, patients must have evidence of baseline pain. Alternatively, in order to adequately evaluate a pain progression response, patients must have evidence of no or minimal pain at baseline. In addition, there was no stratification criteria based on pain intensity, therefore, it uncertain if the treatment arms were balanced with respect to presence or absence of cancer related pain at baseline.

## STUDY ENDPOINT REVIEW

Finally, since trial EFC6193 was an international study, it would be important to include evidence to justify that the pain and analgesic diary were adequately translated and cultural adapted for use in all participating countries and cultures. This evidence has not been submitted.

### 2 ENDPOINT REVIEW

The McGill Melzack Pain Questionnaire-Present Pain Intensity (PPI) was used in pivotal trial EFC6193 both as a component of the secondary endpoint, progression free survival and also in evaluating the secondary endpoints of pain progression and pain response.

#### 2.1 Instruments

##### McGill-Melzack Pain Questionnaire-Present Pain Intensity (PPI)

The McGill-Melzack Pain Questionnaire (See Appendix) was developed in 1975 in order to quantify pain measures. The instrument consists of 3 major measures, one of which is the present pain intensity (PPI). The PPI asks patients to assess their present pain based on the following responses: none, mild, discomfort, distressing, horrible, and excruciating.

(b) (4)

#### 2.2 Language Translation and Cultural Adaptation

Trial EFC6193 was conducted in 26 countries (Argentina, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, Finland, France, Germany, Hungary, India, Italy, Korea, Mexico, Netherlands, Russia, Singapore, Slovakia, South Africa, Spain, Sweden, Taiwan, Turkey, UK, and USA) with 146 active sites out of 155 sites that were initiated.

*Comments: The sponsor has not provided any evidence to justify that the pain and analgesic diary were adequately translated and cultural adapted for use in all participating countries.*

#### 2.3 Protocol and Analysis Plan

The efficacy and safety of cabazitaxel in combination with prednisone were evaluated in a randomized, open-label, international, multi-center phase III study (Study EFC6193) in patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel containing treatment regimen.

*Comments: Open-label clinical trials, where patients and investigators are aware of assigned therapy are rarely adequate to support labeling claims based on PRO instruments. Patients who know they are in active treatment group may overestimate benefit whereas patients who know they are not receiving active treatment may underreport any improvement actually experienced.*

Inclusion Criteria were as follows:

- Diagnosis of histologically or cytologically proven prostate adenocarcinoma, that is refractory to hormone therapy and previously treated with a Taxotere-containing regimen. Patient must have documented progression of disease during or within 6 months

## STUDY ENDPOINT REVIEW

after prior hormone therapy and disease progression during or after Taxotere-containing therapies.

- Patient must have either measurable or non-measurable disease.
  - Patient with measurable disease must have documented progression of disease by RECIST criteria demonstrating at least one visceral or soft tissue metastatic lesion (including new lesion).
  - Patient with non-measurable disease must have documented rising PSA levels or appearance of new lesion.
- Received prior castration by orchiectomy and/or Luteinizing Hormone-Releasing Hormone (LH-RH) agonist with or without antiandrogen, antiandrogen withdrawal, monotherapy with estramustine, or other hormonal agents. (A prior treatment by antiandrogen is not mandatory).
- Life expectancy > 2 months
- Eastern Cooperative Oncology Group (ECOG) performance status 0 – 2
- Age ≥ 18 years

### Exclusion Criteria included the following:

- Previous treatment with mitoxantrone
- Prior radiotherapy to ≥ 40% of bone marrow, and/or brachytherapy
- Prior surgery < 4 weeks of enrollment in the study
- Active secondary cancer including prior malignancy from which the patient has been disease free for ≤ 5 years (However, adequately treated superficial basal cell skin cancer before 4 weeks prior to entry can be eligible to the study)
- Known brain or leptomeningeal involvement
- History of severe hypersensitivity reaction (≥ grade 3) to polysorbate 80 containing drugs
- History of severe hypersensitivity reaction (≥ grade 3) or intolerance to prednisone
- Other concurrent serious illness or medical conditions
- Inadequate organ function as evidenced by the following peripheral blood counts, and serum chemistries at enrollment:
  - Neutrophils ≤ 1.5 x 10<sup>9</sup>/L
  - Hemoglobin ≤ 10 g/dL
  - Platelets ≤ 100 x 10<sup>9</sup>/L
  - Total bilirubin ≥ Upper limit of normal (ULN)
  - AST (SGOT) ≥ 1.5 x ULN
  - ALT (SGPT) ≥ 1.5 x ULN
  - Creatinine ≥ 1.5 x ULN
- Uncontrolled cardiac arrhythmias, angina pectoris, and/or hypertension
- Left ventricular ejection fraction ≤ 50% by multi-gated radionuclide angiography (MUGA) scan (for mitoxantrone arm only)
- Uncontrolled diabetes mellitus
- Active uncontrolled GERD
- Active infection requiring systemic antibiotic or anti-fungal medication
- Participation in another clinical trial with any investigational drug within 30 days prior to study enrollment.

## STUDY ENDPOINT REVIEW

- Concurrent or planned treatment with strong inhibitors of cytochrome P4503A4. (A one week washout period is necessary for patients who are already on these treatments).

Patients were stratified using the following criteria:

- Measurability of disease per RECIST criteria (measurable versus non-measurable disease)
- ECOG performance status (0 or 1 versus 2)

*Comments: The trial inclusion criteria did not require specific baseline pain intensity criteria for enrollment. In order to adequately evaluate a pain palliation response to treatment, patients must have evidence of baseline pain. Alternatively, in order to adequately evaluate a pain progression response, patients must have evidence of no or minimal pain at baseline. Neither criterion was included. In addition, there was no stratification criteria based on pain intensity, therefore, it is uncertain if the treatment arms were balanced with respect to presence or absence of cancer related pain at baseline.*

A total of 755 patients were randomized to receive either cabazitaxel 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. As predefined in the study protocol, patients were required to have progressive disease following completion of Docetaxel-based chemotherapy. Patients with measurable disease were required to have progressive disease determined using the RECIST criteria.

The primary efficacy assessment was overall survival (OS) defined as the time interval from the date of randomization to the date of death due to any cause.

Secondary efficacy assessments included the following:

- Progression free survival (PFS) was evaluated from the date of randomization to the date of tumor progression, PSA progression, pain progression (pain progression supported by clinical evidence and/or radiological of disease progression), or death due to any cause, whichever occurred first
- Tumor lesion assessment (in patients with measurable disease):
  - Objective responses (Complete Response [CR] and Partial Response [PR]) for measurable disease as assessed by Investigators according to RECIST criteria. The confirmation of objective responses was performed by repeat tumor imaging (CT scans, MRI, bone scans) at least 4 weeks after the first documentation of response.
- Time to tumor progression (TTP) was added as a secondary efficacy endpoint in the efficacy analyses. Time to tumor progression was defined as the number of months from the date of randomization to evidence of PD based upon tumor measurements (RECIST criteria). Patients without PD were censored at their last tumor assessment.
- PSA progression (assessed in all patients):
  - In PSA non-responders, the progression was defined as a  $\geq 25\%$  increase over nadir (provided that the increase in the absolute value PSA level was at least 5

## STUDY ENDPOINT REVIEW

ng/mL), confirmed by a second value with a  $\geq 25\%$  increase over baseline at least 1 week later.

- In PSA responders and in patients not evaluable for PSA response at baseline, the progression was defined as a  $\geq 50\%$  increase over the nadir (provided that the increase in the absolute value PSA level was at least 5 ng/mL), confirmed by a second value at least 1 week later.
- PSA response (assessed only in patients with baseline PSA  $\geq 20$  ng/mL): Response required a PSA decrease of  $\geq 50\%$  confirmed by a second PSA value at least 3 weeks later. The duration of PSA response was measured from baseline to the last assessment at which the above criteria are satisfied.
- Pain Progression (assessed in all patients): Pain Progression (cancer related) was defined as an increase of  $\geq 1$  point in the median PPI from its nadir noted on 2 consecutive 3-week-apart visits, or  $\geq 25\%$  increase in the mean AS compared with the baseline score and noted on 2 consecutive 3-week-apart visits, or requirement for local palliative radiotherapy.
- Pain Response (assessed only in patients with median PPI  $\geq 2$  on McGill-Melzack scale and/or mean AS  $\geq 10$  points at baseline): Pain Response was defined as a 2-point or greater reduction from baseline median PPI with no concomitant increase in AS, or a reduction of at least 50% in analgesic use from baseline mean AS (only in patients with baseline mean AS  $\geq 10$ ) with no concomitant increase in pain. Either criterion was maintained for 2 consecutive evaluations at least 3 weeks apart.

Pain was assessed prior to registration, every three weeks, at end of study treatment. In addition, during the first 6 months of the follow-up period, patients were evaluated every 6 weeks for pain progression until documented progression or start of other anticancer therapy, for the rest of the follow-up period patients was evaluated every 3 months with the Present Pain Intensity scale from the McGill-Melzack questionnaire. Pain assessments were averaged over the prior week. The patient was asked to complete the PPI every day for the one week period prior to each evaluation. The questionnaire was to be administered before any treatment infusion occurs. If treatment was delayed, the assessment schedule was defined from the actual date of beginning of treatment. Median PPI and mean AS were calculated only if 5 of the 7 expected values were actually available in the Patient Pain Diary.

Analgesics consumption was assessed with the Pain Medication Log prior to registration, every three weeks, at end of study treatment and then every 6 weeks until pain progression or further anti-tumor therapy. The patient was instructed to record all analgesic use for the one week period prior to each evaluation. Analgesic Score was calculated as the mean daily score of analgesics, averaged over the prior week, using a morphinic equivalent table.

*Comments: The sponsor has not provided any information to justify that the pain progression and pain response definitions are clinically meaningful.*

*The use of the morphinic equivalent table in determining an analgesic score is problematic. It is unclear if similar analgesic scores produce the same degree of analgesia for all patients.*

## STUDY ENDPOINT REVIEW

*The sponsor has not provided a copy of the analgesic log used in the study. Similar to other PRO instruments, it would be important to establish that the analgesic measure, including recall period was appropriate and interpretable for patients.*

Protocol amendments related to pain assessment included the following:

- Modified definition of pain progression that pain had to be cancer-related and pain progression must have been supported by clinical and/or radiological evidence of disease progression. Accordingly, patients were to be removed from study treatment for cancer-related pain progression.
- The change of patient's PPI score on treatment from baseline was compared between the 2 treatment groups. The analysis included all treated patients who had PPI scores at both baseline and on treatment.

### Study Results:

A total of 755 patients were randomized. There were 378 patients randomized to cabazitaxel and 377 randomized to mitoxantrone. Overall survival results for the Jevtana (cabazitaxel) arm versus the control arm are summarized in Table 1.

**Table 1. Efficacy (Overall Survival) of Jevtana in the Treatment of Patients with Hormone Refractory Metastatic Prostate Cancer (Intent-to-Treat Analysis)**

	JEVTANA + Prednisone n=378	Mitoxantrone + Prednisone n=377
<b>Overall Survival</b>		
Number of patients with 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 <sup>1</sup> (95% CI)	0.70 (0.59-0.83)	
p-value	<0.0001	

<sup>1</sup>Hazard ratio estimated using Cox model; a hazard ratio of less than 1 favors JEVTANA

The secondary endpoint of progression free survival is depicted in Table 2, while Table 3 depicts the progression components.

**Table 2. Progression Free Survival**

	MTX+PRED (N=377)	CBZ+PRED (N=378)
Number of patients with PFS events (%)	367 (97.3%)	364 (96.3%)
Median progression free survival in months (95% CI)	1.4 (1.4 - 1.7)	2.8 (2.4 - 3.0)
Hazard ratio (95% CI)	0.74 (0.64-0.86)	
P-value	<0.0001	

Note: A hazard ratio <1 favors cabazitaxel.

PFS was defined as a composite endpoint evaluated from the date of randomization to the date of tumor progression, PSA progression, pain progression, or death due to any cause, whichever occurred first.

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**Table 3. Progression Components**

	MTX+PRED (N=377)	CBZ+PRED (N=378)
<b>Time to tumor progression</b>		
No. of patients with progression (by RECIST) (%)	180 (47.7)	170 (45.0)
Median time to tumor progression (months) (95% CI)	5.4 (4.7 - 6.5)	8.8 (7.4 - 9.6)
Hazard ratio (95% CI)	0.61 (0.49 - 0.76)	
P-value	<0.0001	
<b>PSA progression</b>		
No. of patients with PSA progression (%)	252 (66.8)	252 (66.7)
Median time to PSA progression (months) (95% CI)	3.1 (2.2 - 4.4)	6.4 (5.1 - 7.3)
Hazard ratio (95% CI)	0.75 (0.63-0.90)	
P-value	0.0010	
<b>Pain Progression</b>		
No. of patients with pain progression (%)	98 (26.0)	113 (29.9)
Median time to pain progression (months) (95% CI)	not reached	11.1 (8.0 - .)
Hazard ratio (95% CI)	0.91 (0.69-1.19)	
P-value	0.5192	

Note: A hazard ratio <1 favors cabazitaxel.

A median time to pain progression was 11.1 months in the cabazitaxel group and was not reached in the mitoxantrone group. There was no statistically significant difference between treatment arms in the time to pain progression (p=0.5192) with a HR (95% CI) of 0.91 (0.69 - 1.19). Table 4 denotes the descriptive analysis of pain progression in the ITT population.

**Table 4. Descriptive Analysis of Pain Progression-ITT Population**

	MTX+PRED (N=377)	CBZ+PRED (N=378)
Number of patients with pain progression (%)	98 (26.0%)	113 (29.9%)
Number of patients censored (%)	279 (74.0%)	265 (70.1%)
Median pain progression free in months (95% CI)	Not reached	11.1 (8.0 - .)
Probability of pain progression free at 3 months*	0.71 (0.65-0.76)	0.74 (0.68-0.78)
Probability of pain progression free at 6 months*	0.61 (0.53-0.67)	0.61 (0.55-0.67)
Probability of pain progression free at 9 months*	0.54 (0.45-0.62)	0.53 (0.45-0.60)
Probability of pain progression free at 12 months*	0.54 (0.45-0.62)	0.49 (0.39-0.59)

\*Refer to Kaplan-Meier curve for the interpretation of the probability of pain progression free

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*Comments: A large percentage of patients were censored in each group.*

Table 5 depicts the pain response rate.

**Table 5. Pain Response Rate**

	MTX+PRED (N=377)	CBZ+PRED (N=378)
<b>Pain response rate</b>		
No of patients evaluable <sup>b</sup>	168	174
Pain response rate (%) (95% CI)	7.7 (3.7% to 11.8%)	9.2 (4.9% to 13.5%)
P-value	0.6286	

Pain response was evaluated in patients with a median PPI  $\geq 2$  on McGill-Melzack scale and/or a mean analgesic score  $\geq 10$  points at baseline

A statistically significant difference in pain response between treatment arms was not observed.

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

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ANN M TRENTACOSTI  
05/10/2010

LAURIE B BURKE  
05/10/2010

# DSI CONSULT: Request for Clinical Inspections

**Date:** April 8, 2010

**To:** Constance Lewin, M.D., M.P.H, Branch Chief, GCP1  
Tejashri Purohit-Sheth, M.D., Branch Chief (Acting), GCP2  
Robert Young, M.D., CDER/OC/DSI/GCPBII  
Division of Scientific Investigations, HFD-45  
Office of Compliance/CDER

**Through:** Amy McKee, M.D. and Ian Waxman, M.D. /Clinical Reviewers/Division of  
Drug Oncology Products  
John Johnson, M.D./Clinical Team Leader/DDOP

**From:** Christy Cottrell, Regulatory Health Project Manager/DDOP

**Subject:** **Request for Clinical Site Inspections**

## **I. General Information**

Application#: NDA 201023  
Applicant/ Applicant contact information (to include phone/email):  
sanofi-aventis U.S. LLC  
Attention: Linda Gustavson  
55 Corporate Drive  
Bridgewater, NJ 08807  
P: 908-981-5000  
F: 877-332-5512  
Drug Proprietary Name: Cabazitaxel (XRP6258)  
NME or Original BLA (Yes/No): NME NDA  
Review Priority (Standard or Priority): Priority

Study Population includes < 17 years of age (Yes/No): No  
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Metastatic prostate cancer

PDUFA: October 1, 2010  
Action Goal Date: May 28, 2010  
Inspection Summary Goal Date: May 21, 2010

**II. Protocol/Site Identification**

*Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.*

<b>Site # (Name,Address, Phone number, email, fax#)</b>	<b>Protocol ID</b>	<b>Number of Subjects</b>	<b>Indication</b>
Site 25001 Georges Pompidou/Stephane Oudard Hopital Europeen 20 Rue Leblanc Paris Cedex 15, 75008 France	EFC6193	52	Treatment of adults in combination with prednisone or prednisolone with metastatic prostate cancer who had progression during or after docetaxel-based therapies
Site 792001 Mustafa Ozguroglu Ic Hastaliklari Tibbi Onkoloji A.D. Cerrahpasa Tip Fak. Ic Hast. B.d. Aksaray / Istanbul ISTANBUL 34303	EFC6193	33	Treatment of adults in combination with prednisone or prednisolone with metastatic prostate cancer who had progression during or after docetaxel-based therapies
Site 840011 Mario Eisenberger Sydney Kimmel Cancer Center 1650 Orleans Street, Suite 1 Rm 51 Baltimore, MD 21230	EFC6193	7	Treatment of adults in combination with prednisone or prednisolone with metastatic prostate cancer who had progression during or after docetaxel-based therapies
Site 840077 Shaker Dakhil Cancer Center of Kansas 818 N Emporia S-403 Wixhita, KS 67214	EFC6193	11	Treatment of adults in combination with prednisone or prednisolone with metastatic prostate cancer who had progression during or after docetaxel-based therapies

**III. Site Selection/Rationale**

*Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.*

***Rationale for DSI Audits***

The two international sites were among the sites with the highest enrollment overall in the study as well as the most protocol violations. The domestic sites were among the domestic sites with the highest enrollment and the most protocol violations, as well as a financial conflict of interest.

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects domestically
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

**International Inspections:**

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify): Enrollment of large numbers of study subjects and site-specific protocol violations. This would be the first approval of this new drug and as most of the limited experience with this drug has been at foreign sites, it would be desirable to include at least one foreign site in the DSI inspections to verify the quality of conduct of the study.

**Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.**

**IV. Tables of Specific Data to be Verified (if applicable)**

*If you have specific data that needs to be verified, please provide a table for data verification, if applicable.*

Should you require any additional information, please contact Christy Cottrell, RPM, at 301-796-4256 or Amy McKee, M.D., at 301-796-3909 or Ian Waxman, M.D., at 301-796-5123.

Concurrence: (as needed)

Amy McKee, M.D. and Ian Waxman, M.D., Medical Reviewers  
John Johnson, M.D., Medical Team Leader  
Robert Justice, M.D., Division Director



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/s/

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CHRISTY L COTTRELL  
04/08/2010

AMY E MCKEE  
04/09/2010

IAN M WAXMAN  
04/09/2010

AMNA IBRAHIM  
04/09/2010

Tentative internal goal date for action on the NDA is May 31, 2010  
Signed for Dr John Johnson

ROBERT L JUSTICE  
04/09/2010