

*APPLICATION NUMBER:*  
**201023**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## PATENT INFORMATION

Pursuant to 21 CFR 314.53(d)(1) the patent information for this original application is being submitted concurrently herewith by separate letter addressed to the Central Document Room.

  
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Linda Gustavson, PhD, RAC

Director, U.S. Assoc. Therapeutic Axis Head, Oncology

Regulatory Research and Development Portfolio

Corporate Regulatory Affairs

Sanofi-aventis US

**PATENT INFORMATION SUBMITTED WITH THE FILING  
OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and Composition)  
and/or Method of Use**

NDA NUMBER

201023

NAME OF APPLICANT/NDA HOLDER

sanofi-aventis U.S. LLC

**The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.**

TRADE NAME (OR PROPOSED TRADE NAME)

JEVTANA®

ACTIVE INGREDIENT(S)

cabazitaxel

STRENGTH(S)

Single dose vials containing 60 mg/1.5mL (40 mg/mL)

DOSAGE FORM

concentrate for solution for infusion

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

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**FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number

5,438,072

b. Issue Date of Patent

August 1, 1995

c. Expiration Date of Patent

November 22, 2013

d. Name of Patent Owner

Aventis Pharma S.A.

Address (of Patent Owner)

174 Avenue de France

City/State

75013 Paris

ZIP Code

FRANCE

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Charlotte Barney, Esq.

Address (of agent or representative named in 1.e.)

1041 Route 202/206

City/State

Bridgewater, New Jersey

ZIP Code

08807

FAX Number (if available)

(908) 231-2840

Telephone Number

(908) 231-4551

E-Mail Address (if available)

charlotte.barney@sanofi-aventis.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)		
	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.6 Does the patent claim only an intermediate?		
	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)		
	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
	<input type="checkbox"/> Yes	<input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)	

**5. No Relevant Patents**

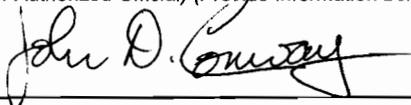
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	<input type="checkbox"/> Yes
---	------------------------------

**6. Declaration Certification**

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)



Date Signed

Feb. 19, 2010

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Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

John D. Conway

Address

sanofi-aventis U.S. Inc.  
1041 Route 202-206

City/State

Bridgewater, New Jersey

ZIP Code

08807

Telephone Number

(908) 231-5617

FAX Number (if available)

(908) 231-2626

E-Mail Address (if available)

john.conway@sanofi-aventis.com

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Food and Drug Administration  
Office of Chief Information Officer (HFA-710)  
5600 Fishers Lane  
Rockville, MD 20857

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**1. GENERAL**

a. United States Patent Number 5,698,582	b. Issue Date of Patent December 16, 1997	c. Expiration Date of Patent July 3, 2012
d. Name of Patent Owner Aventis Pharma S.A.	Address (of Patent Owner) 174 Avenue de France	
	City/State 75013 Paris	
	ZIP Code FRANCE	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)  Charlotte Barney, Esq.	Address (of agent or representative named in 1.e.) 1041 Route 202/206	
	City/State Bridgewater, New Jersey	
	ZIP Code 08807	FAX Number (if available) (908) 231-2840
	Telephone Number (908) 231-4551	E-Mail Address (if available) charlotte.barney@sanofi-aventis.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
	<input type="checkbox"/> Yes	<input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)	

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	<input type="checkbox"/> Yes
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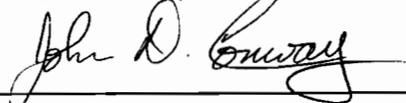
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NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

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Address

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City/State

Bridgewater, New Jersey

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john.conway@sanofi-aventis.com

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**1. GENERAL**

a. United States Patent Number 5,847,170	b. Issue Date of Patent December 8, 1998	c. Expiration Date of Patent March 26, 2016
d. Name of Patent Owner Aventis Pharma S.A.	Address (of Patent Owner) 174 Avenue de France	
	City/State 75013 Paris	
	ZIP Code FRANCE	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
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2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3. Applicant understands Question 2.2 to ask whether the patent claims only a polymorph of the drug substance that is different from that described in the pending NDA. The patent contains claims that encompass any form of the active ingredient, and is submitted for listing on that basis.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
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**3. Drug Product (Composition/Formulation)**

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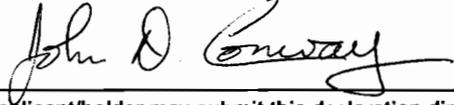
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	<input type="checkbox"/> Yes
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DOSAGE FORM

concentrate for solution for infusion

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number 6,331,635	b. Issue Date of Patent December 18, 2001	c. Expiration Date of Patent March 26, 2016
d. Name of Patent Owner Aventis Pharma S.A.	Address (of Patent Owner) 174 Avenue de France	
	City/State 75013 Paris	
	ZIP Code FRANCE	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)  Charlotte Barney, Esq.	Address (of agent or representative named in 1.e.) 1041 Route 202/206	
	City/State Bridgewater, New Jersey	
	ZIP Code 08807	FAX Number (if available) (908) 231-2840
	Telephone Number (908) 231-4551	E-Mail Address (if available) charlotte.barney@sanofi-aventis.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? <input type="checkbox"/> Yes <input type="checkbox"/> No		

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

**2.1** Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

**2.2** Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

**2.3** If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

**2.4** Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.  
 Applicant understands Question 2.2 to ask whether the patent claims only a polymorph of the drug substance that is different from that described in the pending NDA. The patent contains claims that encompass any form of the active ingredient, and is submitted for listing on that basis.

**2.5** Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

**2.6** Does the patent claim only an intermediate?  Yes  No

**2.7** If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

**3.1** Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

**3.2** Does the patent claim only an intermediate?  Yes  No

**3.3** If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

**4.1** Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

**4.2** Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

**4.2a** If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

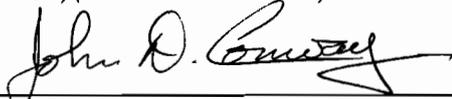
**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)**

Date Signed



Feb 19, 2010

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

<input type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input checked="" type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name John D. Conway	
Address sanofi-aventis U.S. Inc. 1041 Route 202-206	City/State Bridgewater, New Jersey
ZIP Code 08807	Telephone Number (908) 231-5617
FAX Number (if available) (908) 231-2626	E-Mail Address (if available) john.conway@sanofi-aventis.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
Office of Chief Information Officer (HFA-710)  
5600 Fishers Lane  
Rockville, MD 20857

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**PATENT INFORMATION SUBMITTED WITH THE FILING  
OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and Composition)  
and/or Method of Use*

NDA NUMBER

201023

NAME OF APPLICANT/NDA HOLDER

sanofi-aventis U.S. LLC

**The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.**

TRADE NAME (OR PROPOSED TRADE NAME)

JEVTANA®

ACTIVE INGREDIENT(S)

cabazitaxel

STRENGTH(S)

Single dose vials containing 60 mg/1.5mL (40 mg/mL)

DOSAGE FORM

concentrate for solution for infusion

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**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number 6,372,780	b. Issue Date of Patent April 16, 2002	c. Expiration Date of Patent March 26, 2016
d. Name of Patent Owner Aventis Pharma S.A.	Address (of Patent Owner) 174 Avenue de France	
	City/State 75013 Paris	
	ZIP Code FRANCE	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)  Charlotte Barney, Esq.	Address (of agent or representative named in 1.e.) 1041 Route 202/206	
	City/State Bridgewater, New Jersey	
	ZIP Code 08807	FAX Number (if available) (908) 231-2840
	Telephone Number (908) 231-4551	E-Mail Address (if available) charlotte.barney@sanofi-aventis.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		
<input type="checkbox"/> Yes <input type="checkbox"/> No		

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)		
	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.6 Does the patent claim only an intermediate?		
	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)		
	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent) 1 to 5 and 7 to 14	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) Jevtana (a microtubule inhibitor) in combination with prednisone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel containing treatment regimen	

**5. No Relevant Patents**

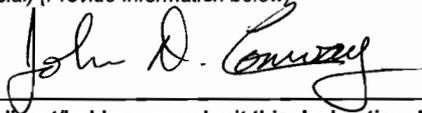
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	<input type="checkbox"/> Yes
---	------------------------------

**6. Declaration/ Certification**

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)



Date Signed

Feb 19, 2010

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Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

John D. Conway

Address

sanofi-aventis U.S. Inc.  
1041 Route 202-206

City/State

Bridgewater, New Jersey

ZIP Code

08807

Telephone Number

(908) 231-5617

FAX Number (if available)

(908) 231-2626

E-Mail Address (if available)

john.conway@sanofi-aventis.com

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Food and Drug Administration  
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Rockville, MD 20857

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**PATENT INFORMATION SUBMITTED WITH THE FILING  
OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and Composition)  
and/or Method of Use*

NDA NUMBER

201023

NAME OF APPLICANT/NDA HOLDER

sanofi-aventis U.S. LLC

**The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.**

TRADE NAME (OR PROPOSED TRADE NAME)

JEVTANA®

ACTIVE INGREDIENT(S)

cabazitaxel

STRENGTH(S)

Single dose vials containing 60 mg/1.5mL (40 mg/mL)

DOSAGE FORM

concentrate for solution for infusion

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**1. GENERAL**

a. United States Patent Number 6,387,946	b. Issue Date of Patent May 14, 2002	c. Expiration Date of Patent March 26, 2016
d. Name of Patent Owner Aventis Pharma S.A.	Address (of Patent Owner) 174 Avenue de France	
	City/State 75013 Paris	
	ZIP Code FRANCE	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)  Charlotte Barney, Esq.	Address (of agent or representative named in 1.e.) 1041 Route 202/206	
	City/State Bridgewater, New Jersey	
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	Telephone Number (908) 231-4551	E-Mail Address (if available) charlotte.barney@sanofi-aventis.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
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2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
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2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
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**3. Drug Product (Composition/Formulation)**

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**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent) 1, 2, 3, 6, 7, and 8	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
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**6. Declaration Certification**

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**Check applicable box and provide information below.**

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name  
John D. Conway

Address  
sanofi-aventis U.S. Inc.  
1041 Route 202-206

City/State  
Bridgewater, New Jersey

ZIP Code  
08807

Telephone Number  
(908) 231-5617

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JEVTANA®

ACTIVE INGREDIENT(S)

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**1. GENERAL**

a. United States Patent Number 7,241,907	b. Issue Date of Patent July 10, 2007	c. Expiration Date of Patent December 10, 2025
d. Name of Patent Owner Aventis Pharma S.A.	Address (of Patent Owner) 174 Avenue de France	
	City/State 75013 Paris	
	ZIP Code FRANCE	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)  Charlotte Barney, Esq.	Address (of agent or representative named in 1.e.) 1041 Route 202/206	
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	ZIP Code 08807	FAX Number (if available) (908) 231-2840
	Telephone Number (908) 231-4551	E-Mail Address (if available) charlotte.barney@sanofi-aventis.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? <input type="checkbox"/> Yes <input type="checkbox"/> No		

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
	<input type="checkbox"/> Yes	<input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)	

**5. No Relevant Patents**

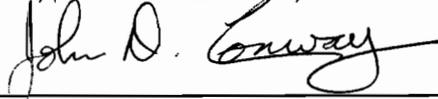
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	<input type="checkbox"/> Yes
---	------------------------------

**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)**



Date Signed

Feb 19, 2010

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

John D. Conway

Address

sanofi-aventis U.S. Inc.  
1041 Route 202-206

City/State

Bridgewater, New Jersey

ZIP Code

08807

Telephone Number

(908) 231-5617

FAX Number (if available)

(908) 231-2626

E-Mail Address (if available)

john.conway@sanofi-aventis.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
Office of Chief Information Officer (HFA-710)  
5600 Fishers Lane  
Rockville, MD 20857

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

## **REQUEST FOR EXCLUSIVITY**

Pursuant to NDA regulation 21 U.S.C. 355(c)(3)(D)(iv) and under the provisions of NDA regulation 21 CFR 314.108, the applicant hereby claims a period of exclusivity of five (5) years from the date of approval of this new drug application (NDA) for the use of cabazitaxel in combination with prednisone in the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel containing treatment regimen.

## EXCLUSIVITY SUMMARY

NDA # 201023

SUPPL # N/A

HFD # 150

Trade Name Jevtana

Generic Name cabazitaxel

Applicant Name sanofi-aventis

Approval Date, If Known June 17, 2010

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505 (b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, **EXPLAIN** why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO



Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====

Name of person completing form: Alice Kacuba for Christy Cottrell

Title: CPMS

Date: 6-21-2010

Name of Office/Division Director signing form: Robert L. Justice, M.D., M.S.

Title: Director, Division of Drug Oncology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	Jevtana

---

**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/

---

ALICE KACUBA  
06/21/2010

ROBERT L JUSTICE  
06/21/2010

## DEBARMENT CERTIFICATION

Sanofi-aventis 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.

  
\_\_\_\_\_

Linda Gustavson, PhD, RAC

Director, U.S. Assoc. Therapeutic Axis Head, Oncology

Regulatory Research and Development Portfolio

Corporate Regulatory Affairs

Sanofi-aventis US

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 201023 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Jevtana Established/Proper Name: cabazitaxel Dosage Form: Injection		Applicant: sanofi-aventis Agent for Applicant (if applicable):
RPM: Christy Cottrell		Division: DDOP
<p><b>NDA:</b> NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2) Efficacy Supplement:   <input type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)</p> <p>(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check box and explain:</p> <p><b><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes   <input type="checkbox"/> Updated   Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p>
<b>❖ Actions</b>		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>September 30, 2010</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None
<b>❖</b> If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics <sup>2</sup>	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority          Chemical classification (new NDAs only): 1</p> <p><input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <span style="margin-left: 200px;">BLAs: Subpart E</span>  <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <span style="margin-left: 100px;"><input type="checkbox"/> Accelerated approval (21 CFR 601.41)</span>  <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <span style="margin-left: 100px;"><input type="checkbox"/> Restricted distribution (21 CFR 601.42)</span></p> <p>Subpart I <span style="margin-left: 200px;">Subpart H</span>  <input type="checkbox"/> Approval based on animal studies <span style="margin-left: 100px;"><input type="checkbox"/> Approval based on animal studies</span></p> <p><input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>Comments:</p>	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>2</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes       No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes       No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If "No," continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes       No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes       No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

*If "No," continue with question (5).*

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
---	--

**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>3</sup>	Included
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) Approval dated June 17, 2010
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	Included; 6-17-10
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	Included; 3-31-10
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	N/A

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 6/18/10

❖ Medication Guide/Patient Package Insert/Instructions for Use ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling. If it is division-proposed labeling, it should be in ttrack-changes format.</li> </ul>	Included; 6-17-10
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	Included; 3-31-10
<ul style="list-style-type: none"> <li>Example of class labeling, if applicable</li> </ul>	N/A
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	Included; 6-17-10
❖ Proprietary Name <ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>Review(s) (<i>indicate date(s)</i>)</li> </ul>	Acceptable; 5/26/10 Review; 5/11/10
❖ Labeling reviews ( <i>indicate dates of reviews and meetings</i> )	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 5/28/10 <input checked="" type="checkbox"/> DRISK 6/4/10 <input checked="" type="checkbox"/> DDMAC 6/15/10 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )	6/9/10
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment ( <i>indicate date</i> )	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>Date reviewed by PeRC <u>4/21/10</u> If PeRC review not necessary, explain: _____</li> <li>Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent ( <i>include certification</i> )	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications ( <i>letters (except action letters), emails, faxes, telecons</i> )	Included
❖ Internal memoranda, telecons, etc.	Included

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.  
Version: 6/18/10

❖ Minutes of Meetings		
• Regulatory Briefing ( <i>indicate date of mtg</i> )		<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )		<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )		<input type="checkbox"/> No mtg 2/23/10
• EOP2 meeting ( <i>indicate date of mtg</i> )		<input type="checkbox"/> No mtg 6/28/06
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )		2/24/09
❖ Advisory Committee Meeting(s)		<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)		
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )		
<b>Decisional and Summary Memos</b>		
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )		<input type="checkbox"/> None 6/17/10
Division Director Summary Review ( <i>indicate date for each review</i> )		<input type="checkbox"/> None 6/17/10
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )		<input type="checkbox"/> None 6/17/10
PMR/PMC Development Templates ( <i>indicate total number</i> )		<input type="checkbox"/> None 10
<b>Clinical Information<sup>5</sup></b>		
❖ Clinical Reviews		
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )		See primary MO review
• Clinical review(s) ( <i>indicate date for each review</i> )		6/15/10
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )		<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )		See primary MO review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )		<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )		<input checked="" type="checkbox"/> Not applicable
❖ Risk Management		
• REMS Documents and Supporting Statement ( <i>indicate date(s) of submission(s)</i> )		<input checked="" type="checkbox"/> None
• REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> )		
• Risk management review(s) and recommendations (including those by OSE and CSS) ( <i>indicate date of each review and indicate location/date if incorporated into another review</i> )		
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )		<input type="checkbox"/> None requested    Included

<sup>5</sup> Filing reviews should be filed with the discipline reviews.  
Version: 6/18/10

<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None See stat TL memo
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 5/26/10
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 5/26/10
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None See primary CP review
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None See primary CP review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 6/2/10
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 6/14/10
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 6/3/10
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 6/3/10
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 6/8/10
• Branch Chief/Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None See primary CMC review
• Product quality review(s) including ONDQA biopharmaceutics reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 6/2/10
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 6/8/10
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) ( <i>indicate date of each review</i> )	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) ( <i>indicate date of each review</i> )	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	See primary CMC review
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) ( <i>date completed must be within 2 years of action date</i> ) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>6</sup></i> )	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER ( <i>date of most recent TB-EER must be within 30 days of action date</i> ) ( <i>original and supplemental BLAs</i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>6</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

## Appendix to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
- (3) **Or** 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) **And** 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.
- (3) **And** 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) **Or** 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.
- (3) **Or** 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 ODE's ADRA.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-201023

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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

06/18/2010

**From:** Cottrell, Christy L.  
**Sent:** Friday, June 11, 2010 11:17 AM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'; Leslie.Aragones@sanofi-aventis.com  
**Subject:** NDA 201023: Carton/container label comments

**Importance:** High  
Linda,

Please refer to your NDA 201023 for cabazitaxel. See below for comments from DMEPA on the carton/container labels.

#### **A. General Comments**

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)
3. 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

6. The entire statement "60 mg/1.5 mL Before First Dilution\*" should have the same prominence as the strength expression.

Feel free to call me with any questions.

Regards,

## Christy

---

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA  
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993

 301.796.4256 (phone) • 301.796.9845 (fax) |  [christy.cottrell@fda.hhs.gov](mailto:christy.cottrell@fda.hhs.gov)



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Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-201023

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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

06/14/2010

**From:** Cottrell, Christy L.  
**Sent:** Thursday, June 10, 2010 11:16 AM  
**To:** Linda.Gustavson@sanofi-aventis.com  
**Subject:** NDA 201023 for cabazitaxel: Patient Package Insert labeling edits

**Importance:** High

**Attachments:** 6-9-10 PPI edits.doc  
Linda,

Attached are the proposed edits to the Patient Package Insert. Please review and provide your counter-proposals by COB tomorrow, Friday, June 11th. As usual, we ask that you accept our revisions and track your counter-proposals.

Let me know if you have any questions.

Regards,  
Christy



6-9-10 PPI  
edits.doc (134 KB)

---

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA  
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993

 301.796.4256 (phone) • 301.796.9845 (fax) |  [christy.cottrell@fda.hhs.gov](mailto:christy.cottrell@fda.hhs.gov)



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in full immediately following this page as B4  
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NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

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CHRISTY L COTTRELL  
06/14/2010



NDA 201023

**NDA ACKNOWLEDGMENT**

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

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

Dear Ms. Gustavson:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Jevtana<sup>®</sup> (cabazitaxel) Injection, 60 mg/1.5 mL

Date of Application: March 31, 2010

Date of Receipt: March 31, 2010

Our Reference Number: NDA 201023

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 30, 2010, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call me at (301) 796-4256.

Sincerely,

*{See appended electronic signature page}*

Christy Cottrell  
Regulatory Project Manager  
Division of Drug Oncology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-201023

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CABAZITAXEL (XRP6258)

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CHRISTY L COTTRELL

06/09/2010

**From:** Cottrell, Christy L.  
**Sent:** Tuesday, June 08, 2010 4:09 PM  
**To:** Linda.Gustavson@sanofi-aventis.com; Leslie.Aragones@sanofi-aventis.com; 'Zareen.Ahmed@sanofi-aventis.com'  
**Subject:** Cabazitaxel CMC PMRs

**Importance:** High  
Linda and team,

We feel that the milestones dates provided for the CMC PMRs are too prolonged. Please provide shorter milestone dates or a justification for why the additional time is needed to complete the PMRs.

Thanks,  
Christy

---

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA  
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993  
 301.796.4256 (phone) • 301.796.9845 (fax) |  [christy.cottrell@fda.hhs.gov](mailto:christy.cottrell@fda.hhs.gov)



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/s/

CHRISTY L COTTRELL  
06/14/2010

**From:** Cottrell, Christy L.  
**Sent:** Tuesday, June 08, 2010 2:44 PM  
**To:** Linda.Gustavson@sanofi-aventis.com; Leslie.Aragones@sanofi-aventis.com  
**Subject:** PMR discussion  
Linda,

We briefly discussed during the telecon that sanofi would provide assumptions for both studies for the PMRs, including the sample sizes. In the interest of time, please provide this information to us as soon as possible.

Christy

---

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA  
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993  
 301.796.4256 (phone) • 301.796.9845 (fax) |  [christy.cottrell@fda.hhs.gov](mailto:christy.cottrell@fda.hhs.gov)



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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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/s/

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CHRISTY L COTTRELL  
06/14/2010



NDA 201023

**FILING COMMUNICATION**

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

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

Dear Ms. Gustavson:

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

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is September 30, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by June 2, 2010.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

**REQUIRED PEDIATRIC ASSESSMENTS**

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

We reference the waiver granted on April 21, 2010, for the pediatric study requirement for this application.

If you have any questions, call me at (301) 796-4256.

Sincerely,

*{See appended electronic signature page}*

Christy Cottrell  
Regulatory Project Manager  
Division of Drug Oncology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

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Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-201023

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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

**From:** Cottrell, Christy L.  
**Sent:** Monday, June 07, 2010 5:03 PM  
**To:** 'Zareen.Ahmed@sanofi-aventis.com'  
**Cc:** Linda.Gustavson@sanofi-aventis.com; Leslie.Aragones@sanofi-aventis.com;  
Kacuba, Alice  
**Subject:** RE: Cabazitaxel: Telecon needed on Monday

**Importance:** High  
Zareen, Linda and Leslie,

See below for the microbiology deficiency. If you agree to modify the storage time at room temperature to (b) (4), there would be no need for a telecon. Please respond at your earliest convenience.

- Microbiological studies in support of the proposed eight-hour post-constitution storage time at room temperature were not provided. The sponsor should provide a risk assessment report summarizing studies that show adventitious microbial contamination does not grow under these conditions. Reference is made to Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7. The report should describe test methods and results that employ a minimum countable inoculum to simulate potential microbial contamination that may occur during product dilution. It is generally accepted that growth is evident when the population increases more than 0.5 Log<sub>10</sub>. The test should be run at the label's recommended storage conditions and be conducted for two to three-times the holding period (the total time between initial vial penetration and the completion of patient infusion) and using the label-recommended fluids. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections.
- The sponsor should revise the proposed post-reconstitution hold period to (b) (4) at room temperature if it cannot provide supporting data for a longer hold period.

Again, sorry for the confusion regarding today's telecon.

Christy

---

**From:** Zareen.Ahmed@sanofi-aventis.com [mailto:Zareen.Ahmed@sanofi-aventis.com]  
**Sent:** Monday, June 07, 2010 3:58 PM  
**To:** Cottrell, Christy L.  
**Cc:** Linda.Gustavson@sanofi-aventis.com; Leslie.Aragones@sanofi-aventis.com  
**Subject:** RE: Cabazitaxel: Telecon needed on Monday

Dear Christy:

I am so very sorry to hear that you were in a car accident this morning. Hope you were not physically hurt, although I know it can be very unsettling and traumatic.

I have not yet received the formal microbiology information request. If you can please forward it to me, we could either respond by email or if needed, discuss during tomorrow's 10:00 am TC.

I hope you feel better.

Thanks,

Zareen

---

**From:** Cottrell, Christy L. [mailto:Christy.Cottrell@fda.hhs.gov]  
**Sent:** Monday, June 07, 2010 3:46 PM  
**To:** Ahmed, Zareen R&D/US  
**Cc:** Gustavson, Linda R&D/US; Aragones, Leslie R&D/US  
**Subject:** RE: Cabazitaxel: Telecon needed on Monday

Zareen, Linda, and Leslie-

My apologies about the telecon this morning. I was in a car accident on the way to work today. When I called Alice, I didn't remember that I had scheduled this telecon! (I think I was in shock or something). Did you receive the microbiology information request yet? If so, is another telecon needed?

Christy

---

**From:** Zareen.Ahmed@sanofi-aventis.com [mailto:Zareen.Ahmed@sanofi-aventis.com]  
**Sent:** Monday, June 07, 2010 10:09 AM  
**To:** Cottrell, Christy L.  
**Cc:** Linda.Gustavson@sanofi-aventis.com; Leslie.Aragones@sanofi-aventis.com  
**Subject:** RE: Cabazitaxel: Telecon needed on Monday

Dear Christy:

Thank you for arranging this morning's 11:30 am TC to discuss a potential microbiology deficiency for the pending cabazitaxel NDA 201023.

We look forward to a productive discussion.

To help facilitate the discussions, we would really appreciate if there are any additional details that you could share before the TC .

I am also including my work and cell phone numbers in case you need to reach me before the teleconference.

Regards,

Zareen

Work: 908-231-3480

(b) (6)

---

**From:** Ahmed, Zareen R&D/US  
**Sent:** Friday, June 04, 2010 7:06 PM  
**To:** 'Cottrell, Christy L.'  
**Cc:** Gustavson, Linda R&D/US; Aragonese, Leslie R&D/US  
**Subject:** RE: Cabazitaxel: Telecon needed on Monday

Dear Christy:

The following is the toll free number and access code for our TC on Monday June 7, 2010 at 11:30 am US EST to discuss a potential microbiology deficiency.

We look forward to talking to you and resolving the matter.

Toll free number: 1-877-771-7176

Access code for participants: 304324

Thanks,

Zareen

---

**From:** Ahmed, Zareen R&D/US  
**Sent:** Friday, June 04, 2010 4:47 PM  
**To:** 'Cottrell, Christy L.'  
**Cc:** Gustavson, Linda R&D/US; Aragonese, Leslie R&D/US  
**Subject:** RE: Cabazitaxel: Telecon needed on Monday

Dear Christy:

Yes, we will be available to have a telecon on Monday, June 7 at 11:30 am to discuss a potential microbiology deficiency.

However, as our microbiology team is based in Europe and have left for the day, it would be helpful if you could please email us the question in advance.

Thanks,

Zareen

---

**From:** Cottrell, Christy L. [mailto:Christy.Cottrell@fda.hhs.gov]  
**Sent:** Friday, June 04, 2010 4:14 PM  
**To:** Gustavson, Linda R&D/US; Aragonés, Leslie R&D/US; Ahmed, Zareen R&D/US  
**Subject:** Cabazitaxel: Telecon needed on Monday

Leslie and Zareen,

We have identified a potential microbiology deficiency and would like to have a telecon to discuss on Monday at 11:30am (ET). Can you confirm that your CMC/Micro staff can be available at that time to meet?

Christy

---

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA  
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993  
 301.796.4256 (phone) • 301.796.9845 (fax) |  christy.cottrell@fda.hhs.gov



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NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

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CHRISTY L COTTRELL  
06/14/2010

**From:** Cottrell, Christy L.  
**Sent:** Friday, June 04, 2010 11:40 AM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'; Leslie.Aragones@sanofi-aventis.com  
**Subject:** FW: NDA 201023 for Cabazitaxel: PMRs

**Importance:** High  
[Linda/Leslie,](#)

When can we expect to receive your proposed milestone dates for the PMRs listed below? We need them ASAP!

Thanks,  
Christy

---

**From:** Cottrell, Christy L.  
**Sent:** Wednesday, June 02, 2010 9:36 PM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'  
**Subject:** NDA 201023 for Cabazitaxel: PMRs  
**Importance:** High

Linda,

Following our telecon regarding the PMRs for Cabazitaxel, we now need you to submit milestone dates for the three PMRs below (b) (4)

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.

Final Protocol Submission: <<insert date>>  
Trial Completion Date: <<insert date>>  
Final Report Submission: <<insert date>>

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.

Final Protocol Submission: <<insert date>>  
Trial Completion Date: <<insert date>>  
Final Report Submission: <<insert date>>

Submit updates on renal toxicity from the next randomized trial every 6 months for 3 years from the initiation of the clinical trial.

Final Protocol Submission: <<insert date>>  
Trial Completion Date: <<insert date>>  
Final Report Submission: <<insert date>>

Please submit the dates ASAP.

Thanks,  
Christy

10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993  
☎ 301.796.4256 (phone) • 301.796.9845 (fax) | ✉ [christy.cottrell@fda.hhs.gov](mailto:christy.cottrell@fda.hhs.gov)



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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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/s/

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CHRISTY L COTTRELL  
06/14/2010

**From:** Cottrell, Christy L.  
**Sent:** Wednesday, June 02, 2010 3:09 PM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'; 'Zareen.Ahmed@sanofi-aventis.com'  
**Subject:** NDA 201023 for Cabazitaxel: PMRs

**Importance:** High

**Follow Up Flag:** Follow up  
**Due By:** Friday, June 04, 2010 5:00 PM  
**Flag Status:** Flagged  
Linda and Zareen,

Below are the two CMC-related PMRs for NDA 201023. We need you to provide the milestone dates **no later than COB on Friday, 6/4.**

Let me know if you have any questions.

Regards,  
Christy

### **PMR #8**

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.

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

Final protocol Submission Date: MM/YR  
Study Completion Date: MM/YR  
Final Report Submission Date: MM/YR

### **PMR #9**

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.).

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

Final protocol Submission Date: MM/YR  
Study Completion Date: MM/YR  
Final Report Submission Date: MM/YR

---

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA  
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993  
 301.796.4256 (phone) • 301.796.9845 (fax) |  [christy.cottrell@fda.hhs.gov](mailto:christy.cottrell@fda.hhs.gov)



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NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

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CHRISTY L COTTRELL  
06/02/2010

**From:** Cottrell, Christy L.  
**Sent:** Wednesday, June 02, 2010 11:38 AM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'  
**Subject:** NDA 201023 for Cabazitaxel: Telecon  
Linda,

We would like to reserve a time for a telecon, if needed, to work out any outstanding labeling or PMR issues for cabazitaxel. Our team is available next Tuesday, 6/8 at 10:00am ET. Can your team be available at that time?

Christy

---

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA  
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993  
 301.796.4256 (phone) • 301.796.9845 (fax) |  [christy.cottrell@fda.hhs.gov](mailto:christy.cottrell@fda.hhs.gov)



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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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CHRISTY L COTTRELL  
06/14/2010



NDA 201023

**INFORMATION REQUEST**

Sanofi-aventis U.S. Inc.

Agent for Sanofi-aventis U.S. LLC

Attention: Linda Gustavson, PhD, RAC

Director, U.S. Assoc. Therapeutic Axis Head, Oncology Regulatory Research and  
Development Portfolio Corporate Regulatory Affairs

200 Crossing Boulevard

Mailstop: BX2-712B

Bridgewater, NJ 08807

Dear Dr. Gustavson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cabazitaxel, 60 mg/1.5 mL, concentrate for solution for infusion.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. Please provide your written response no later than May 30, 2010, in order to continue our evaluation of your NDA.

1. Determine the content of Form B that may be present in the drug substance batches with an (b) (4) of (b) (4)
2. Specify the manufacturing conditions (b) (4) (b) (4) for the mixing and dissolution of drug substance in the drug product manufacturing process. Also, provide data that establishes that the proposed manufacturing process parameters will result in complete dissolution of drug substance with the maximum allowable amount of form B permitted with an (b) (4) content of (b) (4)
3. DMF (b) (4) has been found to be INADEQUATE to support your NDA. Letters dated May 4, 2010, and May 26, 2010, were sent to the DMF holder.

If you have any questions, call Deborah Mesmer, Regulatory Health Project Manager, at 301-796-4023.

Sincerely,

*{See appended electronic signature page}*

Sarah Pope Miksinski, Ph.D.  
Chief, Branch II  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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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WILLIAM M ADAMS

05/26/2010

William Adams, acting for Sarah Pope Miksinski



NDA 201023

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Linda Gustavson, Ph.D, RAC  
Director, U.S. Assoc. Therapeutic Axis Head, Oncology

Dear Dr. Gustavson:

Please refer to your New Drug Application (NDA) submission dated March 30, 2010, received March 31, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cabazitaxel for Injection, 60 mg/1.5 mL.

We also refer to your April 1, 2010, correspondence, received April 1, 2010, requesting review of your proposed proprietary name, Jevtana. We have completed our review of the proposed proprietary name, Jevtana and have concluded that it is acceptable.

The proposed proprietary name, Jevtana, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your April 1, 2010 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sarah Simon, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5205. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Christy Cottrell at (301) 796-4256.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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CABAZITAXEL (XRP6258)

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/s/  
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CAROL A HOLQUIST  
05/26/2010

**From:** Cottrell, Christy L.  
**Sent:** Tuesday, May 25, 2010 12:28 PM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'  
**Subject:** Telecon needed re: PMRs  
Linda,

We would like to schedule a telecon for June 1st at 12:30pm (eastern time) to discuss the PMRs for cabazitaxel. Can you confirm your team's availability? We have some CMC PMRs that we will be sending today, so please make sure your CMC team will be available as well.

Thanks,  
Christy

---

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA  
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993  
 301.796.4256 (phone) • 301.796.9845 (fax) |  [christy.cottrell@fda.hhs.gov](mailto:christy.cottrell@fda.hhs.gov)



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/s/  
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CHRISTY L COTTRELL

06/14/2010

**From:** Cottrell, Christy L.  
**Sent:** Friday, May 21, 2010 1:59 PM  
**To:** Linda.Gustavson@sanofi-aventis.com  
**Cc:** 'Leslie.Aragones@sanofi-aventis.com'  
**Subject:** NDA 201023 for Cabazitaxel: CMC comment  
Linda,

Please refer to the pending NDA 201023 for cabazitaxel. See below for a comment from the CMC team.

- Revise the drug product criterion for (b) (4) such that it is either below the level qualified in the toxicology studies (b) (4) or the qualification threshold of (b) (4) TDI per ICH Q3B guideline. Based on a maximum clinical dose of 25 mg/m<sup>2</sup> and the higher end of body surface area (2.5 m<sup>2</sup>), we calculate the appropriate limit to be (b) (4) (b) (4)

Feel free to contact me with any questions.

Regards,  
Christy

---

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA  
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993

 301.796.4256 (phone) • 301.796.9845 (fax) |  [christy.cottrell@fda.hhs.gov](mailto:christy.cottrell@fda.hhs.gov)



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CABAZITAXEL (XRP6258)

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/s/  
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CHRISTY L COTTRELL  
05/21/2010

**From:** Cottrell, Christy L.  
**Sent:** Wednesday, May 19, 2010 4:09 PM  
**To:** Linda.Gustavson@sanofi-aventis.com  
**Cc:** 'Leslie.Aragones@sanofi-aventis.com'  
**Subject:** NDA 201023 for cabazitaxel: Labeling

**Importance:** High

**Follow Up Flag:** Follow up  
**Due By:** Tuesday, May 25, 2010 5:00 PM  
**Flag Status:** Flagged

**Attachments:** 5-19-10 FDA revised labeling sections to sponsor.doc  
Linda,

Please refer to your pending NDA 201023 for cabazitaxel. Attached is the division's first round of labeling edits for certain sections of the labeling, specifically:

- **Boxed Warning**
- **Indications**
- **Drug Interactions**
- **Use in Specific Populations**
- **Clinical Pharmacology**
- **Nonclinical Toxicology**
- **Clinical Studies**
- **References**

Please accept all of our revisions in this document and then track your counter-proposals. This will make our review much easier! **We would like to receive your counter-proposals by COB next Tuesday, May 25th.**

Feel free to call me with any questions.

Regards,  
Christy



5-19-10 FDA  
revised labeling s...

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Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA  
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993  
☎ 301.796.4256 (phone) • 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov



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10 pages of draft labeling has been withheld in full immediately following this page as B4 CCI/  
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CABAZITAXEL (XRP6258)

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CHRISTY L COTTRELL  
05/19/2010

**From:** Cottrell, Christy L.  
**Sent:** Wednesday, May 19, 2010 1:40 PM  
**To:** Linda.Gustavson@sanofi-aventis.com; 'Leslie.Aragones@sanofi-aventis.com'  
**Subject:** NDA 201023 for Cabazitaxel: PMRs  
Linda,

Please refer to the pending NDA 201023 for cabazitaxel. See below for a list of PMRs for this NDA. We need you to fill in the dates and any other blanks (such as trial names). **Reply requested by Friday, May 21st.**

**PMR #1**

Conduct a Phase 3 randomized controlled trial in patients with hormone refractory metastatic prostate cancer comparing docetaxel/prednisone with cabazitaxel 25 mg/m<sup>2</sup>/prednisone and cabazitaxel 20 mg/m<sup>2</sup>/prednisone as first line therapy. The primary endpoint should be overall survival. The trial should be powered to detect a realistic difference in overall survival. Submit the protocol for agency review prior to commencing the trial.

Final protocol submission Date: MM/YR  
Clinical Trial Completion Date: MM/YR  
Final Report and Dataset Submission Date: MM/YR

**PMR #2**

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

Final Report Submission Date: MM/YR

**PMR #3**

Submit updates on renal toxicity from all active randomized trials <insert trial names> every 6 months for 3 years after the cabazitaxel approval date.

Date of cabazitaxel approval: MM/YR  
Dates of interim Reports every 6 month updates: 1. MM/YR  
2. MM/YR  
3. MM/YR  
4. MM/YR  
5. MM/YR  
Date of Final Report Submission Date: 6. MM/YR

**PMR #4**

Complete and submit the final report of trial TES10884, along with a thorough review of cardiac safety data, for the potential of cabazitaxel on QTc interval prolongation in patients.

Final protocol submission Date: MM/YR

Trial Completion Date: MM/YR

Final Report Submission Date: MM/YR

**PMR #5**

Conduct the trial POP6972 to determine the pharmacokinetics and safety of cabazitaxel in patients with hepatic impairment.

Final protocol submission Date: MM/YR  
Trial Completion Date: MM/YR  
Final Report Submission Date: MM/YR

**PMR #6**

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.

Final protocol submission Date: MM/YR  
Trial Completion Date: MM/YR  
Final Report Submission Date: MM/YR

**PMR #7**

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.

Final protocol submission Date: MM/YR  
Trial Completion Date: MM/YR  
Final Report Submission Date: MM/YR

Feel free to contact me with any questions.

Regards,  
Christy

---

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA  
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993

☎ 301.796.4256 (phone) • 301.796.9845 (fax) | ✉ [christy.cottrell@fda.hhs.gov](mailto:christy.cottrell@fda.hhs.gov)



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NDA-201023

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ORIG-1

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SANOFI AVENTIS  
SPA

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CABAZITAXEL (XRP6258)

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CHRISTY L COTTRELL  
05/19/2010

**From:** Cottrell, Christy L.  
**Sent:** Tuesday, May 18, 2010 3:16 PM  
**To:** Linda.Gustavson@sanofi-aventis.com; 'Leslie.Aragones@sanofi-aventis.com'  
**Subject:** NDA 201023 for Cabazitaxel: Microbiology request for information

**Importance:** High

**Follow Up Flag:** Follow up  
**Due By:** Tuesday, May 25, 2010 12:00 AM  
**Flag Status:** Flagged  
Linda or Leslie,

Please refer to the pending NDA 201023 for cabazitaxel. See below for an information request from the microbiology reviewer.

**Please provide your response by May 25, 2010.**

Sanofi-aventis is requested to respond to the following. If the information is already in the submission, please indicate the submission location.

- (1) For the (b) (4) of the 15 mL glass vials, please provide:
  - (i) The (b) (4) manufacturer and model name or number.
  - (ii) The temperature and (b) (4) speed used for validation studies.
  - (iii) Validation acceptance criteria.
  - (iv) The temperature and (b) (4) speed used for production.
- (2) For environmental monitoring of the (b) (4), please provide the microbial alert and action limits.
- (3) For the endotoxin kinetic-chromogenic testing method described in section 3.2.P.5.3 (Validation of Analytical Procedures), please provide:
  - (i) The maximum valid dilution and routine testing dilution for cabazitaxel concentrate.
  - (ii) The maximum valid dilution and routine testing dilution for cabazitaxel solvent for dilution.
- (4) Please provide a brief description of (b) (4) (b) (4) Include the size, capacity, manufacturer(s), and model name(s) and/or numbers.

(b) (4)

(b) (4)

- (6) For (b) (4) of cabazitaxel concentrate and cabazitaxel solvent for dilution, please provide:

- (7) For the microbial filter retention validation studies presented for cabazitaxel concentrate in section 3.2.P.3.5.2.1.2, please provide:
- (i) The growth medium used to prepare the *B. diminuta* challenge inoculum.
  - (ii) The volume of bacterial suspension used for challenge and the volume tested for growth after filtration.
  - (iii) The time and temperature used for filtrate incubation.
  - (iv) A description of the positive and negative controls, and data for these controls.

Feel free to contact me with any questions.

Regards,  
Christy

---

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA  
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993

 301.796.4256 (phone) • 301.796.9845 (fax) |  [christy.cottrell@fda.hhs.gov](mailto:christy.cottrell@fda.hhs.gov)



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CHRISTY L COTTRELL  
05/18/2010

**From:** Cottrell, Christy L.  
**Sent:** Monday, May 17, 2010 2:11 PM  
**To:** Linda.Gustavson@sanofi-aventis.com; 'Leslie.Aragones@sanofi-aventis.com'  
**Subject:** NDA 201023 for Cabazitaxel: CMC information request

**Importance:** High  
Linda and Leslie,

Please refer to the pending NDA 201023 for Cabazitaxel. See below for a comment from the CMC team:

- For the preparation of the premix solution, the proposed package insert states that the entire contents of the diluent vial (b) (4) is to be transferred to the cabazitaxel vial (b) (4) to obtain at least 6 mL of a premix solution containing approximately 10 mg/mL cabazitaxel. The cabazitaxel vial is manufactured with a (b) (4) overfill and the diluent vial is manufactured with a (b) (4) overfill. Data provided in tables 6, 7 and 8 (NDA section 3.2.P.2.3 Manufacturing Process Development) describes the variations in concentrations of the premix solutions (b) (4) obtained by three operators. We feel that the presence of the excess diluent and cabazitaxel could result in inaccurate dosing. Revise the drug product by decreasing the fill weight of the cabazitaxel vial to a target fill weight of 60 mg of drug, and revise the fill volume/weight of the diluent to just permit the withdrawal of sufficient excess diluent to enable measurement of an exact volume (b) (4) in the syringe which will be transferred into the cabazitaxel vial thus generating a premix solution with a final concentration of 10.0 mg/mL cabazitaxel.

The drug product manufacturing procedure and in-process controls, and section 2.5 of the package insert should be revised appropriately to reflect this change in the cabazitaxel vial and the diluent vial. However, there is no need for sanofi-aventis to submit revised wording for the package insert at this time. If you agree with the recommendation above, the Division will work closely with DMEPA to modify the original proposed package insert to reflect this new manufacturing procedure.

**Please provide a response by COB on Monday, May 24th.** Feel free to contact me with any questions.

Regards,  
Christy

---

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA  
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993  
☎ 301.796.4256 (phone) • 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov



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CHRISTY L COTTRELL  
05/17/2010

**From:** Cottrell, Christy L.  
**Sent:** Tuesday, May 11, 2010 11:13 AM  
**To:** Linda.Gustavson@sanofi-aventis.com  
**Subject:** NDA 201023 for cabazitaxel: Microbiology information request  
Linda,

See below for an inquiry from the microbiology reviewer for cabazitaxel. Additional inquiries may be forthcoming. As with the other disciplines, you may batch your responses when officially submitting to the NDA.

- (1) For the bacterial ingress studies used to validate container-closure integrity, please provide:
  - (i) The number of vials tested.
  - (ii) The number of positive controls utilized.
  - (iii) The number of negative controls utilized.
  - (iv) The type of bacterial growth medium utilized and data demonstrating that the medium could support growth of the challenge microorganism (*Brevundimonas diminuta*).
- (2) Please provide the procedure and validation data for depyrogenation of the grey rubber stoppers used for product closure. If the stoppers are provided ready to sterilize (i.e., already depyrogenated) from the vendor please specify.

Feel free to contact me with any questions.

Regards,  
Christy

---

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA  
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993  
 301.796.4256 (phone) • 301.796.9845 (fax) |  [christy.cottrell@fda.hhs.gov](mailto:christy.cottrell@fda.hhs.gov)



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CHRISTY L COTTRELL

05/11/2010

**From:** Waxman, Ian  
**Sent:** Friday, May 07, 2010 11:18 AM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'  
**Cc:** Cottrell, Christy L.  
**Subject:** Information request  
Hi Linda,

Did patient 710-005-005 have an autopsy performed? If so, can you send the report?

Thanks,  
Ian

Ian Waxman, MD  
Medical Officer  
FDA/CDER/OND/OODP/DDOP  
WO Bldg 22, Rm 2115  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Email: [ian.waxman@fda.hhs.gov](mailto:ian.waxman@fda.hhs.gov)  
Phone: 301-796-5123  
Fax: 301-796-9845

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CHRISTY L COTTRELL

06/14/2010

**From:** Waxman, Ian  
**Sent:** Friday, May 07, 2010 5:28 PM  
**To:** 'Leslie.Aragones@sanofi-aventis.com'  
**Cc:** 'Linda.Gustavson@sanofi-aventis.com'; Cottrell, Christy L.  
**Subject:** Neutropenia Analysis request  
Hi Leslie and Linda,

Can you send an analysis of rates of grade 1-4 and 3-4 neutropenia in patients who received 20mg/m<sup>2</sup> q 3 weekly dosing in the supportive studies? I believe this would include TED6188 (7 patients), TED6190 (20 patients), and ARD6191 (50 patients).

Thank you,  
Ian

---

**From:** Leslie.Aragones@sanofi-aventis.com [mailto:Leslie.Aragones@sanofi-aventis.com]  
**Sent:** Friday, May 07, 2010 2:17 PM  
**To:** Waxman, Ian  
**Cc:** Cottrell, Christy L.; Linda.Gustavson@sanofi-aventis.com  
**Subject:** RE: Analysis request

Dear Ian,  
I am covering for Linda Gustavson, who is out of the office today.

In response to your question, attached is the revised table according to the new categories. The previous conclusion on the effectiveness of G-CSF remains valid.

Best regards,  
Leslie

**Leslie Aragones**  
Global Regulatory Affairs, Oncology  
P: (908) 231-4142  
F: (908) 304-6549  
leslie.aragones@sanofi-aventis.com

---

**From:** Waxman, Ian [mailto:Ian.Waxman@fda.hhs.gov]  
**Sent:** Wednesday, May 05, 2010 1:15 PM  
**To:** Gustavson, Linda R&D/US  
**Cc:** Cottrell, Christy L.  
**Subject:** RE: Analysis request

Hi Linda,

Thank you for providing this data.

Regarding Table 1, could this table be organized by neutrophil count cut-offs (perhaps <250, <500, <750, and <1000 instead? It is difficult to interpret clinically in its current form.

Ian

---

**From:** Linda.Gustavson@sanofi-aventis.com [mailto:Linda.Gustavson@sanofi-aventis.com]  
**Sent:** Tuesday, May 04, 2010 5:07 PM  
**To:** Waxman, Ian  
**Cc:** Cottrell, Christy L.  
**Subject:** RE: Analysis request

Dear Ian,

The team conducted the enclosed analyses to assess the impact of G-CSF treatment and dose reductions on neutrophil count in the cabazitaxel arm of the EFC6193 TROPIC protocol. While there are limitations to the analyses, the results seem to support the conclusion that both G-CSF and dose reductions in certain patients have successfully been used to treat neutropenia following cabazitaxel treatment. Treatment with G-CSF increased the neutrophil nadir values when comparing nadir values before and after G-CSF. Use of G-CSF, dose reduction, or both reduced the decline of neutrophil counts and supported the rapid recovery of neutrophil counts from day 8 to day 15 within a cycle.

Regards,  
Linda

Linda Gustavson, Ph.D., RAC  
Director, R & D Regulatory Affairs  
U.S. Head, Oncology  
Global Regulatory Affairs  
sanofi-aventis US Inc.  
Mail code: BX2-712B  
200 Crossing Blvd, Bridgewater, NJ 08890-0890  
908-304-6221 (work phone)  
203-314-2245 (cell phone)  
fax: 908-304-6549  
email: [linda.gustavson@sanofi-aventis.com](mailto:linda.gustavson@sanofi-aventis.com)

---

**From:** Waxman, Ian [mailto:Ian.Waxman@fda.hhs.gov]  
**Sent:** Thursday, April 15, 2010 10:12 AM  
**To:** Gustavson, Linda R&D/US  
**Cc:** Cottrell, Christy L.  
**Subject:** Analysis request

Hi Linda,

I want to analyze differences in degree of neutropenia in patients who received prophylactic G-CSF by comparing counts obtained in cycles before prophylaxis was begun vs. after prophylaxis was begun.

I think one possible way to do this would be to analyze neutrophil nadirs (mean, median, range) in the cycles before prophylactic G-CSF vs. the cycles after prophylactic G-CSF. Can you ask the cabazitaxel team if they think this would be a good way to analyze the effect of G-CSF on actual neutrophil counts, or if they have ideas for alternative analyses that might be useful? I'd be happy to discuss any ideas right after tomorrow's meeting.

Thanks,  
Ian

Ian Waxman, MD  
Medical Officer  
FDA/CDER/OND/OODP/DDOP  
WO Bldg 22, Rm 2115  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Email: [ian.waxman@fda.hhs.gov](mailto:ian.waxman@fda.hhs.gov)  
Phone: 301-796-5123  
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CABAZITAXEL (XRP6258)

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CHRISTY L COTTRELL

06/14/2010

**From:** Cottrell, Christy L.  
**Sent:** Friday, May 07, 2010 10:46 AM  
**To:** Linda.Gustavson@sanofi-aventis.com; 'Leslie.Aragones@sanofi-aventis.com'  
**Subject:** NDA 201023 for cabazitaxel: Statistical Information Request  
Linda/Leslie,

See below for an information request from the reviewing statistician for NDA 201023 (cabazitaxel):

- For the overall survival analysis in ITT population, there were 242 patients censored for this analysis. Is information on reason of censoring available?
- Where in the submitted data can one locate the 10 patients who were lost to follow-up, as mentioned in your sensitivity analysis for overall survival?

Feel free to contact me with any questions.

Regards,  
Christy

---

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA  
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993

 301.796.4256 (phone) • 301.796.9845 (fax) |  [christy.cottrell@fda.hhs.gov](mailto:christy.cottrell@fda.hhs.gov)



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CHRISTY L COTTRELL  
05/07/2010



NDA 201023

**INFORMATION REQUEST**

Sanofi-aventis U.S. Inc.

Agent for Sanofi-aventis U.S. LLC

Attention: Linda Gustavson, PhD, RAC

Director, U.S. Assoc. Therapeutic Axis Head, Oncology Regulatory Research and  
Development Portfolio Corporate Regulatory Affairs

200 Crossing Boulevard

Mailstop: BX2-712B

Bridgewater, NJ 08807

Dear Dr. Gustavson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cabazitaxel, 60mg/1.5mL, concentrate for solution for infusion.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. Please provide your written response no later than May 21, 2010, in order to continue our evaluation of your NDA.

*For Drug Substance:*

1. Either use the USP<631> Color and Achromicity method for release and stability testing or demonstrate that the USP<631> and Ph. Eur.2.2.2 methods are equivalent.
2. Either use the USP<781> Optical Rotation method for release and stability testing or demonstrate that the USP<781> and Ph. Eur.2.2.7 methods are equivalent.
3. Either use the USP<231> Heavy Metals method for release testing or demonstrate that the USP<231> and Ph. Eur.2.4.8 methods are equivalent.
4. Either use the USP<921> Water Content method for release and stability testing or demonstrate that the USP<921> and Ph. Eur. 2.5.12 or Ph. Eur. 2.5.32 methods are equivalent.
5. Revise the proposed acceptance criterion for (b) (4) (b) (4) to reflect the level observed in the batch release data (b) (4) (u) (4) (b) (4) cabazitaxel drug substance. The therapeutic value of acetone content is (u) (4) based on a (b) (4) molar ratio of cabazitaxel (b) (4) Batch release data for three primary stability batches and three production batches show (b) (4) ranging from (b) (4)

Twelve month primary stability data does not demonstrate any significant change (b) (4) in (b) (4) content when stored at long term storage condition (5 C).

6. Amend the proposed protocol for post-approval stability studies to conduct testing every three months for the first year, every six month for the second year and every 12 month the subsequent years, i.e., 0, 3, 6, 9, 12, 18, 24 and 36 months.

*For Drug Product:*

7. Provide a justification for the proposed (b) (4) overfill (b) (4). The USP<1151>, Pharmaceutical Dosage Forms, recommendation for viscous liquids is (b) (4) excess volume for 1mL labeled size and (b) (4) excess volume for 2mL labeled size.
8. Provide the results from a study using the proposed concentrated solution and diluent which demonstrates that extractables/leachables in the proposed drug product are at acceptable and safe levels. Alternatively, provide justification that structural differences between cabazitaxel and docetaxel would not affect extractables or leachables from the same container closure system used for both products, and also provide reference to NDA 20,449 (Taxotere®).
9. Either use the USP<791> pH method for release and stability testing or demonstrate that the USP<791> and Ph. Eur.2.2.3 methods are equivalent.
10. Either revise the in-process control limit for residual ethanol to not more than (b) (4) or provide data to justify the currently proposed limit of not more than (b) (4). Data generated on cabazitaxel drug product, including one clinical batch, the three primary stability batches, and one production batch, shows levels below (b) (4). In addition, the proposed in-process control limit exceeds the ICH Q3C recommended maximum limit of not more than (b) (4) using Option 1.
11. Provide a copy of the supplier's certificate of analysis for each packaging component, i.e., the glass vial, elastomeric closure and overseal.
12. Amend the proposed protocol for post-approval stability studies to conduct testing every three months for the first year, every six month for the second year and every 12 month the subsequent years, i.e., 0, 3, 6, 9, 12, 18, 24 and 36 months.
13. Regarding the batch analysis data in the nonclinical study reports (module 4 NDA section 4.2.3.2 under Repeat-Dose Toxicity), the co-eluted impurities in the certificate of analysis (COA) differ from those specified in the drug product specification. In the provided COA, impurities (b) (4) are co-eluted while in the drug product specification and other batch analysis data impurities (b) (4) are co-eluted. Clarify this discrepancy.

14. Revise the drug product specification to include a single criterion for each test. The shelf life acceptance criteria of the drug product specification are considered to be the regulatory specification.

*For the Solvent for Dilution:*

15. Amend the proposed protocol for post-approval stability protocols for the full scale validation batches and for the annual batches to conduct testing every three month for the first year and every six month for the second year and yearly thereafter , i.e., 0, 3, 6, 9, 12, 18, 24 and 36 months.

If you have any questions, call Deborah Mesmer, Regulatory Health Project Manager, at 301-796-4023.

Sincerely,

*{See appended electronic signature page}*

Sarah Pope Miksinski, Ph.D.  
Branch Chief  
Division of Pre-Marketing Assessment III  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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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WILLIAM M ADAMS

05/06/2010

William Adams, acting for Sarah Pope Miksinski

**From:** Cottrell, Christy L.  
**Sent:** Thursday, May 06, 2010 11:25 AM  
**To:** 'Leslie.Aragones@sanofi-aventis.com'  
**Cc:** Linda.Gustavson@sanofi-aventis.com  
**Subject:** RE: NDA 201023 for Cabazitaxel: Statistical information request  
[Linda/Leslie](#),

As a follow-up, please provide reason(s) for the discrepancies between CRF and IVRS data on stratification factors.

Thanks,  
Christy

---

**From:** Leslie.Aragones@sanofi-aventis.com [mailto:Leslie.Aragones@sanofi-aventis.com]  
**Sent:** Friday, April 30, 2010 3:20 PM  
**To:** Cottrell, Christy L.  
**Cc:** Linda.Gustavson@sanofi-aventis.com  
**Subject:** RE: NDA 201023 for Cabazitaxel: Statistical information request

Dear Christy,

Please see sanofi-aventis's response below.

FDA statistical reviewer's question:

According to the submitted EFC6193 study data sets, there appear to be a few randomized patients without ECOG performance status data at baseline. Since baseline ECOG performance status is a stratification factor at randomization for the study, this information should not be missing. Please clarify.

Response:

ECOG performance status and measurable disease were stratification variables and the status of each patient was provided from the site to the IVRS at the time of randomization for all patients. An actual SAS dataset (ivrs.xpt) with this information is attached. The variables in this dataset are described in the following table.

Variable	Label	Type	Codes	Format
USUBJID	Unique Subject Identifier	Text		
SUBJID	Subject Identifier for the Study	Text		
ARM	Description of Planned Arm	Text		
ARMN	Planned Arm Number	Integer		
ITT	Intent-to-treat Population	Text	Y	

TTSTR1	Stratification in IVRS (Num)	Integer		
STRC	Stratification in IVRS (Char)	Text		

The site entered the information on the stratification factors particularly ECOG performance status information in the CRF at visit 0 (Page10 of the CRF). In this dataset indeed 6 patients did not have ECOG status recorded at visit 0. In the analysis we used the entries from visit 1 Day 1 instead, for these patients. This imputation seems appropriate as for those 6 patients the dates of visit 1 were very close to the randomization dates (5 of them within 3 days difference and one within 6 days) and one would not expect any change in performance status in a very short period of time..

The comparison of the stratification factors as recorded by the IVRS versus the CRF data showed that for 111 patients (50 patients in the cabazitaxel group and 61 patients in the mitoxantrone group) the classification on the stratification factors in both sources differed. (see attached document ecogdiff\_i.rtf). Most of the differences were in the assessment of measurable disease. ECOG performance status was different between IVRS and CRF in 6 patients in the cabazitaxel arm and 4 patients in the mitoxantrone arm.

The primary analysis for Overall Survival as submitted, used as stratification variables the information recorded in the CRF. The sensitivity analysis using the stratification variables from the IVRS provided similar results compared to the primary analysis as presented in the attached document dp41diff\_i.rtf (p<0.0001, HR=0.67 (0.57 - 0.80)).

Best regards,

Leslie

**Leslie Aragonés**

**Global Regulatory Affairs, Oncology**

P: (908) 231-4142

F: (908) 304-6549

leslie.aragones@sanofi-aventis.com

---

**From:** Cottrell, Christy L. [mailto:Christy.Cottrell@fda.hhs.gov]  
**Sent:** Friday, April 30, 2010 2:29 PM  
**To:** Gustavson, Linda R&D/US; Aragonés, Leslie R&D/US  
**Subject:** FW: NDA 201023 for Cabazitaxel: Statistical information request  
**Importance:** High

Linda/Leslie,

Can you let me know when you will be responding to this inquiry? (I hope you haven't already responded and I missed it!)

Christy

---

**From:** Cottrell, Christy L.  
**Sent:** Monday, April 26, 2010 10:21 AM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'  
**Subject:** NDA 201023 for Cabazitaxel: Statistical information request  
**Importance:** High

Linda,

Please refer to the pending NDA 201023 for cabazitaxel. See below for an inquiry from the statistical reviewer.

- According to the submitted EFC6193 study data sets, there appear to be a few randomized patients without ECOG performance status data at baseline. Since baseline ECOG performance status is a stratification factor at randomization for the study, this information should not be missing. Please clarify.

Feel free to contact me with any questions.

Regards,  
Christy

---

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA  
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993

 301.796.4256 (phone) • 301.796.9845 (fax) |  [christy.cottrell@fda.hhs.gov](mailto:christy.cottrell@fda.hhs.gov)



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SPA

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CHRISTY L COTTRELL

06/14/2010

**From:** Waxman, Ian  
**Sent:** Wednesday, May 05, 2010 1:15 PM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'  
**Cc:** Cottrell, Christy L.  
**Subject:** RE: Analysis request  
[Hi Linda,](#)

[Thank you for providing this data.](#)

[Regarding Table 1, could this table be organized by neutrophil count cut-offs \(perhaps <250, <500, <750, and <1000 instead? It is difficult to interpret clinically in its current form.](#)

[Ian](#)

---

**From:** Linda.Gustavson@sanofi-aventis.com [mailto:Linda.Gustavson@sanofi-aventis.com]  
**Sent:** Tuesday, May 04, 2010 5:07 PM  
**To:** Waxman, Ian  
**Cc:** Cottrell, Christy L.  
**Subject:** RE: Analysis request

[Dear Ian,](#)

[The team conducted the enclosed analyses to assess the impact of G-CSF treatment and dose reductions on neutrophil count in the cabazitaxel arm of the EFC6193 TROPIC protocol. While there are limitations to the analyses, the results seem to support the conclusion that both G-CSF and dose reductions in certain patients have successfully been used to treat neutropenia following cabazitaxel treatment. Treatment with G-CSF increased the neutrophil nadir values when comparing nadir values before and after G-CSF. Use of G-CSF, dose reduction, or both reduced the decline of neutrophil counts and supported the rapid recovery of neutrophil counts from day 8 to day 15 within a cycle.](#)

[Regards,  
Linda](#)

[Linda Gustavson, Ph.D., RAC  
Director, R & D Regulatory Affairs  
U.S. Head, Oncology  
Global Regulatory Affairs  
sanofi-aventis US Inc.  
Mail code: BX2-712B  
200 Crossing Blvd, Bridgewater, NJ 08890-0890  
908-304-6221 \(work phone\)  
203-314-2245 \(cell phone\)  
fax: 908-304-6549  
email: \[linda.gustavson@sanofi-aventis.com\]\(mailto:linda.gustavson@sanofi-aventis.com\)](#)

---

**From:** Waxman, Ian [mailto:lan.Waxman@fda.hhs.gov]  
**Sent:** Thursday, April 15, 2010 10:12 AM  
**To:** Gustavson, Linda R&D/US  
**Cc:** Cottrell, Christy L.  
**Subject:** Analysis request

[Hi Linda,](#)

I want to analyze differences in degree of neutropenia in patients who received prophylactic G-CSF by comparing counts obtained in cycles before prophylaxis was begun vs. after prophylaxis was begun.

I think one possible way to do this would be to analyze neutrophil nadirs (mean, median, range) in the cycles before prophylactic G-CSF vs. the cycles after prophylactic G-CSF. Can you ask the cabazitaxel team if they think this would be a good way to analyze the effect of G-CSF on actual neutrophil counts, or if they have ideas for alternative analyses that might be useful? I'd be happy to discuss any ideas right after tomorrow's meeting.

Thanks,  
Ian

Ian Waxman, MD  
Medical Officer  
FDA/CDER/OND/OODP/DDOP  
WO Bldg 22, Rm 2115  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Email: [ian.waxman@fda.hhs.gov](mailto:ian.waxman@fda.hhs.gov)  
Phone: 301-796-5123  
Fax: 301-796-9845

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CHRISTY L COTTRELL

06/14/2010

**From:** Cottrell, Christy L.  
**Sent:** Friday, April 30, 2010 2:24 PM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'  
**Subject:** NDA 201023 Cabazitaxel: Information Request

**Importance:** High  
Linda,

See below for an information request from the statistical reviewer:

The statistical reviewer is not able to verify this variable DPLASTDT: the last date of alive or dead. Please specify the source data sets and provide the program used for this variable derivation.

Feel free to call me with any questions.

Christy

---

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA  
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993

 301.796.4256 (phone) • 301.796.9845 (fax) |  [christy.cottrell@fda.hhs.gov](mailto:christy.cottrell@fda.hhs.gov)



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CHRISTY L COTTRELL

06/14/2010

**From:** Waxman, Ian  
**Sent:** Wednesday, April 28, 2010 3:39 PM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'  
**Cc:** Cottrell, Christy L.  
**Subject:** Question regarding dose delays and interruptions  
Hi Linda,

Can you clarify the difference between a dose delay and a dose interruption? The ADAE dataset includes both terms.

Thanks again,  
Ian

Ian Waxman, MD  
Medical Officer  
FDA/CDER/OND/OODP/DDOP  
WO Bldg 22, Rm 2115  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Email: [ian.waxman@fda.hhs.gov](mailto:ian.waxman@fda.hhs.gov)  
Phone: 301-796-5123  
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CHRISTY L COTTRELL  
05/07/2010

**From:** Waxman, Ian  
**Sent:** Wednesday, April 28, 2010 12:53 PM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'  
**Cc:** Cottrell, Christy L.  
**Subject:** Information Request - Discontinuations  
Hi Linda,

Can you clarify the reasons for 2 treatment discontinuations on the cabazitaxel arm?

- 1) Patient 380-004-003: medical decision not safety related. Is there any additional information available?
- 2) Patient 826-005-014: abnormal LFTs. LFTs appear relatively unchanged from baseline at time of treatment discontinuation. Is there any additional information available?

Thanks,  
Ian

Ian Waxman, MD  
Medical Officer  
FDA/CDER/OND/OODP/DDOP  
WO Bldg 22, Rm 2115  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

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NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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CHRISTY L COTTRELL  
05/07/2010

**From:** Cottrell, Christy L.  
**Sent:** Tuesday, April 27, 2010 10:50 AM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'  
**Subject:** Cabazitaxel request (not related to the pending NDA)  
Linda,

The information below is not related to the pending NDA for cabazitaxel- just coincidental timing. Please respond.

FDA plans on holding a meeting of the Pediatric Oncology Subcommittee of ODAC in October or November 2010 to focus on optimizing the development of oncology and hematology drugs for pediatric use. The products that will be the focus of this meeting will be those recently approved or those products currently in phase 3 development for adults. We are seeking advice from the subcommittee regarding the potential role of these drugs in pediatric cancers and hematological disorders. In addition, we will seek the Committee's input regarding the optimal design of future clinical studies that may serve as part of a Pediatric Written Request.

We would like to invite Sanofi-Aventis to make a brief presentation at the meeting to provide background information on cabazitaxel to serve as a basis for this discussion. The presentation should be limited to 20 minutes, and include a brief, high-level summary of the following:

1. Regulatory History
2. Preclinical data supporting clinical studies
3. Clinical trial experience in adults (Phase 1, 2, and 3 trials as appropriate)
4. Other clinical trials that are ongoing or completed after approval
5. Post marketing experience
6. Current drug development plan for other indications in adults
7. EMA PIP and any ongoing clinical trials in pediatrics
8. Current or potential challenges that have been identified regarding clinical trials in children (e.g., pediatric formulation issues).

If you agree to participate in the Fall 2010 meeting, we request that you submit a description of the PIP and any ongoing pediatric clinical trials of cabazitaxel outside of the U.S. for our review. We anticipate that one or more planning teleconferences between FDA staff & company representatives may be necessary prior to the meeting. Additional logistical details, including information about the need for an AC briefing document, will follow as planning progresses. The usual timelines for advisory committee meeting preparation will apply to the ODAC Pediatric Subcommittee meeting.

If you have any questions, please do not hesitate to contact Amy McKee at (301)796-3909 or [amy.mckee@fda.hhs.gov](mailto:amy.mckee@fda.hhs.gov), or Dianne Spillman, Oncology Program Lead Project Manager, at (301) 796-1467 or [dianne.spillman@fda.hhs.gov](mailto:dianne.spillman@fda.hhs.gov).

Regards,  
Christy

---

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA  
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993

 301.796.4256 (phone) • 301.796.9845 (fax) |  [christy.cottrell@fda.hhs.gov](mailto:christy.cottrell@fda.hhs.gov)



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CHRISTY L COTTRELL  
04/27/2010

**From:** Waxman, Ian  
**Sent:** Monday, April 26, 2010 3:06 PM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'  
**Cc:** Cottrell, Christy L.  
**Subject:** Blood and Lymphatic Analysis Clarifications  
Hi Linda,

I have a few questions and clarifications.

1. I believe that 356-001-010 (cabazitaxel arm) should have been coded as having grade 3 or grade 4 febrile neutropenia. The patient experienced grade 4 neutropenia on 5/16/08 followed by grade 1 pyrexia (38.3 C) on 5/17/08. The neutropenia was reported as unresolved at the time of death. Please explain why an AE of febrile neutropenia was not captured for this patient. If you agree that such an AE should have been captured, would it be grade 3 or grade 4?

2. I have identified 3 additional patients on the cabazitaxel arm with grade 3 anemia based on CTCAE grading: 203-003-001, 840-008-008, and 840-026-001. Each of these patients is included in your analysis under the grade 2 anemia category. However, each of these 3 required a transfusion and should have been considered to have had a grade 3 event. Please justify your exclusion of these 3 grade 3 anemia patients from the grade 3/4 analysis. It is not appropriate to use strict lab values for grade 3/4 anemia, as CTCAE grading clearly states that transfusion alone is a free-standing criteria for grade 3. It is appropriate to use strict lab values for other hematologic parameters since CTCAE grading is based solely on lab values and does not include a clinical component.

3. Table 2 of your proposed label uses a denominator of 371 patients for adverse events of neutropenia, leukopenia, and thrombocytopenia. However, fewer patients had post-baseline labs drawn. Please explain why you have chosen to use a denominator of 371 for these 3 adverse events.

Thanks,  
Ian

Ian Waxman, MD  
Medical Officer  
FDA/CDER/OND/OODP/DDOP  
WO Bldg 22, Rm 2115  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Email: [ian.waxman@fda.hhs.gov](mailto:ian.waxman@fda.hhs.gov)  
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CHRISTY L COTTRELL  
05/07/2010

**From:** Cottrell, Christy L.  
**Sent:** Monday, April 26, 2010 10:21 AM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'  
**Subject:** NDA 201023 for Cabazitaxel: Statistical information request

**Importance:** High  
Linda,

Please refer to the pending NDA 201023 for cabazitaxel. See below for an inquiry from the statistical reviewer.

- According to the submitted EFC6193 study data sets, there appear to be a few randomized patients without ECOG performance status data at baseline. Since baseline ECOG performance status is a stratification factor at randomization for the study, this information should not be missing. Please clarify.

Feel free to contact me with any questions.

Regards,  
Christy

---

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA  
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993

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CHRISTY L COTTRELL

04/26/2010

**From:** Waxman, Ian  
**Sent:** Friday, April 23, 2010 3:35 PM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'  
**Cc:** Cottrell, Christy L.  
**Subject:** Narrative/CRF Request  
Hi Linda,

Can you provide a narrative and CRF for patient 152-005-004 from the TROPIC study?

Thanks,  
Ian

Ian Waxman, MD  
Medical Officer  
FDA/CDER/OND/OODP/DDOP  
WO Bldg 22, Rm 2115  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Email: [ian.waxman@fda.hhs.gov](mailto:ian.waxman@fda.hhs.gov)  
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CHRISTY L COTTRELL

05/07/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR Patient Reported Outcomes (PRO) ENDPOINTS CONSULTATION</b>		
<b>TO: Study Endpoints and Labeling Development (SEALD)</b> CDER/OND-IO White Oak Bldg 22, Mail Drop 6411 <a href="mailto:SEALD.ENDPOINTS@FDA.HHS.GOV">SEALD.ENDPOINTS@FDA.HHS.GOV</a>		<b>FROM: Review Division: Division of Drug Oncology Products</b> <b>Medical Reviewer: Amy McKee</b> <b>Project Manager: Christy Cottrell</b>		
<b>DATE OF CONSULT REQUEST</b> April 22, 2010	<b>Application# IND/NDA/BLA#</b>  <b>NDA 201023</b>	<b>LETTER # OR SUBMISSION #</b> Original submission	<b>TYPE OF DOCUMENT</b> (Meeting; Protocol/SPA; PDUFA Product Review) New NME NDA	<b>REQUESTED SEALD COMPLETION DATE*</b> <b>May 21, 2010</b>
<b>DRUG ESTABLISHED NAME</b> Cabazitaxel	<b>DRUG TRADE NAME</b> <b>Jevtana</b>	<b>NAME OF SPONSOR</b> Sanofi-aventis	<b>SPONSOR SUBMIT DATE</b> <b>March 31, 2010</b>	
<b>DEVELOPMENT PHASE (E.G., pre-IND/NDA/BLA; IND/BB-IND Phase 1, 2, 3; NDA/BLA):</b> NDA <b>GOAL DATE (if NDA/BLA/SPA):</b> <b>June 11, 2010 (expedited high priority review)</b> <b>ELECTRONIC LINK (if applicable):</b> EDR Location: <a href="\\CDSESUB1\EVSPROD\NDA201023\0005">\\CDSESUB1\EVSPROD\NDA201023\0005</a> Gateway Location: <a href="\\fdswal32\cderesub\inbound\ectd\ci1270144878267.282096@llnap03.te">\\fdswal32\cderesub\inbound\ectd\ci1270144878267.282096@llnap03.te</a> <b>BACKGROUND PACKAGE</b> (deliver PAPER to CDER SEALD Endpoints mailbox in Bldg 22, Rm 6411): N/A <b>MEETINGS (if applicable)</b> (please send invite to <a href="mailto:SEALD.ENDPOINTS@FDA.HHS.GOV">SEALD.ENDPOINTS@FDA.HHS.GOV</a> ) Internal mid-cycle meeting on 5/7; Labeling meetings on 5/11, 5/18, 5/19, 5/24, 5/26, 6/1; Wrap-up meeting on 6/2				
PLEASE make certain the background-briefing package is included with this consult. It should contain the following applicable information needed to start Study Endpoints Review: Protocol or Study ID; Endpoint Concept(s); Instrument(s); Indication(s); Study population(s); Prior related reviews. Division PM, please provide the following specific information on this consult form:  Instrument(s):  Indication(s): Metastatic hormone refractory prostate cancer  Specific Questions/Comments for SEALD: DDOP would like SEALD to review the secondary pain assessment/endpoints for this NDA.   <b>Please confirm whether you can meet the expedited review timeline with a requested completion date of May 21, 2010. You may contact Amy McKee, MD, (clinical reviewer) at 6-3909 for more information/details.</b>				
<b>Requester</b>				
Christy Cottrell, RPM				
<b>Name/Phone number/email address/office location</b>		<a href="tel:301-796-4256">301-796-4256</a> / <a href="mailto:christy.cottrell@fda.hhs.gov">christy.cottrell@fda.hhs.gov</a> / <a href="#">WO22</a> Room 2122		

**Glossary:**

**Concept:** The specific goal of a measurement (i.e. the *thing* that is to be measured by a PRO instrument).

**Instrument:** A means to capture data (e.g. questionnaire, diary) plus all the information and documentation that supports its use. Generally, that includes clearly defined methods and instructions for administration or responding, a standard format for data collection, and well-documented methods for scoring, analysis, and interpretation of results.

\*For voluminous study endpoint submissions (e.g. PRO “dossier” or content validity documentation greater than 50 pages), SEALD requests 60 days after receiving the background/briefing package document to complete the review.

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CHRISTY L COTTRELL

04/22/2010

**From:** Waxman, Ian  
**Sent:** Wednesday, April 21, 2010 10:07 AM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'  
**Cc:** Cottrell, Christy L.  
**Subject:** Information Request: AE Data  
Hi Linda,

Regarding Table 2 (Adverse Reactions) in your proposed label for cabazitaxel:

Please clarify the definition of "all grades"; is this grade 1-4 or grade 1-5?

Also, please clarify whether the grade 3/4 column also includes grade 5 events. Based on our calculations, it appears to include grade 5 events. Discrepancies based on your possible inclusion of grade 5 events are noted for vomiting, abdominal pain, renal failure acute, and dyspnea on the cabazitaxel arm and hematuria and dyspnea on the mitoxantrone arm.

Thanks,  
Ian

Ian Waxman, MD  
Medical Officer  
FDA/CDER/OND/OODP/DDOP  
WO Bldg 22, Rm 2115  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Email: [ian.waxman@fda.hhs.gov](mailto:ian.waxman@fda.hhs.gov)  
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/s/  
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CHRISTY L COTTRELL  
05/07/2010

**From:** Waxman, Ian  
**Sent:** Tuesday, April 20, 2010 11:18 AM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'  
**Cc:** Cottrell, Christy L.  
**Subject:** RE: Information Request  
[I am referring to CSR Table 56. I used all lab data \(ADLB dataset\) collected during from lab day 2 until end of treatment.](#)

Ian

---

**From:** Linda.Gustavson@sanofi-aventis.com [mailto:Linda.Gustavson@sanofi-aventis.com]  
**Sent:** Tuesday, April 20, 2010 11:13 AM  
**To:** Waxman, Ian  
**Cc:** Cottrell, Christy L.  
**Subject:** Re: Information Request

Hi Ian,

**Question:** I am trying to reconcile the blood and lymphatic disorder AE numbers. My numbers do not match for cabazitaxel arm grade 3-4 anemia and grade 1-4 thrombocytopenia. I am also off for mitoxantrone arm gr 1-4 anemia, leukopenia, and thrombocytopenia. Can you tell me which patients are included in your lab data analyses? Is it all patients who received at least one dose of drug?

**Answer:** Please provide us the Table number and the name of the report that you were unable to reconcile, so that we can better assist you.

Here is a general answer to your question. In some tables, we used laboratory data and in some tables we used ae data. When lab data were used, we used only lab tests which were done after Day1 Cycle 1 until 30 days after last treatment infusion. When ae data were used, we used treatment emergent AE (flag aetrem='T'). These selection criteria were used to include the records that showed the results while patients were under study treatment. In the safety section, only patients who received at least one dose of drug were included in the analysis (371 patients each in either group).

Regards,  
Linda

Linda Gustavson, Ph.D., RAC  
Director, R & D Regulatory Affairs  
U.S. Head, Oncology  
Global Regulatory Affairs  
sanofi-aventis US Inc.  
Mail code: BX2-712B  
200 Crossing Blvd, Bridgewater, NJ 08890-0890  
908-304-6221 (work phone)  
203-314-2245 (cell phone)  
fax: 908-304-6549  
email: [linda.gustavson@sanofi-aventis.com](mailto:linda.gustavson@sanofi-aventis.com)

**From:** Waxman, Ian [mailto:Ian.Waxman@fda.hhs.gov]  
**Sent:** Monday, April 19, 2010 5:24 PM  
**To:** Gustavson, Linda R&D/US  
**Cc:** Cottrell, Christy L.

**Subject:** Information Request

Hi Linda,

I am trying to reconcile the blood and lymphatic disorder AE numbers. My numbers do not match for cabazitaxel arm grade 3-4 anemia and grade 1-4 thrombocytopenia. I am also off for mitoxantrone arm gr 1-4 anemia, leukopenia, and thrombocytopenia.

Can you tell me which patients are included in your lab data analyses? Is it all patients who received at least one dose of drug?

Thanks,

Ian

Ian Waxman, MD

Medical Officer

FDA/CDER/OND/OODP/DDOP

WO Bldg 22, Rm 2115

10903 New Hampshire Avenue

Silver Spring, MD 20993

Email: [ian.waxman@fda.hhs.gov](mailto:ian.waxman@fda.hhs.gov)

Phone: 301-796-5123

Fax: 301-796-9845

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Application  
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Submission  
Type/Number

Submitter Name

Product Name

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NDA-201023

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ORIG-1

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SANOFI AVENTIS  
SPA

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CABAZITAXEL (XRP6258)

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CHRISTY L COTTRELL  
05/07/2010

**From:** Waxman, Ian  
**Sent:** Monday, April 19, 2010 5:24 PM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'  
**Cc:** Cottrell, Christy L.  
**Subject:** Information Request  
Hi Linda,

I am trying to reconcile the blood and lymphatic disorder AE numbers. My numbers do not match for cabazitaxel arm grade 3-4 anemia and grade 1-4 thrombocytopenia. I am also off for mitoxantrone arm gr 1-4 anemia, leukopenia, and thrombocytopenia.

Can you tell me which patients are included in your lab data analyses? Is it all patients who received at least one dose of drug?

Thanks,  
Ian

Ian Waxman, MD  
Medical Officer  
FDA/CDER/OND/OODP/DDOP  
WO Bldg 22, Rm 2115  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Email: [ian.waxman@fda.hhs.gov](mailto:ian.waxman@fda.hhs.gov)  
Phone: 301-796-5123  
Fax: 301-796-9845

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NDA-201023

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CABAZITAXEL (XRP6258)

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/s/  
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CHRISTY L COTTRELL  
05/07/2010

**From:** Waxman, Ian  
**Sent:** Friday, April 16, 2010 4:05 PM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'  
**Cc:** Cottrell, Christy L.  
**Subject:** G-CSF analysis  
Hi Linda,

Another way to explore whether patients received prophylactic G-CSF is to separate patients into 2 groups: those who received G-CSF before first onset of neutropenia and those who received G-CSF only after first onset of neutropenia. This may be a more clear approximation of who received truly prophylactic G-CSF, rather than the arbitrary 3 day cut-off. An analysis using this definition of prophylaxis would be useful.

Let me know if questions arise.

Thanks,  
Ian

Ian Waxman, MD  
Medical Officer  
FDA/CDER/OND/OODP/DDOP  
WO Bldg 22, Rm 2115  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Email: [ian.waxman@fda.hhs.gov](mailto:ian.waxman@fda.hhs.gov)  
Phone: 301-796-5123  
Fax: 301-796-9845

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Submission  
Type/Number

Submitter Name

Product Name

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NDA-201023

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ORIG-1

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SANOFI AVENTIS  
SPA

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CABAZITAXEL (XRP6258)

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CHRISTY L COTTRELL

05/07/2010

**From:** Waxman, Ian  
**Sent:** Thursday, April 15, 2010 10:12 AM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'  
**Cc:** Cottrell, Christy L.  
**Subject:** Analysis request  
Hi Linda,

I want to analyze differences in degree of neutropenia in patients who received prophylactic G-CSF by comparing counts obtained in cycles before prophylaxis was begun vs. after prophylaxis was begun.

I think one possible way to do this would be to analyze neutrophil nadirs (mean, median, range) in the cycles before prophylactic G-CSF vs. the cycles after prophylactic G-CSF. Can you ask the cabazitaxel team if they think this would be a good way to analyze the effect of G-CSF on actual neutrophil counts, or if they have ideas for alternative analyses that might be useful? I'd be happy to discuss any ideas right after tomorrow's meeting.

Thanks,  
Ian

Ian Waxman, MD  
Medical Officer  
FDA/CDER/OND/OODP/DDOP  
WO Bldg 22, Rm 2115  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Email: [ian.waxman@fda.hhs.gov](mailto:ian.waxman@fda.hhs.gov)  
Phone: 301-796-5123  
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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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CHRISTY L COTTRELL  
04/15/2010

**From:** Waxman, Ian  
**Sent:** Thursday, April 15, 2010 10:24 AM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'  
**Cc:** Cottrell, Christy L.; Mehrotra, Nitin  
**Subject:** RE: Information Request  
Linda,

Can you send the program and final composite dataset that was used to calculate the table for G-CSF/Neutropenia by cycle?

Ian

---

**From:** Linda.Gustavson@sanofi-aventis.com [mailto:Linda.Gustavson@sanofi-aventis.com]  
**Sent:** Wednesday, April 14, 2010 8:45 AM  
**To:** Waxman, Ian  
**Cc:** Cottrell, Christy L.  
**Subject:** RE: Information Request

Hi Ian,  
Here is the table of neutropenia/GCSF by cycle. As discussed with you and Liji Shen (s-a biostats) on the phone yesterday, we will follow up on your additional request for information regarding the number of missing dates of GCSF administration by cycle.  
Regards,  
Linda

Linda Gustavson, Ph.D., RAC  
Director, R & D Regulatory Affairs  
U.S. Head, Oncology  
Global Regulatory Affairs  
sanofi-aventis US Inc.  
Mail code: BX2-712B  
200 Crossing Blvd, Bridgewater, NJ 08890-0890  
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203-314-2245 (cell phone)  
fax: 908-304-6549  
email: [linda.gustavson@sanofi-aventis.com](mailto:linda.gustavson@sanofi-aventis.com)

---

**From:** Waxman, Ian [mailto:Ian.Waxman@fda.hhs.gov]  
**Sent:** Tuesday, April 13, 2010 9:03 AM  
**To:** Gustavson, Linda R&D/US  
**Cc:** Cottrell, Christy L.  
**Subject:** RE: Information Request

Hi Linda,

Can you ask your team to provide the neutropenia/G-CSF information provided in Table 47 of the Summary of Clinical Safety by each cycle, rather than by cycle 1 vs. cycle 2 to 10?

Thank you,

Ian

Ian Waxman, MD  
Medical Officer  
FDA/CDER/OND/OODP/DDOP  
WO Bldg 22, Rm 2115  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Email: [ian.waxman@fda.hhs.gov](mailto:ian.waxman@fda.hhs.gov)  
Phone: 301-796-5123  
Fax: 301-796-9845

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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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/s/

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CHRISTY L COTTRELL  
05/07/2010

## REQUEST FOR CONSULTATION

TO (Office/Division): **QT IRT**

FROM (Name, Office/Division, and Phone Number of Requestor): **Division of Drug Oncology Products  
Christy Cottrell, RPM**

DATE  
**April 14, 2010**

IND NO.

NDA NO.  
**201023**

TYPE OF DOCUMENT  
**New NME NDA**

DATE OF DOCUMENT  
**March 31, 2010**

NAME OF DRUG  
**Cabazitaxel**

PRIORITY CONSIDERATION  
**High**

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
**May 18, 2010**

NAME OF FIRM: **sanofi-aventis**

### REASON FOR REQUEST

#### I. GENERAL

- |  |   |  |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING              | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING      | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING       | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION                 | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input checked="" type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA                    | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT           |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** DDOP is requesting an IRT consult for NDA 201023 (cabazitaxel) for the treatment of patients with metastatic hormone-refractory prostate cancer who progressed after docetaxel. This application includes one randomized study of cabazitaxel + prednisone vs. mitoxantrone + prednisone, with a safety population of 371 patients per arm. This consult request is for evaluation for QTc abnormalities in patients who received cabazitaxel. The applicant has submitted only one ECG dataset with their NDA submission (ADEG.XPT). This dataset contains only qualitative information. Please note that the applicant is planning to conduct a separate QT study (TES10884-). This QT protocol was submitted on Jan 7, 2010, and was subsequently reviewed by IRT (Dr. Monic Fiszman) and entered into DARRTS on Feb 24, 2010. Please be aware that this NDA is receiving an expedited review and discussion of QT-related portions of the labeling is scheduled to occur at a meeting on May 18, 2010. Links to the submission are:

EDR Location: \\CDSESUB1\EVSPROD\NDA201023\201023.enx

Letter Date: 04/01/2010; Stamp Date: 4/1/2010

EDR Location: \\CDSESUB1\EVSPROD\NDA201023\0005

Gateway Location: \\fdswa132\cderesub\inbound\ectd\ci1270144878267.282096@l1nap03\_te

Please contact Dr. Ian Waxman (MO for safety) at 6-5123 to discuss the expedited timeline for this NDA review and any outstanding questions pertaining to this request.

PM=Christy Cottrell

SIGNATURE OF REQUESTOR

Christy Cottrell

METHOD OF DELIVERY (Check one)

DFS

EMAIL

MAIL

HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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

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/s/

CHRISTY L COTTRELL  
04/14/2010

**From:** Waxman, Ian  
**Sent:** Tuesday, April 13, 2010 9:03 AM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'  
**Cc:** Cottrell, Christy L.  
**Subject:** RE: Information Request  
[Hi Linda,](#)

[Can you ask your team to provide the neutropenia/G-CSF information provided in Table 47 of the Summary of Clinical Safety by each cycle, rather than by cycle 1 vs. cycle 2 to 10?](#)

Thank you,

[Ian](#)

Ian Waxman, MD  
Medical Officer  
FDA/CDER/OND/OODP/DDOP  
WO Bldg 22, Rm 2115  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Email: [ian.waxman@fda.hhs.gov](mailto:ian.waxman@fda.hhs.gov)  
Phone: 301-796-5123  
Fax: 301-796-9845

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Application  
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Submitter Name

Product Name

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NDA-201023

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SANOFI AVENTIS  
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CABAZITAXEL (XRP6258)

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/s/  
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CHRISTY L COTTRELL

05/07/2010

---

**From:** Mesmer, Deborah  
**Sent:** Friday, April 09, 2010 10:55 AM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'  
**Subject:** NDA 201023 : CMC IR 4/9/10

From: Deborah Mesmer, Regulatory Health Project Manager  
FDA/CDER  
Office of New Drug Quality Assessment  
Division of Pre-Marketing Assessment III and Manufacturing Science

To: Linda Gustavson, PhD, RAC

RE: NDA 201023

Please refer to your NDA for Cabazitaxel, 60mg/1.5mL, (b) (4) for solution for infusion.

We have the following request for information.

As soon as feasible, provide a **placebo** sample of the to-be-marketed package, including a full-color sample of the proposed commercial labeling for the drug product.

Ship samples to the following address:

Deborah Mesmer  
Food and Drug Administration  
10903 New Hampshire Avenue  
Building 21, Room 1627, Mail Stop 21-1603  
Silver Spring, MD 20993

Please submit a copy of the cover letter for your sample shipment to your NDA.

Please acknowledge receipt of this message.

If you have any questions, please call Deborah Mesmer, Project Manager for Quality at (301) 796- 4023.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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CABAZITAXEL (XRP6258)

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/s/  
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DEBORAH M MESMER

04/09/2010

**From:** Cottrell, Christy L.  
**Sent:** Thursday, April 08, 2010 12:38 PM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'  
**Subject:** NDA 201023: Clinical pharmacology request for information  
Linda,

See below for a request for information from the clinical pharmacology team regarding NDA 201023 (Cabazitaxel).

**Please address the following data request by 12 April 2010:**

**Study TED6188 and TED6190:**

- We note that the exploratory PK-PD analysis was performed for these two studies for safety endpoints (Neutrophils, WBCs) using WinNonlin. Refer to Section 3.6, 10 and 10.4 of summary of Clinical Pharmacology studies, TED6188 and TED6190, respectively. Please submit the combined PK-PD datasets associated with these analyses. The PK-PD datasets should include demographic factors and all the relevant covariates for each individual. A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Please also submit details of WinNonlin models and outputs wherever applicable.

**Study ARD6191:**

- Please submit the report, datasets and programs for the PK study of ARD6191. The datasets should include demographic factors and all the relevant covariates for each individual. A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Please also submit details of WinNonlin models and outputs where applicable.

Feel free to contact me with any questions.

Regards,  
Christy

---

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA  
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993  
 301.796.4256 (phone) • 301.796.9845 (fax) |  [christy.cottrell@fda.hhs.gov](mailto:christy.cottrell@fda.hhs.gov)



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/s/

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CHRISTY L COTTRELL  
04/08/2010

**From:** Waxman, Ian  
**Sent:** Thursday, April 08, 2010 10:06 AM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'  
**Cc:** Cottrell, Christy L.  
**Subject:** RE: Information Request  
Hi Linda,

I need a bit more clarification regarding your response.

There were 9 deaths on the mitoxantrone arm within 30 days of last dose. Based on what you wrote below, any death within 30 days, regardless of cause, is considered a TEAE. However, in table 38, only 5 of these 9 deaths are considered TEAEs, though all occurred within 30 days of last dose. In table 38 (section: death during treatment phase), why did you include the patients with 840014006 and 250004018 in the TEAE subset rather than the Progression subset of mitoxantrone-treated patients who died within 30 days of last dose?

Thanks,

Ian

---

**From:** Linda.Gustavson@sanofi-aventis.com [mailto:Linda.Gustavson@sanofi-aventis.com]  
**Sent:** Thursday, April 08, 2010 9:01 AM  
**To:** Waxman, Ian  
**Cc:** Cottrell, Christy L.  
**Subject:** RE: Information Request

Hi Ian,

You are correct that in table 38 of the Clinical Study Report (CSR), 4 deaths are due to disease progression and 5 deaths were TEAE, i.e., deaths during the treatment phase (within 30 days) on the mitoxantrone arm.

The patient ID's for the 5 patients with death due to TEAE and the cause of death are as below:

1. 250001027 – Pneumococcal sepsis {PT: Pneumococcal Sepsis}
2. 380003014 – Motor vehicle accident {PT: Multiple fractures}
3. 724004005 – Disease Progression with Pleural Effusion {PT: Pleural Effusion}
4. 840014006 – Disease Progression due to metastatic prostate cancer {PT: Prostate cancer metastatic}
5. 250004018 – Metastasis to the meninges {PT: Metastases to meninges}

These patient ID's with hyperlinks to either narratives (250001027; 380003014; 724004005; 840014006) or case report forms (250004018) are provided in Table 41 of the CSR.

The last 3 patients, although they died of disease progression, were coded as deaths due to TEAE following the Sponsor's data recording conventions because the event occurred within 30 days of last study drug administration. Narratives for patients 840014006 – Disease Progression due to metastatic prostate cancer, and 250004018 – Metastasis to the meninges, were provided on April 7, 2010. As defined in the statistical analysis plan, a treatment emergent adverse event is an event that is new or worsened during the treatment period, regardless of the causes or

relationship to the drug . Therefore, a fatal AE due to the motor vehicle accident or PD will be considered TEAE as long as they are new or meet the criteria for a TEAE.

Regards,  
Linda

Linda Gustavson, Ph.D., RAC  
Director, R & D Regulatory Affairs  
U.S. Head, Oncology  
Global Regulatory Affairs  
sanofi-aventis US Inc.  
Mail code: BX2-712B  
200 Crossing Blvd, Bridgewater, NJ 08890-0890  
908-304-6221 (work phone)  
203-314-2245 (cell phone)  
fax: 908-304-6549  
email: [linda.gustavson@sanofi-aventis.com](mailto:linda.gustavson@sanofi-aventis.com)

---

**From:** Waxman, Ian [mailto:[Ian.Waxman@fda.hhs.gov](mailto:Ian.Waxman@fda.hhs.gov)]  
**Sent:** Wednesday, April 07, 2010 5:24 PM  
**To:** Gustavson, Linda R&D/US  
**Cc:** Cottrell, Christy L.  
**Subject:** RE: Information Request

Hi Linda,

According to the CSR (Table 38), there were 4 disease progression deaths and 5 TEAE deaths during the treatment phase on the mitoxantrone arm.

Can you tell me which 5 mitoxantrone arm deaths within 30 days of last dose were considered to be secondary to TEAEs? It seems that patients 250-004-018 and 840-014-006 were included among these 5 deaths, but as you mentioned in your email earlier today, these deaths should have been considered to be secondary to progressive disease.

Thanks for your clarification.

Ian

---

**From:** Linda.Gustavson@sanofi-aventis.com [mailto:[Linda.Gustavson@sanofi-aventis.com](mailto:Linda.Gustavson@sanofi-aventis.com)]  
**Sent:** Wednesday, April 07, 2010 1:45 PM  
**To:** Waxman, Ian  
**Cc:** Cottrell, Christy L.  
**Subject:** RE: Information Request

Dear Dr. Waxman,

We will submit to the NDA the CRF's for all patients who died within 30 days due to progressive disease. These were not originally submitted in the dossier based on FDA recommendation provided at the preNDA meeting below, to submit deaths within 30 days of last treatment, unless due to progressive disease.

Patient 250004018 died due to an event reported as metastases to the meninges (outcome death). The death was considered progressive disease. There is a mini narrative for this patient on page 119 of the EFC6193 Clinical Study Report (CSR). No narrative or CRFs for this patient was included as they were considered death due to PD.

Patient 840014006 died due to an event reported as metastatic prostate cancer (outcome death). The death was considered progressive disease. This patient had a narrative because the patient had an SAE of confusional state starting on 23 Oct 2007. The patient died on (b) (4) due to the prostate cancer metastatic. CRFs should be currently available for this patient as well. A mini narrative for this patient is on page 120 of the EFC6193 CSR with the hyperlink to the narrative that was included in the submission made on March 31, 2010.

Narratives for both of the patients are attached. Both of these patients were on the mitoxantrone plus prednisone arm of Study EFC6193.

Regards,

Linda

Linda Gustavson, Ph.D., RAC  
Director, R & D Regulatory Affairs  
U.S. Head, Oncology  
Global Regulatory Affairs  
sanofi-aventis US Inc.  
Mail code: BX2-712B  
200 Crossing Blvd, Bridgewater, NJ 08890-0890  
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fax: 908-304-6549  
email: [linda.gustavson@sanofi-aventis.com](mailto:linda.gustavson@sanofi-aventis.com)

5. Does the Agency agree with the proposed electronic data submission proposed in the electronic data submission planning template?

**FDA response: Please provide patient narratives and CRFs for all patients in both treatment groups of study EFC6193 who:**

- **Died within 30 days of last treatment, unless due to progressive disease**
- **Discontinued study drug due to an AE**
- **\*Experienced SAEs**
- **Experienced “events of special interest”**

---

**From:** Waxman, Ian [mailto:ian.waxman@fda.hhs.gov]  
**Sent:** Tuesday, April 06, 2010 5:52 PM  
**To:** Gustavson, Linda R&D/US  
**Cc:** Cottrell, Christy L.  
**Subject:** Information Request

Hi Linda,

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Thanks,

Ian

Ian Waxman, MD  
Medical Officer  
FDA/CDER/OND/OODP/DDOP  
WO Bldg 22, Rm 2115  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Email: [ian.waxman@fda.hhs.gov](mailto:ian.waxman@fda.hhs.gov)  
Phone: 301-796-5123  
Fax: 301-796-9845

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immediately at [ian.waxman@fda.hhs.gov](mailto:ian.waxman@fda.hhs.gov) and delete this e-mail communication from your computer.

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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CHRISTY L COTTRELL  
04/08/2010

## Memorandum of Teleconference

**NDA 201023/ Cabazitaxel/Sanofi Aventis**

**TCON date:** April 7, 2010

**Topics of Discussion:** Environmental assessment submission timing  
Redundant DMF and associated review completion impact

**FDA Attendees:** Richard Lostritto, Sarah Pope Miksinski, Deborah Mesmer

**Sanofi Aventis Attendees:**

Peter Wilson: Environmental Assessment, Manager

Zareen Ahmed: Regulatory CMC Development, Associate Director

Leslie Aragones: Regulatory Affairs Oncology, Regulatory Coordinator

Mark Moyer: VP Regulatory Affairs Oncology, VP Global Regulatory Affairs

Gail Owens: Regulatory CMC Development, Director

Linda Gustavson: Regulatory Affairs Oncology, US Head

Gopi Vudathala: Regulatory Affairs Interface CMC, Associate VP

James Boyd: VP CM

Yvette Gohee: Sanofi-Chimie Regulatory Development

Jacqueline Caniglia: Project Direction

**Agreements reached:**

Sanofi will submit justification in the form of references to their previous applications to support their claim for categorical exclusion from the environmental assessment. They will submit the references by email to Deborah Mesmer.

Sanofi will consider if they can remove one of the DMFs (and associated manufacturing establishment) for the (b) (4). They will respond by the week of April 12, 2010, whether they can do this. FDA requested that if Sanofi removes a site, that they provide specific information as to what is in the NDA for the two remaining sites. (That is, FDA doesn't want to review information that would be remaining in the application from a third site that had been removed.)

FDA mentioned that if one site is removed, Sanofi can amend post-approval to add the third site for manufacture of (b) (4).

Refer also to information request below

-----  
**From:** Mesmer, Deborah

**Sent:** Wednesday, April 07, 2010 12:50 PM

**To:** 'Linda.Gustavson@sanofi-aventis.com'

**Cc:** Cottrell, Christy L.  
**Subject:** NDA 201023 TCON - April 7,2010  
**Importance:** High

Dear Dr. Gustavson,

Thank you for agreeing to the TCON for NDA 201023 this afternoon at 3:30 p.m. I have received your call-in number of:

866-680-0168  
Participant 786065

The topics of discussion will be:

- 1) Environmental assessment submission timing
- 2) Redundant DMF and associated review completion impact

With regard to the environmental assessment, we have the following request:

Indicate the earliest date by which you can provide an environmental assessment for the drug substance that includes for the yew plants the harvesting practices and permits (if applicable) as well as a certification statement that the harvest is not harmful to the environment. Note that the lack of this information in the original submission is a potential refuse-to-file issue. Environmental assessment information is an integral part of the multidisciplinary CMC review and the necessary process by which we conduct CMC reviews is delayed until we have this information. We recommend that we receive this information within two weeks of this communication.

Sincerely,

Debbie Mesmer

Deborah Mesmer  
Regulatory Health Project Manager  
FDA/CDER  
Office of New Drug Quality Assessment  
Division of Pre-Marketing Assessment III and Manufacturing Science  
301-796-4023  
deborah.mesmer@fda.hhs.gov

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Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-201023

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ORIG-1

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SANOFI AVENTIS  
SPA

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CABAZITAXEL (XRP6258)

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/s/  
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DEBORAH M MESMER

04/09/2010

**From:** Waxman, Ian  
**Sent:** Wednesday, April 07, 2010 5:24 PM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'  
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Narratives for both of the patients are attached. Both of these patients were on the mitoxantrone plus prednisone arm of Study EFC6193.

Regards,

Linda

Linda Gustavson, Ph.D., RAC  
Director, R & D Regulatory Affairs  
U.S. Head, Oncology  
Global Regulatory Affairs  
sanofi-aventis US Inc.  
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**Sent:** Tuesday, April 06, 2010 5:52 PM  
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**Cc:** Cottrell, Christy L.  
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Thanks,

Ian

Ian Waxman, MD  
Medical Officer  
FDA/CDER/OND/OODP/DDOP  
WO Bldg 22, Rm 2115  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Email: [ian.waxman@fda.hhs.gov](mailto:ian.waxman@fda.hhs.gov)  
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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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/s/

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CHRISTY L COTTRELL  
04/08/2010

**From:** McKee, Amy  
**Sent:** Wednesday, April 07, 2010 2:51 PM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'  
**Cc:** Cottrell, Christy L.  
**Subject:** Cabazitaxel information request  
Linda,

I am conducting the efficacy review for NDA 201023 and am hoping you can point me in the right direction. Which dataset contains the raw data which were used for the analysis of the primary efficacy endpoint of overall survival? Thank you for your help.

Amy

Amy E. McKee, M.D.  
Medical Officer  
FDA/CDER/OND/OODP/DDOP  
White Oak, Building 22 Room 5232  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
(P) 301-796-3909  
(F) 301-796-9849  
amy.mckee@fda.hhs.gov

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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04/08/2010

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WO Bldg 22, Rm 2115  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Email: [ian.waxman@fda.hhs.gov](mailto:ian.waxman@fda.hhs.gov)  
Phone: 301-796-5123  
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/s/

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04/08/2010

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CHRISTY L COTTRELL  
04/07/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR DDMAC LABELING REVIEW CONSULTATION</b> <b>**Please send immediately following the Filing/Planning meeting**</b>	
TO: <b>CDER-DDMAC-RPM</b>		FROM: (Name/Title, Office/Division/Phone number of requestor) <b>Division of Drug Oncology Products Christy Cottrell, RPM</b>	
REQUEST DATE <b>April 6, 2010</b>	IND NO.	NDA/BLA NO. <b>NDA 201023</b>	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW) <b>New NME NDA</b>
NAME OF DRUG <b>Cabazitaxel</b>	PRIORITY CONSIDERATION <b>High priority</b>	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) <b>May 15, 2010</b>
NAME OF FIRM: <b>Sanofi-aventis</b>		PDUFA Date: <b>October 1, 2010</b>	
<b>TYPE OF LABEL TO REVIEW</b>			
<b>TYPE OF LABELING:</b> (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)		<b>TYPE OF APPLICATION/SUBMISSION</b> <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	
		<b>REASON FOR LABELING CONSULT</b> <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION	
<b>EDR link to submission:</b> EDR Location: <a href="\\CDSESUB1\EVSPROD\NDA201023\0005">\\CDSESUB1\EVSPROD\NDA201023\0005</a> Gateway Location: <a href="\\fdswa132\cderesub\inbound\ectd\ci1270144878267.282096@llnap03.te">\\fdswa132\cderesub\inbound\ectd\ci1270144878267.282096@llnap03.te</a>			
<b>Please Note:</b> There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.			
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> DDOP is planning an expedited 8-week review of this high priority NDA. Target goal date is May 26, 2010.  Mid-Cycle Meeting: May 7, 2010  Labeling Meetings: May 11 at 3:00pm, May 18 at 1:00pm, May 19, at 2:30pm, May 24 at 2:00pm, May 26 at 1:00pm, and June 1 at 1:00pm  Wrap-Up Meeting: June 2 at 1:00pm			
SIGNATURE OF REQUESTER <b>Christy Cottrell</b>			
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> eMAIL <input type="checkbox"/> HAND	

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-201023

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ORIG-1

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SANOFI AVENTIS  
SPA

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CABAZITAXEL (XRP6258)

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CHRISTY L COTTRELL

04/06/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>OSE</b> <b>Attention: Sarah Simon</b>		FROM: Division of Drug Oncology Products Christy Cottrell, RPM		
DATE April 6, 2010	IND NO.	NDA NO. NDA 201023	TYPE OF DOCUMENT New NME NDA	DATE OF DOCUMENT March 31, 2010
NAME OF DRUG Cabazitaxel	PRIORITY CONSIDERATION High priority	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE May 15, 2010	
NAME OF FIRM: sanofi-aventis				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY	<input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): New NME NDA	
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> As previously discussed during planning meetings, DDOP is planning an expedited 8-week review of this application. Requesting OSE review of package insert, carton/container labels and attendance at labeling meetings. Links to the submission are below: EDR Location: <a href="\\CDSESUB1\EVSPROD\NDA201023\0005">\\CDSESUB1\EVSPROD\NDA201023\0005</a> Gateway Location: <a href="\\fdswa132\cderesub\inbound\ctd\ci1270144878267.282096@l1nap03">\\fdswa132\cderesub\inbound\ctd\ci1270144878267.282096@l1nap03</a> te				
PDUFA date is October 1, 2010. Target action date is May 26, 2010. Requesting completed OSE review by May 15, 2010. DMEPA reviewer already assigned: Lubna Najam Awaiting DRISK reviewer assignment.				
DDOP MO: Ian Waxman/Amy McKee DDOP RPM: Christy Cottrell				
SIGNATURE OF REQUESTER Christy Cottrell		METHOD OF DELIVERY (Check one) X DARRTS <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

Application  
Type/Number

Submission  
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Submitter Name

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ORIG-1

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SPA

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CABAZITAXEL (XRP6258)

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/s/  
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CHRISTY L COTTRELL

04/06/2010

**From:** Waxman, Ian  
**Sent:** Monday, April 05, 2010 12:12 PM  
**To:** 'Linda.Gustavson@sanofi-aventis.com'  
**Cc:** Cottrell, Christy L.  
**Subject:** RE: Cabazitaxel review question  
[Hi Linda,](#)

I am trying to locate a CRF for patient 840-071-004 (EFC6193), but cannot seem to find one. Can you tell me if this CRF was submitted? Were CRFs submitted for all patients? If not, which ones are missing?

Thanks,

Ian

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**From:** Linda.Gustavson@sanofi-aventis.com [mailto:Linda.Gustavson@sanofi-aventis.com]  
**Sent:** Friday, April 02, 2010 2:27 PM  
**To:** Waxman, Ian  
**Subject:** RE: Cabazitaxel review question

Before Amendment 1, the dose and schedules of investigational products were:

- Arm A: XRP6258, 20 mg/m<sup>2</sup>, as a 1-hour iv infusion, every 3 weeks.
- Arm B: XRP6258, 10 mg/m<sup>2</sup>, as a weekly 1-hour iv infusion (Days 1, 8, 15, 22), every 5 weeks.
- Arm C: XRP9881, 90 mg/m<sup>2</sup>, as a 1-hour iv infusion, every 3 weeks.

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**From:** Waxman, Ian [mailto:Ian.Waxman@fda.hhs.gov]  
**Sent:** Friday, April 02, 2010 2:21 PM  
**To:** Gustavson, Linda R&D/US  
**Subject:** RE: Cabazitaxel review question

Can you also tell me what the weekly dose was?

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**From:** Linda.Gustavson@sanofi-aventis.com [mailto:Linda.Gustavson@sanofi-aventis.com]  
**Sent:** Friday, April 02, 2010 2:17 PM  
**To:** Waxman, Ian  
**Cc:** Cottrell, Christy L.  
**Subject:** RE: Cabazitaxel review question

Dear Dr. Waxman,

Study ARD6191 was originally planned to compare cabazitaxel q3 weekly, cabazitaxel q1 weekly and another taxane larotaxel (XRP9881). Due to low enrollment the protocol was amended and subsequently patients were only further enrolled in the cabazitaxel q3 weekly arm.

In total 71 patients were treated with the q3 weekly regimen. There were 13 patients who had been treated in the cabazitaxel q1 weekly arm. The study report does not provide a comprehensive analysis on safety for these 13 patients but presents individual patient profiles in Appendix C 4.2 of the study report and the SAE narratives of those patients in section 14.5 of the

study report. However, the data from these 14 patients were included in the integrated summary of safety and are described together with data from another weekly study TED6189 in the Summary of Clinical Safety in section 2.7.4 of the submission. Therefore, the data from those 13 patients were included in the electronic datasets.

Regards,  
Linda

Linda Gustavson, Ph.D., RAC  
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U.S. Head, Oncology  
Global Regulatory Affairs  
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203-314-2245 (cell phone)  
fax: 908-304-6549  
email: [linda.gustavson@sanofi-aventis.com](mailto:linda.gustavson@sanofi-aventis.com)

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**From:** Waxman, Ian [mailto:[Ian.Waxman@fda.hhs.gov](mailto:Ian.Waxman@fda.hhs.gov)]  
**Sent:** Friday, April 02, 2010 11:41 AM  
**To:** Gustavson, Linda R&D/US  
**Cc:** Cottrell, Christy L.  
**Subject:** Cabazitaxel review question

Hi Linda,

I am conducting a safety review for NDA 201023 and am having difficulty reconciling patient numbers for supportive study ARD6191.

The study synopsis includes 71 treated patients, all of whom received q3 weekly dosing. The dataset, however, contains an additional 13 patients who received weekly dosing. Are these additional 13 patients documented anywhere in the study report synopsis? Was the protocol design changed?

Thanks,  
Ian

Ian Waxman, MD  
Medical Officer  
FDA/CDER/OND/OODP/DDOP  
WO Bldg 22, Rm 2115  
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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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/s/

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CHRISTY L COTTRELL  
04/05/2010

**From:** Waxman, Ian  
**Sent:** Friday, April 02, 2010 11:41 AM  
**To:** 'linda.gustavson@sanofi-aventis.com'  
**Cc:** Cottrell, Christy L.  
**Subject:** Cabazitaxel review question  
Hi Linda,

I am conducting a safety review for NDA 201023 and am having difficulty reconciling patient numbers for supportive study ARD6191.

The study synopsis includes 71 treated patients, all of whom received q3 weekly dosing. The dataset, however, contains an additional 13 patients who received weekly dosing. Are these additional 13 patients documented anywhere in the study report synopsis? Was the protocol design changed?

Thanks,  
Ian

Ian Waxman, MD  
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NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

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CHRISTY L COTTRELL  
04/05/2010

**From:** Cottrell, Christy L.  
**Sent:** Tuesday, March 23, 2010 10:35 AM  
**To:** 'Mark.Moyer@sanofi-aventis.com'; 'Linda.Gustavson@sanofi-aventis.com'  
**Subject:** NDA 201023: PK request  
Mark and Linda,

See below for a PK request for information to be submitted with the NDA.

In your NDA submission, please submit the pharmacokinetic dataset including individual concentration vs. time and corresponding pharmacokinetic parameters by patient as SAS transport files. The following are the general expectations for submitting pharmacometric data and models:

- All datasets used for model development and validation should be submitted as a SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets.
- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt).
- A model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Let me know if you have any questions.

Regards,  
Christy Cottrell

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Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA  
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Application  
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Submission  
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Submitter Name

Product Name

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NDA-201023

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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  
03/23/2010