CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-449/S-018

Correspondence

DUPLICATE

Aventis Pharmaceuticals

SE1-018
BS

Aventis

RECEIVED
OCT 3 0 2002
HFD-150 / CDER

October 28, 2002

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

NDA 20-449/S-018
Taxotere® (docetaxel) for Injection Concentrate
October 23rd FDA Statistical Comments

Dear Dr. Pazdur:

Reference is made to NDA 20-449 for Taxotere® (docetaxel) Injection Concentrate and to our pending supplemental New Drug Application S-018 submitted on February 1, 2002 for the use of Taxotere® plus cisplatin for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received chemotherapy for this condition. Additional reference is made to the Division's statistical comments contained in the October 23, 2002 fax. We are now providing a response to the Division's comments.

RESPONSE STATISTICIANS COMMENT

The sponsor is in agreement with the reviewers' conclusion that docetaxel combined with cisplatin (D75+Cis) is non-inferior to vinorelbine+cisplatin (V+Cis).

However, the sponsor would like to address the following two aspects:

Primary model for analysis

The FDA reviewers' analysis is based on a stratified model. The sponsors primary analysis to test non-inferiority used a stratified and covariate adjusted Cox proportional hazards model. This model was pre-specified in section 10.1 of the Statistical Analysis Plan (SAP) as the primary method to assess non-inferiority. The SAP was finalized prior to the interim analysis and submitted to the agency on August 2nd 2000.

Based on the stratified and covariate adjusted Cox proportional hazards model, the hazard ratio of control over test becomes 0.843 (or 1.183 if calculated as test over control as presented in the application) compared to 0.884 based on a stratified Cox proportional hazards model. The application of a stratified model should be considered as a sensitivity analysis and indeed supports the conclusion based on the primary analysis.

ITT population vs All randomized patients.

According to the statistical analysis plan, patients who were misdiagnosed and were identified as not having NSCLC were excluded from the ITT population. Two patients were identified as not having NSCLC (patient 41011 with oat cell carcinoma and patient 12017 with pancreatic carcinoma). The sponsor used the ITT population as defined above for the analysis of survival data. The reviewer's analysis is based on all randomized patients including these two patients. Although the sponsor considers this as a minor difference it should be noted that all analyses presented in the submission are based on the ITT population as defined in the statistical analysis plan.

In general, the sponsor would like to point out that the draft CLINICAL STUDIES section of the package insert submitted with the sNDA reflects the analyses specified in the SAP.

If you have any questions, please contact the undersigned at (908) 304-6471.

Sincerely,

Cheryl Anderson
Therapeutic Area Head, Oncology
Drug Regulatory Affairs

DUPLICATE

Aventis Pharmaceuticals

Aventis

NDA SUPP AMEND
SE1-018
BM

September 30, 2002

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

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OCT 0 1 2002
HFD-150 / CDER

NDA 20-449/S-018
Taxotere® (docetaxel) for Injection Concentrate
September 24th FDA Request for Additional Information

Dear Dr. Pazdur:

Reference is made to NDA 20-449 for Taxotere® (docetaxel) Injection Concentrate and to our pending supplemental New Drug Application S-018 submitted on February 1, 2002 for the use of Taxotere® plus cisplatin for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received chemotherapy for this condition. Additional reference is made to the Division's request for additional information contained in the September 24th fax. We are now providing a response to the Division's request for information as Attachment 1.

If you have any questions, please contact the undersigned at (908) 304-6471.

Sincerely,

Cheryl Anderson
Therapeutic Area Head, Oncology
Drug Regulatory Affairs

Attachment(s)

ORIGINAL

Aventis Pharmaceuticals

NDA SUPP AMEND
SE1 - 018
BM

October 17, 2002

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

RECEIVED
OCT 21 2002
HFD-150 / CDER

NDA 20-449/S-018
Taxotere® (docetaxel) for Injection Concentrate
October 10th FDA Request for Additional Information

Dear Dr. Pazdur:

Reference is made to NDA 20-449 for Taxotere® (docetaxel) Injection Concentrate and to our pending supplemental New Drug Application S-018 submitted on February 1, 2002 for the use of Taxotere® plus cisplatin for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received chemotherapy for this condition. Additional reference is made to the Division's request for additional information contained in the October 10, 2002 fax. We are now providing a response to the Division's request for information.

QUESTION 1

In section 9.2.1 (Methods for QOL) of the study report for TAX326, it is stated that a general rule was set for the first level of missing data: if more than 1/3 of the items were missing, the QOL assessment was not evaluable. Otherwise, the missing values were replaced by the overall mean of the given item. Please provide a justification for such an approach, including references.

RESPONSE

The methodology used for missing data as described in section 9.2.1 of the study report is only relevant for the patient-rated and the observer-rated subscales of the LCSS, for which the total scores were calculated.

There is no consensus on how to deal with missing items in a rating scale and there is no literature that specifically addresses missing items for the LCSS subscales. However, three general methods are recommended by experts in the field (Ref.1 and2): (1) Treat the score for the scale as missing (2) Simple mean imputation and (3) General imputation methods including regression imputation.

As pre-specified in the Statistical Analysis Plan for this study, a general rule was applied: At least 2/3 of the items (6 of the 9 items for the patient-rated scale and 4 of the 6 items for the observer-rated scale) had to be rated to consider the respective subscale to be evaluable. When a larger

number of items is missing the first method seemed reasonable to handle missing items, particularly when calculating total scores for the scales, versus other methods with imputation algorithms.

In the actual data only 4 patients (0.5%) were excluded from the analysis of the patient-rated subscale and 1 patient (0.1%) from the observer-rated subscale for a sole reason of more than 1/3 of items were missing.

In a situation where 1/3 of the items or less were missing the missing items were replaced by the overall mean of the given item. In the actual data, 474 items (0.8%) were imputed. This procedure was also pre-specified in the statistical analysis plan. This method is widely used and recommended by the experts from the references provided.

1. Fayers, P.M. & Machin, D. (2000) Quality of life: Assessment, analysis and interpretation John Wiley and Sons: West Sussex, England ; pp.232-235.
2. Curran, D., Fayers, P.M.,Molenbrerghs, G., & Machin, D. (1998) Analysis of incomplete quality of life data in clinical trials in Quality of Life Assessment in Clinical Trials (Editors: Staquet, Hayes, & Fayers) Oxford University Press Inc.: New York, NY ; pp.257-261.

If you have any questions, please contact the undersigned at (908) 304-6471.

Sincerely,

Cheryl Anderson
Therapeutic Area Head, Oncology
Drug Regulatory Affairs

Attachment

DUPLICATE

NDA SUPP AMEND
SE1-018
BM

Aventis Pharmaceuticals

October 14, 2002

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

RECEIVED
OCT 15 2002
HFD-150 / CDER

NDA 20-449/S-018
Taxotere® (docetaxel) for Injection Concentrate
October 10th FDA Request for Additional Information

Dear Dr. Pazdur:

Reference is made to NDA 20-449 for Taxotere® (docetaxel) Injection Concentrate and to our pending supplemental New Drug Application S-018 submitted on February 1, 2002 for the use of Taxotere® plus cisplatin for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received chemotherapy for this condition. Additional reference is made to the Division's request for additional information contained in the October 10, 2002 fax. We are now providing a response to the Division's request for information.

QUESTION 1

For adverse event (AE) analysis by age (Tables 61 and 62 of study report for TAX326) and gender (Tables 63 and 64) were AEs included irrespective of whether they were present at baseline or was an emergent strategy used as with the sponsor's main analysis of AEs?

RESPONSE

The sponsor confirms for the adverse event analysis for age and gender, the treatment emergent concept was used as with the sponsor's main analysis of AEs.

If you have any questions, please contact the undersigned at (908) 304-6471.

Sincerely,

Cheryl Anderson
Therapeutic Area Head, Oncology
Drug Regulatory Affairs

Table 2 : AE by Maximum Grade, COSTART term, and Treatment Group

Adverse Event	Docetaxel Cisplatin N = 406	Docetaxel Carboplatin N = 401	Vinorelbine Cisplatin N = 396
Asthenia Severity			
1	121	105	111
2	128	126	131
3	49	42	56
4	1	2	1
TOTAL	299 (74%)	275 (69%)	299 (76%)
Pain Severity			
1	127	119	126
2	119	135	142
3	50	55	48
4	0	3	2
TOTAL	296 (73%)	312 (79%)	318 (80%)
Anorexia Severity			
1	88	64	65
2	59	60	74
3	21	12	20
4	1	0	1
TOTAL	169 (42%)	136 (34%)	160 (40%)
Peripheral Edema Severity			
1	80	58	48
2	54	35	25
3	2	3	1
4	1	1	0
TOTAL	137 (34%)	97 (24%)	74 (19%)
Myalgia Severity			
1	44	52	33
2	25	11	12
3	3	3	1
4	0	0	0
TOTAL	72 (18%)	66 (16%)	46 (12%)
Arthralgia Severity			
1	39	41	31
2	26	23	17
3	2	3	4
4	0	0	0
TOTAL	67 (17%)	67 (17%)	52 (13%)
Constipation Severity			
1	75	71	104
2	43	34	44
3	6	2	13
4	0	1	0

TOTAL	124 (31%)	108 (27%)	161 (41%)
Nail disorder Severity			
1	40	30	2
2	12	11	1
3	3	0	0
4	0	0	0
TOTAL	55 (14%)	41 (10%)	3 (<1%)
Hemoptysis Severity			
1	78	73	59
2	11	16	12
3	1	5	1
4	2	1	0
TOTAL	82 (20%)	95 (24%)	72 (18%)
Dehydration Severity			
1	11	3	5
2	18	7	16
3	9	7	15
4	3	0	2
TOTAL	41 (10%)	17 (4%)	38 (10%)
Pleural Effusion Severity			
1	65	71	56
2	20	30	28
3	11	10	6
4	0	0	1
TOTAL	96 (24%)	111 (28%)	91 (23%)
Dizziness Severity			
1	22	18	45
2	14	7	9
3	0	1	1
4	0	0	0
TOTAL	36 (9%)	26 (6%)	55 (14%)

Aventis Pharmaceuticals

September 5, 2002

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

SE1-018
BM

NDA 20-449/S-018
Taxotere® (docetaxel) for Injection Concentrate
August 26th FDA Request for Additional Information

Dear Dr. Pazdur:

Reference is made to NDA 20-449 for Taxotere® (docetaxel) Injection Concentrate and to our pending supplemental New Drug Application S-018 submitted on February 1, 2002 for the use of Taxotere® plus cisplatin for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received chemotherapy for this condition. Additional reference is made to the following:

- The Division's request for information contained in the August 26, 2002 fax. Specific reference is made to question number two, wherein the Division requested CRFs for the 45 of 52 patients listed as having a change in staging in the revised Table 17 (the Division had been able to locate 7 of the 52 patients in the application).

- The August 29, 2002 response to the August 26th fax, in which we identified an additional 6 patients whose case reports had been submitted in the application and committed to providing the CRF's for the remaining 39 patients electronically by September 6th.

By this letter we are notifying the Division that case reports for 39 patients 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

Attached for your convenience, is a copy of the cover letter sent to the Central Document Room.

Should you have any questions or require additional information, please do not hesitate to contact the undersigned at (908) 304-6471.

Sincerely,

Cheryl Anderson
Therapeutic Area Head, Oncology
Drug Regulatory Affairs

Attachment

Aventis Pharmaceuticals

Aventis

August 29, 2002

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

NDA 20-449/S-018
Taxotere® (docetaxel) for Injection Concentrate
August 26th FDA Request for Additional Information

Dear Dr. Pazdur:

Reference is made to NDA 20-449 for Taxotere® (docetaxel) Injection Concentrate and to our pending supplemental New Drug Application S-018 submitted on February 1, 2002 for the use of Taxotere® plus cisplatin for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received chemotherapy for this condition. Additional reference is made to the Division's request for additional information contained in the August 26, 2002 fax. We are now providing a response to the Division's request for information as Attachment 1.

If you have any questions, please contact the undersigned at (908) 304-6471.

Sincerely,

Cheryl Anderson
Therapeutic Area Head, Oncology
Drug Regulatory Affairs

Attachment(s)

SE1-018

DUPLICATE

Aventis Pharmaceuticals

Aventis

August 20, 2002

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

RECEIVED
AUG 2 8 2002
HFD-150 / CDER

NDA 20-449/S-018
Taxotere® (docetaxel) for Injection Concentrate
August 15 & 16th FDA Request for Additional Information

Dear Dr. Pazdur:

Reference is made to NDA 20-449 for Taxotere® (docetaxel) Injection Concentrate and to our pending supplemental New Drug Application S-018 submitted on February 1, 2002 for the use of Taxotere® plus cisplatin for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received chemotherapy for this condition. Additional reference is made to the Division's request for additional information contained in the August 15th and August 16th faxes. We are now providing a response to the Division's request for information as Attachment 1.

If you have any questions, please contact the undersigned at (908) 304-6471.

Sincerely,

Cheryl Anderson
Therapeutic Area Head, Oncology
Drug Regulatory Affairs

Attachment

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

Aventis Pharmaceuticals

DUPLICATE

Aventis

August 19, 2002

NDA SUPPLEMENT

SE1-018
BM

RECEIVED
AUG 2 0 2002
HFD-150 / CDER

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

NDA 20-449/S-018
Taxotere® (docetaxel) for Injection Concentrate
August 13th FDA Request for Additional Information

Dear Dr. Pazdur:

Reference is made to NDA 20-449 for Taxotere® (docetaxel) Injection Concentrate and to our pending supplemental New Drug Application S-018 submitted on February 1, 2002 for the use of Taxotere® plus cisplatin for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received chemotherapy for this condition. Additional reference is made to the Division's request for additional information contained in the August 13, 2002 telefax. We are now providing a response to the Division's request for information as Attachment 1.

At this time we would like to inform the Division of a correction to our August 8, 2002 response to the Division's August 7th information request. In that response, we incorrectly identified the variable that was used in all analyses for the clinical stage at randomization as the variable "DIAGEXP". In fact, for all analyses the variable "STAGE" (stage at the time of central randomization) was used. The variable DIAGEXP identifies the stage recorded at randomization on the CRF and may not be the same value as the variable STAGE. Please refer to Attachment 2 for a detailed explanation of this correction.

Finally, for the convenience of the reviewer, we have included the original Tables 16, 17 and 19 from the TAX 326 study report in this submission as Attachment 3.

If you have any questions, please contact the undersigned at (908) 304-6471.

Sincerely,

Cheryl Anderson
Therapeutic Area Head, Oncology
Drug Regulatory Affairs

Attachment(s)

DUPLICATE

Aventis Pharmaceuticals

Aventis

NDA SUPP AMEND
SE1-018
(BM)

August 13, 2002

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

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AUG 1 4 2002
HFD-150 / CDER

NDA 20-449/S-018
Taxotere® (docetaxel) for Injection Concentrate
FDA Request for Additional Information

Dear Dr. Pazdur:

Reference is made to NDA 20-449 for Taxotere® (docetaxel) Injection Concentrate and to our pending supplemental New Drug Application S-018 submitted on February 1, 2002 for the use of Taxotere® plus cisplatin for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received chemotherapy for this condition. Additional reference is made to the Division's request for additional information contained in the August 5, 2002 and August 6, 2002 telefaxes. We are now providing a response to the Division's request for information as Attachment 1.

If you have any questions, please contact the undersigned at (908) 231-6471.

Sincerely,

Cheryl Anderson

Cheryl Anderson
Therapeutic Area Head, Oncology
Drug Regulatory Affairs

Attachment(s)
Desk Copy: Ms. Ann Staten, Project Manager (HFD-150)

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

DUPLICATE

Aventis Pharmaceuticals

Aventis

August 8, 2002

NDA SUPP AMEND

SE1-018
BM

RECEIVED
AUG 12 2002
HFD-150 / CDER

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

NDA 20-449/S-018
Taxotere® (docetaxel) for Injection Concentrate
FDA Request for Additional Information

Dear Dr. Pazdur:

Reference is made to NDA 20-449 for Taxotere® (docetaxel) Injection Concentrate and to our pending supplemental New Drug Application S-018 submitted on February 1, 2002 for the use of Taxotere® plus cisplatin for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received chemotherapy for this condition. Additional reference is made to the Division's request for additional information contained in the August 7, 2002 telefax. In this telefax, the medical reviewer made the following request:

"It is not clear where the listing for the clinical stage at randomization is found in the datasets (?UPAT). In the UPAT dataset, DIAGSTG provides clinical stage, but a significant number of patients have a staging of I, II or IIIA, which implies that this was the clinical stage at diagnosis. Please identify the listing which provides clinical stage at enrollment/randomization."

We are now providing the following response to the Division's request. The clinical stage at randomization is located in the dataset UPAT under the variable name "DIAGEXP" [extent disease is coded as "2 = Metatstatic (IV), 3=Locally advanced (IIIB)]. The clinical stage at initial diagnosis is located in the dataset UPAT under the variable name "DIAGSTG". The pathological stage at the initial diagnosis is located in the dataset UPAT under the variable name "DIAGPST". For all analyses, the stage at randomization (DIAGEXP) was used.

If you have any questions, please contact the undersigned at (908) 231-6471.

Sincerely,

Cheryl Anderson

Cheryl Anderson
Therapeutic Area Head, Oncology
Drug Regulatory Affairs

Desk Copy: Ms. Ann Staten, Project Manager (HFD-150)

DUPLICATE

Aventis Pharmaceuticals

SUPPL NEW CORRESP

SNC to
SE1-018

July 1, 2002

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

NDA 20-449/S-018
Taxotere® (docetaxel) for Injection Concentrate
General Correspondence: Copy of Cover Letter and Table of Contents for the SAS Codes

Dear Dr. Pazdur:

Reference is made to NDA 20-449 for Taxotere® (docetaxel) for Injection Concentrate and to our pending supplemental New Drug Application S-018 submitted on February 1, 2002 for the use of Taxotere® plus cisplatin for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received chemotherapy for this condition. Reference is also made to the June 28, 2002 phone conversation between Marion Ceruzzi of Aventis and Ann Staten of the DODP. In that conversation, Ms Staten requested a paper copy of the Table of Contents for the re-submission of the SAS codes under "General Correspondence". Also included is a copy of the cover letter provided to the Electronic Document Room for the CD-ROM containing the SAS codes.

If you have any questions concerning this submission, please contact the undersigned at (908) 231-5828.

Sincerely,

Marion Ceruzzi

Marion Ceruzzi, Ph.D.
US Regulatory Liaison

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

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

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Aventis Pharmaceuticals	July 1, 2002
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
(908) 231-5828	(908) 304-6317
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
200 Crossings Boulevard PO Box 6890 Bridgewater, NJ 08807-0890	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 20-449/S-018

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
docetaxel	Taxotere for Injection Concentrate

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

CODE NAME *(If any)* RP 56976

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

(PROPOSED) INDICATION(S) FOR USE:

APPLICATION INFORMATION

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

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

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

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

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

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

REASON FOR SUBMISSION

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

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

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

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

This application contains the following items: *(Check all that apply)*

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

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, 211or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 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 review and, to the best of my knowledge are certified to be true and accurate.

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

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Marion J. Ceruzzi	Marion Ceruzzi, Ph.D. US Regulatory Liaison	July 1, 2002

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
200 Crossings Boulevard Bridgewater, NJ 08807-0890	(908) 231-5828

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:

epartment of Health and Human Services
Food and Drug Administration
CBER, 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.

Aventis Pharmaceuticals

June 28, 2002

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

NDA 20-449/S-018
TAXOTERE® (docetaxel) for Injection Concentrate

Gentlemen:

Reference is made to our New Drug Application for TAXOTERE® (docetaxel) for Injection Concentrate, NDA 20-449 and to our pending supplemental New Drug Application (S-018) submitted on February 1, 2002 for the use of TAXOTERE® plus cisplatin for the treatment of patients with unresectable locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received chemotherapy for this condition. Additional reference is made to the following:

- The fax from the Division of Oncology Drug Products dated May 28, 2202 requesting the SAS codes that produced statistical results of all efficacy endpoints.
- The June 14, 2002 submission of the SAS codes in paper format to the Division of Oncology Drug Products and in electronic format to the Central Document Room.
- The June 19, 2002 fax from the Electronic Document Room Staff notifying the Sponsor that the datasets provided were in non archival format (i.e. were not sent as SAS transport file), the folder structure was not consistent with the guidance and a TOC, 356H and cover letter were not included on the CD-ROM.
- The June 20, 2002 telephone conversation between Ms. Carole Crowley of Aventis and Mr. Randy Levin of the Agency. In that discussion, Mr. Levin indicated the Sponsor should provide the SAS programs as ASCII files with the "sas" extension. He also indicated if the Sponsor is submitting programs that were used in the statistical analysis software to arrive at the final analysis for the principal efficacy and safety data, those programs should be placed in the appropriate subfolder of the crt folder.
- The June 27, 2002 email from Ms. Carole Crowley from Aventis to Mr. Randy Levin of the Agency asking for responses to various questions concerning the re-submission of the SAS codes in electronic format and to the subsequent phone conversation between Ms. Carole Crowley of Aventis and Mr. Randy Levin of the Agency where the responses to those questions were discussed.

Attached herewith please find one (1) CD-ROM containing the SAS codes, the cover letter, 356H and TOC.

Sincerely,

Marion Ceruzzi

Marion Ceruzzi, Ph.D.
US Regulatory Liaison

Encl.: 1 CD-ROM

SAS PROGRAMS FOR EFFICACY ANALYSES

Program Name	FSR Table Number and Description	LOCATION
Backinit	PROGRAM INITIATION FILE REQUIRED FOR ALL SAS PROGRAMS	Crt\programs\backinit.sas
xpt	CONVERT XPT DATA FILE TO SAS DATASETS	Crt\programs\xpt.sas
eff_g00_11a	4.1.1A NONPARAMETRIC ANALYSIS OF COVARIANCE FOR SURVIVAL ITT POPULATION D75+CIS75 VS. V25X4+CIS100	Crt\programs\eff_g00_11a.sas
eff_g00_11b	4.1.1B SURVIVAL ANALYSIS - STRATIFIED LOG-RANK TEST ITT POPULATION D75+CIS75 VS. V25X4+CIS100	Crt\programs\eff_g00_11b.sas
eff_g00_11c	4.1.1C SURVIVAL ANALYSIS - PROPORTIONAL HAZARDS REGRESSION ITT POPULATION D75+CIS75 VS. V25X4+CIS100	Crt\programs\eff_g00_11c.sas
eff_g00_11d	4.1.1D SURVIVAL ANALYSIS - TEST OF NON-INFERIORITY ITT POPULATION D75+CIS75 VS. V25X4+CIS100	Crt\programs\eff_g00_11d.sas
eff_g00_11e	4.1.1E NONPARAMETRIC ANALYSIS OF COVARIANCE FOR SURVIVAL CENSORING FOR FURTHER THERAPY ITT POPULATION D75+CIS75 VS. V25X4+CIS100	Crt\programs\eff_g00_11e.sas
eff_g00_12a	4.1.2A TIME TO DISEASE PROGRESSION - NONPARAMETRIC ANCOVA D75+CIS75 VS. V25X4+CIS100	Crt\programs\eff_g00_12a.sas
eff_g00_12b	4.1.2B TIME (CYCLES) TO DISEASE PROGRESSION - NONPARAMETRIC ANCOVA D75+CIS75 VS. V25X4+CIS100	Crt\programs\eff_g00_12b.sas
eff_g00_13a	4.1.3A FREQUENCIES OF BEST OVERALL RESPONSE D75+CIS75 VS. V25X4+CIS100	Crt\programs\eff_g00_13a.sas
eff_g00_13b	4.1.3B DURATION OF RESPONSE - CR + PR: NONPARAMETRIC ANCOVA D75+CIS75 VS. V25X4+CIS100	Crt\programs\eff_g00_13b.sas
eff_g00_13c	4.1.3C DURATION OF RESPONSE (CYCLES) - CR + PR: NONPARAMETRIC ANCOVA D75+CIS75 VS. V25X4+CIS100	Crt\programs\eff_g00_13c.sas
eff_g00_14	4.1.4 SUMMARY OF WEIGHT CHANGE FROM BASELINE DURING THE CHEMOTHERAPY PERIOD ITT POPULATION D75+CIS75 VS. V25X4+CIS100	Crt\programs\eff_g00_14.sas

Program Name	FSR Table Number and Description	LOCATION
eff_g00_15	4.1.5 SUMMARY OF OPIOID ANALGESIC CONSUMPTION FOR TUMOR RELATED PAIN ITT POPULATION D75+CIS75 VS. V25X4+CIS100	Crt\programs\eff_g00_15.sas
eff_g00_16	4.1.6 SUMMARY OF PERFORMANCE STATUS CHANGE FROM BASELINE DURING THE CHEMOTHERPY PERIOD ITT POPULATION D75+CIS75 VS. V25X4+CIS100	Crt\programs\eff_g00_16.sas
eff_g00_17a1	4.1.7A1 QOL COMPLIANCE IN THE FIRST 6 CYCLES ITT POPULATION D75+CIS75 VS. V25X4+CIS100	Crt\programs\eff_g00_17a1.sas
eff_g00_17a2	4.1.7A2 PROPORTION OF PATIENTS WITH EVALUABLE LCSS ASSESSMENTS ITT POPULATION D75+CIS75 VS. V25X4+CIS100	Crt\programs\eff_g00_17a2.sas
eff_g00_17b	4.1.7B SUMMARY AND ANALYSIS OF COVARIANCE FOR LCSS AND EQ5D GLOBAL HEALTH STATUS CHANGE FROM BASELINE TO LAST ON-TREATMENT ASSESSMENT ITT POPULATION SECTION: EFFICACY D75+CIS75 VS. V25X4+CIS100	Crt\programs\eff_g00_17b.sas
eff_g00_17c	4.1.7C LONGITUDINAL ANALYSIS FOR LCSS AND EQ5D GLOBAL HEALTH STATUS CHANGE FROM BASELINE ITT POPULATION D75+CIS75 VS. V25X4+CIS100	Crt\programs\eff_g00_17c.sas
eff_g00_17d	4.1.7D LOGIT ANALYSIS OF DROP-OUT IN QUALITY OF LIFE USING THE GLOBAL HEALTH STATUS ITT POPULATION D75+CIS75 VS. V25X4+CIS100	Crt\programs\eff_g00_17d.sas
eff_g00_17pm	4.1.7PM PATTEN MIXTURE LONGITUDINAL ANALYSIS FOR LCSS AND EQ5D GLOBAL HEALTH STATUS CHANGE FROM BASELINE ITT POPULATION D75+CIS75 VS. V25X4+CIS100	Crt\programs\eff_g00_17pm.sas
eff_g00_17e	4.1.7E SUMMARY AND ANALYSIS OF CHANGE FROM BASELINE FOR EQ5D PATIENT-RATED ITEMS ITT POPULATION D75+CIS75 VS. V25X4+CIS100	Crt\programs\eff_g00_17e.sas
eff_g00_21a	4.2.1A NONPARAMETRIC ANALYSIS OF COVARIANCE FOR SURVIVAL ITT POPULATION D75+CB6(AUC) VS. V25X4+CIS100	Crt\programs\eff_g00_21a.sas
eff_g00_21b	4.2.1B SURVIVAL ANALYSIS - STRATIFIED LOG-RANK TEST ITT POPULATION D75+CB6(AUC) VS. V25X4+CIS100	Crt\programs\eff_g00_21b.sas
eff_g00_21c	4.2.1C SURVIVAL ANALYSIS - PROPORTIONAL HAZARDS REGRESSION ITT POPULATION D75+CB6(AUC) VS. V25X4+CIS100	Crt\programs\eff_g00_21c.sas

Program Name	FSR Table Number and Description	LOCATION
eff_g00_21d	4.2.1D SURVIVAL ANALYSIS - TEST OF NON-INFERIORITY ITT POPULATION D75+CB6(AUC) VS. V25X4+CIS100	Crt\programs\eff_g00_21d.sas
eff_g00_21e	4.2.1E NONPARAMETRIC ANALYSIS OF COVARIANCE FOR SURVIVAL CENSORING FOR SUBSEQUENT THERAPY ITT POPULATION D75+CB6(AUC) VS. V25X4+CIS100	Crt\programs\eff_g00_21e.sas
eff_g00_22a	4.2.2A TIME TO DISEASE PROGRESSION - NONPARAMETRIC ANCOVA D75+CB6(AUC) VS. V25X4+CIS100	Crt\programs\eff_g00_22a.sas
eff_g00_22b	4.2.2B TIME (CYCLES) TO DISEASE PROGRESSION - NONPARAMETRIC ANCOVA D75+CB6(AUC) VS. V25X4+CIS100	Crt\programs\eff_g00_22b.sas
eff_g00_23a	4.2.3A FREQUENCIES OF BEST OVERALL RESPONSE D75+CB6(AUC) VS. V25X4+CIS100	Crt\programs\eff_g00_23a.sas
eff_g00_23b	4.2.3B DURATION OF RESPONSE - CR + PR: NONPARAMETRIC ANCOVA D75+CB6(AUC) VS. V25X4+CIS100	Crt\programs\eff_g00_23b.sas
eff_g00_23c	4.2.3C DURATION OF RESPONSE (CYCLES) - CR + PR: NONPARAMETRIC ANCOVA D75+CB6(AUC) VS. V25X4+CIS100	Crt\programs\eff_g00_23c.sas
eff_g00_24	4.2.4 SUMMARY OF WEIGHT CHANGE FROM BASELINE DURING THE CHEMOTHERAPY PERIOD ITT POPULATION D75+CB6(AUC) VS. V25X4+CIS100	Crt\programs\eff_g00_24.sas
eff_g00_25	4.2.5 SUMMARY OF OPIOID ANALGESIC CONSUMPTION FOR TUMOR RELATED PAIN ITT POPULATION D75+CB6(AUC) VS. V25X4+CIS100 SECTION: EFFICACY	Crt\programs\eff_g00_25.sas
eff_g00_26	4.2.6 SUMMARY OF PERFORMANCE STATUS CHANGE FROM BASELINE DURING THE CHEMOTHERPY PERIOD ITT POPULATION D75+CB6(AUC) VS. V25X4+CIS100	Crt\programs\eff_g00_26.sas
eff_g00_27a1	4.2.7A1 QOL COMPLIANCE IN THE FIRST 6 CYCLES ITT POPULATION D75+CB6(AUC) VS. V25X4+CIS100	Crt\programs\eff_g00_27a1.sas
eff_g00_27a2	4.2.7A2 PROPORTION OF PATIENTS WITH EVALUABLE LCSS ASSESSMENTS ITT POPULATION D75+CB6(AUC) VS. V25X4+CIS100	Crt\programs\eff_g00_27a2.sas

Program Name	FSR Table Number and Description	LOCATION
eff_g00_27b	4.2.7B SUMMARY AND ANALYSIS OF COVARIANCE FOR LCSS AND EQ5D GLOBAL HEALTH STATUS CHANGE FROM BASELINE TO LAST ON-TREATMENT ASSESSMENT ITT POPULATION D75+CB6(AUC) VS. V25X4+CIS100	Crt\programs\eff_g00_27b.sas
eff_g00_27c	4.2.7C LONGITUDINAL ANALYSIS FOR LCSS AND EQ5D GLOBAL HEALTH STATUS CHANGE FROM BASELINE ITT POPULATION D75+C6(AUC) VS. V25X4+CIS100	Crt\programs\eff_g00_27c.sas
eff_g00_27d	4.2.7D LOGIT ANALYSIS OF DROP-OUT IN QUALITY OF LIFE USING THE GLOBAL HEALTH STATUS ITT POPULATION D75+CB6(AUC) VS. V25X4+CIS100	Crt\programs\eff_g00_27d.sas
eff_g00_27pm	4.2.7PM PATTEN MIXTURE LONGITUDINAL ANALYSIS FOR LCSS AND EQ5D GLOBAL HEALTH STATUS CHANGE FROM BASELINE ITT POPULATION D75+CB6(AUC) VS. V25X4+CIS100	Crt\programs\eff_g00_27pm.sas
eff_g00_27e	4.2.7E SUMMARY AND ANALYSIS OF CHANGE FROM BASELINE FOR EQ5D PATIENT-RATED ITEMS ITT POPULATION D75+CB6(AUC) VS. V25X4+CIS100	Crt\programs\eff_g00_27e.sas
eff_gf0_11a	4.1.1A ADJUSTED SURVIVAL ITT POPULATION D75+CIS75 VS. V25X4+CIS100 - OVERALL, BY STAGE AND BY REGION	Crt\programs\eff_gf0_11a.sas
eff_gf0_11b	4.1.1B UNADJUSTED SURVIVAL ITT POPULATION D75+CIS75 VS. V25X4+CIS100	Crt\programs\eff_gf0_11b.sas
eff_gf0_11e	4.1.1E ADJUSTED SURVIVAL CENSORING FOR FURTHER THERAPY ITT POPULATION D75+CIS75 VS. V25X4+CIS100	Crt\programs\eff_gf0_11e.sas
eff_gf0_11f	4.1.1F UNADJUSTED SURVIVAL CENSORING FOR FURTHER THERAPY ITT POPULATION D75+CIS75 VS. V25X4+CIS100	Crt\programs\eff_gf0_11f.sas
eff_gf0_17c	4.1.7C QUALITY OF LIFE SCORES MEAN CHANGE FROM BASELINE ITT POPULATION D75+CIS75 VS. V25X4+CIS100	Crt\programs\eff_gf0_17c.sas
eff_gf0_17d	4.1.7D QUALITY OF LIFE SCORES MEAN CHANGE FROM BASELINE ITT POPULATION D75+CIS75 VS. V25X4+CIS100 COMPLETERS AND NON-COMPLETERS HEALTH STATE TODAY	Crt\programs\eff_gf0_17d.sas

SAS MACROS FOR THE EFFICACY ANALYSES PROGRAMS

Macro Name	Location
adj_ano	Crt\programs\adj_ano.sas
adj_ano2	Crt\programs\adj_ano2.sas
ahvl_ux	Crt\programs\ahvl_ux.sas
baes	Crt\programs\baes.sas
calculat	Crt\programs\calculat.sas
cmh_wls	Crt\programs\cmh_wls.sas
conf	Crt\programs\conf.sas
countby	Crt\programs\countby.sas
countlev	Crt\programs\countlev.sas
d01	Crt\programs\d01.sas
d02	Crt\programs\d02.sas
d05	Crt\programs\d05.sas
d05_5.01bx	Crt\programs\d05_5.01bx.sas
dd02	Crt\programs\dd02.sas
fact326	Crt\programs\fact326.sas
fsrmttl	Crt\programs\fsrmttl.sas
fsrtitl	Crt\programs\fsrtitl.sas
gnote	Crt\programs\gnote.sas
gnote1	Crt\programs\gnote1.sas
gnotecgm	Crt\programs\gnotecgm.sas
gnote_h2	Crt\programs\gnote_h2.sas
gnote_h3	Crt\programs\gnote_h3.sas
gnote_l	Crt\programs\gnote_l.sas
gnote_l2	Crt\programs\gnote_l2.sas
gnote_l3	Crt\programs\gnote_l3.sas
gnote_l4	Crt\programs\gnote_l4.sas
gnote_l_backup	Crt\programs\gnote_l_backup.sas
graph	Crt\programs\graph.sas
imp326	Crt\programs\imp326.sas
kmest	Crt\programs\kmest.sas
lifet	Crt\programs\lifet.sas
lifewls2	Crt\programs\lifewls2.sas
lifewls3	Crt\programs\lifewls3.sas
lifewls4	Crt\programs\lifewls4.sas
life_wls	Crt\programs\life_wls.sas
life_wls_ck	Crt\programs\life_wls_ck.sas
make_ndp	Crt\programs\make_ndp.sas
make_pv	Crt\programs\make_pv.sas

Macro Name	Location
median1	Crt\programs\median1.sas
median1_old	Crt\programs\median1_old.sas
median2	Crt\programs\median2.sas
median3	Crt\programs\median3.sas
median3y	Crt\programs\median3y.sas
median3z	Crt\programs\median3z.sas
medianrp	Crt\programs\medianrp.sas
plot1	Crt\programs\plot1.sas
plot1cgm	Crt\programs\plot1cgm.sas
plot1cgm_backup	Crt\programs\plot1cgm_backup.sas
plot1_1	Crt\programs\plot1_1.sas
plot1_tst	Crt\programs\plot1_tst.sas
plot2cgm	Crt\programs\plot2cgm.sas
plot95c2	Crt\programs\plot95c2.sas
plot95c3	Crt\programs\plot95c3.sas
plot95ci	Crt\programs\plot95ci.sas
plotcgm	Crt\programs\plotcgm.sas
plotck	Crt\programs\plotck.sas
plotslid	Crt\programs\plotslid.sas
plotslid3	Crt\programs\plotslid3.sas
plottcgm	Crt\programs\plottcgm.sas
plotxcgm	Crt\programs\plotxcgm.sas
pltw95	Crt\programs\pltw95.sas
rrci	Crt\programs\rrci.sas
rsvector	Crt\programs\rsvector.sas
runsur3a	Crt\programs\runsur3a.sas
sgl001	Crt\programs\sgl001.sas
stalista	Crt\programs\stalista.sas
subgrp	Crt\programs\subgrp.sas
sub_an12	Crt\programs\sub_an12.sas
sub_anal	Crt\programs\sub_anal.sas
sub_anal2	Crt\programs\sub_anal2.sas
surv320f	Crt\programs\surv320f.sas
survq2	Crt\programs\survq2.sas
svscores	Crt\programs\svscores.sas
symbol	Crt\programs\symbol.sas
symbol1	Crt\programs\symbol1.sas
symbol1x	Crt\programs\symbol1x.sas
symbol1xx	Crt\programs\symbol1xx.sas
symbol2	Crt\programs\symbol2.sas
symbol2x	Crt\programs\symbol2x.sas
symbol_1	Crt\programs\symbol_1.sas

Macro Name	Location
t320fmt1	Crt\programs\t320fmt1.sas
t326cfmt	Crt\programs\t326cfmt.sas
tablist	Crt\programs\tablist.sas
tess	Crt\programs\tess.sas
test_sum	Crt\programs\test_sum.sas
t_fsr	Crt\programs\t_fsr.sas
var_cat	Crt\programs\var_cat.sas
wt_ttp	Crt\programs\wt_ttp.sas
xcal_01	Crt\programs\xcal_01.sas
xformat	Crt\programs\xformat.sas
xrep_01	Crt\programs\xrep_01.sas
zascii	Crt\programs\zascii.sas
zformat	Crt\programs\zformat.sas
zwrap	Crt\programs\zwrap.sas
_1on1	Crt\programs_1on1.sas
_1on1a	Crt\programs_1on1a.sas
_2on1	Crt\programs_2on1.sas
_2on1fs	Crt\programs_2on1fs.sas
_r1on1	Crt\programs_r1on1.sas

DUPLICATE

Aventis Pharmaceuticals

SUPPL NEW CORRESP

SNC to
SE1-018

June 21, 2002

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

RECEIVED
JUN 2 4 2002
HFD-150 / CDER

NDA 20-449/S-018
Taxotere® (docetaxel) for Injection Concentrate
General Correspondence: Request for Cover Letters sent to the Dept. of Scientific Investigation

Dear Dr. Pazdur:

Reference is made to NDA 20-449 for Taxotere® (docetaxel) for Injection Concentrate and to our pending supplemental New Drug Application S-018 submitted on February 1, 2002 for the use of Taxotere® plus cisplatin for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received chemotherapy for this condition. Reference is also made to the June 19, 2002 phone conversation between Marion Ceruzzi of Aventis and Ann Staten of the DODP. In that conversation, Ms Staten requested the Cover Letters of all correspondence to the Dept. of Scientific Investigation regarding the above supplemental application to be submitted as "General Correspondence".

Enclosed herewith are the June 17, June 18 and June 21 Cover Letters to Dr. Khin Maung U, M.D. Division of Scientific Investigations regarding documentation submitted per his request for the U.S. sites of Dr. Pendergrass, Fossella and Lynch as well as for the Brazilian site for Dr. Rodriguez.

If you have any questions concerning this submission, please contact the undersigned at (908) 231-5828.

Sincerely,

Marion Ceruzzi

Marion Ceruzzi, Ph.D.
US Regulatory Liaison

Desk Copy: Ms. Ann Staten, Project Manager (HFD-150)

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

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

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Aventis Pharmaceuticals	June 21, 2002
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
(908) 231-5828	(908) 304-6317
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
200 Crossings Boulevard PO Box 6890 Bridgewater, NJ 08807-0890	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 20-449/S-018

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
docetaxel	Taxotere for Injection Concentrate

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

CODE NAME *(If any)* RP 56976

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

(PROPOSED) INDICATION(S) FOR USE:

APPLICATION INFORMATION

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

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

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

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

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

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

REASON FOR SUBMISSION

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

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

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

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

This application contains the following items: *(Check all that apply)*

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

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, 211or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 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 review and, to the best of my knowledge are certified to be true and accurate.

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

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Marion Ceruzzi	Marion Ceruzzi, Ph.D. US Regulatory Liaison	June 21, 2002

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
200 Crossings Boulevard Bridgewater, NJ 08807-0890	(908) 231-5828

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:

epartment of Health and Human Services
ood and Drug Administration
CBER, 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.

DUPLICATE

Aventis Pharmaceuticals

NDA SUPP AMEND
SE1-018
BS

June 14, 2002

RECEIVED
JUN 18 2002
HFD-150 / CDER

RECEIVED
JUN 17 2002
CDR/CDER

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

NDA 20-449/S-018

TAXOTERE® (docetaxel) for Injection Concentrate

Gentlemen:

Attached herewith please find one (1) CD ROM containing the SAS codes requested by Ms. Ann Staten of the Division of Oncology Drug Products in a fax dated May 28, 2002. Ms Staten requested the SAS codes for our pending supplemental New Drug Application (S-018 submitted to the Division of Oncology Drug Products on February 2, 2002 to NDA 20-449 Taxotere® (docetaxel) for Injection Concentrate) submitted in electronic format. For your convenience, we are enclosing the instructions for loading the data and running the efficacy programs. This information is also contained in the CD-ROM.

Also attached for your convenience is a copy of the cover letter accompanying the paper copy of the SAS codes that were sent to the Division of Oncology Drug Products.

Sincerely,

for

Marion Ceruzzi, Ph.D.
US Regulatory Liaison

Encl.: 1 CD-ROM

DUPLICATE

Aventis Pharmaceuticals

Aventis

June 14, 2002

SUPPLEMENT REQUESTED
SNC 10
SE1-018

RECEIVED
JUN 17 2002
HFD-150 / CDER

Richard Pazdur, M.D.
Director
Center for Drug Evaluation and Research
Division of Oncology Drug Products (HFD-150)
1451 Rockville Pike
Rockville, MD 20852
Attn: Division Document Room #3067

NDA 20-449/S-018
TAXOTERE® (docetaxel) for Injection Concentrate

Dear Dr. Pazdur:

Reference is made to our New Drug Application for TAXOTERE® (docetaxel) for Injection Concentrate, NDA 20-449 and to our pending supplemental New Drug Application (S-018) submitted on February 2, 2002 for the use of TAXOTERE® plus cisplatin for the treatment of patients with unresectable locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received chemotherapy for this condition. Additional reference is made to the fax from the Division dated May 28, 2202 requesting the SAS codes that produced statistical results of all efficacy endpoints and to a telephone conversation on June 6, 2002 between Ms. Ann Staten of the Division and Dr. Marion Ceruzzi of Aventis. In this conversation, Ms. Staten indicated the SAS codes should be provided in paper and electronic format; the electronic version should be sent to the Central Document Room and the paper copy should be sent to the Division's Document Room. She indicated that SAS data file format is acceptable and that all of the efficacy endpoints, primary as well as secondary and quality of life should be included.

We are now providing a paper copy of the SAS codes as requested. The copy of the electronic components 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

Should you have any questions or require additional assistance, please do not hesitate to contact me at (908) 231-5828.

Yours sincerely,

for

Marion Ceruzzi, Ph.D.
US Regulatory Liaison

Desk Copy : (Letter only) Ms. Ann Staten, Project Manager, Division of Oncology Drug Products (HFD-150)

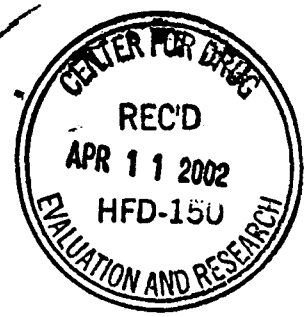
DUPLICATE

Aventis Pharmaceuticals

April 8, 2002

Richard Pazdur, M.D.
Director
Center for Drug Evaluation and Research
Division of Oncology Drug Products (HFD-150)
1451 Rockville Pike
Rockville, MD 20852
Attn: Division Document Room #3067

NDA SUPP AMEND
SE1-018
BM



NDA 20-449/S-018
TAXOTERE® (docetaxel) for Injection Concentrate

Dear Dr. Pazdur:

Reference is made to our New Drug Application for TAXOTERE® (docetaxel) for Injection Concentrate, NDA 20-449 and to our supplemental New Drug Application (S-018) submitted on February 2, 2002 for the use of TAXOTERE® plus cisplatin for the treatment of patients with unresectable locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received chemotherapy for this condition. Additional reference is made to the presentation by Aventis of the NSCLC application to the Division on March 13, 2002. After the meeting, Ms. Ann Staten, Dr. Donna Griebel and Dr. Ramzi Dagher and I met to discuss the specifics of the application. During this discussion the Division requested we provide the survival and overall response by investigator for protocol RP56976V_326 (TAX 326). The reviewers requested that Table 4 (Number of Randomized, Eligible and Evaluable Patients for Response by Investigator by Country) in the final study report for TAX 326 (Overall submission volume 82, Item 8 volume number 49 page 142) be revised to incorporate information on survival and overall response.

We are now providing a copy of the March 13 presentation and the survival and overall response information for each investigator participating in TAX 326. The survival and response information requested for TAX 326 is contained in the table titled "Number of Randomized, Eligible, Evaluable Patients for Response, Survival and Overall Response by Investigator by Country for Protocol RP 56976V-326 (TAX 326)."

Should you have any questions or require additional assistance, please do not hesitate to contact me at (908) 453-2192.

Yours sincerely,

Martha Propsner

Martha Propsner, US Liasion
Drug Regulatory Affairs

Desk Copy: Ms. Ann Staten, Project Manager, Division of Oncology Drug Products (HFD-150)

Aventis Pharmaceuticals Inc. · Aventis Pharmaceuticals Products Inc. · www.aventis.com
Route 202-206 · PO Box 6800 · Bridgewater, NJ 08807-0800 · Telephone (908) 231-4000

DUPLICATE

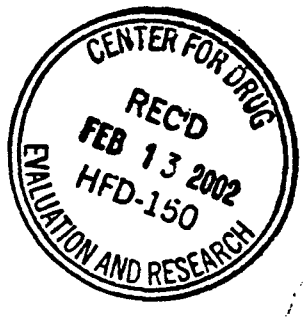
Aventis Pharmaceuticals

Aventis

February 11, 2002

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

SNC



NDA 20-449

TAXOTERE® (docetaxel) for Injection Concentrate

Dear Dr. Pazdur:

Reference is made to the New Drug Application (NDA) for TAXOTERE® (docetaxel) for Injection Concentrate, NDA 20-449. Additional reference is made to our supplemental New Drug Application submitted on February 1, 2002 for the use of TAXOTERE® plus cisplatin for the treatment of patients with unresectable locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received chemotherapy for this condition.

Following the submission of the above referenced application, we discovered a problem with our publishing system wherein the copy of the cover letter provided in the review copy did not contain periods, decimal points or colons. Additionally, we would like to provide an updated version of the Statement of Organization that more fully explains the volumization schema for the application's Table of Contents. We are now providing a corrected cover letter that includes the appropriate punctuation and an updated Statement of Organization. These documents should replace those previously provided in the application.

Yours sincerely,

Steve Caffé, M.D.
Vice President, Regulatory Affairs – North America

SC/mp

Desk copy: Ms. Ann Staten, Project Manager, HFD-150 (10 copies)

Aventis Pharmaceuticals Inc. · Aventis Pharmaceuticals Products Inc. · www.aventis.com
Route 202-206 · PO Box 6800 · Bridgewater, NJ 08807-0800 · Telephone (908) 231-4000

DUPLICATE

Aventis Pharmaceuticals

Aventis

NDA NO 20-449 REF NO. 018
NDA SUPPL FOR SE8-018

February 1, 2002

Richard Pazdur, M D , Director
Division of Oncology Drug Products (HFD-150)
Food and Drug Administration, CDER
Woodmont Office Complex 2, Document Room
1451 Rockville Pike
Rockville, MD 20852

NDA 20-449

TAXOTERE® (docetaxel) for Injection Concentrate

SUPPLEMENTAL NEW DRUG APPLICATION

TAXOTERE® in Combination With Cisplatin for the Treatment of Patients with Unresectable Locally Advanced or Metastatic Non-small Cell Lung Cancer Who Have not Previously Received Chemotherapy for this Condition

Dear Dr Pazdur

Reference is made to the New Drug Application (NDA) for TAXOTERE® (docetaxel) for Injection Concentrate, NDA 20-449 approved on May 14, 1996 for the treatment of patients with locally advanced or metastatic breast cancer who have progressed or relapsed during anthracycline based therapy Reference is also made to the supplemental new drug application (s-NDA) S-005, approved December 23, 1999, for the use of TAXOTERE® for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy Reference is also made to s-NDA S-011, approved on December 23, 1999, for the use of TAXOTERE® for the treatment of locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy

In accordance with 21 CFR §314 50 and §314 71, Aventis Pharmaceuticals hereby submits a supplemental New Drug Application to support the use of **TAXOTERE® plus cisplatin for the treatment of patients with unresectable locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received chemotherapy for this condition.** The proposed dosing regimen is TAXOTERE® 75mg/m^2 administered intravenously over one hour immediately followed by cisplatin 75mg/m^2 administered over 30-60 minutes, every three weeks

The proposed new indication is supported by the results of two independent, well-controlled, phase III trials:

- Study TAX 326 titled "A multicenter, multinational, randomized Phase III study of docetaxel (RP 56976) plus cisplatin versus docetaxel plus carboplatin versus vinorelbine plus cisplatin in chemotherapy-naïve patients with unresectable locally advanced and/or recurrent (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer"
- Study TAX — titled "A multicenter randomized Phase III study of docetaxel plus best supportive care versus best supportive care in chemotherapy naïve patients with metastatic or unresectable localized non-small cell lung cancer"

Aventis Pharmaceuticals Inc Aventis Pharmaceuticals Products Inc www aventis com
Route 202-206 PO Box 6800 Bridgewater, NJ 08807-0800 Telephone (908) 231-4000

Additionally, this efficacy supplement is supported by a series of Phase I studies (TAX 012, TAX 018, TAX 060) which established the maximum tolerated dose, the recommended dose and contributed pharmacokinetic and drug-drug interaction data It is also supported by three uncontrolled Phase II studies (TAX 018, TAX 020 and TAX 260) which provided preliminary evidence of anti-tumor activity and additional tolerability data for the claimed regimen

Study TAX — establishes the activity of docetaxel as a single agent in the target population Study TAX — compared the effect on survival of docetaxel as a single agent versus best supportive care in chemotherapy naïve patients with locally advanced, recurrent or metastatic NSCLC and good performance status Study TAX was

TAX — might serve as a supportive docetaxel single-agent trial in a future application for the first-line treatment of NSCLC which would include additional randomized controlled trials of the safety and efficacy of docetaxel as part of combination therapy Data from TAX — included in this application.

Study TAX 326 establishes the safety and efficacy of TAXOTERE® in combination with cisplatin versus an active control, vinorelbine plus cisplatin, in the proposed indication For the docetaxel plus cisplatin group, in comparison to the vinorelbine plus cisplatin control group, the median survival was 11 3 months versus 10 1 months, respectively, and the 2-year survival was 21% versus 14%, respectively The hazard ratio was 1 183, in favor of docetaxel plus cisplatin, with a 95% CI of 1 008 to 1 388 Under the most conservative criteria set by the Agency, the confidence level was 98 9% that docetaxel plus cisplatin preserved more than 75% of the survival benefit of the control group This application also provides information establishing that vinorelbine plus cisplatin is an appropriate active control

In study TAX 326, a series of secondary endpoints demonstrated additional clinically relevant benefits Tumor shrinkage was increased, and tumor-related impact on the patient clinical status was improved, as evidenced by improved patient self-administered pain scores and global quality of life scores, less deterioration of the Karnofsky performance status over time and less frequent weight loss

The proposed docetaxel plus cisplatin regimen is safe and well tolerated in the target population and the benefit/risk ratio is favorable In study TAX 326, the median relative dose intensity for docetaxel and cisplatin was 97%, and the proportion of patients discontinuing treatment as a result of an adverse event was 15 8% Docetaxel plus cisplatin compared favorably to vinorelbine plus cisplatin, as evidenced by fewer severe, life-threatening or grade 3 and 4 toxicities (51 7% vs 59 6%, respectively), fewer adverse events leading to hospitalizations (40 8% vs 46 7%, respectively), and fewer adverse events leading to discontinuations (15 8% vs 23 0%, respectively) The incidence of death within 30 days following the last infusion of treatment (7 6% vs 9 3%, respectively), and the incidence of death due to toxicity (2 2% vs 2 0%, respectively) were low and similar between the two regimens The administration of docetaxel plus cisplatin was associated with less nausea/vomiting and less hematological toxicity compared to control, while the relative incidences of neurological toxicities and of renal adverse events were similar Grade 3 and 4 diarrhea was observed with a low but increased frequency in the docetaxel plus cisplatin treatment group, compared to the vinorelbine plus cisplatin treatment group (6 7% and 2 8%, respectively), but the incidence of discontinuation due to diarrhea remained low (<1%) in both treatment groups The safety profile observed for docetaxel plus cisplatin in the target population was consistent with that known for each agent in different tumor types and in particular for docetaxel 75 mg/m^2 as second-line treatment for NSCLC The toxicities are known, predictable and manageable Elderly patients did not differ from younger patients in their tolerance to test treatment, relative to the safety profile of the active control regimen

For the TAXOTERE® plus carboplatin treatment group, compared with the vinorelbine plus cisplatin group, the median survival time was 9 4 months versus 9 9 months, respectively The 2-year survival rate was 18% vs 14%, respectively The hazard ratio was 1 048 (95% CI=0 894, 1 229), in favor of the docetaxel plus carboplatin treatment group

We look forward to the Agency's feedback and guidance on this issue

Over the course of the development of this indication, the following agreements have been made between the Agency and the applicant

- All relevant safety data from phase I, II and III trials should be presented however, because of differences in doses and dosing schedules, these data need not be integrated
- To represent the collective post-marketing experience of docetaxel, an overview assessment is presented with a copy of the Periodic Safety Update Reports (PSURs) compiled according to ICH E2 recommendations In parallel, available information on the use of TAXOTERE® in combination with cisplatin is presented
- In accordance with 21 CFR §314 55(c) Aventis Pharmaceuticals requested a waiver to perform studies in pediatric age groups relative to this application The Division granted a waiver for pediatric studies for this application as reflected in the pre s-NDA meeting minutes
- As agreed during the pre-sNDA meeting, an electronic copy of the case report forms without hypertext links is being provided An electronic copy of the case report forms including bookmarks for visit and domain, but without hypertext links between data corrections forms and case report form pages is being provided

The organization of this application is in accordance with 21 CFR §314 50 All applicable 356h items, except Item 11 (Case Report Tabulations for TAX 326) and Item 12 (Case Report Forms) are being submitted as a paper archival copy and a review copy Items 11 and 12 are being submitted as an electronic archival copy in accordance with the January 1999 guidance "Providing Regulatory Submissions in Electronic Format – General Considerations" Aventis Pharmaceuticals Inc certifies that all electronic media is free from computer virus The virus scan was performed using Symantec's Norton Antivirus Corporation Edition, Full version 7 0, Scan engine version 1 1 1 11 The Virus Pattern File is Version 40123A, issued on January 22, 2002

This application consists of 185 volumes The pagination of the application reflects the technical section numbers that coincide with the Contents of Application section of FDA form 356h The overall application pagination numbers are located at the bottom right corner of each page, representing Item number, volume number and page number, each volume begins on page 1 Outer jackets are numbered sequentially, volume 1 through 185 Please note, individual reports within the technical sections retain their original internal page numbers that relate to the table of contents of the individual report in addition to the overall application pagination

Technical sections for Nonclinical Pharmacology and Toxicology and Clinical Microbiology are not relevant to this efficacy supplement and are therefore, not included

The proposed package insert is provided in Microsoft Word for Windows ™ Version 6 0 format in the archival copy of the submission Underscore and strikethrough reflect the proposed modifications

Ten (10) additional copies of volumes 1-3 will be submitted under separate cover to Ms Ann Staten, Project Manager Additionally, a paper review copy of Item 12 (Case Report Forms) will be provided for review purposes within 60 days of this submission

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 $156,660 00 was submitted under check number 0007282281 on January 21, 2002 with a User Fee Identification Number 4241

As required by §306(k)(1) of the Generic Drug Enforcement Act [21 U S C §335a(k)(1)], we hereby certify that, in connection with this application, Aventis Pharmaceuticals did not, and will not use, in any capacity, the services of any person debarred under subsections 306(a) or (b) of the Act

In accordance with 21 CFR § 54 *et seq*, certification regarding the financial interests and arrangements of investigators who participated in covered clinical studies is provided in Volume 1 We have carefully reviewed the Phase II trials which support the claimed indication and we have concluded that these studies do not qualify as covered clinical studies since they do not contribute to the confirmation of efficacy and no single investigator made a significant contribution to the demonstration safety

The archival copy of the electronic components of this supplemental 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

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

We would like to thank the Division for their invitation to present an overview of this supplemental application to the review team We would like to propose March 13 –15 as potential dates for this presentation

On behalf of Aventis Pharmaceuticals, we look forward to working with the Division to facilitate the review of this application Should you have any questions or require additional information to facilitate the review, please contact Ms Martha Propsner, at (908) 231-3841, or via fax at (908) 541-5274 or, in her absence, Steve Caffé, M D at (908) 231-5863

Yours sincerely,

Steve Caffé mp

Steve Caffé, M D
Vice President, Head GRAMS – North America

SC/mp

Cc Ms Ann Staten, Project Manager, HFD-150 (via fax)

DUPLICATE

Aventis Pharmaceuticals

Aventis

RECEIVED
FEB 01 2002
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February 1, 2002

SE8-018
BL SNC

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Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

CENTER FOR DRUG
REC'D
FEB 04 2002
HFD-150
EVALUATION AND RESEARCH

NDA 20-449

TAXOTERE® (docetaxel) for Injection Concentrate

SUPPLEMENTAL NEW DRUG APPLICATION

TAXOTERE® in Combination With Cisplatin for the Treatment of Patients with Unresectable Locally Advanced or Metastatic Non-small Cell Lung Cancer Who Have not Previously Received Chemotherapy for this Condition

Gentlemen:

Attached herewith please find one (1) DLT tape for Item 11 and Item 12, representing the electronic components for a supplemental New Drug Application submitted to the Division of Oncology Drug Products for NDA 20-449 Taxotere® (docetaxel) for Injection Concentrate. The indication for this supplement is "TAXOTERE® in Combination With Cisplatin for the Treatment of Patients with Unresectable Locally Advanced or Metastatic Non-small Cell Lung Cancer Who Have not Previously Received Chemotherapy for this Condition." Also enclosed, one (1) CD-ROM containing the draft labeling for this submission.

A copy of the cover letter for the above-referenced application is enclosed.

Sincerely,

Martha Propsner
US Liaison, Drug Regulatory Affairs

Encl.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-449/S-018

PRIOR APPROVAL SUPPLEMENT

Aventis Pharmaceuticals Products Inc
Route 202-206
PO Box 6800
Bridgewater , NJ 08807-2800

Attention: Steve Caffe, M.D.
Vice President, Head GRAMS – North America

Dear Dr. Caffe:

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

NDA Number: 20-449

Supplement Number: S-018

Review Priority Classification: Standard (S)

Date of Supplement: February 1, 2002

Date of Receipt: February 1, 2002

This supplement proposes the following change(s): To support the use of Taxotere plus cisplatin for the treatment of patients with unresectable locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received chemotherapy for this condition.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 2, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be December 1, 2002 and the secondary user fee goal date will be February 1, 2003.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
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: Division Document Room #3067
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, call Ann Staten, Project Manager, at (301) 594-5770.

Sincerely,

/S/

{See appended electronic signature page}

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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
3/14/02 11:40:29 AM
Signed for Dotti Pease