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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-449/S-028

Administrative

3 Pages Redacted of
Deliberative Process
§ 552(b)(5)

NDA 20449
Taxotere (Docetaxel)

Aventis, Inc.

patcert.pdf, pg 1



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

Statements of Claimed Exclusivity and Associated Certification

This letter serves as an official request for a period of extended marketing exclusivity under 21 CFR Part 314.50(j) and 21 CFR Part 108(b)(5), for docetaxel. As a new supplemental application, containing a report of a new clinical investigation (RP56976V - 327 (TAX 327) that was conducted and sponsored by the applicant under IND 35,555, and that is essential to the approval of this supplemental application, docetaxel is entitled to three (3) years of exclusivity.

To the best of the applicant's knowledge, the clinical investigation (TAX 327) included in this application meets the definition of "new clinical investigation" set forth in 21 CFR Part 314.108(a). In a literature search conducted by the applicant, no published or otherwise publicly available study reports were found for clinical investigations that are relevant to the conditions for which the applicant is seeking approval, *i.e.*, demonstration *via* Phase III pivotal study of significantly increased overall survival resulting from use of docetaxel in combination with prednisone in the treatment of androgen-independent (hormone-refractory) metastatic prostate cancer. The applicant was the sponsor named in Form FDA-1571 for IND 35,555, under which study TAX 327 was conducted.

NDA 20449
Taxotere (Docetaxel)

Aventis, Inc.

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

Patent Information and Certification

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

NDA 20449 Department of Health and Human Services
 Taxotere (Docetaxel) Food and Drug Administration

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

**PATENT INFORMATION SUBMITTED WITH THE
 FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
 (Active Ingredient), Drug Product (Formulation and
 Composition) and/or Method of Use*

NDA NUMBER
 20-449 (Supplemental - Prostate)
 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)
 Docetaxel

STRENGTH(S)
 Single dose vials containing 20mg(0.5 ml) or 80mg(2.0 ml)
 BQ 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.

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

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

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

1. GENERAL

a. United States Patent Number 4,814,470	b. Issue Date of Patent 3/21/1989	c. Expiration Date of Patent 5/14/2010
---	--------------------------------------	---

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:

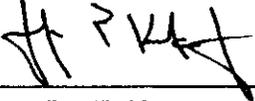
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

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

NDA 20449 6. Declaration Certification Taxol® (Docetaxel)	Aventis, Inc.	patcert.pdf, pg 5
<p>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.</p> <p>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</p>		
<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</p> <div style="text-align: center; font-size: 2em; margin-top: 10px;">  </div>		<p>Date Signed 11/17/2003</p>
<p>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).</p>		
<p>Check applicable box and provide information below.</p>		
<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official	
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official	
<p>Name Joseph P. Kirk Jr.</p>		
<p>Address Aventis Pharmaceuticals Inc. 1041 Route 202-206 - P.O. Box 6800</p>	<p>City/State Bridgewater, New Jersey</p>	
<p>ZIP Code 08807-0800</p>	<p>Telephone Number 908 231-5916</p>	
<p>FAX Number (if available) 908 231-2840</p>	<p>E-Mail Address (if available) joseph.kirk@aventis.com</p>	
<p>The public reporting burden for this collection of information has been estimated to average 9 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:</p> <p style="text-align: center;"> Food and Drug Administration CDER (HFD-007) 5600 Fishers Lane Rockville, MD 20857 </p> <p style="text-align: center; font-style: italic;"> <i>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.</i> </p>		

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

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
└ ───────────┘ However, the patent does not specifically claim any └
┘ of the active ingredient, and therefore the answer to Question 2.2 is "no".

NDA 20449
Taxotere (Docetaxel)

Aventis, Inc.

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

Patent Information and Certification

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

NDA 20449 Department of Health and Human Services
Taxotere (Docetaxel) Food and Drug Administration

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

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

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

NDA NUMBER

20-449 (Supplemental - Prostate)

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)

Docetaxel

STRENGTH(S)

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

5,438,072

b. Issue Date of Patent

8/1/1995

c. Expiration Date of Patent

11/22/2013

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

6.1 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.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> 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

The public reporting burden for this collection of information has been estimated to average 9 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:

Food and Drug Administration
 CDER (HFD-007)
 5600 Fishers Lane
 Rockville, MD 20857

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NDA 20449
Taxotere (Docetaxel)

Aventis, Inc.

patcert.pdf, pg 11



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

Patent Information and Certification

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

NDA 20449 Department of Health and Human Services
Taxotere (Docetaxel) Food and Drug Administration

Form Approved OMB No. 0910-9513
Patent Form 2012
Expiration Date: 07/31/06
See OMB Statement on Page 3.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
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NDA NUMBER

20-449 (Supplemental - Prostate)

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)

Docetaxel

STRENGTH(S)

Single dose vials containing 20mg(0.5 ml) or 80mg(2.0 ml)
EQ 40mg Base/ml

DOSAGE FORM

Sterile Solution

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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)

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Vice President, Global Patent Litigation

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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?

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

Yes No

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.

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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

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6. Declaration Certification
(axotere (Docstaxel))

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

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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

The public reporting burden for this collection of information has been estimated to average 9 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:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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

NDA 20449
Taxotere (Docetaxel)

Aventis, Inc.

patcert.pdf, pg 15



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

Patent Information and Certification

Form FDA 3542a for United States Patent No. 5,698,582

NDA 20449 Department of Health and Human Services
Taxotere (Docetaxel) Food and Drug Administration

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

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

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

NDA NUMBER

20-449 (Supplemental - Prostate)

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)

Docetaxel

STRENGTH(S)

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.

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

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

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

1. GENERAL

a. United States Patent Number
5,698,582

b. Issue Date of Patent
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)

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

Louis J. Wille
Vice President, Global Patent Litigation

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

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

6.1 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.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> 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

The public reporting burden for this collection of information has been estimated to average 9 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:

Food and Drug Administration
 CDER (HFD-007)
 5600 Fishers Lane
 Rockville, MD 20857

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

EXCLUSIVITY SUMMARY FOR NDA # 20-449 SUPPL # 028

Trade Name Taxotere Generic Name docetaxel

Applicant Name Aventis HFD # 150

Approval Date If Known May 19, 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 / / 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 / / 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 Written Request?

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

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

YES /___/ NO /_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 /___/ NO /___/

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

NDA# _____
NDA# _____
NDA# _____

2. Combination product.

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

YES /___/ NO /___/

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

NDA# _____
NDA# _____
NDA# _____

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

PART III THREE-YEAR EXCLUSIVITY FOR 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:

Tax327

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"):

_____TAX 327_____

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 # 35,555YES /_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 Ann Staten Date
Title:

Signature of Office/ Date
Division Director Richard Pazdur, MD

Form OGD-011347 Revised 05/10/2004

cc:

Archival NDA

HFD- /Division File

HFD- /RPM

HFD-610/Mary Ann Holovac

HFD-104/PEDS/T.Crescenzi

**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
5/19/04 09:10:47 AM

Richard Pazdur
5/19/04 11:33:26 AM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 20-449 Supplement Type (e.g. SE5): SE1 Supplement Number: 028

mp Date: 1-27-04 Action Date: PDUFA 7-27-04

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: treatment of patients with hormone refractory prostate 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: _____

If studies 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.

Section 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

cc: NDA 20-449/s-028
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

Debarment Certification

December 2, 2003

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.

A handwritten signature in cursive script, appearing to read "Cheryl L. Anderson".

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

Date : May 18, 2004

From : Ramzi Dagher, MD ; Primary Reviewer and Team Leader for NDA 20449 / S-028

To : Addendum to DSI consult

Inspection of two sites in Europe was originally contemplated as outlined in the DSI consult. However, given the large number of patients enrolled (1006) in this global study, and based on the objective nature of the primary endpoint used (survival), it is unlikely that inspections would have altered interpretation of the data. Therefore, the DSI team was informed that inspection of the two sites would not be necessary.

**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

5/18/04 10:48:14 AM

CSO

SUPPLEMENT AMENDMENT

RECEIVED
APR 29 2004
CDR / CDER



DUPLICATE

RECEIVED

MAY 3 2004

DDR-150/CDER

April 28, 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-028: TAXOTERE® (docetaxel) Injection Concentrate

Amendment to Pending Application

*Patient Survival Status Forms for Twelve Case Report Forms
that were Submitted for Study TAX 327*

Dear Dr. Pazdur:

With this letter, Aventis Pharmaceuticals Inc. (Aventis) is submitting information to the pending supplemental New Drug Application (sNDA) 20-449/S-028 concerning twelve patients who were included in study RP 56976V-327 (TAX 327).

Reference is made to the January 26, 2004 submission by Aventis of the subject sNDA, which contained efficacy and safety data to support approval for TAXOTERE in combination with prednisone as a treatment for patients with androgen-independent (hormone-refractory) metastatic prostate cancer.

Reference is also made to a pre-sNDA correspondence between the FDA and Aventis regarding submission of Case Report Forms (CRFs) for selected patients included in study TAX 327. In its pre-sNDA briefing document dated August 26, 2003 (Serial No. 1116), Aventis proposed to submit CRFs for all deaths related to study treatment, for deaths that occurred during the treatment phase, or for deaths occurring within 30 days after the last infusion of study treatment. In addition, Aventis proposed to submit CRFs for all patients who discontinued study treatment due to an adverse event. The FDA indicated its concurrence with this proposal in a September 24, 2003 electronic mail message from Commander Ann Staten, FDA, to Dr. Michael Rozycki, Aventis, and the sNDA that was submitted on January 26, 2004 was in conformance with this approach.

Aventis has become aware that the information that was included for some CRFs in the submission of sNDA 20-449/S-028 did not reflect the entire contents of the original CRF. Specifically, Aventis has identified twelve (12) patients for whom information derived from one component of the CRF, the Patient Survival Status Form (PSSF), was not complete. The PSSF records either the Date Last Known Alive or Date of Death; in the latter case, the Date of Death captured on the PSSF should be the same as that captured on the Death Report Form of the CRF.

In all 12 cases, the PSSF information in the source Case Report Form was complete and up-to-date; however, during the process of scanning the CRF to produce electronic PDF files for inclusion in the Common Technical Document, some PSSF-related documents were inadvertently omitted. In all cases, correct Date Last Known Alive and Date of Death information was captured in the Case Report Tabulations and in data sets used for the statistical analysis of TAX 327.

With this submission, Aventis is providing the PSSF-related information that was inadvertently omitted from the original submission of sNDA 20-449/S-028. A detailed description of this information is as follows:

- **Patient 00301 (Site AR00014).** The PSSF for this patient indicates a Date Last Known Alive of April 1, 2003. However, this PSSF was not scanned with the remainder of the CRF information and was not included in the original sNDA submission. The present submission contains the PSSF that was missing from the original submission. The study database contains the correct Date Last Known Alive of April 1, 2003.
- **Patient 03201 (Site BE20534).** The PSSF included in the original sNDA submission indicated a Date Last Known Alive of February 14, 2003. Also submitted in the original sNDA was a Data Clarification Form indicating that two PSSFs were available for that patient, one with a Date Last Known Alive of February 14, 2003 and the other with a Date Last Known Alive of March 24, 2003, and that the one dated February 14, 2003 should be deleted. The PSSF containing the correct Date Last Known Alive of March 24, 2003 was not scanned with the remainder of the CRF information and was not included in the original sNDA submission. The present submission contains the two PSSFs and the Data Clarification Form. The study database contains the correct Date Last Known Alive of March 24, 2003.
- **Patient 08102 (Site CA21916).** A PSSF indicating the same Date of Death as that recorded on the Death Report Form was not scanned with the remainder of the CRF information and was not included in the original sNDA submission. The present submission contains the PSSF that was missing from the original submission. The study database contains the correct Date of Death of [redacted].
- **Patient 08105 (Site CA21916).** A PSSF indicating the same Date of Death as that recorded on the Death Report Form was not scanned with

the remainder of the CRF information and was not included in the original sNDA submission. The present submission contains the PSSF that was missing from the original submission. The study database contains the correct Date of Death of []

- **Patient 08108 (Site CA21916).** A PSSF indicating the same Date of Death [] as that recorded on the Death Report Form was not scanned with the remainder of the CRF information and was not included in the original sNDA submission. The present submission contains the PSSF that was missing from the original submission. The study database contains the correct Date of Death of []
- **Patient 08118 (Site CA21916).** A PSSF indicating the same Date of Death [] [] as that recorded on the Death Report Form was not scanned with the remainder of the CRF information and was not included in the original sNDA submission. The present submission contains the PSSF that was missing from the original submission. The study database contains the correct Date of Death of []
- **Patient 08202 (Site CA00064).** The PSSF for this patient indicates a Date Last Known Alive of March 27, 2003. However, this PSSF was not scanned with the remainder of the CRF information and was not included in the original sNDA submission. The present submission contains the PSSF that was missing from the original submission. The study database contains the correct Date Last Known Alive of March 27, 2003.
- **Patient 11512 (Site FR21814).** The PSSF included in the original sNDA submission indicated a Date Last Known Alive of May 19, 2003. However, a second PSSF indicating a Date Last Known Alive of March 24, 2003 was not scanned with the remainder of the CRF information and was not included in the original sNDA submission. The correct Date Last Known Alive is March 24, 2003, since that is the date closest to data cut-off. The present submission contains the PSSF that was included with the original sNDA as well as the PSSF that was missing. The study database contains the correct Date Last Known Alive of March 24, 2003.
- **Patient 19001 (Site LB00001).** No PSSF was included in the original sNDA submission. A Data Clarification Form included in the sNDA submission referred to two PSSFs, one with a Date Last Known Alive of March 20, 2003 and the other with a Date Last Known Alive of March 24, 2003, and indicating that the PSSF with Date Last Known Alive of March 20, 2003 should be deleted. The present submission contains the Data Clarification Form that was missing from the original submission, as well as the two PSSFs that were missing from the original submission. The study database contains the correct Date Last Known Alive of March 24, 2003.

- Patient 30601 (Site US04504).** A PSSF indicating the same Date of Death as that recorded on the Death Report Form was not scanned with the remainder of the CRF information and was not included in the original sNDA submission. The present submission contains the PSSF that was missing from the original submission. The study database contains the correct Date of Death of [redacted].
- Patient 30603 (Site US04504).** A PSSF indicating the same Date of Death as that recorded on the Death Report Form was not scanned with the remainder of the CRF information and was not included in the original sNDA submission. The present submission contains the PSSF that was missing from the original submission. The study database contains the correct Date of Death of [redacted].
- Patient 31003 (Site US20055).** A PSSF indicating the same Date of Death as that recorded on the Death Report Form was not scanned with the remainder of the CRF information and was not included in the original sNDA submission. The present submission contains the PSSF that was missing from the original submission. The study database contains the correct Date of Death of [redacted].

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 following table.

Folder/File Name	Description
W20449	
amendtoc.pdf	Submission table of contents
cover.pdf	Submission cover letter
356h.pdf	FDA Form 356h
\cfr	Item 12 folder
crftoc.pdf	CRF table of contents
\ 327	Folder containing data for study TAX 327
\ar00014	Folder for site AR00014
\00301	PSSF documentation for patient 00301
\be20534	Folder for site BE20534
\03201	PSSF documentation for patient 03201
\ca21916	Folder for site CA21916
\08102	PSSF documentation for patient 08102
\08105	PSSF documentation for patient 08105

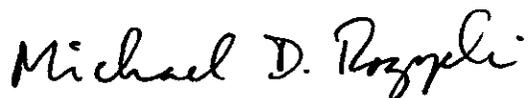
Folder/File Name	Description
\08108	PSSF documentation for patient 08108
\08118	PSSF documentation for patient 08118
\ca00064	Folder for site CA00064
\08202	PSSF documentation for patient 08202
\fr21814	Folder for site FR21814
\11512	PSSF documentation for patient 11512
\lb00001	Folder for site LB00001
\19001	PSSF documentation for patient 19001
\us04504	Folder for site US04504
\30601	PSSF documentation for patient 30601
\30603	PSSF documentation for patient 30603
\us20055	Folder for site US20055
\31003	PSSF documentation for patient 31003

The PSSF that was missing from the CRF for patient 301 (site AR00014) was already identified in an April 14, 2004 electronic mail message from Dr. Rozycki to Commander Staten. That electronic mail message also contained a copy of the missing PSSF as an attachment in PDF format.

The approximate size of this electronic submission is less than 2 MB. The CD-ROM has been scanned and found to be free of any known computer viruses (Symantec Antivirus Corporate Edition, Program Version 7.50.846, current virus definition 4/21/04, version 60421ai, Scan Engine 4.1.0.6).

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, Ph.D.
Director, Regulatory Affairs

Enc: Form FDA 356h
One (1) CD-ROM

4/19/04

PROJECT MANAGER REVIEW OF LABELING

NDA 20-449/S-028

Drug: Taxotere (docetaxel) Concentrate for Injection,
20 mg and 80 mg
Applicant: Aventis
Submission Date: January 26, 2004
Receipt Date: January 27, 2004

BACKGROUND:

On April 24, 2003, NDA 20-449/S-016 was approved, which provided for revisions to the labeling in response to the Agency request for improvement in the statements made regarding the overfill volumes of the concentrate and diluent vials as result of postmarketing medication error reports received by OPDRA.

The final printed labeling (FA) for S-016 was submitted electronically on May 16, 2003 and it was accepted on June 9, 2003.

This new supplement (S-028) provides for the following new proposed indication: "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.

DOCUMENTS REVIEWED:

I compared the electronic Word version of the proposed draft package insert text submitted January 26, 2004 for S-028 against the electronic version of the final printed labeling for S-016 submitted on May 16, 2003.

REVIEW:

The only changes in the new version are those the sponsor proposes for this supplement. The summary of changes in the proposed labeling as compared to the S-016 final printed labeling are as follows:

PATIENT INFORMATION LEAFLET

The revision date has been changed.
Prostate cancer has been added as a new indication.
"such as" has replaced "called" in the reference to dexamethasone.
The premedication charts have been revised to accommodate the premedication regimen for prostate cancer.

PRESCRIBING INFORMATION

The revision date has been changed.

HUMAN PHARMACOKINETICS

A paragraph has been added to discuss the pharmacokinetics of docetaxel/prednisone combination therapy.

CLINICAL STUDIES

A new subsection has been added to describe clinical study results from TAX 327.

INDICATIONS

An indication for the treatment of Androgen Independent (Hormone Refractory) Metastatic Prostate Cancer with Taxotere combined with prednisone has been added.

WARNINGS

The premedication regimen for prostate cancer has been added under the premedication subsection.

PRECAUTIONS

A paragraph describing safety and effectiveness in elderly patients versus younger in the study TAX 327 has been added under the Geriatric Use subsection.

ADVERSE REACTIONS

The introductory paragraph has been rearranged to accommodate the new prostate indication.

An additional subheading "Monotherapy with Taxotere for Locally Advanced or Metastatic Breast Cancer After Failure of Prior Chemotherapy" has been added for the Breast Cancer indication

The subsection "Clinically Important Treatment Emergent Adverse Events Regardless of Relationship in Patients with Prostate Cancer who Received TAXOTERE in Combination with Prednisone (TAX 327)" has been added to display safety results from TAX 327.

DOSAGE AND ADMINISTRATION

A new subsection "Prostate Cancer" has been added to include dosage for the Taxotere and prednisone combination regimen.

The premedication regimen for prostate cancer has been added under the premedication subsection. Dosage Adjustments During Treatment

A sub-section "Combination Therapy with TAXOTERE for Prostate Cancer" has been added to include dosage adjustments for the Taxotere and prednisone combination regimen.

NDA 20-449/S-028

Page 3

CONCLUSION - RECOMMENDED REGULATORY ACTION:

The proposed draft package insert text submitted on January 26, 2004 with tracked changes is attached.

With the concurrence of the Medical 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

35 pages redacted from this section of
the approval package consisted of draft labeling

**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
4/19/04 03:15:29 PM
CSO

Dotti Pease
4/19/04 03:19:46 PM
CSO

Staten, Ann M

From: Michael.Rozycki@aventis.com
Sent: Wednesday, April 14, 2004 5:24 PM
To: statena@cder.fda.gov
Subject: RE: query regarding docetaxel prostate NDA

Dear Ann,

Please forward the following response to the reviewer.

At each follow-up visit, the date of last contact was recorded on the CRF Follow-Up Status Form (FUS/FVS/FDS, Page F.U.1) in the variable D_LCONT which is part of the dataset PATST.XPT. In addition, all subjects who did not have a death report form (DRF) in the database were recontacted to determine their survival status as of the cut-off date of March 24, 2003. This information was recorded on a special CRF Patient Survival Status Form (PSSF) with the variable D_LCONT as the last known alive date. Data from the PSSF is provided in a separate file, PSSF.XPT. To establish the actual date for censoring if the subject was alive, data from the PSSF were used for the derived dataset UPAT.XPT.

Of 1006 subjects randomized, 557 died and 449 subjects were censored in the survival analysis. 442 out of 449 subjects were known to be alive on or after March 24, 2003, and were censored on that date. The remaining 7 subjects were censored on the last date known to be alive prior to March 24, 2003, as recorded on the PSSF of the CRF. The censoring rules were executed as predefined in the Statistical Analysis Plan.

For patient AR00014-306, who was alive at study cutoff, the PSSF is included in the CRF for that patient and shows D_LCONT=26 March 2003.

Patient AT21958-02404 died on [(D_DRF=[] in UPAT.XPT) and was not censored.

For patient AR00014-301, who was alive at study cutoff, the PSSF was inadvertently omitted from the CSR that was included in the submission. A copy of that PSSF is attached to this e-mail, and shows D_LCONT = 01APR2003.

We are investigating why the PSSF for patient AR00014-0301 was omitted from the CRF that was submitted for that patient in the CTD. We expect to provide follow-up information for this issue at the beginning of next week.

Please let me know if you have any further questions regarding this matter.

Sincerely,
Michael Rozycki

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: Staten, Ann M [mailto:STATENA@cder.fda.gov]

4/19/2004

Sent: Tuesday, April 13, 2004 9:06 AM
To: Rozycki, Michael PH/US
Subject: query regarding docetaxel prostate NDA
Importance: High

Dear Mike,

We have the following urgent request for the prostate supplement NDA 20-449/S-028.

Please let me know if you have any questions.

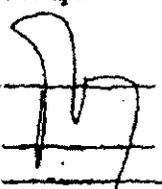
Sincerely,

Ann

In a random review of CRF's for 50 patients from 28 sites and in comparing information from the CRF to that in the Dataset UPAT.XPT,

we observed that three patients were censored on the study cutoff date of 3/24/03 although their last known date alive according to last contact occurred prior to that. Please clarify whether there is any additional contact information for those patients justifying such an approach, and whether this occurred with other patients. The three patients' ID numbers and dates of randomization and last known contact are listed below:

Site #	Patient ID#	Date of Randomization	Date of last known contact
AR00014	301	9/13/00	alive 7/11/01
AR00014	306	5/21/01	alive 1/10/02
AR21958	02404	3/8/01	alive 6/5/01

Patient Survival Status Form	
PI Name: DANIEL CAUPOS	Inv. No.: R R 0 0 0 1 4 <small>(enter 6-digit digit number)</small>
Patient Number: 0 0 3 0 1 <small>(enter 5-digit number)</small>	Patient Initials: E J <small>(if no initial, enter e-1)</small>
Please contact the patient <i>now</i> to determine their survival status :	
Is the patient known to be dead ? If yes, please complete the date of death and send us the Death Report Form (DRF) :	
Date of Death:	0 0 / 0 0 0 / 2 0 0 0 <small>(Format: dd/mm/yyy, e.g., 01/Jan/2003)</small>
If no, what is the last date the patient was known to be alive ?	
Date Last Known Alive:	0 1 / A P R / 2 0 0 3 <small>(Format: dd/mm/yyy, e.g., 01/Jan/2003)</small>
Includes <u>confirmed</u> Lost to Follow Up patients, as well as patients still in Follow Up that were unable to be contacted on or after 24 March 2003. Date provided should be the last date the patient was known to be alive, based on doctor visit, telephone contact, or information from patient's doctor, family member or friend.	
Signature of Primary Investigator or Sub-Investigator designated to complete above information.	
Investigator Name:	Daniel CAUPOS
Investigator Signature:	

3/30/04



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-449/S-028

**PRIOR APPROVAL SUPPLEMENT
FILING COMMUNICATION**

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-028

Review Priority Classification: Priority (P)

Date of supplement: January 26, 2004

Date of receipt: January 27, 2004

This supplemental application proposes the following change: Taxotere in combination with prednisone as a treatment for patients with androgen independent (hormone refractory) metastatic prostate cancer.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on March 27, 2004 in accordance with 21 CFR 314.101(a). The user fee goal date will be July 27, 2004.

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

NDA 20-449/S-028

Page 2

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 requirement. We are waiving the requirement for pediatric studies for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this supplement 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
3/30/04 09:03:30 AM
Signed for Dotti Pease

Aventis Pharmaceuticals



March 29, 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

NDA 20-449: TAXOTERE[®] (docetaxel) Injection Concentrate

Amendment to Pending Application

Response to FDA Request for Information for Pre-Approval Inspection

Dear Dr. Pazdur:

With this letter, Aventis Pharmaceuticals Inc. (Aventis) is submitting information requested by the Food and Drug Administration (FDA) Division of Scientific Investigation (DSI), in preparation for Pre-Approval Inspections to support the Agency's review of the pending supplemental New Drug Application (sNDA) 20-449/S-028.

Reference is made to the January 26, 2004 submission by Aventis of the subject sNDA, which contained efficacy and safety data to support approval for TAXOTERE in combination with prednisone as a treatment for patients with androgen-independent (hormone-refractory) metastatic prostate cancer.

Reference is also made to a March 1, 2004 telephone discussion between Dr. David Gan, FDA DSI, and Dr. Michael Rozycki, Aventis, in which Dr. Gan indicated that he was working to arrange Pre-Approval Inspections of two investigators for study RP 56976V-327 (TAX 327), in support of the FDA's review of the subject sNDA. The investors to be inspected were ☐

☐ Dr. Gan indicated that he needed the following information in order to prepare for these inspections:

- Contact information, investigator CVs, and FDA Forms 1572 for each of the two sites to be inspected.

- Monitor name and monitoring logs for the two sites to be inspected.
- Randomization lists for each site.
- Total patients entered and discontinued (with reason why for the latter) at each site.
- Evaluability of each patient at the two sites.
- Reportable SAEs and deaths by patient at each site.
- Protocol deviations and violations for each site.
- Results of primary efficacy endpoints for patients at the two sites.
- Data tabulations for each patient at the two sites to be inspected.

Finally, reference is made to a series of telephone and e-mail exchanges between Dr. Leslie Ball, FDA DSI, Commander Ann Staten, FDA Division of Oncology Drug Products (DODP), and Dr. Rozycki between March 16, 2004 and March 18, 2004, in which it was agreed that, contrary to the earlier discussion between Dr. Gan and Dr. Rozycki, data tabulations for each patient would not need to be submitted. Dr. Ball requested that the remainder of the information requested by Dr. Gan be submitted electronically to DODP as an amendment to the sNDA, with notification to DSI when the submission had taken place.

With this letter, and in accordance with the FDA's January 1999 "Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDA," Aventis is submitting the information requested by DSI in preparation for its Pre-Approval Inspections. [

] 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 following table.

Folder/File Name	Description
W20449	
cover.pdf	Submission cover letter
356h.pdf	FDA Form 356h
amendtoc.pdf	Submission table of contents
\clinstat	Item 8/10 folder
\ 327	Folder containing data for study TAX 327
\ [Information []
site contact.pdf	Contact information for []
monitoringinfo.pdf	Monitor contact information and site monitoring log
currentprotocol.pdf	Current protocol for TAX 327 used for [] site

Folder/File Name	Description
protocolamendment.pdf	Protocol amendments 1, 2, 3, 4, and 5 of TAX 327, specific for _____ site
_____ .pdf	<i>Curriculum vitae</i> for _____
fda1572.pdf	Form FDA 1572 for _____
horticv.pdf	<i>Curriculum vitae</i> for _____
tables.pdf	Tables containing the following information for _____ site: <ul style="list-style-type: none"> • Patient randomization • Eligibility, evaluability, discontinuation, and survival information • SAEs, including deaths • Protocol deviations • Protocol violations • Primary endpoint information
_____	Information for _____
_____ site contact.pdf	Contact information for _____
monitoringinfo.pdf	Monitor contact information and site monitoring log
currentprotocol.pdf	Current protocol for TAX 327 used for _____ site
protocolamendment.pdf	Protocol amendments 1, 2, 3, 4, and 5 of TAX 327, specific for _____ site
_____ .pdf	<i>Curriculum vitae</i> for _____
fda1572.pdf	Form FDA 1572 for _____
_____ .pdf	<i>Curriculum vitae</i> for _____
_____ .pdf	<i>Curriculum vitae</i> for _____
_____ .pdf	<i>Curriculum vitae</i> for _____
_____ .pdf	<i>Curriculum vitae</i> for _____
tables.pdf	Tables containing the following information for _____ site: <ul style="list-style-type: none"> • Patient randomization • Eligibility, evaluability, discontinuation, and survival information • SAEs, including deaths • Protocol deviations • Protocol violations • Primary endpoint information

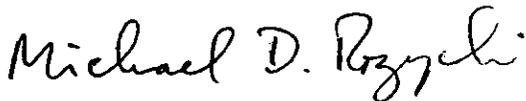
NDA 20-449
March 29, 2004
Page 4 of 4

The protocol and amendments used at _____ site differ slightly from those used at _____ site, in that the versions of the protocol and amendments used in _____ (as well as certain other countries) allowed for the use of prednisolone instead of prednisone. In addition, the current protocol, version 4, for study TAX 327 was updated on October 1, 2001, and includes changes resulting from Amendments 1, 2, and 3. It does not incorporate the changes resulting from Amendments 4 and 5. However, all protocol amendments, including Amendments 4 and 5, are included in the file *protocolamendment.pdf* for each investigator site.

The approximate size of this electronic submission is 26 MB. The CD-ROM has been scanned and found to be free of any known computer viruses (Symantec Antivirus Corporate Edition, Program Version 7.50.846, current virus definition 3/22/04 version 60223g, Scan Engine 4.1.0.6).

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, Ph.D.
Director, Regulatory Affairs

Enc: Form FDA 356h
One (1) CD-ROM

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Dr. Michael Rozycki **From:** Amy Baird, CSO

Fax: 908-304-6549 **Fax:** (301) 827-4590

Phone: 908-304-6412 **Phone:** (301) 594-5779

Pages (including cover): 1 **Date:** February 20, 2004

Re: NDA 20-449/S-028 Taxotere (docetaxel) Injection. Specifically, your submission dated January 26, 2004, which provides for the androgen independent (hormone refractory) prostate cancer indication.

Urgent For Review Please Comment Please Reply Please Recycle

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

● **Comments:**

The following request is per the clinical and statistical review teams.

Your electronic submission provides two datasets in which a date of death is recorded (DRF.XPT and PSSF.XPT). In both cases, the date of death is listed under the D_DRF column as a 5 digit number which is not interpretable. Please provide a dataset which includes date of death and date of randomization as dates including month, day and year presented uniformly.

Please call should you have any questions.

Thank you,

Amy Baird

/s/

RECEIVED

JAN 27 2004

CDR/CDER



NDA NO. 20-449 REF NO. 028

NDA SUPPL FOR SE2-028

January 26, 2004

DUPLICATE

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

SE2-028

RECEIVED

JAN 29 2004

DDR-150/CDER

NDA 20-449: Taxotere[®] (docetaxel) Injection Concentrate
Prior Approval Supplement: Androgen Independent (Hormone Refractory) Prostate Cancer

Dear Dr. Pazdur:

Provided herewith, in accordance with 21 CFR Section 314.70, is a Supplemental New Drug Application (sNDA) that contains clinical safety and efficacy data to support approval for Taxotere[®] in combination with prednisone as a treatment for patients with androgen independent (hormone refractory) metastatic prostate cancer. The proposed regimen is Taxotere 75 mg/m² administered every 3 weeks as a one-hour infusion, with prednisone 5 mg administered orally, twice daily.

This application includes results from one prospective, multicenter, randomized Phase III study (TAX327), which compared the efficacy and safety of two doses and schedules of Taxotere (every 3 weeks and weekly, in combination with prednisone) to that of the approved regimen of mitoxantrone combined with prednisone. This trial, which enrolled 1006 subjects (of whom 65.5% were aged 65 years old or more) demonstrated a statistically significant overall survival advantage for both the every 3 weeks Taxotere/prednisone regimen, (p=0.0094, hazard ratio=0.761, 95% CI [0.619-0.936]) and for the two Taxotere groups combined, (p=0.0398, hazard ratio=0.834, 95% CI [0.701-0.992]) compared to the mitoxantrone regimen. In addition, the study examined cross-arm comparisons for a variety of important secondary efficacy measures, including endpoints associated with pain response rate, PSA response rate, tumor response rate, progression-free survival, quality of life, performance status and weight gain. While treatment-emergent adverse events were more frequent in the Taxotere every 3 weeks treatment group compared with mitoxantrone every 3 weeks treatment group, no substantial differences were seen in discontinuations from treatment due to drug toxicity, death within 30 days of last infusion, toxic death or incidence per cycle of serious adverse events.

NDA 20,449 Efficacy Supplement

January 26, 2004

Page 2

Overall, the benefit of Taxotere, including a significant survival and pain control advantage, clearly outweighs the risks of therapy in this uniformly fatal disease, and represents a significant addition to the therapeutic armamentarium, which has lacked any chemotherapeutic agent producing clinical benefits above and beyond that of symptom pain control. It is therefore respectfully requested that FDA consider assigning a priority review clock to this application.

This sNDA was the subject of a pre-sNDA meeting request, (dated July 31, 2003, Serial No. 1110, IND 35,555). FDA responses to the pre-sNDA questions posed by Aventis, (questions that were designed to optimize for an efficient review of the application), were considered by Aventis as complete enough to allow for the expedient preparation of the application without the need for a pre-sNDA meeting. With the submission of this application, and to further optimize for an efficient review of this application, Aventis personnel will work with FDA to schedule a meeting as soon as possible so that an overview of the application content can be presented to relevant Review Staff. Aventis would like to propose February 24, March 15, or March 24 as potential dates for this meeting. Further, Aventis would like to extend an offer of a demonstration of this electronic application as well. This demonstration may be scheduled either in conjunction with the submission overview meeting or as a separate meeting, depending on the preference of the Division Review Staff.

This submission contains an original cover letter, Form FDA 356h, and Module 1 of the CTD, including originals of all signed forms. In accordance with the 1999 FDA Guideline for Industry, "Providing Regulatory Submissions in Electronic Format", a copy of this cover letter, Form FDA 356h, and digital tape containing the full contents of the application have been sent under separate cover to:

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

Under separate cover, the User Fee for this supplemental New Drug Application has been submitted according to the Prescription Drug User Fee Act. A fee of \$286,750 was submitted via check number November 25, 2003 with User Fee Identification Number 4670.

NDA 20,449 Efficacy Supplement

January 26, 2004

Page 3

A complete index for the contents of this application is provided in this application. The electronic archival copy of this application consists of 1 DLT 35/70 Digital Tape (approximately 3.8 GB). Aventis certifies that all electronic media have been scanned and found to be free of any known computer viruses (Symantec Antivirus Corporate Edition, Program Version 8.1.0.825, current DEFS 1/18/04 rev. 19, Scan Engine 4.2.0.7). We look forward to working closely with FDA Review Staff so that the application review can be as efficient as possible.

Dr. Michael Rozycki will have primary responsibility for responding to any Agency requests on the application. He may be reached at 908-304-6412, or by fax at 908-304-6549.

Sincerely,



Cheryl Anderson
Senior Director and Oncology Therapeutic Area Head
Global Regulatory Liaison
Aventis Pharmaceuticals, Inc.
Mail Code: BX2-209G
200 Crossing Boulevard
PO Box 6890
Bridgewater, NJ 08807-0890
Telephone 908 394 6471
Fax 908 304 6549
E-mail: Cheryl.anderson2@aventis.com

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, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

RECEIVED
JAN 27 2004
CDR/CDER

APPLICANT INFORMATION

NAME OF APPLICANT Aventis Pharmaceuticals	DATE OF SUBMISSION January 26, 2003
TELEPHONE NO. (Include Area Code) (908) 304-6412	FACSIMILE (FAX) Number (Include Area Code) (908) 304-6549
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 200 Crossing Boulevard PO Box 6890 Bridgewater, NJ 08807-0890	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 20-449		
ESTABLISHED NAME (e.g., Proper name, USPU/SAN name) docetaxel	PROPRIETARY NAME (trade name) IF ANY Taxotere® Injection Concentrate	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) (2R,3S)-N-carboxy-3-phenylisoserine, N-tert-butyl ester, 13-ester with 5b-20-epoxy-1,2a,4,7b,10b,13a-hexahydroxytax-11-en-9-one 4-acetate 2-benzate trihydrate	CODE NAME (if any) XRP6976J	
DOSAGE FORM: Concentrate for Infusion	STRENGTHS: 20 mg and 80 mg	ROUTE OF ADMINISTRATION: Intravenous
(PROPOSED) INDICATION(S) FOR USE: TAXOTERE in combination with prednisone is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer		

APPLICATION INFORMATION

APPLICATION TYPE (check one)	<input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)	<input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
	<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)	
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE	<input checked="" type="checkbox"/> 505 (b)(1)	<input type="checkbox"/> 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)	<input type="checkbox"/> ORIGINAL APPLICATION	<input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION
	<input type="checkbox"/> PRESUBMISSION	<input type="checkbox"/> RESUBMISSION
	<input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT
	<input type="checkbox"/> LABELING SUPPLEMENT	<input checked="" type="checkbox"/> EFFICACY SUPPLEMENT
	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT	<input type="checkbox"/> OTHER
IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:		
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY	<input type="checkbox"/> CBE	<input type="checkbox"/> CBE-30
	<input checked="" type="checkbox"/> Prior Approval (PA)	
REASON FOR SUBMISSION Initial sNDA Submission		

PROPOSED MARKETING STATUS (check one)	<input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx)	<input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
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NUMBER OF VOLUMES SUBMITTED	eCTD	THIS APPLICATION IS	<input type="checkbox"/> PAPER	<input checked="" type="checkbox"/> PAPER AND ELECTRONIC	<input type="checkbox"/> 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.

See original NDA submission dated July 27, 1994

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
IND 35,555

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 (1)(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)

CERTIFICATION

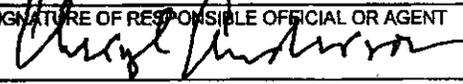
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. 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, 680 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 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 Cheryl Anderson, Senior Director & Therapeutic Area Head Global Regulatory Liaison, Oncology	DATE 26 Jan 2003
ADDRESS (Street, City, State, and ZIP Code) 200 Crossing Boulevard Bridgewater, NJ 08807-0890		TELEPHONE NUMBER (908) 304-6471

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
BER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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.

1.3 Comprehensive Table of Contents

Description	Archive copy folder/file name
1.1 Cover letter	<i>\cover.pdf</i>
1.2 FDA form 356h	<i>\356h.pdf</i>
1.4 Administrative Documents	
1.4.1 Patent Information	<i>other\patinfo.pdf</i>
1.4.2 Patent Certification	<i>other\patcert.pdf</i>
1.4.3 Debarment certification	<i>other\debar.pdf</i>
1.4.4 Field copy certification	<i>other\fieldcer.pdf</i>
1.4.5 User Fee Cover Sheet	<i>other\userfee.pdf</i>
1.4.6 Financial Disclosure	<i>other\financial.pdf</i>
1.4.7 Letters of authorization for reference to other applications	<i>other\authoriz.pdf</i>
1.4.8 Waiver requests	<i>other\waiver.pdf</i>
1.4.9 Environmental assessment or request for categorical exclusion	<i>other\environ.pdf</i>
1.4.10 Statements of claimed exclusivity and associated certifications	<i>other\exclusiv.pdf</i>
1.5 Prescribing information	
Labeling Table of Contents	<i>labeling\labeltoc.pdf</i>
1.5.1 Proposed labeling text	<i>labeling\proposed.pdf</i>
1.5.2 Current labeling text	<i>labeling\current.pdf</i>
1.5.3 Approved labeling text	<i>labeling\approved.pdf</i>
1.6 Annotated labeling text	<i>labeling\summary.pdf</i>
1.7 Labeling History	<i>labeling\history.pdf</i>
1.8 Documentation on the INN and USAN	<i>other\inn and usan.pdf</i>
1.9 Summary of all the interactions with FDA	<i>other\interactions.pdf</i>
1.10 Post-marketing risk management plans	<i>other\post-marketingriskmanagement.pdf</i>

Module 2 Table of Contents

Description	Archive copy folder/file name
2.1 CTD Table of Contents	<i>summary\sumtoc.pdf</i>
2.2 CTD Introduction	<i>summary\2.2 ctd introduction.pdf</i>
2.3 Quality Overall Summary	<i>summary\2.3 quality overall summary.pdf</i>
2.4 Nonclinical Overview	<i>summary\2.4 non clinical overview.pdf</i>
2.5 Clinical Overview	<i>summary\2.5 clinical overview.pdf</i>
2.6 Nonclinical Written and Tabulated Summary	<i>summary\2.6 nonclinical summary.pdf</i>
2.7 Clinical Summary	
2.7.1 Biopharmaceutic and Analytical Methods Summary	<i>summary\2.7.1 biopharm summary.pdf</i>
2.7.2 Clinical Pharmacology Summary	<i>summary\2.7.2 clinical pharmacology summary.pdf</i>
2.7.3 Clinical Efficacy Summary	<i>summary\2.7.3 clinical efficacy summary.pdf</i>
2.7.4 Clinical Safety Summary	<i>summary\2.7.4 clinical safety summary.pdf</i>
2.7.5 Literature References	<i>summary\2.7.5 literature references.pdf</i>
2.7.6 Synopses of individual studies	<i>summary\2.7.6 synopses of individual studies.pdf</i>

Module 5 Clinical Table of Contents

Description	Archive copy folder/file name
5.1 Table of Contents	<i>clinstat\clintoc.pdf</i>
5.2 Tabular Listing of all Clinical Studies (clinstat)	<i>clinstat\5.2tabularlistingofallclinicalstu.pdf</i>
5.3 Clinical Study Reports and Related Information	
5.3.1 Reports of Biopharmaceutic Studies	<i>clinstat\5.3.1 reports of biopharmaceutic studies.pdf</i>
5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials	<i>clinstat\5.3.2 reports of studies pertinent to pharmacokinetics using human biomat.pdf</i>
5.3.3 Reports of Human Pharmacokinetics (PK) Studies	<i>clinstat\5.3.3 reports of human pharmacokinetics (pk) studies.pdf</i>
5.3.4 Reports of Human Pharmacodynamics (PD) Studies	<i>clinstat\5.3.4 reports of human pharmacodynamics (pd) studies.pdf</i>
5.3.5 Reports of Efficacy and Safety Studies	
5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication	
5.3.5.1.1 Study 327	<i>clinstat\5.3.5.1.1 study 327\327.pdf</i>
5.3.5.1.1 Study 327a	<i>clinstat\5.3.5.1.1 study 327\327a.pdf</i>
5.3.5.1.1 Study 327b	<i>clinstat\5.3.5.1.1 study 327\327b.pdf</i>
5.3.5.2 Study Reports of Uncontrolled Clinical Studies	<i>clinstat\5.3.5.2 uncontrolled clinical studies.pdf</i>

5.3.5.3 Reports of Analyses of Data from More Than One Study	<i>clinstat\5.3.5.3 analyses of data.pdf</i>
5.3.5.4 Other Study Reports	<i>clinstat\5.3.5.4 other study reports.pdf</i>
5.3.6 Reports of Postmarketing Experience	
5.3.6 .1 PSUR 10	<i>clinstat\5.3.6 psur10.pdf</i>
5.3.6 .2 PSUR 11	<i>clinstat\5.3.6 psur11.pdf</i>
5.3.6 .3 PSUR 12	<i>clinstat\5.3.6 psur12.pdf</i>
5.3.7 Case Report Forms and Individual Patient Listings	
5.3.7.1 Case Report Tabulations (CRTs) and Patient Listings	<i>crt\crttoc.pdf</i>
5.3.7.2 Case Report Forms (CRFs)	<i>crf\crftoc.pdf</i>
5.4 Publications	
Abratt 2003	<i>clinstat\pubs\abratt2003.pdf</i>
Baille 1997	<i>clinstat\pubs\baille1997.pdf</i>
Beer 2001	<i>clinstat\pubs\beer2001.pdf</i>
Berry 2001	<i>clinstat\pubs\berry2001.pdf</i>
Berry 2002	<i>clinstat\pubs\berry2002.pdf</i>
Bruno 1996	<i>clinstat\pubs\bruno1996.pdf</i>
Bruno 1998	<i>clinstat\pubs\bruno1998.pdf</i>
Bruno 2001	<i>clinstat\pubs\bruno2001.pdf</i>
Bublely 1999	<i>clinstat\pubs\bublely1999.pdf</i>
Dawson 1998	<i>clinstat\pubs\dawson1998.pdf</i>
DiPaola 1999	<i>clinstat\pubs\dipaola1999.pdf</i>
DMPKFR 2405	<i>clinstat\pubs\dmpkfr2405.pdf</i>
DMPK2104 Addendum #2	<i>clinstat\pubs\dmpk2104addendum#2.pdf</i>
FDA End of Phase II Mtg	<i>clinstat\pubs\fdaendofphaseiimtg.pdf</i>

FDA comments Bonferroni	<i>clinstat\pubs\fdacommentsonbonferroni.pdf</i>
FDA comments TAX327 SAP	<i>clinstat\pubs\fdacommentstax327sap.pdf</i>
FDA comments TAX327 protocol	<i>clinstat\pubs\fdacommentstax327protocol.pdf</i>
FDA pre-sNDA comments	<i>clinstat\pubs\fdapre-sndacommentson.pdf</i>
FDA 04-03-03	<i>clinstat\pubs\fd_04_03_03.pdf</i>
Foa 2002	<i>clinstat\pubs\foa2002.pdf</i>
French Agency 99-08-31	<i>clinstat\pubs\frenchagency99_08_31.pdf</i>
French Agency 00-04-07	<i>clinstat\pubs\frenchagency00_04_07.pdf</i>
Friedland 1999	<i>clinstat\pubs\friedland1999.pdf</i>
Gaffar 2003	<i>clinstat\pubs\gaffar2003.pdf</i>
Gravis 2003	<i>clinstat\pubs\gravis2003.pdf</i>
Hainsworth 1999	<i>clinstat\pubs\hainsworth1999.pdf</i>
Halabi 2003	<i>clinstat\pubs\halabi2003.pdf</i>
Hirschfeld 2002	<i>clinstat\pubs\hirschfeld2002.pdf</i>
Hirth 2000	<i>clinstat\pubs\hirth2000.pdf</i>
Hudes 1999	<i>clinstat\pubs\hudes1999.pdf</i>
Johnson 1985	<i>clinstat\pubs\johnson1985.pdf</i>
Johnson 2003	<i>clinstat\pubs\johnson2003.pdf</i>
Kantoff 1999	<i>clinstat\pubs\kantoff1999.pdf</i>
Laber 2003	<i>clinstat\pubs\laber2003.pdf</i>
Lindsted 1996	<i>clinstat\pubs\lindsted1996.pdf</i>
Listing of Taxotere HRPC Studies	<i>clinstat\pubs\listingoftaxoterehrpcstudies.pdf</i>
Lu-Yao 1997	<i>clinstat\pubs\lu-yao1997.pdf</i>
Marre 1996	<i>clinstat\pubs\marre1996.pdf</i>
MDA-ID-00156	<i>clinstat\pubs\mda-id-00156.pdf</i>
Millikan 1999	<i>clinstat\pubs\millikan1999.pdf</i>
Moore 1994	<i>clinstat\pubs\moore1994.pdf</i>
Muc 2000 SA00-221	<i>clinstat\pubs\muc2000sa00-221.pdf</i>
Myers 1999	<i>clinstat\pubs\myers1999.pdf</i>
Newling 1997	<i>clinstat\pubs\newling1997.pdf</i>

Oudard 2003	<i>clinstat\pubs\oudard2003.pdf</i>
O'Saughnessy1991	<i>clinstat\pubs\osauehnessv1991.pdf</i>
Parkin 1997	<i>clinstat\pubs\parkin1997.pdf</i>
Petrioli 2003	<i>clinstat\pubs\petrioli2003.pdf</i>
Pichard 1992	<i>clinstat\pubs\pichard1992.pdf</i>
Picus 1999	<i>clinstat\pubs\picus1999.pdf</i>
Ries 1973	<i>clinstat\pubs\ries1973.pdf</i>
Ries 1975	<i>clinstat\pubs\ries1975.pdf</i>
Ries 2000	<i>clinstat\pubs\ries2000.pdf</i>
Saxman 1992	<i>clinstat\pubs\saxman1992.pdf</i>
Scher 1994	<i>clinstat\pubs\scher1994.pdf</i>
Scher 1999	<i>clinstat\pubs\scher1999.pdf</i>
Schilsky 2002	<i>clinstat\pubs\schilsky2002.pdf</i>
Small 1997	<i>clinstat\pubs\small1997.pdf</i>
Small 2000	<i>clinstat\pubs\small2000.pdf</i>
Small 2001	<i>clinstat\pubs\small2001.pdf</i>
Smith 1998	<i>clinstat\pubs\smith1998.pdf</i>
Spontaneous AEs by PT	<i>clinstat\pubs\spontaneous aes by pt.pdf</i>
Spontaneous AEs by SOC	<i>clinstat\pubs\spontaneous aes by soc.pdf</i>
Standford 1999	<i>clinstat\pubs\standford1999.pdf</i>
Tannock 1989	<i>clinstat\pubs\tannock1989.pdf</i>
Tannock 1996	<i>clinstat\pubs\tannock1996.pdf</i>
Tax-FR1-29916	<i>clinstat\pubs\tax-fr1-29916.pdf</i>
XRP6976-6006	<i>clinstat\pubs\xrp6976-6006.pdf</i>
XRP6976-7001	<i>clinstat\pubs\xrp6976-7001.pdf</i>
Yamamoto 2000	<i>clinstat\pubs\yamamoto2000.pdf</i>
2002 INDAR SWOG 9916letter	<i>clinstat\pubs\2002indarswog9916letter.pdf</i>

4 Pages Redacted of
Deliberative Process
§ 552(b)(5)

9/25/03

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

A 20-449	Efficacy Supplement Type SE-1	Supplement Number 028
Drug: Taxotere (docetaxel)		Applicant: Aventis
RPM: Ann Staten		HFD-150 Phone # 301-594-0490
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
• Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
• Chem class (NDAs only)		
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		7-27-04
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that form FDA-3542a was submitted.		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	X
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	() Yes, Application # _____ (x) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	
	X 5-17-04
❖ Actions	
• Proposed action	(x) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(x) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(x) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	() None (X) Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	X PM 4-19-04; DDMAC 4-15-04
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	n/a
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	n/a
• Applicant proposed	n/a
• Reviews	n/a
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	n/a
• Documentation of discussions and/or agreements relating to post-marketing commitments	n/a
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
	X
❖ Memoranda and Telecons	
	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	X 5-12-04
• Pre-NDA meeting (indicate date)	X 9-23-03
• Pre-Approval Safety Conference (indicate date; approvals only)	X ODS attended labeling mtg 5-5-04
• Other	

❖ Advisory Committee Meeting	
• Date of Meeting	n/a
• 48-hour alert	n/a
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	Division Director
❖ Clinical review(s) (indicate date for each review)	X 5-17-04
❖ Microbiology (efficacy) review(s) (indicate date for each review)	n/a
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	n/a
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	n/a
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Demographic Worksheet (NME approvals only)	n/a
❖ Statistical review(s) (indicate date for each review)	See Medical review
❖ Biopharmaceutical review(s) (indicate date for each review)	X 5-10-04
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	n/a
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	n/a see memo to file 5-18-04
• Bioequivalence studies	n/a
❖ CMC review(s) (indicate date for each review)	X 4-19-04
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	X see CMC review
• Review & FONSI (indicate date of review)	n/a
• Review & Environmental Impact Statement (indicate date of each review)	n/a
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	n/a
❖ Facilities inspection (provide EER report)	Date completed: () Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested () Not yet requested
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	n/a
❖ Nonclinical inspection review summary	n/a
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	n/a
❖ CAC/ECAC report	n/a

9/25/03

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 20-449 Supplement # SE1-028

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

Applicant: Aventis Pharmaceuticals

Date of Application: January 26, 2004
Date of Receipt: January 27, 2004
Date clock started after UN:
Date of Filing Meeting: March 26, 2004
Filing Date: March 27, 2004
Action Goal Date (optional): July 27, 2004 User Fee Goal Date: July 27, 2004

Indication(s) requested: **Prostate Cancer:** TAXOTERE in combination with prednisone is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic prostate 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

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) ____5-12-99__ NO
 If yes, distribute minutes before filing meeting.

• Pre-NDA Meeting(s)? Date(s) ____9-23-03__ 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.

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___ 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

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On Original**

**Appears This Way
On Original**

9/25/03

ATTACHMENT
MEMO OF FILING MEETING

DATE: 3-26-04

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: Baird, YHsieh, Dagher, Abraham, Rahman, Sridhara, Pazdur

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Dr. Ramzi Dagher
Secondary Medical:	Dr. Grant Williams
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: YES Requested 2-26-04
- Advisory Committee Meeting needed? NO
- 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

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.

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

EXPECTED REVIEW COMPLETION:

Clinical/Stat combined review: End of April

Biopharm: End of April

ACTION ITEMS:

1. Document filing issues/no filing issues conveyed to applicant by Day 74. (done: 3-30-04)
2. The following consultants should be cleared to assist in the review of this supplement: Dr. Donna Przepiorka, Dr. Maha Hussain and Dr. Bruce Redman. (done: 3-29-04)
3. Contact JoAnn Minor to identify a patient consultant. (done: 3-29-04)
4. No team meetings are needed (labeling meeting scheduled for 5-5-04 9:30am CR C)

Ann Staten, RD
Regulatory Project Manager, HFD-150

Staten, Ann M

From: Staten, Ann M
Sent: Wednesday, September 24, 2003 11:33 AM
To: Michael. Rozycki (Michael.Rozycki@aventis.com)
Subject: HRPC responses attached
Importance: High

Hi Mike,

Attached are the FDA answers to your questions. You have the option of canceling our meeting of September 29, 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

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10/9/2003

PROPOSED DISCUSSION QUESTIONS

General Application Format and Content

1. Aventis plans to submit a supplemental New Drug Application (sNDA) to support the use of TAXOTERE as a treatment for hormone-refractory prostate cancer. The application will include data from the Phase III Study TAX327. 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 C.

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. 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. Narratives will be submitted for deaths that occurred during the treatment phase or within 30 days after the last infusion of study treatment.

Does the FDA concur with this approach?

FDA Response: Yes. Please have CRF's for all deaths available for submission upon request as needed.

4. It is anticipated that the key information for an assessment of safety in the hormone-refractory prostate cancer setting will be generated out of the TAX327 study. 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 hormone-resistant prostate 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 hormone-refractory prostate 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 C. 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: 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. Hyperlinks are desirable but not required.

8. Data sets for study TAX327 will be provided at the time of the submission in a SAS transport file format (.XPT), as defined by logical panels, e.g., efficacy, adverse events, laboratory tests, etc. These data sets will include original CRF data as well as derived data. A typical example of the define.pdf document is attached in Appendix D. (Some of these files may have sizes larger than 50 MB.)

8a. Included in Appendix E 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 the raw data where the efficacy variables were derived.

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. Please also include the following:

- a) SAS programs that produced all derived efficacy variables from the raw data;
- b) SAS programs that produced all of the efficacy results

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 datasets; it is not planned to provide paper copies of any listings.

Does the FDA agree with this proposal?

FDA Response:

Yes. Please include all patients who died of any cause during the study and all patients who dropped out during the course of the study in association with any adverse experience, whether or not thought to be drug related.

Adverse Event Analyses

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 arms 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 arms. The table in Appendix F displays the planned analyses with regard to the principle of treatment-emergent adverse events (TEAEs) or all adverse events (ALL AEs).

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. See also # 12.

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 arms in TAX327 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 setting of hormone-refractory prostate 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 setting of hormone-refractory prostate 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. 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.

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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.

Drug	Number Exposed To Study Drug	Number Exposed To Reference Drug	Number Exposed To Both Drugs
Gender	Males	All Females	Females >50
Age:	0-≤1 Mo.	>1 Mo.-≤ 2Year	>2-≤12
Race	White	Black	Other

Other

**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
10/9/03 02:27:13 PM

Kevin Ridenhour
10/10/03 08:47:49 AM

INTERNAL MEETING MINUTES

MEETING DATE: September 23, 2003

IND/NDA IND 35,555 Meeting Request Submission Date: July 31, 2003 (NB10)
FDA Response Date: August 14, 2003
Briefing Document Submission Date: August 26, 2003 (NB16)

DRUG: Taxotere (docetaxel)
SPONSOR/APPLICANT: Aventis

TYPE of MEETING:

1. Pre-sNDA
2. Indication: []

FDA PARTICIPANTS:

Richard Pazdur, MD, Director, Division of Oncology Drug Products
Ramzi Dagher, M.D., Medical Team Leader
Kevin Ridenhour, MD, Medical Reviewer
Peiling Yang, PhD, Statistician
Atiqur Rahman, Ph.D., Clinical Pharmacology Team Leader
Ann Staten, RD, Project Manager
Justina Molzon, Common Technical Document advisor

MEETING OBJECTIVES:

To discuss the format and content of the sNDA submission (Taxotere in combination with prednisone in patients with androgen-independent, including HRPC, metastatic prostate cancer); electronic submission in ICH-CTD format; and general regulatory considerations.

BACKGROUND: Following the internal pre-meeting on 9-23-03, FDA's response was sent to the sponsor via E-mail on 9-24-03 (attached). The sponsor cancelled the meeting since further clarification was not needed.

ACTION ITEMS:

There were no unresolved issues or discussion points.

 /S/
Ann Staten Date
Project Manager
Minutes preparer

Concurrence Chair: /S/
Kevin Ridenhour, M.D. Date
Medical Reviewer

Attachments: FDA e-mail dated 9-24-03

37 Pages Redacted of
Deliberative Process
§ 552(b)(5)

Withheld

30

**page(s) of trade
secret
and/or confidential
commercial
information**

(b4)