CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-449/s-029

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

Aventis Pharmaceuticals

Aventis Pharmaceuticals, Inc.
200 Crossings Blvd., P.O. Box 6890
Bridgewater, NJ 08807-0890

Patent Information and Certification

Forms FDA 3542a for the following patents are included in Section 1.4.2:

United States Patent No. 4,814,470
United States Patent No. 5,438,072
United States Patent No. 5,714,512
United States Patent No. 5,698,582

Aventis Pharmaceuticals

Aventis Pharmaceuticals, Inc.
200 Crossings Blvd., P.O. Box 6890
Bridgewater, NJ 08807-0890

Patent Information and Certification

Forms FDA 3542a for United States Patent No. 4,814,470

Department of Health and Human Services
Food and Drug Administration

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

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
20-449 (Supplemental - Breast adjuvant)

NAME OF APPLICANT / NDA HOLDER
Aventis Pharmaceuticals Inc.

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)
Taxotere®

ACTIVE INGREDIENT(S)	STRENGTH(S)
Docetaxel	Single dose vials containing 20mg(0.5 ml) or 80mg(2.0 ml) EQ 40mg Base/ml

DOSAGE FORM
Sterile Solution

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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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	b. Issue Date of Patent	c. Expiration Date of Patent
4,814,470	3/21/1989	5/14/2010

d. Name of Patent Owner	Address *(of Patent Owner)*	
Aventis Pharma S.A	20 avenue Raymond Aron	
	City/State: 92160 Antony France	
	ZIP Code:	FAX Number *(if available)*: 011 49 69 305 80556
	Telephone Number: 011 49 69 305 6181	E-Mail Address *(if available)*: markus.jacobi@aventis.com

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)	Address *(of agent or representative named in 1.e.)*	
Louis J. Wille Vice President, Global Patent Litigation	Aventis Pharmaceuticals Inc. 1041 Route 202-206 - P.O. Box 6800	
	City/State: Bridgewater, NJ	
	ZIP Code: 08807-0800	FAX Number *(if available)*: 908 231-2691
	Telephone Number: 908 231-5721	E-Mail Address *(if available)*: lou.wille@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?	☒ 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.		
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 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, 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 *(as listed in the patent)*	Does the patent claim 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 approved 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
	11/17/2003

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 Joseph P. Kirk Jr.	
Address Aventis Pharmaceuticals Inc. 1041 Route 202-206 - P.O. Box 6800	City/State Bridgewater, New Jersey
ZIP Code 08807-0800	Telephone Number 908 231-5916
FAX Number *(if available)* 908 231-2840	E-Mail Address *(if available)* joseph.kirk@aventis.com

Notes to Form FDA 3542a for U.S. Patent 4,814,470 submitted for sNDA 20-449 (Taxotere®) (Supplemental – Breast adjuvant)

Note to Question 2.2: U.S. Patent No.4,814,470 claims the active ingredient of the drug product Taxotere® as a compound, and these claims are not limited to specific polymorphic forms. However, the patent does not specifically claim any particular polymorph of the active ingredient, and therefore the answer to Question 2.2 is "no".

Aventis Pharmaceuticals

Aventis Pharmaceuticals, Inc.
200 Crossings Blvd., P.O. Box 6890
Bridgewater, NJ 08807-0890

Patent Information and Certification

Forms FDA 3542a for United States Patent No. 5,438,072

Department of Health and Human Services
Food and Drug Administration

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

Form Approved: OMB No. 0910-0513
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NDA NUMBER
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NAME OF APPLICANT / NDA HOLDER
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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)
Taxotere®

ACTIVE INGREDIENT(S)	STRENGTH(S)
Docetaxel	Single dose vials containing 20mg(0.5 ml) or 80mg(2.0 ml) EQ 40mg Base/ml

DOSAGE FORM
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1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,438,072	8/1/1995	11/22/2013

d. Name of Patent Owner	Address *(of Patent Owner)*	
Aventis Pharma S.A.	20 avenue Raymond Aron	
	City/State: 92160 Antony France	
	ZIP Code	FAX Number *(if available)*: 011 49 69 305 80556
	Telephone Number: 011 49 69 305 6181	E-Mail Address *(if available)*: markus.jacobi@aventis.com

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)	Address *(of agent or representative named in 1.e.)*	
☞ Louis J. Wille Vice President, Global Patent Litigation	Aventis Pharmaceuticals Inc. 1041 Route 202-206 - P.O. Box 6800	
	City/State: Bridgewater, NJ	
	ZIP Code: 08807-0800	FAX Number *(if available)*: 908 231-2691
	Telephone Number: 908 231-5721	E-Mail Address *(if available)*: lou.wille@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

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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.		
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 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, 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 *(as listed in the patent)*	Does the patent claim 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 approved 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

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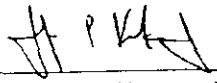	11/17/2003

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

Name Joseph P. Kirk Jr.	
Address Aventis Pharmaceuticals Inc. 1041 Route 202-206 - P.O. Box 6800	City/State Bridgewater, New Jersey
ZIP Code 08807-0800	Telephone Number 908 231-5916
FAX Number *(if available)* 908 231-2840	E-Mail Address *(if available)* joseph.kirk@aventis.com

Aventis Pharmaceuticals

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200 Crossings Blvd., P.O. Box 6890
Bridgewater, NJ 08807-0890

Patent Information and Certification

Forms FDA 3542a for United States Patent No. 5,714,512.

Department of Health and Human Services
Food and Drug Administration

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

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NDA NUMBER
20-449 (Supplemental - Breast adjuvant)

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1. GENERAL

a. United States Patent Number
5,714,512

b. Issue Date of Patent
2/3/1998

c. Expiration Date of Patent
7/3/2012

d. Name of Patent Owner
Aventis Pharma S.A.

Address *(of Patent Owner)*
20 avenue Raymond Aron

City/State
92160 Antony France

ZIP Code

FAX Number *(if available)*
011 49 69 305 80556

Telephone Number
011 49 69 305 6181

E-Mail Address *(if available)*
markus.jacobi@aventis.com

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)

Louis J Wille
Vice President, Global Patent Litigation

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City/State
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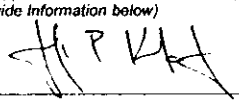	11/17/2003

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5,698,582

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12/16/1997

c. Expiration Date of Patent
7/3/2012

d. Name of Patent Owner
Aventis Pharma S A

Address *(of Patent Owner)*
20 avenue Raymond Aron

City/State
92160 Antony France

ZIP Code

FAX Number *(if available)*
011 49 69 305 80556

Telephone Number
011 49 69 305 6181

E-Mail Address *(if available)*
markus.jacobi@aventis com

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)

Louis J. Wille
Vice President, Global Patent Litigation

Address *(of agent or representative named in 1 e)*
Aventis Pharmaceuticals Inc
1041 Route 202-206 -P.O. Box 6800

City/State
Bridgewater, NJ

ZIP Code
08807-0800

FAX Number *(if available)*
908 231-2691

Telephone Number
908 231-5721

E-Mail Address *(if available)*
lou.wille@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?	☐ 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.		
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 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, 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 *(as listed in the patent)*	*Does the patent claim 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 approved labeling.)*		

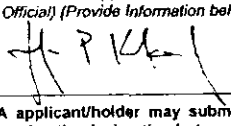
5. No Relevant Patents

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
	11/17/2003

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 Joseph P. Kirk Jr.	
Address Aventis Pharmaceuticals Inc. 1041 Route 202-206 - P.O. Box 6800	City/State Bridgewater, New Jersey
ZIP Code 08807-0800	Telephone Number 908 231-5916
FAX Number *(if available)* 908 231-2840	E-Mail Address *(if available)* joseph.kirk@aventis.com

EXCLUSIVITY SUMMARY FOR NDA # _20-449_____ SUPPL #__029_____

Trade Name ___Taxotere Generic Name __docetaxel_____

Applicant Name __Aventis_____ HFD # ___HFD-150_____

Approval Date If Known ___August 18, 2004_____

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 question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_X_/ NO /___/

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

___505 (b) (1)___SE1__

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 /_x_/ 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 /_x_/ NO /___/

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

_____3 years_____

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

YES /___/ NO /_x_/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen 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 /__x/

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 /_x_/ NO /___/

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

NDA# ____20-449_____ ___Taxotere (docetaxel)

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 NDA'S 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 /__x/ 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 /_x_/ 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 /_x_/

(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 /_x_/

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 /__x/

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 /_x_/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 35,555 YES /__X/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

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 /_x__/

If yes, explain: _____

_____

Signature Date
Title:

Signature of Office/ Date
Division Director

Form OGD-011347 Revised 05/10/2004

Aventis Pharmaceuticals

Aventis

Aventis Pharmaceuticals, Inc.
200 Crossing, Blvd., P.O. Box 6890
Bridgewater, NJ 08807-0890

Debarment Certification

February 17, 2004

Aventis Pharmaceutical Inc. hereby certifies that it has not used and will not use in any capacity the services of any person debarred pursuant to section 306(a) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 335(a) and (b)] in connection with this application.

Cheryl L. Anderson
Senior Director and Therapeutic Area Head, Oncology

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 20-449 Supplement Type (e.g. SE5): SE1 Supplement Number: 029

Stamp Date: 3-17-04 Action Date: PDUFA 9-17-04

HFD -150 Trade and generic names/dosage form: Taxotere (docetaxel) for injectable concentrate

Applicant: Aventis Therapeutic Class: 1P

Indication(s) previously approved: breast and NSCLC.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Taxotere® in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node-positive breast cancer.

Is there a full waiver for this indication (check one)?

☑ Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☑ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed

☐ **Other:**_____

udies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

ection D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager
Ann Staten

cc: NDA 20-449/s-029
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Aventis Pharmaceuticals, Inc.
200 Crossing, Blvd., P.O. Box 6890
Bridgewater, NJ 08807-0890

User Fee Cover Sheet

Form FDA 3397 is included in Section 1.4.5.1
A copy of User Fee Check is included in Section 1.4.5.2

NDA 20449 Taxotere (Docetaxel)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

user fee.pdf pg 2

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS
Aventis Pharmaceuticals Inc.
200 Crossing Boulevard, Mail Stop
BX2-209G
POBox 6890
Bridgewater, NJ 08807-0890

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
20,449

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____ (APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER *(Include Area Code)*
(908) 304-6471

3. PRODUCT NAME
TAXOTERE® (docetaxel)

6. USER FEE I D NUMBER
4700

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

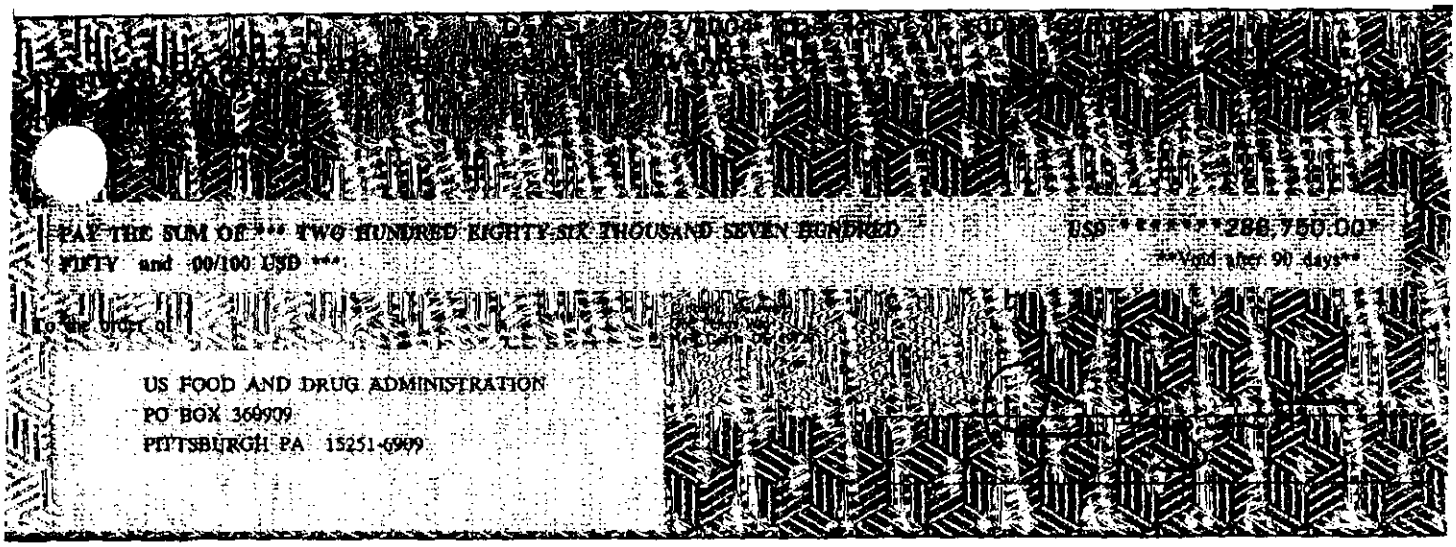
☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FORTHIS APPLICATION?
☐ YES ☒ NO
(See item 8, reverse side if answered YES)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Cheryl D. Anderson	Senior Director and Therapeutic Area Head, Oncology	1/30/2004

FORM FDA 3397 (1/03)

PSC Media Arts (301) 443-6690 EF



⑈0009162536⑈ ⑆031100209⑆ 38645293⑈

Aventis

Date :	Vendor:	Page :	Check No.:
02/03/2004	10155891	1/ 1	0009162536

Date	Reference/	Document	Text	Gross Amount	Discount	Net Amount
004	INV013004	1900701949	Give:F.Lee-UserFee4700-TaxotereBreastAdjuvant	286,750.00	0.00	286,750.00

*******286,750.00*

AI

752940

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 20-449 Supplement # SE1-029

Trade Name: Taxotere Injection Concentrate
Generic Name: docetaxel
Strengths: 20 mg and 80 mg

Applicant: Aventis Pharmaceuticals

Date of Application: March 17, 204
Date of Receipt: March 17, 2004
Date clock started after UN:
Date of Filing Meeting: May 13, 2004
Filing Date: May 16, 2004
Action Goal Date (optional): September 17, 2004 User Fee Goal Date: September 17, 2004

Indication(s) requested: Taxotere® in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node-positive breast cancer.

Type of Original NDA: (b)(1) _____ (b)(2) _____
OR
Type of Supplement: (b)(1) ____X____ (b)(2) _____
NOTE: 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). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S _____ P ____X____
Resubmission after withdrawal? _____ Resubmission after refuse to file? ___ _____
Chemical Classification: (1,2,3 etc.) _____
Other (orphan, OTC, etc.) ___ ____

User Fee Status: Paid ___X____ Exempt (orphan, government) ___ _____
Waived (e.g , small business, public health) _ _____

Form 3397 (User Fee Cover Sheet) submitted: YES X NO
User Fee ID # ____4700_____
Clinical data? YES ___X___ NO, Referenced to NDA # _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES NO X

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? YES NO X

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

Is the application affected by the Application Integrity Policy (AIP)? YES NO X
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES X NO
- Was form 356h included with an authorized signature? YES X NO
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES X NO
  If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A YES X NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?
  All in an eNDA in CTD format

  Additional comments:
- If in Common Technical Document format, does it follow the guidance? N/A YES X NO
- Is it an electronic CTD? N/A YES NO X
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- Patent information submitted on form FDA 3542a? YES X NO
- Exclusivity requested? YES, _3_____years NO
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES X NO
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., *"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application."* Applicant may not use wording such as "To the best of my knowledge . . . ."

- **Financial Disclosure forms included with authorized signature?** YES X NO
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? N/A YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES X NO
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

- List referenced IND numbers:

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 8-21-03 NO
  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES X NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? N/A X YES NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A X YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A X YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?
  N/A YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO
  If no, did applicant submit a complete environmental assessment? YES NO

If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? N/A YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #:
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").
- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

  YES NO
- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO
- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

  ____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

  ____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

  ____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

  ____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

  IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

  ____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

  ____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications

that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

Formatted: Bullets and Numbering

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)
____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:
  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

    YES NO
  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

    YES NO
  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

    N/A YES NO
  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

    N/A YES NO
- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):
  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

    YES NO
  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

    YES NO
  - EITHER
    The number of the applicant's IND under which the studies essential to approval were conducted.

    IND # _____ NO

    OR

    A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

    N/A YES NO
- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

  YES NO

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT

MEMO OF FILING MEETING

DATE: 5-13-04

BACKGROUND:
(Provide a brief background of the drug, e.g., it was already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Staten, YHsieh, Dagher, Abraham, Rahman, Li, Sridhara, Williams, Cortazar

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	Dr. Pat Cortazar
Secondary Medical:	Dr. Ramzi Dagher
Statistical:	Dr. Ning Li
Pharmacology:	N/A
Statistical Pharmacology:	N/A
Chemistry:	N/A
Environmental Assessment (if needed):	Dr. Yung-Ao Hsieh
Biopharmaceutical:	Dr. Sophia Abraham
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	Dr. David Gan
Regulatory Project Management:	Ann Staten
Other Consults:	Joseph Grill (DDMAC)

Per reviewers, are all parts in English or English translation? **YES**
If no, explain:

CLINICAL FILE __✔__ REFUSE TO FILE ____

- Clinical site inspection needed: **TBD**
- Advisory Committee Meeting needed? **TBD**
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A

CLINICAL MICROBIOLOGY NA __✔__ FILE _____ REFUSE TO FILE _____

STATISTICS FILE __✔__ REFUSE TO FILE _____

BIOPHARMACEUTICS FILE __✔__ REFUSE TO FILE _____

- **Biopharm. inspection needed:** **NO**

PHARMACOLOGY NA ___✔___ FILE _____ REFUSE TO FILE _____

- GLP inspection needed: **NO**

CHEMISTRY FILE ___✔___ REFUSE TO FILE _____

- Establishment(s) ready for inspection? N/A
- Microbiology N/A

ELECTRONIC SUBMISSION:
Any comments: **None**

Biopharm.: Clin Pharm section to be submitted at the end of March per pre-sNDA agreement – need raw data in SAS format.

REGULATORY CONCLUSIONS/DEFICIENCIES.

_____ The application is unsuitable for filing. Explain why:

___✔___ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

___✔___ No filing issues have been identified.

___none___ Filing issues to be communicated by Day 74. List (optional):

EXPECTED REVIEW COMPLETION:
Clinical: August 1st
Stat: After August 10th
Biopharm: August 1st

ACTION ITEMS:

1. Document filing issues/no filing issues conveyed to applicant by Day 74. (done: 5-19-04)
2. The following consultants should be cleared to assist in the review of this supplement: TBD if needed.
3. DSI memo – Pat to select sites asap if needed
4. One team meeting is needed (medical and Statistics only w/ TLs)
5. Two labeling meetings to be scheduled. Done: 8-4-04 and 8-10-04

_Ann Staten, RD_____
Regulatory Project Manager, HFD-150

Staten, Ann M

From: Cortazar, Patricia
nt: Thursday, May 27, 2004 3:00 PM
Staten, Ann M
cc: Dagher, Ramzi; Pazdur, Richard; Li, Ning; Sridhara, Rajeshwari; Abraham, Sophia
Subject: DSI consult

I did a preliminary review of the primary efficacy endpoint by sites and the results are very even. Therefore, I do not recommend a DSI inspection. At this point the data looks very solid with similar results across centers.
Ann:
Please let the DSI division that an inspection would not be necessary.
thanks,

Patricia Cortazar, MD
Medical Officer
Division of Oncology Drug Products
FDA

PROJECT MANAGER REVIEW OF LABELING

NDA 20-449/S-029

Drug:	**Taxotere (docetaxel) Concentrate for Injection, 20 mg and 80 mg**
Applicant:	**Aventis**
Submission Date:	**March 17, 2004**
Receipt Date:	**March 17, 2004**

BACKGROUND:

On May 19, 2004, NDA 20-449/S-028 was approved, which provided for "Taxotere in combination with prednisone as a treatment for patients with androgen independent (hormone refractory) metastatic prostate cancer" as well as several other revisions to the package insert.

The final printed labeling (FA) for S-028 was submitted electronically on May 27, 2004 and it was accepted on June 21, 2004.

This new supplement (S-029) provides for the following new proposed indication: "TAXOTERE in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer." as well as other revisions.

On June 23, 2004, Aventis provided an electronic copy of the package insert which combined the approved labeling from S-028 into the proposed labeling for S-029.

DOCUMENTS REVIEWED:

I compared the electronic Word version of the proposed draft package insert text for S-029 against the electronic version of the final printed labeling for S-028 submitted on May 27, 2004.

REVIEW:

The only changes in the new version are those the sponsor proposes for this supplement.

CONCLUSION - RECOMMENDED REGULATORY ACTION:

The proposed draft package insert for S-029 with tracked changes is attached.

With the concurrence of the Medical, Statistical and Clinical Pharmacology reviewers, this labeling may be approved (see their reviews).

___ *{See appended electronic signature page}*_
Ann Staten, Regulatory Health Project Manager
___*{See appended electronic signature page}*_
Dotti Pease, Chief, Project Manager Staff

7 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Staten, Ann M

From: Staten, Ann M
Sent: Tuesday, August 26, 2003 11:21 AM
To: Michael. Rozycki (Michael.Rozycki@aventis.com)
Subject: Follow-up questions for presNDA meeting (adj. Breast)
Importance: High

Hi Mike,

Attached is our response to your submission dated 8-22-03 (serial number 1115).

Please let me know if you need anything else.

Sincerely,

Ann

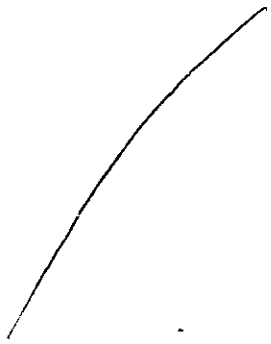
1. Aventis Follow-Up Comment and Question #1: Aventis expects to submit the sNDA on or about January 29, 2004. At present, patient accrual to Study XRP6976D/1001 is ongoing, and as such, Aventis cannot commit to the submission of a final study report before the end of May 2004. Aventis believes that the mature efficacy data and the clinical safety experience which will be included with Study TAX316, and supported by the safety data from Study GEICAM 9805, does not warrant delaying the submission of the sNDA until the availability of a final report for Study XRP6976D/1001. Hence, Aventis proposes to submit the final report for Study XRP6976D/1001 after the initial submission of the subject sNDA, but before the end of May 2004.

Does FDA agree with this timeframe for the submission of a final report for Study XRP6976D/1001?

FDA Response

Yes, we agree. However, delay of your submission of the final study report for Study XRP6976D/1001 may delay our completion of the review and final action on the sNDA submission.

2. Aventis Follow-Up Comment and Question #2; In the original question in the briefing document, Aventis offered to include supportive pharmacokinetic reports for the following four additional studies in the sNDA submission:



In the original question, Aventis indicated that it does not regard these additional studies as being capable, separately or in combination, of confirming the absence of an interaction among all of the constitutive agents of the TAC treatment regimen. Aventis does not plan to include case report forms or SAS datasets containing tabulations of analytical results (including, but not limited to, efficacy, safety, dosing, and baseline demographics results) with the sNDA

submission, but will provide available data to FDA reviewers upon request. The FDA response of August 21 did not comment on the Aventis proposal for submission of these studies.

Does the FDA agree that the submission of pharmacokinetic information for Studies — escribed above would be helpful in assessing potential pharmacokinetic interactions?

FDA Response

No, we do not agree that the above studies will be helpful in assessing potential pharmacokinetic interactions. These studies are not relevant to the sNDA submission since dosing schedules and patient populations may differ from those recommended for the TAC combination. In addition, the potential pharmacokinetic interactions — n these studies may differ than that for the triple TAC combination.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Ann Staten
9/25/03 01:47:33 PM

Patricia Cortazar
9/26/03 11:47:07 AM

Aventis Pharmaceuticals

August 18, 2004

Food and Drug Administration
Attention: Richard Pazdur, M.D.
Director, Division of Oncology Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont 2 Room
1451 Rockville Pike
Rockville, MD 20852

Supplemental NDA 20-449/S-029: TAXOTERE® (docetaxel) Injection Concentrate

Amendment to Pending Supplemental NDA

Responses to FDA Requests for Information

Dear Dr. Pazdur:

Reference is made to the March 17, 2004 submission of supplemental New Drug Application (sNDA) 20-449/S-029, and to a request from Cmdr. Ann Staten (FDA) to Daniel Bollag (Aventis) during a telephone conversation on August 18, 2004. In the August 18 conversation, Cmdr. Staten requested that the final changes proposed for the adjuvant breast cancer indication communicated to FDA via electronic mail on August 18 be submitted to the supplemental NDA.

With this letter, Aventis is submitting to sNDA 20-449/S-029 the proposed label changes which were sent to the FDA via electronic mail today (see Appendix).

Aventis certifies that all electronic media are free from computer virus. The virus scan for this submission was performed using Symantec's Norton Antivirus Corporate Edition, Version 7.50.846, Scan Engine Version 4.1.0.6. The Virus Definition File is Version 60816c, issued August 16, 2004.

Aventis considers the information included in this submission to be confidential and proprietary, and requests that no portion thereof be disclosed to third parties, under the Freedom of Information Act or otherwise, without first obtaining written permission from the applicant under 21 CFR 314.430.

If you have any questions or require additional information to facilitate the review, please contact me at (908) 304-6431 (Fax: 908-304-6531), or in my absence, Cheryl Anderson at (908) 304-6471.

Sincerely,

Daniel M. Bollag, Ph.D.
Director
US Regulatory Affairs

Enclosures: Form FDA 356h
Appendix
1 CD, <1 MB

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER
NDA #20-449/S-029

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Aventis Pharmaceuticals, Inc	August 18, 2004
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(908) 304-6431	(908)-541-5274
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 200 Crossing Blvd., Route 202-206 P.O. Box 6890 Bridgewater, NJ 08807-0890	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State,, ZIP Code, telephone & FAX number)* IF APPLICABLE N/A

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* NDA #20-449

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY- ALVESCO™
Docetaxel	TAXOTERE Injection Concentrate

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
(2R,3S)-N-carboxy-3-phenylisoserine,N-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate

CODE NAME *(If any)*
XRP 6976

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Concentrate for Infusion	20 mg and 80 mg	Intravenous infusion

(PROPOSED) INDICATION(S) FOR USE:
—

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION:
Response to FDA Request for Information

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED N/A THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☒ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name,address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* – *Response to FDA Request for Information*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601 12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
DM Bollag	Daniel M. Bollag, Ph.D. Director, U.S. Regulatory Affairs	08/18/04

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Aventis Pharmaceuticals, Inc. Route 202-206 POBox 6800 Bridgewater, NJ 08807-0890	(908) 304-6431

Public reporting burden for this collection of information is estimated to average 24 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
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

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.

Bollag, Daniel PH/US

From: Bollag, Daniel PH/US
Sent: Wednesday, August 18, 2004 2:07 PM
To: 'statena@cder.fda.gov'
Cc: Bollag, Daniel PH/US
Subject: NDA 20-449/S-029: final label changes
Signed By: daniel.bollag@aventis.com
Security Label: Signed & encrypted
Contacts: Ann Staten

Hello Ann,

As we discussed a few minutes ago, here are the changes to the label and postmarketing commitment statements that you sent to us this morning. The Word document has the changes highlighted in revision marks.

Label:
At the time of this interim analysis, based on a total of 219 deaths, overall survival was longer for TAC than FAC (hazard ratio=0.69, 2-sided 95% CI=0.53, 0.90). (See Figure Y). There will be further analysis at the time survival data mature.

Postmarketing commitment:
To submit a complete report of the updated TAX316 data to verify the efficacy based on 700 events of DFS and safety of Taxotere in the adjuvant treatment of women with operable node-positive breast cancer and to submit the final analysis of overall survival (expected to occur in 2010).

Best regards, Dan

_____ Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

___1___ § 552(b)(5) Draft Labeling

SE1-029 BLA NDA SUPPL AMEND

DUPLICATE

Aventis

August 5, 2004

Food and Drug Administration
Attention: Richard Pazdur, M.D.
Director, Division of Oncology Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont 2 Document Room
1451 Rockville Pike
Rockville, Maryland 20852

RECEIVED
AUG - 6 2004
DDR-150/CDER

Supplemental NDA 20-449/S-029: TAXOTERE® (docetaxel) Injection Concentrate

Amendment to Pending Supplemental NDA
Response to July 30, 2004 FDA Request for Information

Dear Dr. Pazdur:

Reference is made to the March 17, 2004 submission of supplemental New Drug Application (sNDA) 20-449/S-029.

Reference is also made to an electronic mail message received from the Food and Drug Administration (FDA) on July 30, 2004, requesting information pertaining to the review of sNDA 20-449/S-029. With this letter, Aventis is responding to the FDA's request for information.

Question 1. *Please explain what type of additional radiotherapy the following patients had and the difference with protocol radiotherapy: 32311, 27601, 17423.*

Aventis Response. Patient 32311 (TAC) had a left quadrantectomy on —. She received 2 cycles of treatment (the last TAC cycle was given on February 16, 1999) and then discontinued due to AE (allergy). She then received additional chemotherapy with FAC starting on —. She received adjuvant radiotherapy to the left breast (50 Gy) from — , which was reported as "Adjuvant Radiotherapy as per Protocol" in listing L26. This radiotherapy was also reported as radiotherapy to the left breast in the module "Non-Systemic Anti-Cancer Therapy," as shown in listing L31.

Patient 27601 (FAC) had a right lumpectomy on —. She received the maximum treatment of 6 cycles, with the last cycle given on April 17, 1998. She had adjuvant radiotherapy to the right breast (50 Gy) and right supraclavicular region (50 Gy) from — 1998, as well as a boost to the right breast (10 Gy) from — (reported as "Adjuvant Radiotherapy as per Protocol" in listing L26). This radiotherapy was also incorrectly reported in the module "Non-Systemic Anti-Cancer Therapy" as radiotherapy to the right breast, as shown in listing L31.

Patient 17423 (TAC) had a right lumpectomy on — She withdrew consent before the first administration of study drug (reason: "unhappy with assignment with treatment arm"). She then received adjuvant chemotherapy with AC-Taxol from — She had adjuvant radiotherapy to

the right breast (5040 cGy) from — and to the right axillary region (1080 cGy) from — (reported as "Adjuvant Radiotherapy as per Protocol" in listing L26). This radiotherapy was also reported in the module "Non-Systemic Anti-Cancer Therapy" as radiotherapy to the right breast, as shown in listing L31.

In summary, all three patients received adjuvant radiotherapy following adjuvant chemotherapy. However, patients 32311 and 17423 did not receive the full 6 cycles of assigned chemotherapy. Nevertheless, in each case, the radiotherapy could be considered as "per protocol," i.e., no "extra" radiotherapy was given.

Question 2. *It is very important to find the reason why patient 25501 received radiotherapy to C7 - D11. Please submit information on radiation oncologist clinical notes, imaging before radiation,etc.*

Aventis Response. On August, 2, 2004 Aventis sent the following response to the FDA via electronic mail:

> "Per our July 8, 2004 response to the July 6, 2004 information request, subject 25501 had a baseline bone scan and bone x-ray that were suspicious but inconclusive for bone metastasis. At cycle 3, repeat imaging confirmed the bone metastasis, and the TNM status at baseline was therefore changed to M1 by IRF. Hence, this patient is considered to have had a DFS event at baseline, and all radiotherapy received by this patient was by definition post-DFS. The CRF does not capture the reason for radiotherapy under such circumstances."

It should be clarified that, contrary to what was stated in the above response, patient 25501 was not considered to have had a DFS event at baseline. Rather, she was considered to be metastatic at baseline. According to the Intention to Treat principle, her DFS was to be calculated once she had relapsed, which in this case was when she showed progression of her metastatic disease on January 1, 2001. Thus, a breast cancer relapse (BCR) was assigned on this date, as shown in listing L30. After 6 cycles of FAC (the last cycle was given on November 16, 1998) and before her BCR, she had radiotherapy to the spine (C7-D11) from — as well as chemotherapy (Taxotere on — and bisphosphonates (pamidronate on —) as described in listing L31.

A copy of this submission was forwarded to Commander Ann Staten (FDA) via electronic mail on August 5, 2004. Please contact Cheryl Anderson at 908-304-6471, for all matters regarding this submission.

Sincerely,

Michael D. Rozycki

Michael D. Rozycki, Ph.D.
Director, Regulatory Affairs

Enc: Form FDA 356

SE1.029_BM
DUPLICATE

Aventis

August 4, 2004

NDA SUPPL AMEND

Food and Drug Administration
Attention: Richard Pazdur, M.D.
Director, Division of Oncology Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont 2 Document Room
1451 Rockville Pike
Rockville, Maryland 20852

RECEIVED
AUG - 5 2004
DDR-150/CDER

Supplemental NDA 20-449/S-029: TAXOTERE® (docetaxel) Injection Concentrate

Amendment to Pending Supplemental NDA

Responses to FDA Requests for Information

Dear Dr. Pazdur:

Reference is made to the March 17, 2004 submission of supplemental New Drug Application (sNDA) 20-449/S-029.

Reference is also made to electronic mail queries received from the Food and Drug Administration (FDA) on June 15, 16, 17, 22, July 6 (2 queries), 8, 9, 12 (2 queries), 13, 14, 19, and 27, 2004, requesting information pertaining to the review of sNDA 20-449/S-029. Aventis provided responses *via* electronic mail to these information requests on June 18 (2 responses), 22, 23, July 8 (4 responses), 14 (2 responses), 15, 16 (2 responses), 20, 21, and 28, 2004.

With this letter, Aventis is submitting to sNDA 20-449/S-029 the responses, listed above, that have previously been sent to the FDA *via* electronic mail. These responses are included herewith in the Appendix.

Please contact me at 908-304-6412 (Fax: 908-304-6549) or, in my absence, Cheryl Anderson at 908-304-6471, for all matters regarding this submission.

Sincerely,

Michael D. Rozycki

Michael D. Rozycki, Ph.D.
Director, Regulatory Affairs

Enc: Form FDA 356h
Appendix

Aventis Pharmaceuticals Inc. • 200 Crossing Boulevard • PO Box 6890 • Bridgewater, NJ 08807-0890 • www.aventis.com
Telephone (908) 304-7000

DUPLICATE

NDA SUPPL AMEND
SE1-029-BM

August 3, 2004

RECEIVED
AUG - 4 2004
DDR-150/CDER

Food and Drug Administration
Attention: Richard Pazdur, M.D.
Director, Division of Oncology Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont 2 Document Room
1451 Rockville Pike
Rockville, Maryland 20852

Supplemental NDA 20-449/S-029: TAXOTERE® (docetaxel) Injection Concentrate

Amendment to Pending Supplemental NDA

Response to FDA Requests for Information

Dear Dr. Pazdur:

Reference is made to the March 17, 2004 submission of supplemental NDA 20-449/S-029.

With this letter, Aventis is submitting responses to the following information requests received from Cmdr. Ann Staten, Food and Drug Administration, Division of Oncology Drug Products, on July 29, 2004 via electronic mail:

Question 1: *Please provide the definition for the HORMONOREC dataset. We need definition of ERSTA and PGRSTA 1,2,3,4 and A.*

Response to Question 1: The codes used are as follows: 1 = Negative; 3 = Positive; 4 = Not Assessable; A = Not Done, when confirmed by the investigator (i.e., "Not Done" box checked for Biochemical Method or Immunocytochemistry tests on page B-9 of the case report form). The number "2" is not used.

Question 2: *You reported — ypersensitivity reactions on the proposed labeling. Please explain what type of reactions and submit all the information or explain where is the information located in the Study Report.*

Response to Question 2: Hypersensitivity reactions reported in the proposed labeling consist of all events reported as "allergy" in Table 47 of the TAX 316 clinical study report; namely, literal terms from investigators that were coded to the NCI term "allergy", as well as events identified with the preprinted term "allergy" on the case report form. The term "hypersensitivity" was chosen for labeling purposes in lieu of "allergy" in order maintain consistency in the TAXOTERE labeling.

Aventis Pharmaceuticals Inc. • 200 Crossing Boulevard • PO Box 6890 • Bridgewater, NJ 08807-0890 • www.aventis.com
Telephone (908) 304-7000

Question 3: *Please send all the information you have regarding the three patients with leukemia e.g. cytogenetics, classification, etc.*

Response to Question 3: At the time of submission of the sNDA (March 17, 2004), three cases of leukemia (patients 13510, 24105, and 40701) were reported in the clinical database for study TAX 316. A fourth case (patient 10621) was also reported in the study report for TAX 316 because this case occurred after the data base lock for the second interim analysis for TAX 316 but prior to the submission of the sNDA. Comparative information for patients 13510, 24105, 40701, and 10621 is included in the Table in Appendix 1 to this submission. Additional information is available in the CIOMS forms for these patients, included in Appendix 2.

A fifth case, patient 27602, involves possible myelodysplastic syndrome, but was reported as non-serious and unrelated to study chemotherapy according to the investigator. This case was reported in the 120-day safety update for sNDA 20-449/S-029 that was submitted on July 16, 2004. Information for this case is not included in the table in Appendix 1.

A copy of this submission was forwarded via electronic mail to Cmdr. Staten on August 2, 2004. Please contact me at 908-304-6412 (Fax: 908-304-6549) or, in my absence, Cheryl Anderson at 908-304-6471, for all matters regarding this submission.

Sincerely,

Michael D. Rozycki

Michael D. Rozycki, Ph.D.
Director, Regulatory Affairs

Enc: Form FDA 356h
2 Appendices

Staten, Ann M

From: Gohel, Lopa
Sent: Tuesday, August 03, 2004 2:34 PM
To: Staten, Ann M
Subject: RE: taxotere labeling meeting

Hi Ann:
I reviewed the label and do not have any comments at this time.
Thanks,
Lopa

-----Original Message-----
From: Staten, Ann M
Sent: Tuesday, August 03, 2004 10:08 AM
To: Gohel, Lopa
Subject: RE: taxotere labeling meeting

-----Original Message-----
From: Gohel, Lopa
Sent: Tuesday, August 03, 2004 10:03 AM
To: Staten, Ann M
Subject: taxotere labeling meeting

Hi Ann:
I am not in the office tomorrow and will be unable to attend the taxotere labeling meeting. Do you have a copy of the label that I can review and send for comments if necessary?

Thanks,
Lopa

3 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Staten, Ann M

From: Staten, Ann M
Sent: Friday, July 30, 2004 10:14 AM
To: 'Michael.Rozycki@aventis.com'
Subject: NDA information request s-029

Importance: High

Mike,

Here is another information request.

Please submit ASAP the following information:

- Please explain what type of additional radiotherapy the following patients had and the difference with protocol radiotherapy: 32311, 27601, 1743
- It is very important to find the reason why patient 25501 received radiotherapy to C7 - D11. Please submit information on radiation oncologist clinical notes, imaging before radiation,etc.

Thank you,

Ann

Staten, Ann M

From: Staten, Ann M
Sent: Thursday, July 29, 2004 10:22 AM
To: 'Michael.Rozycki@aventis.com'
Subject: FW: TAXOTERE nda INFO REQUEST

Importance: High

Here is another.

Thanks!

You reported ~ hypersensitivity reactions on the proposed labeling. Please explain what type of reactions and submit all the information or explain where is the information located in the Study Report.

APPEARS THIS WAY
ON ORIGINAL

Staten, Ann M

From: Staten, Ann M
Sent: Thursday, July 29, 2004 10:39 AM
To: 'Michael.Rozycki@aventis.com'
Subject: Urgent Taxotere NDA info request

Importance: High

Please see below request to be submitted asap.

Thanks!

Please provide the definition for the HORMONOREC dataset. We need definition of ERSTA and PGRSTA 1,2,3,4 and A.

APPEARS THIS WAY
ON ORIGINAL

Staten, Ann M

From: Staten, Ann M
Sent: Thursday, July 29, 2004 10:41 AM
To: 'Michael.Rozycki@aventis.com'
Subject: FW: Taxotere NDA information request

And another! I am sorry for not batching the requests.

Thanks,
ann

Please send all the information you have regarding the three patients with leukemia e.g. cytogenetics, classification, etc..

APPEARS THIS WAY
ON ORIGINAL

Staten, Ann M

From: Staten, Ann M
Sent: Tuesday, July 27, 2004 12:46 PM
To: 'Michael.Rozycki@aventis.com'
Subject: Taxotere info request

Importance: High

Dear Mike,

Here is another request from the medical review:

Please submit an adverse event narrative for patient 10403 whose cause of death was stated in the Study Report as "cardiopathy".

Thanks,
Ann

Staten, Ann M

From: Staten, Ann M
Sent: Wednesday, July 14, 2004 3:09 PM
To: 'Michael.Rozycki@aventis.com'
Subject: Taxotere NDA information request

Hi Mike,

Here is another quest for clarification just received.

The number of patients who had breast conserving surgery and mastectomy from Tables 18 and 24 are not the same. Please explain the difference.

Thanks,
Ann

Staten, Ann M

From: Staten, Ann M
Sent: Tuesday, July 13, 2004 9:33 AM
To: 'Michael.Rozycki@aventis.com'
Subject: Taxotere NDA information request

Dear Mike,

Here are three more information requests.

1. Please explain why the number of events from Table 29 of the Study Report (316.pdf, pg 136) and Tables from 3785, 3786, 3787 are not the same. For example:
   - the number of patients with distant relapse are 115 (TAC) and 158 (FAC) on Table 29 and 116 (TAC), 159 (FAC) on page 3785.
   - the number of patients with second primary malignancies are 20 (TAC) and 26 (FAC) on Table 29 and 29 (TAC), 34 (FAC) on page 3786 and 3787.

2. The number of patients with contralateral breast cancer from table 9 (page 136) and page 3787 is not the same. Please explain the difference and separate DCIS from invasive breast cancer.

3. Please provide the following information in a table:

Site of loco-regional recurrence	TAC arm	FAC arm
Total # with locoregional recurrence		
Chest wall		
Ipsilateral breast		
Other regional lymph nodes		
Axillary lymph nodes		

Thanks!
Ann

APPEARS THIS WAY
ON ORIGINAL

Staten, Ann M

From: Staten, Ann M
Sent: Monday, July 12, 2004 12:06 PM
To: 'Michael.Rozycki@aventis.com'
Subject: Taxotere NDA information request

Dear Mike,

We have 2 additional requests:

1. Please submit detailed information on post-study therapy for all patients who withdrew or had an event.

2. Did any patient receive bisphosphonates after randomization? If the answer is yes, please provide detailed information.

Thanks,
Ann

APPEARS THIS WAY
ON ORIGINAL

Pease, Dorothy W

From: Pease, Dorothy W
nt: Monday, July 12, 2004 8:28 AM
: 'Michael.Rozycki@aventis.com'
Cc: Staten, Ann M
Subject: Taxotere NDA 20-449/S029

Another clinical request:

The study report states (section 6.3.4.2) that 10 patients received prior anti-tumor treatments such as surgery, radiotherapy, chemotherapy (TAC) and hormonotherapy. Please submit detailed information including patient identification, treatments received and timing with respect to randomization.

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products, HFD-150
301-594-5742/301-594-0498 (fax)

Pease, Dorothy W

Fr: Cortazar, Patricia
Friday, July 09, 2004 2:47 PM
Pease, Dorothy W
Cc: Dagher, Ramzi; Cortazar, Patricia
Subject: Taxotere NDA info request

Dotti:
Please send the following information request to the sponsor.

- The study report states (section 6.3.4.2) that 10 patients received prior anti-tumor treatments such as surgery, radiotherapy, chemotherapy (TAC) and hormonotherapy. Please submit detailed information including patient identification, treatments received and timing with respect to randomization.

Thanks

Patricia Cortazar, MD
Medical Officer
Division of Oncology Drug Products
FDA

APPEARS THIS WAY
ON ORIGINAL

Pease, Dorothy W

From: Michael.Rozycki@aventis.com
Sent: Friday, July 09, 2004 11:35 AM
To: PEASE@cder.fda.gov
Cc: STATENA@cder.fda.gov
Subject: RE: Taxotere 20-449/S029

Dotti,

I have received the request and will provide an answer ASAP.

Thanks,
-Mike

Michael Rozycki, Ph.D.
Director, Oncology Regulatory Affairs
Global Regulatory Liaison, TAXOTERE
Aventis Pharmaceuticals, Inc.
Mail Code BX2-209G
200 Crossing Boulevard
Bridgewater, NJ 08807
Phone: 908-304-6412
Fax: 908-304-6549

-----Original Message-----
From: Pease, Dorothy W [mailto:PEASE@cder.fda.gov]
Sent: Friday, July 09, 2004 7:43 AM
To: Rozycki, Michael PH/US
Cc: Staten, Ann M
Subject: RE: Taxotere 20-449/S029

Additional request:

Please describe the following data from Table 27 "Major Protocol Deviations During Follow-up":

- **Patient ID, hormonal therapy received and reason for deviation from protocol.**
- **Patient ID, type of surgery and reason**
- **Patient ID, radiation therapy and reason**
- **Please confirm other therapies were ovarian ablation and reason for protocol deviation.**

Reason ER PR positive patients did not received hormonal therapy.

Dotti

Pease, Dorothy W

entered in DFS

From: Pease, Dorothy W
Sent: Friday, July 09, 2004 7:43 AM
To: 'Michael.Rozycki@aventis.com'
Cc: Staten, Ann M
Subject: RE: Taxotere 20-449/S029

Additional request:

Please describe the following data from Table 27 "Major Protocol Deviations During Follow-up":

- **Patient ID, hormonal therapy received and reason for deviation from protocol.**
- **Patient ID, type of surgery and reason**
- **Patient ID, radiation therapy and reason**
- **Please confirm other therapies were ovarian ablation and reason for protocol deviation.**

Reason ER PR positive patients did not received hormonal therapy.

Dotti

APPEARS THIS WAY
ON ORIGINAL

7/8/04 To PC

Pease, Dorothy W

From: Michael.Rozycki@aventis.com
Sent: Thursday, July 08, 2004 2:32 PM
To: PEASE@cder.fda.gov
Cc: statena@cder.fda.gov
Subject: RE: Additional Taxotere questions

Dear Dottie,

Please forward the following response to the Reviewer.

Question 1. Patient 11803 had 2 cycles of TAC and withdrew due to G3 skin (according to the Listing of treatment discontinuation due to AE). I can not find this information in the CRF. Please direct me where can I find the information in the CRF and specify the type of skin event.

Response: For patient 11803, the CRF entries in the AE module appear on CRF page C6, cycle 2, as follows: AE= Skin; grade= 3; serious= no; stop date=ongoing; action taken=1 (i.e. discontinued); relation to study drug=3 (i.e. probable). This information is displayed in Stat Table 1.04a as well as in listings L14 (AEs) and L25 (reason for discontinuation from study treatment).

There is no verbatim description of the AE provided by the investigator other than the NCI-CTC term "Skin". Referring to NCI-CTC version 1.0 definitions (as provided in the study CRF completion guidelines as well as in the study protocol in Appendix 3), Grade 3 for the term "Skin" means "generalized, symptomatic macular, papular, or vesicular eruption".

Question 2. Please explain the location in the electronic submission for the "listing of patients with non protocol therapy reasons for treatment discontinuation". Your response to a previous FDA information request did not include AEs that cause treatment discontinuation for patients: 22502, 21202, 21731,20803, 21312,25501, 23904, 13705, 17608, 27601, 28402, 17423, 30301 and 40401.

Response: The listing, "Listing of patients with non protocol therapy - reasons for treatment discontinuation" was created *ad hoc* to answer the Reviewer's question of June 22, 2004 (see response to Reviewer submitted via e-mail on June 23, 2004). This listing does not appear *per se* in the electronic submission of the sNDA (March 17, 2004), but data used to produce this listing was extracted from Statistical Table 3.12 and listing L25 (reason for discontinuation from study treatment), which are included in the electronic submission.

Of the 14 patients listed in the question, 13 did not discontinue due to AEs. 22502, 25501, 27601 (all FAC) and 23904 (TAC) completed the maximum of 6 cycles as per protocol (see L25), and their discontinuation was not caused by any AEs. 21202, 20803, 21312, 13705, 17423 (all FAC) discontinued due to "consent withdrawn", all of them because they refused the assigned treatment and wanted to receive the experimental arm (see L25, Stat Table 1.04c). Again, their discontinuation was not caused by any AEs. 17608 (TAC) received 2 cycles of treatment and then discontinued due to "consent withdrawn"; the reason cited was "does not want anymore Taxotere". AEs present at the last cycle (= cycle 2) are listed in Stat Table 1.04c and in listing L14. None of them caused treatment discontinuation for this patient. The following subjects discontinued due to "OTHER" (their discontinuation was not caused by any AEs): 21731 (TAC- not treated), reason = "pt ineligible due to low neutrophil count prior to first infusion"; 28402 (FAC 4 cycles), reason = "Doctor wished to treat with Taxol"; AEs present at last cycle (= cycle 4) are listed in L14: 30301 (FAC- not treated), reason = "misunderstanding of post admission excusion criteria".

Patient 40401 (TAC) did discontinue after 3 cycles due to a grade 1 fever in absence of infection (see L14, L25, Stat Table 1.04a). This patient is listed in the "listing of patients with non protocol therapy - reasons for treatment discontinuation" that was attached to the Sponsor's response e-mail of June 23, 2004.

Please let me know if there are any further questions.

Thanks and best regards,
-Mike

Michael Rozycki, Ph.D.
Director, Oncology Regulatory Affairs
Global Regulatory Liaison, TAXOTERE

inc. outgoing e-mails + 4 responses

Pease, Dorothy W

From: Pease, Dorothy W
Sent: Friday, July 09, 2004 7:29 AM
To: Cortazar, Patricia
Cc: Staten, Ann M
Subject: FW: Request re: Taxotere for Adj. Breast CA

mmsinfo.txt
(445 B)

-----Original Message-----
From: Michael.Rozycki@aventis.com [mailto:Michael.Rozycki@aventis.com]
Sent: Thursday, July 08, 2004 4:20 PM
To: PEASE@cder.fda.gov
Cc: STATENA@cder.fda.gov
Subject: FW: Request re: Taxotere for Adj. Breast CA

Dear Dottie,

My deepest apologies but I need to correct this response again. The corrected response to the first question should read as follows:

Question 1. Please explain if patients # 12212, 20613, 21204 and 25501 had biopsy confirmation of metastatic disease at baseline.

esponse: For each of these 4 patients (12212, 20613, 21204, and 25501), metastatic disease at baseline was determined only by imaging: there was no confirmation by biopsy. In each case. the original TNM status entry in the CRF was M0.

- In two of these cases (20613 and 25501), the original CRF entries for imaging at baseline were consistent with such an M0 status. However, the actual findings were unconfirmed. As the subjects progressed into treatment, further imaging demonstrated that these initial suspicious but unconfirmed-for-tumor images were in fact truly indicative of metastatic spots at baseline. More specifically, subject 20613 had a bone scan at baseline with suspicious spots, which at cycle 3 of study treatment was confirmed to be evidence of metastasis. Subject 25501 had a baseline bone scan and bone X-ray that were both suspicious, but inconclusive. At cycle 3, repeat imaging proved these images to be indicative of metastasis. By IRF, in both cases, the TNM status at baseline was then changed to M1.
- For the other two cases (12212 and 21204), the original CRF entries for imaging at baseline were inconsistent with such an M0 status. 12212 had baseline liver involvement evidence based on US, suspicious at the time of randomization but then later confirmed at cycle 6 by repeat exam to be indicative of liver tumor spot. The original CRF entry was made at the time when such a conclusion was reached, thus indicated liver lesion =yes, even though the same CRF said M0. M0 was later changed to M1 by IRF. A similar situation occurred for subject 21204, who at baseline had a suspicious ipsilateral supraclavicular node, which was confirmed via cycle 2 imaging.

Again, my apologies for this confusion.

Best regards,
-Mike
Michael Rozycki, Ph.D.
Director, Oncology Regulatory Affairs
Global Regulatory Liaison, TAXOTERE
Aventis Pharmaceuticals, Inc
Mail Code BX2-209G
) Crossing Boulevard
.dgewater, NJ 08807
Phone: 908-304-6412
Fax: 908-304-6549

Pease, Dorothy W

From: Cortazar, Patricia
Sent: Thursday, July 08, 2004 3:21 PM
To: Pease, Dorothy W
Subject: Taxotere NDA information request

Dotti:
Please forward the following.

Please describe the following data from Table 27 "Major Protocol Deviations During Follow-up":

- **Patient ID, hormonal therapy received and reason for deviation from protocol.**
- **Patient ID, type of surgery and reason**
- **Patient ID, radiation therapy and reason**
- **Please confirm other therapies were ovarian ablation and reason for protocol deviation.**
- **Reason ER PR positive patients did not received hormonal therapy.**

Thank you
Patricia Cortazar, MD
Medical Officer
Division of Oncology Drug Products
FDA

APPEARS THIS WAY
ON ORIGINAL

Pease, Dorothy W

From: Michael.Rozycki@aventis.com

Sent: Thursday, July 08, 2004 3:17 PM

To: PEASE@cder.fda.gov

Cc: STATENA@cder.fda.gov

Subject: FW: Request re: Taxotere for Adj. Breast CA

Dear Dottie,

My previous reply contained a small but significant error. The first bullet of the response to question 1 should read: "In two of these cases (20613 and 25501), the original CRF entries for imaging at baseline were inconsistent with such an M0 status."

The entire corrected response should read:

Question 1. Please explain if patients # 12212, 20613, 21204 and 25501 had biopsy confirmation of metastatic disease at baseline.

Response: For each of these 4 patients (12212, 20613, 21204, and 25501), metastatic disease at baseline was determined only by imaging; there was no confirmation by biopsy. In each case, the original TNM status entry in the CRF was M0.

- In two of these cases (20613 and 25501), the original CRF entries for imaging at baseline were inconsistent with such an M0 status. However, the actual findings were unconfirmed. As the subjects progressed into treatment, further imaging demonstrated that these initial suspicious but unconfirmed-for-tumor images were in fact truly indicative of metastatic spots at baseline. More specifically, subject 20613 had a bone scan at baseline with suspicious spots, which at cycle 3 of study treatment was confirmed to be evidence of metastasis. Subject 25501 had a baseline bone scan and bone X-ray that were both suspicious, but inconclusive. At cycle 3, repeat imaging proved these images to be indicative of metastasis. By IRF, in both cases, the TNM status at baseline was then changed to M1.
- For the other two cases (12212 and 21204), the original CRF entries for imaging at baseline were consistent with such an M0 status. 12212 had baseline liver involvement evidence based on US, suspicious at the time of randomization but then later confirmed at cycle 6 by repeat exam to be indicative of liver tumor spot. The original CRF entry was made at the time when such a conclusion was reached, thus indicated liver lesion =yes, even though the same CRF said M0. M0 was later changed to M1 by IRF. A similar situation occurred for subject 21204, who at baseline had a suspicious ipsilateral supraclavicular node, which was confirmed via cycle 2 imaging.

My apologies for any confusion.

Best regards,
-Mike

Michael Rozycki, Ph.D.
Director, Oncology Regulatory Affairs
Global Regulatory Liaison, TAXOTERE
Aventis Pharmaceuticals, Inc.
Mail Code BX2-209G
200 Crossing Boulevard
Bridgewater, NJ 08807
Phone: 908-304-6412
Fax 908-304 6549

-----Original Message-----
From: Rozycki, Michael PH/US
Sent: Thursday, July 08, 2004 2:50 PM
To: 'PEASE@cder.fda.gov'
Cc: 'STATENA@cder.fda.gov'

Subject: RE: Request re: Taxotere for Adj. Breast CA

Dear Dottie,

Please forward the following response to the reviewer.

Question 1. Please explain if patients # 12212, 20613, 21204 and 25501 had biopsy confirmation of metastatic disease at baseline.

Response: For each of these 4 patients (12212, 20613, 21204, and 25501), metastatic disease at baseline was determined only by imaging; there was no confirmation by biopsy. In each case, the original TNM status entry in the CRF was M0.

- In two of these cases (20613 and 25501), the original CRF entries for imaging at baseline were consistent with such an M0 status. However, the actual findings were unconfirmed. As the subjects progressed into treatment, further imaging demonstrated that these initial suspicious but unconfirmed-for-tumor images were in fact truly indicative of metastatic spots at baseline. More specifically, subject 20613 had a bone scan at baseline with suspicious spots, which at cycle 3 of study treatment was confirmed to be evidence of metastasis. Subject 25501 had a baseline bone scan and bone X-ray that were both suspicious, but inconclusive. At cycle 3, repeat imaging proved these images to be indicative of metastasis. By IRF, in both cases, the TNM status at baseline was then changed to M1.
- For the other two cases (12212 and 21204), the original CRF entries for imaging at baseline were consistent with such an M0 status. 12212 had baseline liver involvement evidence based on US, suspicious at the time of randomization but then later confirmed at cycle 6 by repeat exam to be indicative of liver tumor spot. The original CRF entry was made at the time when such a conclusion was reached, thus indicated liver lesion =yes, even though the same CRF said M0. M0 was later changed to M1 by IRF. A similar situation occurred for subject 21204, who at baseline had a suspicious ipsilateral supraclavicular node, which was confirmed via cycle 2 imaging.

Question 2. Please explain which regional lymph nodes were found metastatic and method of diagnosis for patients # 24507, 18302 and 26807.

Response:
For all subjects entered in the study, pathological node status as determined on the basis of pathological review of resected lymph nodes was required and eligibility for the study was defined as pN status = pN1 [mobile ipsilateral axillary node(s)].
Upon review and monitoring of source data, all three index subjects (24507, 18302 and 26807) were confirmed pN2 [ipsilateral lymph node(s) fixed to one another or adjacent structure].

In two cases (24507 and 18302) such a pN stage was mentioned at time of randomization request, but this information was mis-analyzed. the subject deemed eligible and thus randomized. In the third case, (26807), (26807), the original entry indicated pN1, which was later changed by investigator to pN2 as a result of the sponsor review on-site of source documents against the CRF.

No information is available in the database and CRF beyond pN2 regarding the exact anatomical location of those ipsilateral fixed axillary nodes.

Please let me know if there are any further questions.

Thanks and best regards,
-Mike

Michael Rozycki, Ph.D.
Director, Oncology Regulatory Affairs
Global Regulatory Liaison, TAXOTERE
Aventis Pharmaceuticals, Inc

Pease, Dorothy W

From: Cortazar, Patricia
Sent: Thursday, July 08, 2004 11:36 AM
To: Pease, Dorothy W
Cc: Dagher, Ramzi; Cortazar, Patricia
Subject: Taxotere NDA question to sponsor

Dotti:
Please submit the following information request to the sponsor:

- **Please send complete information on the number of cycles received of non-allowed chemotherapy and reasons for receiving non protocol therapy for patients in the attached table:**

Non- allowed erapy.doc (64 K

Thank you,
Patricia Cortazar, MD
Medical Officer
Division of Oncology Drug Products
FDA

Patient ID	TAC Arm 745 (100%)		FAC Arm746 (100%)	
	TAC	Other therapy received/ reason	FAC	Other therapy received/ reason
12502	1	FAC/ AE: G3 vomiting, skin		
22502			6	FEC/Thiotepa
11207	1	AC/ AE:G3 stomatitis, abdominal pain, anorexia		
21202				FAC plus Taxotere
21716	2	FAC/ AE: G2 diarrhea, nausea		
21728	1	FAC/ AE: G3 allergy		
21731		FAC		
21733	3	FAC/ AE: G3 allergy		
11803	2	AC/ AE: G3 skin		
12103	2	FAC/ AE: diarrhea		
12109	4	FAC/ AE increased creatinine		
12308	4	FAC/ AE: fever with no infection		
12314	3	FAC/ AE: fever with no infection		
12317	4	FAC/ AE: generalized edema		
22312	2	FAC/ AE: G3 allergy		
22702	2	FAC/ AE: G2 allergy		
12002	1	AC/ AE: abdominal pain, stomatitis, nausea		
22004	3	AC/ AE: G3 pulmonary		
20803			0	AC followed by Taxol
21312				TAC
12211	5	FAC/ AE: fever with no infection, cardiac arhythmia		
12214	3	TFA		
25501			6	Taxotere/Pamidronate
15002	1	AC/ AE: enteritis		
15006	1	AC/ AE: G4 allergy		
25010	4	Epirubicin/Cyclophosphamide/ AE: fever with no infection		
16301			3	Metotrexate/5FU/Genoxal
13418	1	FAC/ AE: G2 allergy		
26802	5	AC/ AE: G2 neurosensory		
23904	6	5FU/Carboplatin/Vblastin		
13705			0	TAC
32311	2	FAC/ AE: G3 allergy		
17608	2	AC		
27601			6	HDCT
27602	5	Thiotepa/Mitoxantrone/aminof/ AE: fever with no infection		
17902	2	FAC/ AE: G3 allergy		
28402			4	Taxol
17206	2	FAC/ AE: cardiac ischemia		
29701	3	AC/ AE: fever with no infection		
17423			0	AC/Taxol
18001	2	CMF/ AE: G3 infection		
19201	1	AC/ AE: G3 allergy		
30301			0	AC
42001			0	TAC
40401	3	AC/ AE: fever with no infection		

Need to
enter in DFI

Pease, Dorothy W

From: Pease, Dorothy W
Sent: Thursday, July 08, 2004 11:26 AM
To: 'Michael.Rozycki@aventis.com'
Cc: Staten, Ann M
Subject: Taxotere 20-449/S030

7-9-04

Please refer to your supplemental new drug application NDA 20-449 S-030, dated 5-Apr-04. This application provides for manufacturing and site changes for the manufacture for the drug substance docetaxel. Additionally, changes in test procedures/specifications are proposed for some reagents. However, we are unable to find any description and discussion on the intended reagent changes in Sections 1 (Introduction) and 2 (Results obtained with proposed Changes and Justification). Please indicate the proposed changes involve only the reagents related to the ——— changes.

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products, HFD-150
301-594-5742/301-594-0498 (fax)

Pease, Dorothy W

From: Dagher, Ramzi
Sent: Wednesday, July 07, 2004 3:07 PM
To: 'michael.rozycki@aventis.com'
Cc: Pease, Dorothy W; Staten, Ann M
Subject: taxotere approval summary for prostate cancer

CCRprostate.doc (151 KB)

Dear Mike,

If you could have any comments or suggestions to us by close of business Monday, that would be great.

Best Regards,

Ramzi Dagher,
DODP

Aventis Pharmaceuticals, Inc.
Mail Code BX2-209G
200 Crossing Boulevard
Bridgewater, NJ 08807
Phone: 908-304-6412
Fax: 908-304-6549

-----Original Message-----
From: Pease, Dorothy W [mailto:PEASE@cder.fda.gov]
Sent: Tuesday, July 06, 2004 4:27 PM
To: Rozycki, Michael PH/US
Subject: Additional Taxotere questions

- Patient 11803 had 2 cycles of TAC and withdrew due to G3 skin (according to the Listing of treatment discontinuation due to AE). I can not find this information in the CRF. Please direct me where can I find the information in the CRF and specify the type of skin event.
- Please explain the location in the electronic submission for the "listing of patients with non protocol therapy reasons for treatment discontinuation". Your response to a previous FDA information request did not include AEs that cause treatment discontinuation for patients: 22502,21202, 21731,20803, 21312,25501, 23904, 1370517608, 27601, 28402, 17423, 30301 and 40401.

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products, HFD-150
301-594-5742/301-594-0498 (fax)

Need to enter in DFS

Pease, Dorothy W

From: Pease, Dorothy W
Sent: Tuesday, July 06, 2004 4:27 PM
To: 'Michael.Rozycki@aventis.com'
Subject: Additional Taxotere questions

- Patient 11803 had 2 cycles of TAC and withdrew due to G3 skin (according to the Listing of treatment discontinuation due to AE). I can not find this information in the CRF. Please direct me where can I find the information in the CRF and specify the type of skin event.
- Please explain the location in the electronic submission for the "listing of patients with non protocol therapy reasons for treatment discontinuation". Your response to a previous FDA information request did not include AEs that cause treatment discontinuation for patients: 22502,21202, 21731,20803, 21312,25501, 23904, 1370517608, 27601, 28402, 17423, 30301 and 40401.

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products, HFD-150
301-594-5742/301-594-0498 (fax)

Mail Code BX2-209G
200 Crossing Boulevard
Bridgewater, NJ 08807
Phone: 908-304-6412
Fax: 908-304-6549

-----Original Message-----
From: Pease, Dorothy W [mailto:PEASE@cder.fda.gov]
Sent: Tuesday, July 06, 2004 7:45 AM
To: Rozycki, Michael PH/US
Cc: Staten, Ann M
Subject: Request re: Taxotere for Adj. Breast CA

Request from our medical reviewer:

For the patients found with metastatic disease at baseline:

- Please explain if patients # 12212, 20613, 21204 and 25501 had biopsy confirmation of metastatic disease at baseline.
- Please explain which regional lymph nodes were found metastatic and method of diagnosis for patients # 24507, 18302 and 26807.

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products, HFD-150
301-594-5742/301-594-0498 (fax)

Pease, Dorothy W

From: Michael.Rozycki@aventis.com
Sent: Tuesday, July 06, 2004 9:37 AM
To: PEASE@cder.fda.gov
Cc: STATENA@cder.fda.gov
Subject: RE: Request re: Taxotere for Adj. Breast CA

Thanks, Dotti. I will discuss with our Taxotere team and provide you with an answer ASAP.

Best regards,
-Mike

Michael Rozycki, Ph.D.
Director, Oncology Regulatory Affairs
Global Regulatory Liaison, TAXOTERE
Aventis Pharmaceuticals, Inc.
Mail Code BX2-209G
200 Crossing Boulevard
Bridgewater, NJ 08807
Phone: 908-304-6412
Fax: 908-304-6549

-----Original Message-----
From: Pease, Dorothy W [mailto:PEASE@cder.fda.gov]
Sent: Tuesday, July 06, 2004 7:45 AM
To: Rozycki, Michael PH/US
Cc: Staten, Ann M
Subject: Request re: Taxotere for Adj. Breast CA

Request from our medical reviewer:

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Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products, HFD-150
301-594-5742/301-594-0498 (fax)

in DFS

Pease, Dorothy W

From: Pease, Dorothy W
Sent: Tuesday, July 06, 2004 7:45 AM
To: 'Michael.Rozycki@aventis.com'
Cc: Staten, Ann M
Subject: Request re: Taxotere for Adj. Breast CA

Request from our medical reviewer:

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- Please explain if patients # 12212, 20613, 21204 and 25501 had biopsy confirmation of metastatic disease at baseline.
- Please explain which regional lymph nodes were found metastatic and method of diagnosis for patients # 24507, 18302 and 26807.

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products, HFD-150
301-594-5742/301-594-0498 (fax)

Pease, Dorothy W

From: Cortazar, Patricia
Sent: Thursday, July 01, 2004 5:14 PM
To: Pease, Dorothy W
Subject: Info request to sponsor of NDA 20449 (taxotere adjuvant breast)

Dotti:
Please send the following information request to Aventis.
Thanks
For the patients found with metastatic disease at baseline:

- Please explain if patients # 12212, 20613, 21204 and 25501 had biopsy confirmation of metastatic disease at baseline.
- Please explain which regional lymph nodes were found metastatic and method of diagnosis for patients # 24507, 18302 and 26807.

Patricia Cortazar, MD
Medical Officer
Division of Oncology Drug Products
FDA

Staten, Ann M

From: Staten, Ann M
Sent: Thursday, June 17, 2004 12:43 PM
'Michael.Rozycki@aventis.com'
Subject: Taxotere information request s-029

Hi Mike,

Here is another request from the medical officer.

Thanks,
Ann

Please complete the following information:

- **Patient # 30806 past history of neoplasm other than breast carcinoma from Table #15. Could not find the data from listings L08A or L08B.**
- **Patient # 10703 had negative margins according to listing L04. Please explain discrepancy between Table 14 and L04.**
- **Patients#s: 11302, 12608, 26604, 13612, 17404 and 26608 had positive margins. Please confirm if these patients had additional surgery and or radiotherapy.**
- **Sites of distant metastases at diagnoses for patients# 12212 (from L04 page 456), 27302, 20613, 21204, 25501.**

Staten, Ann M

From: Staten, Ann M
Sent: Wednesday, June 16, 2004 1:20 PM
'Michael.Rozycki@aventis.com'
Subject: Taxotere NDA information request

Importance: High

Dear Mike,

We have the following additional information request to be submitted:

Table 2 Distribution of patients randomized by treatment and length of follow-up.

Length of Follow-up (months)TAC Arm	FAC Arm	All Patients	
< 12			
12-to <18			
18- to <24			
24- to <30			
30 to <36			
36 to <42			
42 to <48			
48 to <54			
54 to <60			
> 60			

Thanks
Ann

Staten, Ann M

From: Staten, Ann M
Sent: Tuesday, June 15, 2004 4:01 PM
To: 'Michael.Rozycki@aventis.com'
Subject: NDA 20-449/S-029 Taxotere question

Dear Michael,

We have the following information request:

Please explain the discrepancy between the number of patients per STUDY SITE/COUNTRY (Argentina, Canada, Egypt, Hungary, South Africa, Sweden, UK and USA) from "Randomized patients by Country", page 818 and "List of principal investigators", page 1295 of the Clinical Study Report.

Sincerely,
Ann

SE1-029-BB

DUPLICATE RECEIVED

JUN 0 4 2004

CDR / CDER

Aventis

June 3, 2004

RECEIVED

JUN - 8 2004

DDR-150/CDER

Food and Drug Administration
Attention: Richard Pazdur, M.D.
Director, Division of Oncology Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont 2 Document Room
1451 Rockville Pike
Rockville, Maryland 20852

SE1-029-BB

Supplemental NDA 20-449/S-029: TAXOTERE® (docetaxel) Injection Concentrate

Amendment to Pending Supplemental NDA

Pharmacokinetics Data for Final Report, Study XRP6976D/1001

Dear Dr. Pazdur:

With this letter, Aventis Pharmaceuticals Inc. (Aventis) is submitting pharmacokinetics data in SAS format for the final report for Study XRP6976D/1001, a pharmacokinetic interaction study of TAXOTERE® in combination with doxorubicin and cyclophosphamide, as an amendment to the pending supplemental New Drug Application (sNDA) 20-449/S-029. The sNDA was submitted to the FDA on March 17, 2004, and the report for Study XRP6976D/1001 was submitted on May 26, 2004.

In accordance with the FDA's January 1999 "*Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDA*," this submission consists of an original cover letter and Form FDA 356h, and one (1) CD-ROM containing the entire submission contents, as described in the table on the following page.

The approximate size of this electronic submission is 1.4 MB. The CD-ROM has been scanned and found to be free of any known computer viruses (Norton Antivirus Corporate Edition, Program Version 7.50.846, Scan Engine 4.1.0.6; Virus Definition File version 60602q, dated 6/2/2004).

Aventis Pharmaceuticals Inc. • 200 Crossing Boulevard • PO Box 6890 • Bridgewater, NJ 08807-0890 • www.aventis.com
Telephone (908) 304-7000

DUPLICATE

May 26, 2004

Food and Drug Administration
Attention: Richard Pazdur, M.D.
Director, Division of Oncology Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont 2 Document Room
1451 Rockville Pike
Rockville, Maryland 20852

Supplemental NDA 20-449/S-029: TAXOTERE® (docetaxel) Injection Concentrate

Amendment to Pending Supplemental NDA

Final Report for Pharmacokinetics Study XRP6976D/1001

Dear Dr. Pazdur:

With this letter, Aventis Pharmaceuticals Inc. (Aventis) is submitting a Final Report for Study XRP6976D/1001, a pharmacokinetic interaction study of TAXOTERE® in combination with doxorubicin and cyclophosphamide, as an amendment to the pending supplemental New Drug Application (sNDA) 20-449/S-029. This sNDA was submitted to the FDA on March 17, 2004 and contained clinical efficacy and safety data to support approval for TAXOTERE in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable, node-positive breast cancer.

Reference is made to the subject sNDA, and to an August 22, 2003 submission by Aventis to IND 35,555 (Serial No. 1115), in which Aventis proposed to submit the final report for study XRP6976D/1001 after the initial submission of the sNDA, but before the end of May 2004. On August 26, 2003, the FDA replied that it was in agreement with this timeframe.

Study XRP6976D/1001 was a multicenter, open-label, cross-over, randomized pharmacokinetic study of doxorubicin in combination with cyclophosphamide, with or without TAXOTERE (TAC versus AC treatments), in the treatment of advanced breast cancer patients. The results of this study showed that the pharmacokinetics of doxorubicin and cyclophosphamide were unchanged across the AC and TAC treatments, and that TAXOTERE pharmacokinetics in the presence of cyclophosphamide and doxorubicin were unchanged compared to monotherapy. Overall, no pharmacokinetic interaction was evidenced.

MEMORANDUM OF TELEPHONE CONVERSATION
DIVISION OF ONCOLOGY DRUG PRODUCTS

DATE: August 16, 2004 (2:00pm-2:30pm)

SUBJECT: NDA 20-449/S-029 Taxotere (docetaxel)

Discussion:

Dr. Mortimer was consulted regarding the supplemental application for Taxotere in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node-positive breast cancer. Dr. Mortimer concurred with the Division's decision to approve this application.

Ann Staten, RD
Regulatory Health Project Manager

Patricia Cortazar, MD
Medical Reviewer

Attachment: FDA review summary (handout)

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

/s/

Ann Staten
8/17/04 12:44:33 PM
CSO

MEMORANDUM OF TELEPHONE CONVERSATION
DIVISION OF ONCOLOGY DRUG PRODUCTS

DATE: August 13, 2004 (3:30pm-4:00pm)

SUBJECT: NDA 20-449/S-029 Taxotere (docetaxel)

Discussion:

Dr. Martino was consulted regarding the supplemental application for Taxotere in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node-positive breast cancer. Dr. Martino concurred with the Division's decision to approve this application.

Ann Staten, RD
Regulatory Health Project Manager

Patricia Cortazar, MD
Medical Reviewer

Attachment: FDA review summary (handout)

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

/s/

Ann Staten
8/17/04 12:38:27 PM
CSO

MEMORANDUM OF TELEPHONE CONVERSATION
DIVISION OF ONCOLOGY DRUG PRODUCTS

DATE: August 12, 2004 (11:30am-12:00pm)

SUBJECT: NDA 20-449/S-029 Taxotere (docetaxel)

Discussion:

Natalie Compagni Portis was consulted regarding the supplemental application for Taxotere in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node-positive breast cancer. Ms. Portis concurred with the Division's decision to approve this application.

Ann Staten, RD
Regulatory Health Project Manager

Patricia Cortazar, MD
Medical Reviewer

Attachment: FDA review summary (handout)

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

/s/

Ann Staten
8/17/04 12:49:55 PM
CSO

INTERNAL MEETING MINUTES

MEETING DATE: August 19, 2003

IND/NDA IND 35,555 Meeting Request Submission Date: July 2, 2003 (NB01)
FDA Response Date: July 8, 2003
Briefing Document Submission Date: July 29, 2003 (NB07)
August 22, 2003 (NB15)

DRUG: Taxotere (docetaxel)

SPONSOR/APPLICANT: Aventis

TYPE of MEETING:

1. Pre-sNDA

2. Indication: Taxotere in combination with doxorubicin and cyclophosphamide, is indicated for the adjuvant treatment of patients with operable breast cancer

FDA PARTICIPANTS:
Richard Pazdur, MD, Director, Division of Oncology Drug Products
Ramzi Dagher, M.D., Medical Team Leader
Patricia Cortazar, MD, Medical Reviewer
Kevin Ridenhour, MD, Medical Reviewer
Peiling yang, PhD, Statistician
Gary Gensinger, Office of Information Management
Sophia Abraham, Ph.D., Clinical Pharmacology Reviewer
Ann Staten, RD, Project Manager
Farid Berhammou for Justina Molzon, CTD consultant

MEETING OBJECTIVES:

To discuss the format and content of the sNDA electronic submission in ICH-CTD format and general regulatory considerations.

BACKGROUND: Following the internal pre-meeting on 8-19-03, FDA's response was sent to the sponsor via E-mail on 8-21-03 (attached). The sponsor requested clarification from the Clinical Pharmacology reviewer (serial number B15) and after receiving our 8-26-03 response (attached), Aventis cancelled the meeting since further clarification was not needed.

ACTION ITEMS:

There were no unresolved issues or discussion points.

Concurrence Chair: _____/_____

Ann Staten Date
Project Manager
Minutes preparer

Patricia Cortazar, M.D. Date
Medical Reviewer

Attachments: FDA e-mails dated 8-21-03 and 8-26-03

Staten, Ann M

From: Staten, Ann M

Sent: Thursday, August 21, 2003 9:22 AM

To: Michael. Rozycki (Michael.Rozycki@aventis.com)

Subject: IND 35,555 Responses to Adj Breast meeting package

Importance: High

Please refer to you submissions dated July 2 and 29, 2003 requesting a pre-sNDA meeting.

Attached are the FDA answers to your questions. You have the option of canceling our meeting of August 27, 2003 if these answers are clear to you. If you choose to have the meeting, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan, for which you would like FDA feedback, should be submitted as a new meeting request. Please let me know as soon as possible if you are canceling the meeting.

Sincerely,

Ann

General Application Content and Format

1. This application will be prepared in the Common Technical Document (CTD) format. The Table of Contents of the application, in CTD format, is attached as Appendix A in this briefing document for the meeting.

   Does the Agency agree that the overall format for the planned application should allow for efficient review?

   FDA Response: Yes.

2. Aventis does not plan to submit any separate document equivalent to the former Item 10 (Statistical) of the NDA. All the statistical information will be included in the individual study reports in Module 5.

   Does the FDA concur with this approach?

   FDA Response: Yes

3. For studies TAX316 and GEICAM 9805, case report forms will be provided for deaths (all deaths related to study treatment, or deaths that occurred during the treatment phase or within 30 days after the last infusion of study treatment) and for each patient who discontinued due to an adverse event.

   Does the FDA concur with this approach?

   FDA Response: No. Please submit narratives, CRF and CRT from all deaths for our review. CRF and CRT from patients who died from disease progression are important to confirm the primary endpoint. CRT and CRF should also be provided for all patients who died of any cause during the study or within 30 days after the last dose of study drug.

4. It is anticipated that the key information for an assessment of safety in the adjuvant treatment setting for breast cancer will be generated out of study TAX316; interim data will be provided from study GEICAM 9805. However, to comply with the CTD requirement for inclusion of the Periodic Safety Update Report (PSUR), Aventis proposes the following approach:

   - PSURs that were already submitted via inclusion within the approved NDA supplement S-018 (first-line, non-small cell lung carcinoma) will be referenced to the previous submission.
   - Additional PSURs issued subsequent to the submission of supplement S-018 will be included within the planned electronic sNDA for adjuvant treatment of breast cancer.

   Does the FDA agree with this approach to compliance with the requirement for including PSURs?

FDA Response: Yes.

5. Due to the fact that early breast cancer does not occur in pediatric patients, it is proposed that the requirement for inclusion of pediatric data be waived in conjunction with the submission of the subject planned supplementary application.

   Given the status of the pediatric rule, should Aventis plan to include a waiver request within the planned application? If so, does the FDA agree with this waiver request?

   FDA Response: FDA is currently enjoined from enforcing the Pediatric Rule. Therefore, a waiver request is not applicable at this time.

Electronic Submission

6. Aventis intends to submit the TAXOTERE sNDA as an electronic NDA (e-NDA) in accordance with the January 1999 Guidance for Industry, "*Providing Regulatory Submissions in Electronic Format – NDA*" and the August 2001 Guidance for Industry, "*Submitting Marketing Applications According to ICH-CTD Format – General Considerations*". Each modular component of the CTD will be mapped to a corresponding e-NDA folder. As an example, a proposed Table of Contents for CTD Module 5 is included after the overall CTD Table of Contents in Appendix A. In the Table of Contents for Module 5, the column on the left shows the CTD module 5 structure, while the column on the right shows the file name and file path of each component document within the e-NDA folder structure.

   Does the FDA have any specific recommendations or requests for the electronic submission that could ease the review?

   FDA Response: The proposed submission of electronic data is apparently adequate. Raw data should be submitted in SAS transport format. Submission of all primary datasets in a usable format is a critical element of the electronic submission. It will be helpful if we can take a look at a sample of the datasets, before the NDA submission.

7. Case report forms (CRFs) will be submitted electronically as bookmarked PDF files; data correction forms (DCF) will be provided at the front of each CRF. The DCFs will be bookmarked, however, there will be no hyperlink from the DCF to the corresponding page of the CRF.

   Does the FDA concur with this approach?

   FDA Response: Yes. We prefer to have hyperlinks, however, they are not required.

8. SAS data sets for TAX316 and GEICAM 9805 will be provided at the time of the submission in a SAS transport file format (.XPT) as defined by logical panels, e.g., efficacy (TAX316 only), adverse events, laboratory tests, etc. These data sets will

include original CRF data as well as derived data. An example of the define.pdf document is attached in Appendix F. (It is expected that 4 files will have a size greater than 50 MB: Adverse Events (65 MB), Laboratory Data (95 MB), Prior and Concomitant Medications (100 MB), and Other Procedures (55MB)).

8a. Included in Appendix G is a user dataset documentation example. Does the FDA agree that this format will meet the reviewer's needs?

FDA Response: Please provide electronic SAS formats that you created for efficacy variables (i.e., Format Library). Please submit a sample of the efficacy raw and derived datasets before the NDA submission.

8b. Aventis plans to provide the analysis programs for the analysis of Disease-Free Survival (DFS) and Overall Survival (OS) in a format that will allow execution of the programs using a SAS PC version 8.2. Does the FDA agree with this plan?

FDA Response: Yes

8c. Do FDA personnel agree that further dialogue on dataset presentation, programs, and CRFs that would be expressly designed to ensure mutual understanding of the optimal format to ease application review, should take place in short-term follow-up to the pre-sNDA meeting?

FDA Response: Yes

9. Referring to the FDA Guidance for Industry, "*Providing Regulatory Submissions in Electronic Format – NDA*" (January 1999) [Page 50], Aventis does not plan to include any Patient Profiles with this submission.

   Does the FDA agree with this plan?

   FDA Response: Yes. However, during the review we may ask for specific analyses that arise.

10. Data will be submitted electronically as SAS datasets. Therefore, it is not planned to submit patient listings which would present the raw data and derived data from all patients. However, we will provide supportive patient listings for selected summary tables (e.g., listings of deaths occurring within 30 days from last infusion). These patient listings will be provided electronically in SAS data sets; it is not planned to provide paper copies of any listings.

    Does the FDA agree with this proposal?

FDA Response:

Yes. Please also include the following:

- **all patients who died of any cause during the study or within 30 days after the last dose of study drug.**

- **All patients who dropped out during the course of the trial in association with any adverse experience, whether or not thought to be drug related.**

Additional FDA Request:

- **Please include in your submission all of the raw data in a SAS transport file format from which the derived efficacy variables are calculated.**

- **Please include in your submission the electronic SAS programs that produced (a) all derived efficacy variables from the raw data, and (b) all of the efficacy results.**

TAX316 Analysis and Safety Data Presentation

11. It is planned that the analyses of adverse events will include treatment-emergent adverse events (adverse events that developed or worsened in severity during treatment), and all adverse events that occurred under treatment irrespective of whether they occurred before treatment started. Aventis understands that both concepts for the evaluation of adverse events are important. The primary and comprehensive analysis of safety will be based on the "treatment-emergent" principle, and this analysis will comprise the basis upon which conclusions will be drawn regarding the safety profile of TAXOTERE within the investigational arm of the pivotal trial. However, the results of all adverse events will be presented as well to ensure an adequate description and conclusion of the safety profile of the investigational arm. The table in Appendix H displays the planned analyses with regard to the principle of treatment-emergent adverse events (TEAEs) or all adverse events (ALL AE's).

    Does the FDA agree that the proposed safety analyses will allow for an objective assessment of TAXOTERE associated adverse events, and that these analyses will address the needs of FDA Review Staff?

    FDA Response: Yes.

12. It should be noted that for purposes of draft labeling submission, Aventis plans to base labeling on treatment-emergent adverse events that are "clinically meaningful". The judgment of which adverse events are "clinically meaningful" will be made by analyzing those that occurred in patients in the TAXOTERE arm in TAX316 with respect to frequency and severity. Specific safety domains, including rare events or events deemed class-specific for the drugs used in the combination, will be considered. It is the Sponsor's intention to present in labeling those adverse events that facilitate prescriber recognition of important toxicities associated with this therapeutic regimen in

the adjuvant treatment setting for breast cancer. TAXOTERE has been marketed since 1996; thus, its general safety profile is well appreciated and is reflected in the current label. The Sponsor's intention to focus on clinically meaningful events in the adjuvant treatment setting for breast cancer is also to avoid additional "long and exhaustive lists" of adverse events that have the potential to be added to this label for this indication and the additional planned indications. This intention is concordant with the May 2000 FDA Draft Guidance on the adverse reaction section of the labeling. Recent announcements by FDA policy staff, in general, support this direction.

Does the FDA agree that the treatment-emergent adverse event analyses output may be acceptable for presentation within the proposed product labeling?

FDA Response: Yes. You may make a proposal regarding what is clinically meaningful. However, FDA will evaluate all adverse events to reach a conclusion regarding the safety profile of docetaxel within this setting. Determination of what is clinically meaningful is a review issue.

GEICAM Study 9805 Interim Safety Data

13. GEICAM 9805 is an on-going study, from which interim safety data of the same treatment regimen used in the pivotal study, TAX316, will be submitted in order to provide as complete information as possible on the benefit/risk profile of the TAC treatment regimen. The Sponsor expects the submitted safety data for study GEICAM 9805 to include, but not be limited to:

    - Patient demographics at baseline – overall statistics
    - Existing signs and symptoms at baseline – overall statistics
    - Treatment exposure and dosing - overall statistics
    - Treatment discontinuations – overall statistics and patient listings
    - All adverse events under treatment and treatment-emergent adverse events – overall statistics:
        - Overview
        - Grading
        - Adverse events leading to discontinuations
        - Adverse events starting or worsening during follow-up
    - Fever, neutropenia, infection, and other specific toxicities – overall statistics
    - Serious adverse events - overall statistics and listings of events
    - Deaths – overall statistics, listings of events, and causes of death

    The Sponsor plans to report the safety results for studies TAX316 and GEICAM 9805 from separate databases.

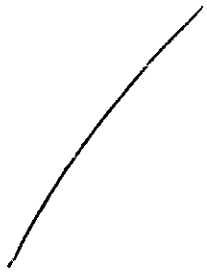
Does the FDA agree that the proposed submission of safety data for study GEICAM 9805 would be of value to the FDA in assessing the overall benefit/risk profile of TAXOTERE in the adjuvant treatment setting for breast cancer?

FDA Response: Yes.

Pharmacokinetic Studies

14. The planned application will include information that supports a conclusion that there is no pharmacokinetic interaction between docetaxel and the other drugs in the TAC combination. Contained within Appendix I of this submission is the protocol for study XRP6976D/1001 (*A pharmacokinetic interaction study of docetaxel (RP56976, TAXOTERE) 75 mg/m^2 i.v. on the combination therapy doxorubicin (50 mg/m^2 i.v.) and cyclophosphamide (500 mg/m^2 i.v.) in the treatment of advanced breast cancer*), submitted to IND 35,555 on May 30, 2003 (Serial No. 1096), to examine for the potential pharmacokinetic interaction between docetaxel and doxorubicin/ cyclophosphamide. This ongoing study was designed to collect such data from a total of twenty-four (24) patients. At the time of the submission of the subject application, it is anticipated that pharmacokinetic data from twenty-four (24) patients will not be available. Therefore, it is proposed that a final report for study XRP6976D/1001 will be submitted after the initial submission of the subject sNDA. Aventis proposes to submit this report before the end of May, 2004. This report would include all safety, pharmacokinetics, and efficacy data for all patients.

    In addition, supportive pharmacokinetic reports for the following additional studies will be included in the sNDA submission.



    The Sponsor does not regard studies as being capable, separately or in combination, of confirming the absence of an interaction among all of the constitutive agents of the TAC treatment regimen. Hence, the Sponsor does not plan to include case report forms or SAS datasets containing tabulations of analytical results (including, but not limited to, efficacy, safety, dosing, and baseline demographics results) with the submission. The Sponsor will provide available data to FDA reviewers upon request.

Does the FDA agree that the submission of pharmacokinetic information as described above will be useful in assessing potential pharmacokinetic interactions?

FDA Response:

Yes, we agree that Study XRP6976D/1001 is useful in assessing potential pharmacokinetic interactions between docetaxel and the other drugs in the TAC combination. Therefore, we strongly recommend that you include the final report and results for Study XRP6976D/1001 in the sNDA submission at the time of submission.

APPEARS THIS WAY
ON ORIGINAL

OTHER FDA COMMENTS:

REGULATORY

1. NDA/sNDA Presentations to CDER's Division of Oncology

The Center for Drug Evaluation and Research's Division of Oncology Drug Products implemented an initiative in which we request an NDA/sNDA applicant to present their NDA/sNDA to Division personnel shortly after NDA/sNDA submission and before the expected NDA/sNDA filing date. This initiative allows the applicant to present an overview of the entire NDA/sNDA to the review team and interested Division personnel.

These presentations are generally expected to last one hour followed by a half-hour question and answer session. The applicant, not consultants, should present important information on each technical aspect (i.e., clinical, statistical, CMC, pre-clinical pharmacology and toxicology, and clinical pharmacology and biopharmaceutics) of the NDA/sNDA. In addition to providing an overview of the NDA/sNDA, the applicant should present their reasons for why the Division or the Office of Drug Evaluation I should approve their NDA/sNDA.

Please contact your Project Manager shortly after NDA/sNDA submission to schedule a date for your presentation. Alternatively, you may provide available dates in the cover letter of your NDA/sNDA and we will try to accommodate them.

2. Financial Disclosure Final Rule

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective and any study in which a single investigator makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 "*Guidance for Industry: Financial Disclosure By Clinical Investigators*" (posted on the Internet 3/27/2001) at http://www.fda.gov/oc/guidance/financialdis.html.

3. Pediatric Exclusivity

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study

Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

4. DEMOGRAPHICS

In response to a final rule published 2-11-98, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this analysis. To assist you in this regard, the following table is a suggestion for presentation of the numeric patient demographic information. This data, as well as the pertinent analyses, should be provided in the NDA.

Please provide information for each category listed below from the primary safety database excluding PK studies.

CATEGORY		NUMBER EXPOSED TO STUDY DRUG	NUMBER EXPOSED TO STUDY DRUG	NUMBER EXPOSED TO STUDY DRUG
Gender	Males	All Females	Females >50	
Age:	0-≤1 Mo.	>1 Mo.-≤ 2Year	>2-≤12	
	12-16	17-64	≥65	
Race:	White	Black	Asian	
	Other			

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-449/S-029

PRIOR APPROVAL SUPPLEMENT

Aventis Pharmaceuticals, Inc.
200 Crossing Boulevard
P.O. Box 6890
Bridgewater, NJ 08807-0890

Attention: Michael Rozycki, Ph.D.
Director, US Regulatory Affairs

Dear Dr. Rozycki:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Taxotere® (docetaxel) for Injection Concentrate, 20 mg and 80 mg

NDA Number: 20-449

Supplement number: S-029

Review Priority Classification: Priority (P)

Date of supplement: March 17, 2004

Date of receipt: March 17, 2004

This supplemental application proposes the following change: Taxotere® in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node-positive breast cancer.

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 16, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 17, 2004.

Under 21 CFR 314.102(c), you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Division of Oncology Drug Products, HFD-150
Attention: Division Document Room, 3067
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Attention: Document Room 3067
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, call Ann Staten, Regulatory Project Manager, at (301)594-0490.

Sincerely,

{See appended electronic signature page}

Dotti Pease
Chief, Project Manager Staff
Division of Oncology Drug Products

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

/s/

Ann Staten
4/15/04 10:52:02 AM
Signed for Dotti Pease

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Martha Propsner, Aventis	**From:**	Ann Staten, Project Manager
Fax:	908-304-6317	**Fax:**	301-827-4590
Phone:	908-231-3841	**Phone:**	301-594-5770
Pages:	1	**Date:**	April 26, 2002

Re: IND 35,555 –TAX316 serial number 1009 (3-28-02)

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Dear Martha:

The review is complete and we have the following statistical comments:

1. The changes made in the SAP/protocol regarding the nominal significance levels used in the remaining analyses (the second interim and the final analyses) are acceptable.

2. The Agency would like to emphasize that any efficacy claim will be solely based on the primary statistical analysis of the primary endpoint. Other analyses, such as Cox model and modified Kolmogorov-Smirnov test, may be regarded as supportive only if the primary analysis demonstrates a statistically significant result; otherwise, such analyses will be regarded as exploratory. All pre-specified covariates should be included in the Cox model.

Sincerely,

Ann

Ann

INTERNAL MEETING MINUTES

MEETING DATE: February 11,2002

IND/NDA IND 35,555 Meeting Request Submission Date: December 17, 2001 (N987)
Briefing Document Submission Date: January 22, 2002 (993)

DRUG: Taxotere (docetaxel)

SPONSOR/APPLICANT: Aventis

TYPE of MEETING:

1. **Other; guidance on statistical analysis plan**

FDA PARTICIPANTS:
Donna Griebel, MD, Medical Team Leader
Ramzi Dagher, M.D., Medical Reviewer
Ning Li, Ph.D., Statistician
Dotti Pease for Ann Staten, RD, Project Manager

MEETING OBJECTIVES:

1. To discuss the statistical strategy for an additional interim analysis and the consequences for the final analysis (TAX 316 Taxotere in comboination with doxorubicin and cyclophosphamide as adjuvant treatment of operable breast cancer w/positive axillary nodes.)

BACKGROUND: Following the internal pre-meeting on 2-11-02, FDA's responses were sent to the sponsor in a facsimile dated 2-12-02 (attached). The sponsor requested that the meeting be cancelled since clarification was not needed.

ACTION ITEMS:

There were no unresolved issues or discussion points.

_____/_____
Ann Staten Date
Project Manager
Minutes preparer

Concurrence Chair: _____/_____
Ramzi Dagher, M.D. Date
Medical Reviewer

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Martha Propsner, Aventis	**From:**	Ann Staten, Project Manager
Fax:	908-231-3716	**Fax:**	301-827-4590
Phone:	908-231-3841	**Phone:**	301-594-5770
Pages:	2	**Date:**	February 12, 2002
Re:	IND 35,555; serial no. 987 and 993		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Dear Ms. Propsner,

Attached are the FDA answers to your questions. You have the option of canceling our meeting of February 14, 2002 if these answers are clear to you. If you choose to have the meeting, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan, for which you would like FDA feedback, should be submitted as a new meeting request. Please let me know as soon as possible if you are canceling the meeting.

Questions:

1. Does the Agency agree on the proposed strategy for interim and final analyses for the TAX 316 study?

FDA Response: Since the first interim analysis used an alpha of 0.001, there is 0.049 left for the rest of the analysis. We suggest the sponsor use either one of the following approaches to adjust the overall alpha :

   a. You can split 0.049 for the remaining two analyses (Say 0.001 and 0.048)

   b. Use O'Brien-Fleming's method for the rest of the two analyses based upon 0.049 level.

2. Aventis believes that positive results from the TAX 316 additional analysis (as proposed in the enclosed SAP amendment) would support a claim for the use of Taxotere in combination with doxorubicin and cyclophosphamide as adjuvant treatment of operable breast cancer with —

Does the Agency agree?

FDA : This will be a review issue.

3. With respect to the regulatory assessment of the future filing, does the Agency have any concern with the plan to disseminate the October 2001 interim analysis results by the non-Aventis members of the Steering Committee at the next ASCO meeting?

FDA : From a regulatory perspective, we have no grounds for objecting to this planned presentation.

Please call me with any questions.

Sincerely,

Ann

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

/s/

Ann Staten
2/21/02 11:13:33 AM

Ramzi Dagher
2/21/02 11:37:34 AM