CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-449/S-018

Administrative Documents

Item 13 -Patent/Exclusivity Information

1)	Active Ingredient(s)	docetaxel
2)	Strength(s)	80 mg and 20 mg
3)	Trademark	Taxotere® (docetaxel) for Injection Concentrate, 20 mg, 80 mg
4)	Dosage Form (Route of Administration):	sterile solution
5)	Application Firm Name	Aventis Pharma
6)	IND Number.	[redacted]
7)	NDA Number	20-449
8)	Approval Date.	May 14, 1996
9)	Exclusivity -- date first ANDA could be submitted or approved and length of exclusivity period	Pursuant to Sections 505(c)(3)(D), 505(j)(4)(D) or 527(a) of the Federal Food, Drug and Cosmetic Act, no ANDA may be approved with an effective date which is prior to 3 years after the date of approval of this application
10)	Applicable patent numbers and expiration date of each	4,814,470, expires May 14, 2010 5,438,072, expires November 22, 2013 5,698,582, expires July 3, 2012 5,714,512, expires July 3, 2012 5,750,561, expires July 3, 2012

11) To the best of our knowledge, each of the clinical investigations included in this application meets the definition of "new clinical investigation" set forth in 21 CFR 314 108(a)

A list of all published studies or publicly available reports of clinical investigations known to the applicant through a literature search that are relevant to the conditions for which we are seeking approval is attached We have thoroughly searched the scientific literature and, to the best of our knowledge, the list is complete and accurate and, in our opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of the conditions for which we are seeking approval without reference to the new clinical investigation(s) in the application The reasons that these studies or reports are insufficient are presented in the attachment as well.

Item 13. Patent Information

1)	Patent number	4,814,470
2)	Date of expiration	May 14, 2010
3)	Type of patent	drug substance, drug product
4)	Name of patent owner	Rhône-Poulenc Rorer S A , formerly known as Rhône-Poulenc Sante
5)	U.S representative	Aventis Pharma

The undersigned declares that Patent No 4,814,470 covers the formulation, composition, and/or method of use of Applicant's Taxotere® (docetaxel) product This product is the subject of this application for which approval is being sought

Signed: _____ Date 01-08-02

Name. Ross J Oehler

Title. Vice President, US Patent Operations
Aventis Pharmaceuticals

Item 13. Patent Information

1)	Patent number	5,438,072
2)	Date of expiration	November 22, 2013
3)	Type of patent	drug product
4)	Name of patent owner	Rhône-Poulenc Rorer S.A.
5)	U S. representative	Aventis Pharma

The undersigned declares that Patent No 5,438,072 covers the formulation, composition, and/or method of use of Applicant's Taxotere® (docetaxel) product This product is the subject of this application for which approval is being sought

Signed _____ Date· 01-08-02
Name Ross J. Oehler
Title Vice President, US Patent Operations
Aventis Pharmaceuticals

Item 13. Patent Information

1)	Patent number	5,750,561
2)	Date of expiration	July 3, 2012
3)	Type of patent	drug product
4)	Name of patent owner	Rhône-Poulenc Rorer S.A
5)	U S representative	Aventis Pharma

The undersigned declares that Patent No 5,750,561 covers the formulation, composition, and/or method of use of Applicant's Taxotere® (docetaxel) product. This product is the subject of this application for which approval is being sought

Signed _____ Date 01-08-02
Name Ross J. Oehler
Title Vice President, US Patent Operations
Aventis Pharmaceuticals

Item 13. Patent Information

1)	Patent number	5,698,582
2)	Date of expiration	July 3, 2012
3)	Type of patent	drug product
4)	Name of patent owner	Rhône-Poulenc Rorer S A
5)	U S. representative	Aventis Pharma

The undersigned declares that Patent No 5,698,582 covers the formulation, composition, and/or method of use of Applicant's Taxotere® (docetaxel) product This product is the subject of this application for which approval is being sought

Signed _____ Date 01-08-02

Name Ross J Oehler

Title Vice President, US Patent Operations
Aventis Pharmaceuticals

Item 13. Patent Information

1)	Patent number	5,714,512
2)	Date of expiration	July 3, 2012
3)	Type of patent	drug product
4)	Name of patent owner	Rhône-Poulenc Rorer S A
5)	U S. representative	Aventis Pharma

The undersigned declares that Patent No 5,714,512 covers the formulation, composition, and/or method of use of Applicant's Taxotere® (docetaxel) product. This product is the subject of this application for which approval is being sought

Signed  Date 01-08-02

Name Ross J. Oehler

Title Vice President, US Patent Operations
Aventis Pharmaceuticals

EXCLUSIVITY SUMMARY for NDA # 20-449 SUPPL # 018

Trade Name Taxotere Generic Name docetaxel

Applicant Name Aventis Pharmaceuticals HFD- 150
Approval Date November 27, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

   a) Is it an original NDA? YES/___/ NO /___/

   b) Is it an effectiveness supplement? YES /_X_/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE1

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

      YES /_X_/ NO /___/

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

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

   d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

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

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

YES /___/ NO /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /__X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

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

YES /__X_/ NO /___/

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

NDA # 20-449 Taxotere

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 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 9:**

(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:

Investigation #1, Study # TAX326

Investigation #2, Study #

Investigation #3, Study #

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

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

Investigation #1	YES /___/	NO /_X__/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

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

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

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

Investigation #1 YES /___/ NO /__X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(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"):

Investigation # TAX326 , Study # "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"

Investigation #_, Study #

Investigation #__, Study #

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 # _____ YES /_X__/	NO /___/ Explain:
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain:

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

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

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

YES /___/ NO /__X_/

If yes, explain: _____

_____

_____

Ann Staten,RD
Signature of Preparer Date
Title: Project Manager

Richard Pazdur,MD
Signature of Office or Division Director Date

cc:
Archival NDA
HFD- 150 /Division File
HFD- 150 /AStaten
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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
11/27/02 02:24:17 PM

Richard Pazdur
11/27/02 02:33:08 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 20-449 Supplement Type (e.g. SE5): SE1 Supplement Number: s-018

Stamp Date: February 1, 2002 Action Date: December 1, 2002

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

Applicant: Aventis Therapeutic Class: 5010100

Indication(s) previously approved: Metastatic breast cancer

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

Number of indications for this application(s): 1

Indication #1: Non-small cell lung cancer

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

- ☐ X 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
- ☒ X 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
HFD-950/ Terrie Crescenzi
HFD-960/Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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
10/7/02 03:17:09 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-449/011,012

AUG 10 1999

Rhone-Poulenc Rorer
500 Arcola Road, H-14
P.O. Box 1200
Collegeville, PA 19426-0107

Attention: Max W. Talbott, Ph.D., Vice President
Worldwide Regulatory Affairs

Dear Dr. Talbott:

Reference is made to your correspondence dated June 23 and 30, 1999, requesting waivers of pediatric studies under 21 CFR 314.55(c).

We have reviewed the information you have submitted and agree that a waiver is justified for Taxotere (docetaxel) for the treatment of patients with locally advanced or metastatic non-small cell lung cancer, after failure of prior chemotherapy, and for the treatment of patients with chemotherapy-naive locally advanced or metastatic non-small cell lung cancer for the pediatric population.

Accordingly, waivers for pediatric studies for these applications are granted under 21 CFR 314.55 at this time.

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

Sincerely,

/S/ M.D.

Robert L. Justice, M.D.
Acting Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ITEM 16: DEBARMENT CERTIFICATION

As required by Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 335a(k)), as amended by the Generic Drug Enforcement Act of 1992, Aventis Pharmaceuticals hereby certifies 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.

Team Leader Summary

N20-449 SE018
Drug: **Taxotere**
Applicant: **Aventis**
Date of Submission: **February 1, 2002**
Date Review Complete: **November 27, 2002**
Medical Team Leader: **Donna J. Griebel, MD**

In December 1999, docetaxel was approved as monotherapy for locally advanced (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer after failure of prior platinum-based chemotherapy (NDA Supplement 011). Although two doses were studied, 100 mg/m^2 and 75 mg/m^2, only 75 mg/m^2 was approved because the higher dose was associated with excess toxicity (early toxic deaths). The approval was based on two randomized, controlled studies. A statistically significant survival benefit was noted in the comparison of docetaxel to best supportive care. A second study that randomized docetaxel 75 mg/m^2 against investigator choice of either vinorelbine (30 mg/m^2 weekly x 3) or ifosfamide, resulted in no statistically significant survival difference. A higher proportion of 1-year survivors was noted in the docetaxel arm in both studies.

The applicant has

data from a single randomized, controlled trial that compared docetaxel 100 mg/m^2 (the dose associated with excessive toxicity in the second line setting) to best supportive care, which had been shown in meta-analysis to be inferior to early cisplatin based chemotherapy regimens.

treatment with docetaxel was associated with a statistically significant survival benefit in the submitted study, 6.0 months (95% CI 5.0, 8.0) on the docetaxel arm vs. 5.7 months (95% CI 4.4, 6.8), p=0.03. The survival benefit of docetaxel did not outweigh the significant risk associated with docetaxel 100mg/m^2. The standard of care at the time of the review was cisplatin based doublet therapy and the FDA's approvals of three such doublets had been based on comparisons to older cisplatin based treatments. Best supportive care was an outdated comparator arm by the time of submission of these docetaxel first-line non-small cell lung carcinoma treatment data. The median survival and proportion of one year survivorship associated with docetaxel 100 mg/m^2 monotherapy was very similar in cross-study comparison to that of older cisplatin based regimens that had since been supplanted by the newer doublet therapies associated with superior survival. The docetaxel 100 mg/m^2 dose had been associated with unacceptably high treatment related mortality in the second-line setting (5% in one trial and 14% in the other), and in the first-line setting treatment related mortality associated with this dose was 6.5%. The proportion of deaths within 30 days of treatment at this dose level was 14% and 27% in the second line setting, and 17% in the first-line setting.

The current NDA supplemental application (S018) again presents data to support docetaxel's use in the first-line setting. In this submission a lower dose of docetaxel, 75 mg/m^2 , was combined in a doublet with cisplatin 75 mg/m^2 (q 3 weeks) and compared to an FDA approved cisplatin doublet, vinorelbine 25 mg/m^2 weekly x 3 + cisplatin 100 mg/m^2 x 1; cycled q 4 weeks. The vinorelbine + cisplatin doses used in this study were recently incorporated into the vinorelbine label after FDA review of the SWOG study that revealed a significant survival advantage associated with this doublet (in these doses) compared to single agent cisplatin. (The original

approval of vinorelbine in combination with cisplatin was based on a study in which higher doses of vinorelbine and cisplatin, 30 mg/m^2 weekly + 120 mg/m^2 , were associated with a significant survival advantage (adjusted analysis) in comparison to cisplatin + vindesine. Vinorelbine single agent treatment was also associated with a statistically significant survival benefit when compared to 5-FU+leucovorin in Stage IV patients with non-small cell lung carcinoma.)

The study submitted for review in this application (TAX326) had 3 arms: the vinorelbine + cisplatin control arm and two docetaxel doublets, docetaxel + cisplatin and docetaxel + carboplatin. It was designed to compare each docetaxel arm to the control arm, and the primary endpoint was survival. In a Kaplan-Meier log rank analysis, with adjustment for more than one comparison, neither docetaxel doublet was superior to the vinorelbine + cisplatin control, although there was a survival trend favoring the docetaxel + cisplatin arm. The Kaplan-Meier estimate of median survival in the docetaxel +cisplatin group was 10.9 months compared to 10.0 months on the cisplatin + vinorelbine arm. The estimated hazard ratio (docetaxel + cisplatin / vinorelbine +cisplatin) was 0.88 (CI=0.74-1.06). The Kaplan –Meier estimate of median survival on the docetaxel + carboplatin arm was 9.1 months. Secondary endpoints revealed a higher overall response rate that was not statistically significant when adjusted for multiple comparisons in the docetaxel + cisplatin arm compared to the vinorelbine control arm, (31.6% vs. 24.4%, respectively) and time to progression was similar (21.4 weeks vs. 22.1 weeks, respectively). The assessment interval was longer on the vinorelbine arm because treatment was administered on a 4 week cycle compared to every 3 weeks on the docetaxel arms.

The applicant proposed that treatment with docetaxel + cisplatin, if not superior, was non-inferior to vinorelbine + cisplatin with respect to survival. The difficulties associated with a making such a noninferiority comparison include the existence of only a single trial comparing the two treatment regimens and the existence of only a single trial that establishes the treatment effect of vinorelbine in combination with cisplatin at the doses utilized in the TAX 326 (30mg/m^2 and 100 mg/m^2, respectively).

The FDA examined the question of non-inferiority by first establishing the treatment effect of the control arm regimen, (vinorelbine 30 mg/m^2 weekly x 3 + cisplatin 100 mg/m^2; 4 week cycle). This was done utilizing the data from a SWOG study reported by Wozniak, et al in JCO (1998). Median survival was 8 months on the vinorelbine arm vs. 6 months on the cisplatin control arm. Neither this SWOG study nor TAX326 enrolled patients with performance status 2. Only 8% of the SWOG study patients had Stage IIIB disease (all limited to patients with effusion or multiple pulmonary nodules), compared to a third of the patients enrolled in TAX 326. On TAX 326 25% of patients on the docetaxel arm were female, while a third of patients in the SWOG study were female. The relative distribution of these characteristics between studies is relevant because they are prognostic factors in advanced non-small cell lung carcinoma. Patients with PS 2 have a worse prognosis. Females and patients with Stage IIIB disease tend to have a better prognosis. Of these major prognostic factors, only the proportion of Stage IIIB patients enrolled in the study was notably different between studies. A higher proportion of Stage IIIB patients in TAX326 could explain the apparently longer median survival observed with vinorelbine +cisplatin treatment in that study compared to the median observed with this treatment in the SWOG study. Important incremental differences in study populations could impact on the reliability of noninferiority conclusions.

The 95% confidence interval of the hazard ratio for vinorelbine + cisplatin/ cisplatin was (0.65, 0.86) in the SWOG study that was solely relied upon for establishing the treatment effect of the active control. The upper limit of the confidence interval, which is associated with the least possible survival effect of the addition of vinorelbine to cisplatin (from the comparison to

cisplatin in the SWOG study) was used to begin the noninferiority analysis. Although the sponsor utilized a non-parametric covariate-adjusted stratified log rank test in its calculations of treatment effect within TAX326, the FDA considered the stratified log rank test to be the appropriate analysis, particularly given that the treatment effect of the active control from the historical data was calculated with a log rank test. The upper bound , 0.86, was then used to calculate the hazard ratio that would be expected if a minimum of 50% of the treatment effect of the vinorelbine combination was retained, 0.927. The ratio of this calculated 50% retention hazard ratio (0.927) and the upper bound of the 95%CI for the active control treatment effect (vinorelbine added to cisplatin) then provides the upper limit cutoff of the hazard ratio for the comparison of interest in TAX326, docetaxel + cisplatin / vinorelbine + cisplatin, and assures at least 50% retention of the treatment effect from the active control arm (addition of vinorelbine to cisplatin). This calculated upper bound was 1.078. The adjusted 97.65% confidence interval for the hazard ratio of survival comparison of docetaxel+cisplatin / vinorelbine + cisplatin observed in TAX 326 was (0.737, 1.059), and 1.059 falls below the calculated boundary for preservation of at least 50% of the active control effect. [An adjusted confidence interval was utilized because there were more than one comparison included in the efficacy analysis (two docetaxel arms compared to the vinorelbine arm), and there had been an interim analysis.]

The next step after establishing that the addition of docetaxel to cisplatin preserved at least 50% of the treatment effect of the active control was to estimate the minimum retention of effect that was actually observed in TAX 326. This calculation began with multiplying the upper bound of the confidence interval for the hazard ratio of the comparison of docetaxel + cisplatin/ vinorelbine + cisplatin in TAX 326, (0.737, 1.059) times the upper bound of the hazard ratio for the active control historical comparison of the addition of vinorelbine to cisplatin (0.86 for vinorelbine+cisplatin/cisplatin). The value that results, 0.91, is the derived hazard ratio for the addition of docetaxel to cisplatin relative to cisplatin. The proportion of the reserved treatment effect of the active control arm is then calculated by the ratio (1-0.91) ÷ (1.0.86), or *ln*0.91/*ln* 0.86. This calculation reveals an estimated minimum retention of active control effect of 62%.

The biometrics review team performed a number of sensitivity analyses that included an alternative method of noninferiority analysis, the Rothman et al approach (see Biometrics review), which estimated a 76% preservation of active control effect. Other analyses included adjustments for stage reported at randomization (some were in error), adjudicated stage (corrected to actual stage at randomization), adjusted proportional hazards model, and unstratified log rank test. These sensitivity analyses in general confirmed the retention of at least 50% of the treatment effect of the active control.

The biometrics and medical review teams concurred that the addition of docetaxel to cisplatin retained at least 62% of the active control effect (addition of vinorelbine to cisplatin). A conservative analysis of noninferiority had been applied, and the success in showing retention of over 50% of the treatment effect was likely attributable to the fact that the survival effect of the docetaxel+cisplatin regimen in the study had come close to achieving statistically significant superiority. The active control arm regimen has been included in FDA approved labeling for vinorelbine and was considered by the review team to be a relevant control arm for a noninferiority analysis. The application was considered approvable based on noninferior effectiveness, but that effectiveness had to be examined in light of safety. A persuasively inferior safety profile associated with the docetaxel arm would have provided a strong argument for nonapproval, given the fact that superior efficacy had not been established.

Neither arm was clearly superior to the other in terms of toxicity. Safety review revealed that treatment related mortality was 2% in each arm. Comparison of deaths that occurred within 30

days of study treatment, a mortality comparison that removes potential bias of investigator/sponsor assignment of attribution in an unblinded trial, revealed similarity between arms, 9.3% on the vinorelbine arm vs. 7.6% on the docetaxel arm. Withdrawal from the study for adverse events occurred in 16% of patients on the docetaxel arm compared to 23% of patients in the vinorelbine control arm. With regard to hematological toxicities, the two treatment arms were similar, except that the vinorelbine arm was associated with a higher overall rate of grade ¾ anemia (25% vs. 7% on the docetaxel arm). Rates of infection and febrile neutropenia were similar between arms. Diarrhea occurred with greater frequency on the docetaxel arm, both in overall and grade ¾ diarrhea (47% and 7% vs. 25% and 3% on the vinorelbine arm). There was a higher incidence of hypersensitivity reactions on the docetaxel arm, 12% overall vs. 4% on the vinorelbine arm, and a higher rate of fluid retention, 54% overall vs. 42% overall. The rate of alopecia and nail disorder was higher on the docetaxel arm. There was a higher rate of vomiting, both overall and grade ¾ on the vinorelbine arm (61% and 16% vs. 55% and 8% on the docetaxel arm). Incidence of neurosensory and neuromotor events was similar between arms. Rates of asthenia, anorexia and skin changes were similar between arms. There was no new toxicity associated with docetaxel when it was combined with cisplatin in this study, and the toxicities observed in each arm were those that would be anticipated with each regimen.

The docetaxel + carboplatin arm in TAX326 was not associated with a superior median survival and it could not be shown that this combination retains at least 50% of the vinorelbine combination treatment effect. Although this suggests within trial inconsistency in the evidence of effectiveness associated with docetaxel in this disease, it must be noted that the literature provides no clear evidence that carboplatin has similar efficacy to cisplatin in this disease and there is some literature to suggest that it is inferior. Certainly carboplatin has been shown to be inferior to cisplatin in the setting of testicular carcinoma. The lack of evidence of effectiveness for the docetaxel + carboplatin doublet could well have been attributed to the substitution of carboplatin in the doublet.

The FDA review team recommends approval of the docetaxel + cisplatin combination regimen for the treatment of patients with unresectable, locally advanced (Stage IIIB) or metastatic non-small cell lung cancer who have not previously received chemotherapy, based on a noninferiority analysis that estimated at least 62% retention of the active control arm treatment effect, and a toxicity profile that was not clearly worse than that of the control arm. There is clear prior evidence supporting docetaxel's activity in this disease, data that have been reviewed by the FDA. As a single agent it demonstrated statistically significantly superior survival compared to best supportive care in the first-line treatment setting (the same setting as the current indication), and it has demonstrated survival benefit as monotherapy in the second line treatment of non-small cell lung carcinoma. The active control arm in the noninferiority comparison had relevance, as it is an FDA approved treatment regimen for this disease. Although there were some clear limitations to the reliability of the noninferiority comparison, which were outlined in this review, the estimated retention of over half of the control effect with a conservative approach to analysis of noninferiority (relative to the Rothman, et al approach described in detail in the Biometrics review), the fact that this retention was related to the strong trend toward superiority associated with the docetaxel regimen, and the prior evidence of docetaxel's activity in this disease contributed to the decision for approval. The safety review did not provide clear evidence that either regimen was superior to the other.

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/s/

Donna Griebel
11/27/02 08:21:14 PM
MEDICAL OFFICER

PROJECT MANAGER REVIEW OF LABELING

NDA 20-449/S-018

Drug: **Taxotere (docetaxel) Injection, 20mg and 80mg**

Applicant: **Aventis Pharmaceutical Products, Inc.**

Submission Date: **February 1, 2002**
Receipt Date: **February 1, 2002**

BACKGROUND:

Aventis submitted a "Changes Being Effected" (CBE) labeling supplement (S-017) dated January 9, 2002 to provide for additions to the ADVERSE REACTIONS section, Post-Marketing Experience subsection of the package insert. This supplement was approved on July 9, 2002.

However, the sponsor agreed to make the following changes:

Under **Post-marketing Experiences,** subsection **Gastrointestinal,** replace the last sentence "Rare occurrences of dehydration as a consequence to gastrointestinal events, gastrointestinal perforation, ischemic colitis, colitis, intestinal obstruction, ileus, and neutropenic enterocolitis have been reported."
with the following:

> "Gastrointestinal: abdominal pain, anorexia, constipation, duodenal ulcer, esophagitis, gastrointestinal hemorrhage, gastrointestinal perforation, ischemic colitis, colitis, intestinal obstruction, ileus, neutropenic enterocolitis and dehydration as a consequence to gastrointestinal events have been reported."

Under **Post-marketing Experiences,** subsection **Opthalmologic,** replace the last sentence "Rare cases of lacrimal duct obstruction resulting in excessive tearing have been reported primarily inpatients receiving other anti-tumor agents concomitantly." with the following:

> "Excessive tearing which may be attributable to lacrimal duct obstruction has been reported."

The current supplement S-018 provides for the use of Taxotere in conjunction with cisplatin for first line NSCLC. It also proposes revisions in the Human Pharmacokinetics section.

DOCUMENTS REVIEWED:

I compared the approved January 9, 2002 CBE against the proposed draft labeling in S-018 dated February 1, 2002.

REVIEW:

I found that all of the proposed changes to the package insert were identified by the underline and strikethrough feature.

CONCLUSION - RECOMMENDED REGULATORY ACTION:

In this supplement, the sponsor has correctly identified all of the proposed changes to the package insert using the underline and strikethrough feature. This supplement may be approved with the concurrence of the medical, clinical pharmacology and statistics reviewers.

If approved, the supplement should include the changes recommended in the S-017 approval letter as stated above under "**BACKGROUND: **".

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

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

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/s/

Ann Staten
8/29/02 01:54:10 PM
CSO

Dotti Pease
9/3/02 11:36:59 AM
CSO

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

MEMORANDUM OF TELEPHONE CONVERSATION
DIVISION OF ONCOLOGY DRUG PRODUCTS

DATE: November 14, 2002 (3:00pm-3:30pm)

SUBJECT: NDA 20-449/S-018 Taxotere (docetaxel)

Discussion:

Dr. Lippman was consulted regarding the supplemental application for Taxotere in combination with cisplatin in first line non-small cell lung carcinoma (study TAX326). After clarification from the Division regarding non-inferiority analyses that were conducted, Dr. Lippman concurred with the Division's decision to approve this application.

/S/

Ann Staten, RD
Regulatory Health Project Manager

/S/

Ramzi Dagher, MD
Medical Reviewer

MEETING MINUTES

DATE: November 29, 2001 **TIME:** 9:30 am **LOCATION:** Conference Room G

IND/NDA IND [redacted] Meeting Request Submission Date: September 26, 2001 (N971)
Briefing Document Submission Date: October 26, 2001 (N976);
November 1, 2001 (N977)
Other submissions: November 13, 2001 (N979)

DRUG: Taxotere (docetaxel)

SPONSOR/APPLICANT: Aventis Pharmaceuticals

TYPE of MEETING:

1. Pre-sNDA

2. Proposed Indication: Taxotere in combination with platinum agents for the treatment of patients with unresectable locally advanced or metastatic non-small cell lung cancer.

FDA PARTICIPANTS:
Richard Pazdur, M.D., Director, Division of Oncology Drug Products
Donna Griebel, M.D., Medical Team Leader, Division of Oncology Drug Products
Alison Martin, M.D., Medical Team Leader, DODP, (internal meeting only)
Ramzi Dagher, M.D., Medical Reviewer
Lilia Talrico, M.D., Associate Director
Gang Chen, Ph.D., Statistician, Team Leader
Ning Li, Ph.D., Statistician
Sophia Abrahams, Ph.D., Clinical Pharmacology Reviewer
Khin U, M.D., Division of Scientific Investigation (internal meeting only)
Ann Staten, Project Manager

INDUSTRY PARTICIPANTS:
Steve Caffe, M.D., Head, US Regulatory
Sol Rajfer, M.D., Head, Global Clinical
Jean-Pierre Bizzari, M.D., Vice President, Clinical Development-Oncology
Antoine Yver, M.D., Senior Director, Global Clinical Development-Oncology
Francis Gamza, M.D., Associate Director, Associate Global Clinical Manager
Jocelyn Berille, M.D., Director, Associate Global Clinicial Manager
Martin Roessner, M.S., Therapeutic Area Head, Oncology, Global Biostatistics
Alf Gruener, M.D., Global Project Team Leader
Yong Kim, Ph.D., Group Head, Biostatistics
Jeffrey Barrett, Ph.D., F.C.P., Head Global Biopharmaceutics
Sanjukta Bhaduri, Director, Global Pharmacoviligance and Epidemiology
Martha Propsner, Regulatory Trategic Liaison

Philippe Serrano, Global Regulatory Strategic Liaison
Stewart Mittnacht, Head, Global and North America Submissions

November 29, 2001 pre-sNDA meeting

MEETING OBJECTIVES:

To discuss the filing of a supplement for Taxotere in combination with platinum agents for the treatment of patients with unresectable locally advanced or metastatic non-small cell lung cancer.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

QUESTION 1:

Aventis believes that the benefit/risk ratio of the docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 combination regimen q 3 weeks in the treatment of chemotherapy-naïve patients with unresectable locally advanced or metastatic non-small cell lung cancer is favorable based on the overall evidence of effectiveness and the unremarkable safety profile of this regimen as observed in study TAX 326.

Does the Agency agree?
We discourage the registration approach for the combination regimen indication in first-line treatment of nonsmall cell lung cancer based on noninferiority as described in the briefing document for the following reasons.

1. The proposal hinges on a single trial that in fact includes two noninferiority comparisons, one of which appears unlikely to establish noninferiority (docetaxel/carboplatin). A single trial is an insufficient database for clearly establishing noninferiority, and it would be particularly problematic if a co-existing noninferiority comparison is not supportive. Should you choose to pursue this registration approach, retention of 75% of the control effect must be convincingly demonstrated in both comparisons. The same alpha planned for the superiority test should be used (0.014 one sided).

   The docetaxel/carboplatin vs. vinorelbine/cisplatin may not represent a feasible noninferiority comparison because it fails to isolate the effect of docetaxel. The single agent efficacy of carboplatin and its contribution to the treatment effect of the regimen will need to be clearly defined before the relevance of this comparison can be accepted as a second noninferiority comparison.

2. As stated in the previous meeting response (February 22, 2001), the noninferiority analysis of TAX326 hinges on a comparison of the relative contributions of vinorelbine and docetaxel to each cisplatin based regimen. You must build a convincing meta-analysis to define vinorelbine's treatment effect in this disease, and it appears that this will be difficult. The recently reviewed SWOG study that isolated the contribution of vinorelbine to the cisplatin combination is a single study. If the treatment effect of the control can only be established on the basis of a single historical trial, the between-study

variability cannot be assessed, and the within-trial variability associated with the estimate of the control effect may be underestimated. The estimate of control effect in this situation should be based on the lower (or upper) bound of the 95% CI (two-sided).

3. As stated in our previous meeting where we discussed a potential noninferiority analysis of TAX326, imbalances across studies in important prognostic factors or supportive care will be an important hurdle to establishing a claim of noninferiority (e.g. TAX 326 had a higher proportion of Stage III patients than the SWOG trial). Heterogeneity in study populations could render noninferiority analyses uninterpretable. Adjustment of the control effect would be necessary, and may still leave questions regarding the validity of the conclusions if the analysis is based on a limited study database. Similarly, should there be within-study imbalances detected in the review of TAX 326 that favor the docetaxel arm (e.g. distribution of pleural effusions in the IIIB patients), this too would render the noninferiority analysis uninterpretable.

4. Consistency of the supportive secondary endpoints must be factored into the analysis. It is concerning that TTP appears numerically inferior in both docetaxel arms. It is impossible to exclude that this is a true reflection of treatment effect, even if the differences in assessment schedules between arms are acknowledged. These secondary endpoints appear particularly weak for the carboplatin/docetaxel doublet, which again raises concerns about inconsistency of the results.

5. The evaluation of the clinical relevance of a noninferiority analysis of two cytotoxic regimens involves examining whether there are advantages relative to the standard comparator arm that make it important for the new treatment to be available to patients. The TAX 326 safety data presented in the background package suggests both regimens are associated with significant toxicity, with some differences. There appears to be more vomiting and anemia associated with vinorelbine/cisplatin, and more diarrhea and fluid retention with the docetaxel doublets. Important toxicities like neutropenia, neutropenic fever and infection appear similar among arms (although infection is somewhat higher with the docetaxel/carboplatin doublet). Deaths within 30 days of treatment are slightly higher on the vinorelbine/cisplatin arm (9% vs. 8% on the docetaxel doublets) and the data presented showed treatment discontinuation for adverse events was higher on the vinorelbine arm (23% vs. 16% in the docetaxel/cisplatin doublet and 9% in the docetaxel/carboplatin doublet). The safety advantage of the docetaxel doublets over cisplatin/vinorelbine is not striking and its relevance would be a review issue. Other available information available on the docetaxel/cisplatin doublet would be factored into the review, including the results of ECOG 1594 where docetaxel/cisplatin was reportedly not well tolerated by performance status 2 patients.

QUESTION 2:

Aventis believes that the benefit/risk ratio of the docetaxel 75 mg/m^2 and carboplatin AUC 6 combination regimen q 3 weeks is also favorable in the same population, based on the consistent evidence of efficacy and the favorable safety profile of this regimen as observed in study TAX 326.

Does the Agency agree?

See answer to Question 1.

QUESTION 3:

Based on the assertions above, Aventis Pharmaceuticals Inc. is proposing the indication for TAXOTERE in patients with non-small cell lung cancer be extended to include the treatment of chemo-naïve patients in combination with platinum agents. The proposed draft indication is:
"Taxotere® is indicated for the treatment of patients with unresectable locally advanced or metastatic non-small cell lung cancer in combination with platinum agents in patients who have not previously received chemotherapy for this condition"
The recommended dosage regimen is docetaxel 75 mg/m^2 in combination with cisplatin 75 mg/m^2 or carboplatin dosed to an AUC of 6 mg/mL·min according to the Calvert formula, repeated every 3 weeks.

Does the Agency agree?

See answer to Question #1.

QUESTION 4:

All safety data from Phase I, II and III (TAX 326 and TAX) trials will be presented. However, because of differences in doses and dosing schedules, these data will not be integrated.

Will the Agency accept this approach for presentation of safety data in the ISS?

FDA Response: Yes.

QUESTION 5:

To represent the collective post-marketing experience of docetaxel worldwide, the Sponsor proposes to include an overview assessment of the post-marketing experience with docetaxel as reflected in Periodic Safety Update Reports (PSURs).

Will the Agency accept this approach for presentation of the post-marketing experience for docetaxel?

FDA Response: Yes. In addition, available information on the use of taxotere in combination with carboplatin or cisplatin should be presented separately.

QUESTION 6:

In accordance with 21 CFR Part 54, Financial Disclosure by Clinical Investigators, the Sponsor proposes to provide certification for clinical investigators involved in the adequate and well-controlled Phase III studies (TAX and TAX 326) only.

Does the Agency agree?

FDA Response: No. The requirement to collect financial disclosure information applies to all studies that the FDA relies on to establish that the product is effective, or that makes a significant contribution to demonstration of safety. (see Guidance for Industry: Financial Disclosure By Clinical Investigators at http://www.fda.gov/oc/guidance/financialdis.html.) (Phase 2 studies of the combinations would contribute to the database upon which FDA makes a determination of safety.)

BACKGROUND

The application will be comprised of a pivotal study (TAX 326) that is a controlled study of docetaxel in combination with platinum agents (cisplatin or carboplatin) and an active control arm consisting of vinorelbine plus cisplatin. To support the activity of docetaxel in the proposed indication, the application will include the results of a controlled study of docetaxel monotherapy in non-small cell lung cancer (TAX). The application will be further supported by five (5) Phase I and four (4) Phase II uncontrolled studies of combination therapy in the proposed indication.

This application will be primarily a paper submission; however, we wish to make the Division aware of certain electronic files and datasets that will be provided in addition to or in lieu of a paper copy. A complete description of the data that will be included in each section of the proposed application is displayed in the attached table.

QUESTION 7:

ITEMS 1-8, 13, 14, 16, and 18

The application's Index, Summary, Labeling, Chemistry Manufacturing and Controls, Nonclinical Pharmacology and Toxicology, Human Pharmacokinetics and Bioavailabiliy, Clinical Data, Patent Information, Patent Certification, Debarment Certification, (Items 1 – 8, 13,

14, 16, and 18 of the application) will be provided as paper copy (for both review and archival) with the exception of labeling that will be provided as a paper copy and a Word document.

Will the Division accept this approach for providing information for the sections detailed above?

FDA Response: Electronic submission (SAS transport files) of clinical data consisting of the pivotal phase 3 trial TAX 326 and PK/Bioavailability (TAX012, TAX018, and TAX049 is acceptable.

QUESTION 8:

ITEM 10 (STATISTICAL)

The Statistical section (Item 10) will be cross-referenced to the Clinical data section (Item 8), by providing a Table of Contents for Item 8. An additional paper copy of Item 8 will be provided for the Statistical Officer's review.

Will the Division accept this approach for the Statistical Section?

FDA Response: Yes.

QUESTION 9:

ITEM 11 (CASE REPORT TABULATIONS)

The Case Report Tabulations (Item 11) will be provided electronically for TAX 326 only; tabulations for all other studies will be included as part of the final study reports in the clinical data section (Item 8). The Case Report Tabulations will be cross-referenced to the Clinical Data section (Item 8), by providing a Table of Contents for Item 8. An additional paper copy of Item 8 will be provided to the Reviewer, upon request.

Will the Division accept this approach for providing Case Report Tabulations?

FDA Response: Yes.

QUESTION 10:

ITEM 12 (CASE REPORT FORMS)

Case Report Forms (Item 12) will be submitted electronically for all studies. Case report forms (CRFs) will be bookmarked but the CRF correction forms will not be hyperlinked to the

corresponding page in the CRF. The CRF for each patient, consisting of the correction forms followed by the case report form pages, will be provided as a single electronic file in pdf format. 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.

Will the Division accept this approach for the submission of Case Report Forms?

FDA Response: We request that you provide hyperlinking between the CRF correction form and the corresponding page in the CRF. An electronic copy of the CRFs without hypertext links would also be acceptable for this application. A paper copy of the CRFs may be provided for review purposes upon submission of the application or within 60 days from the submission of the application.

CRF's should be available at the site for inspection. Once sites are selected for inspection, the sponsor should send a random sample of CRF's to DSI in paper form.

OTHER FDA COMMENTS:

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, or that 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 Final Rule**

We have reviewed the information you have submitted and agree that a waiver is justified for Taxotere for the treatment of patients with first-line treatment of nonsmall cell lung cancer for the pediatric population. Accordingly, a waiver for pediatric studies for this application is granted under 21 CFR 314.55 at this time.

4. **Pediatric Exclusivity**

Under the Food and Drug Administration Modernization Act, you have the opportunity for an exclusivity extension if Taxotere is appropriate for an indication in pediatrics. If you choose to pursue pediatric exclusivity, your plans for a pediatric drug development, in the form of a Proposed Pediatric Study Request (PPSR), should be submitted so that we can consider issuing a Written Request.

Please refer to the "*Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505 A of the Federal Food, Drug and Cosmetic Act*" at Drug Information Branch (301) 827-4573 or http://www.fda.gov/cder/guidance/index.htm. You should also refer to our division's specific guidance on pediatric oncology Written Requests which is at http://www.fda.gov/cder/guidance/3756dft.htm.

The meeting was concluded at 11 p.m. There were no unresolved issues or discussion points.

/S/
Ann Staten
Project Manager
Minutes preparer

Concurrence Chair:

/S/
Ramzi Dagher, M.D./Date
Medical Officer

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/s/

Ann Staten
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Ramzi Dagher
12/18/01 02:37:53 PM

MEETING MINUTES

DATE: February 22, 2001 **TIME:** 10:00 am **LOCATION:** Conference Room B

IND/NDA IND [redacted] Meeting Request Submission Date: December 22, 2001 (N907)
Briefing Document Submission Date: December 22, 2001 (N907)
Other submissions: January 26, 2001 (N913)

DRUG: Taxotere (docetaxel)

SPONSOR/APPLICANT: Aventis Pharmaceuticals

TYPE of MEETING:

1. Other - Non-inferiority Statistical Analysis Plan

2. Proposed Indication: First-Line Non-Small Cell Lung Cancer

FDA PARTICIPANTS:
Robert Temple, M.D., Director, Office of Drug Evaluation I (ODEI) (industry meeting only)
Richard Pazdur, M.D., Director, Division of Oncology Drug Products (internal meeting only)
Donna Griebel, M.D., Medical Team Leader, Division of Oncology Drug Products
Ramzi Dagher, M.D., Medical Reviewer
Isagani Chico, M.D., Medical Reviewer (internal meeting only)
George Chi, Ph.D., Director, Division of Biometrics I (industry meeting only)
Gang Chen, Ph.D., Statistician, Team Leader
Ning Li, Ph.D., Statistician
Dianne Spillman, Project Manager (internal meeting only)
Ann Staten, Project Manager (industry meeting only)

INDUSTRY PARTICIPANTS:
Jean-Pierre Bizzari, M.D., Vice President, Clinical Research Oncology
Marion Ceruzzi, Aventis Regulatory Affairs
Christopher Griffith, Aventis Regulatory Affairs
Frank Gamza, M.D., Associate Director, Clinical Research Oncology
Alf Gruener, M.D., Senior Director, Clinical Research
Sylvain Durrleman, M.D., Head, Global Biometrics & Data Management
Yong Kim, Ph.D., Associate Director, Biostatistics
[redacted]
Philippe Serrano, Associate Director, Global Regulatory Affairs
[redacted]

MEETING OBJECTIVES:

February 22, 2001 meeting – 1st line NSCLC

1. To discuss the non-inferiority statistical analysis plan.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

ECOG 1594 SAP

1. In previous correspondence dated October 11, 2000, the Agency indicated that the major steps to establishing non-inferiority are determining the treatment effect associated with the control arm and demonstrating that a clinically acceptable proportion of that treatment effect is retained by the new therapy. After a thorough review of the literature no reference was found to support the comparison of the standard therapy, paclitaxel + cisplatin versus placebo or best supportive care in patients with NSCLC. Therefore, Aventis is postulating an effect size of survival difference between paclitaxel plus cisplatin and placebo at 25% based on clinical judgement and applying 50% preservation from placebo in determination of the non-inferiority margin.

   Does the FDA agree with this Aventis proposal?

   FDA: No. Without data to support the treatment effect of paclitaxel + cisplatin compared to placebo or best supportive care, the combination of paclitaxel + cisplatin cannot be used as a comparator arm to support the efficacy of docetaxel + cisplatin in a non-inferiority analysis. It is not acceptable to postulate an effect size based on clinical judgment alone. The effect size must be based on clinical data.

   Have you examined whether the necessary data to establish the treatment effect of the ECOG 1594 comparator arm gemcitabine + cisplatin exist?

   Aventis: Aventis will take this under consideration.

2. Although the design of study ECOG 1594 has 4 arms with 3 pairwise comparisons to the control arm, the primary comparison for Aventis is only one test arm, docetaxel plus cisplatin, compared to the control arm, paclitaxel plus cisplatin. Therefore, there is no issue of multiplicity.

   Does the FDA agree with this Aventis view?

   FDA: Yes, we agree.

Tax326 SAP

February 22, 2001 meeting – 1st line NSCLC

1. In previous correspondence dated October 31, 2000, the Agency indicated that certain percentage preservation of the standard therapy survival effect related to placebo should be used to determine the non-inferiority margin. After a thorough review of the literature no reference was found to support the comparison of the standard therapy, vinorelbine + cisplatin versus placebo or best supportive care in patients with NSCLC. Therefore, Aventis is postulating an effect size of survival from placebo at 20% based on a clinical judgement and applying 50% preservation from placebo in determination of the non-inferiority margin.

   Does the FDA agree with this Aventis proposal?

   FDA: No. A study has demonstrated superior survival associated with single agent vinorelbine compared to placebo (5-FU + LV), and treatment with the combination regimen vinorelbine + cisplatin has demonstrated superior survival compared to single agent vinorelbine. The noninferiority analysis of relevance in the comparison of the docetaxel + cisplatin combination to vinorelbine + cisplatin is the comparison of the docetaxel and vinorelbine contributions to each of these regimens (since cisplatin is included in both regimens). The proposal to retain 50% of the treatment effect of the combination compared to placebo is not appropriate because it ignores cisplatin's contribution to the incremental increase in survival (as demonstrated by the superiority of cisplatin + vinorelbine vs. vinorelbine). Because of this, a much more conservative proposal for preservation of effect is necessary.

   We remind you that even if a case for non-inferiority in efficacy could be made using this trial (TAX 326), relative toxicity will be considered in the final decision regarding approval.

   The trial would have to be well conducted and the secondary endpoints should favor the docetaxel arm. Relative distribution of prognostic factors among trials and dose intensities will also have to be examined to assess comparability of studies.

2. Does the FDA agree with the separate inference domains for the two pairwise comparisons to the active control [docetaxel+cisplatin vs. vinorelbine+cisplatin and docetaxel+carboplatin vs. vinorelbine+cisplatin] and that the error rate per comparison (as opposed to the experimentwise error rate) has the primary relevance in this study design as stated in the SAP (page 7)?

   Quote from page 7 of the SAP - ***"The purpose of including the two docetaxel combinations with different platinum compounds in this study is to provide for the treatment choices between geographical regions of cancer treatment, i.e., a cisplatin combination is almost always necessary in regions with economic priorities, while a carboplatin combination is highly preferred in other regions due to ease of administration and less toxicity anticipated. In a sense, the two independent docetaxel combinations corresponding to two separate***

studies comparing to the standard vinorelbine combination merged into a single study to achieve efficiency in the conduct of the trial, especially, for rapid enrollment of patients through one global study protocol. Thus, the two pairwise comparisons of each docetaxel combination against the same control are viewed as separate inference domains (as would apply in the setting of two separate studies), and hence, no adjustment for the type 1 error rate is considered necessary. "

FDA: We agree with the sponsor that the use of the Hochberg method and the intended definition of statistical significance, as described on page 20 of the SAP, i.e., "statistical significant will apply to both comparisons if both have $p<0.05$ or it will apply to one of them if it has $p<0.028$."

The meeting was concluded at 11 a.m. There were no unresolved issues or discussion points.

/S/
Ann Staten
Project Manager
Minutes preparer

Concurrence Chair:

/S/
Donna Griebel, M.D./Date
Medical Officer

/s/

Ann Staten
4/11/01 02:33:07 PM

Donna Griebel
4/12/01 03:10:29 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Kelly B. Pendergrass, M.D.
Kansas City Oncology & Hematology Group
6724 Troost Avenue, Suite 710
Kansas City, Missouri 64131

SEP 26 2002

Dear Dr. Pendergrass:

Between July 22 and July 25, 2002, Mr. Carl J. Montgomery, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol # RP56976 entitled: "A Multicenter, Multinational, Randomized Phase III Study of Docetaxel (RP56976, Taxotere®) Plus Cisplatin versus Docetaxel (RP56976, Taxotere®) Plus Carboplatin versus Vinorelbine Plus Cisplatin in Chemotherapy-Naive Patients with Unrespectable Locally Advanced and/or Recurrent (Stage IIIb) or Metastatic (Stage IV) Non-Small Cell Lung Cancer") of the investigational drug Taxotere® (docetaxel), performed for Aventis. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections, designed to validate clinical studies on which drug approval may be based and to ensure that the rights, safety and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did adhere to FDA regulations governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Montgomery during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter, at the address given below.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 1000118420
CFN: 19-31935
Field Classification:
Headquarters Classification:
___x_1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

If Headquarters classification is a different classification, explain why: The district classified OAI based on the charge that the pharmacist, ——— diluted the chemotherapeutic agents. I do not think this is Dr. Pendergrass's responsibility.

cc:
HFA-224
HFD- 150 Doc.Rm. NDA# 20-449/S-018
HFD- 150 Review Div.Dir. (Richard Pazdur, MD)
HFD- 150 MO (Ramzi Dagher, MD)
HFD- 150 PM (Ann Staten)
HFD-46/47c/r/s/ GCP File #3113
HFD-46/47 GCP Reviewer (David Gan, MD, Dr.PH., MPH)
HFD-46/47 CSO (Carolanne Currier)
HFR- SW 350 DIB (Mary Waleske)
HFR- SW 350 Bimo Monitor /Field Investigator (Carl J Montgomery)
r/d: (DG):7/5/02;9/11/02
reviewed:kmu:9/5/02
f/t:**ml: 9/11/02**
O:\Gan\letters\Auditletter.pendergrass0802.doc

Reviewer Note to Rev. Div. M.O.

This was a clinical investigator assignment issued to validate the data being used in support of NDA 20449. Fourteen subjects were enrolled. Records for all 14 subjects were reviewed during the inspection. There were no deficiencies found. However, there appears to be a problem with the compounding of the chemotherapeutic agents used during this trial. This clinical investigator utilized the services of ——— was arrested in 2001 by FBI/OCI and charged with dilution of chemotherapeutic agents and he has pled guilty. Further follow-up of this matter is pending. Until the compounding issue is resolved, I recommend that the data from this study not be used in support an approval decision for this NDA.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

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

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

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

1. APPLICANT'S NAME AND ADDRESS

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

2. TELEPHONE NUMBER *(Include Area Code)*

(908) 231-3841

3. PRODUCT NAME

Taxotere (docetaxel) for Injection Concentrate

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

20-449

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

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

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

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4241

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

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

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

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

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

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

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO

(See item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes 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
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
	Steve Caffe, M.D. Vice President, Head GRAMS –N.A.	January 21, 2002

FORM FDA 3397 (4/01)

Created by PSC Media Arts (301) 443-2454 EF

1-1-15

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 20-449 /SE1 - 018

Drug Taxotere (docetaxel) Applicant Aventis

RPM Ann Staten Phone 301-594-0490

■505(b)(1)
☐505(b)(2) Reference listed drug

☐Fast Track ☐Rolling Review Review priority: ■ S ☐P

Pivotal IND(s)

Application classifications:
Chem Class 1S (new indication)
Other (e.g., orphan, OTC) Orphan designation received after NDA submission

PDUFA Goal Dates:
Primary December 1, 2002
Secondary

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ■ User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption

- Action Letter..... ■AP ☐ AE ☐NA

- Labeling & Labels
  FDA revised labeling and reviews..... X 11-27-02
  Original proposed labeling (package insert, patient package insert) X
  Other labeling in class (most recent 3) or class labeling..... N/a
  Has DDMAC reviewed the labeling? ..... ■ Yes (include review) ☐ No
  Immediate container and carton labels ..... N/a
  Nomenclature review ..... N/a

- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ■ is not on the AIP.
  Exception for review (Center Director's memo)..... N/a
  OC Clearance for approval..... N/a

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) ☐ Materials requested in AP letter

- Post-marketing Commitments
  - Agency request for Phase 4 Commitments..... N/a
  - Copy of Applicant's commitments ..... N/a

- Was Press Office notified of action (for approval action only)?..... ■ Yes ☐ No
  - Copy of Press Release or Talk Paper..... N/a

- Patent
  - Information [505(b)(1)] X
  - Patent Certification [505(b)(2)]..... N/a
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)]..... N/a

- Exclusivity Summary X

- Debarment Statement X

- Financial Disclosure
  - No disclosable information X
  - Disclosable information – indicate where review is located ..... Page 23

- Correspondence/Memoranda/Faxes X

- Minutes of Meetings X
  - Date of EOP2 Meeting _____
  - Date of pre NDA Meeting 11-29-01; 2-22-01
  - Date of pre-AP Safety Conference N/a

- Advisory Committee Meeting ..... N/a
  - Date of Meeting ..... N/a; Lippman t-con 11-14-02
  - Questions considered by the committee ..... N/a
  - Minutes or 48-hour alert or pertinent section of transcript ..... N/a

- Federal Register Notices, DESI documents ..... N/a

CLINICAL INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) ..... X 11/29/02

- Clinical review(s) and memoranda ..... X 11/27/02

- Safety Update review(s) ..... N/a

- Pediatric Information
  ■ Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
  Pediatric Page..... X
  ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ■Not Applicable

- Statistical review(s) and memoranda X

- Biopharmaceutical review(s) and memoranda..... X

- Abuse Liability review(s) ..... N/a
  Recommendation for scheduling ..... N/a

- Microbiology (efficacy) review(s) and memoranda ..... N/a

- DSI Audits X
  ☐Clinical studies ☐ bioequivalence studies ..... _____

CMC INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- CMC review(s) and memoranda X

- Statistics review(s) and memoranda regarding dissolution and/or stability ..... N/a

- DMF review(s) ..... N/a

- Environmental Assessment review/FONSI/Categorical exemption ..... X- see CMC review

- Micro (validation of sterilization) review(s) and memoranda ..... N/a

- Facilities Inspection (include EES report)
  Date completed N/a ..... ☐ Acceptable ☐ Not Acceptable

- Methods Validation ..... ☐ Completed ☐ Not Completed

PRECLINICAL PHARM/TOX INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- Pharm/Tox review(s) and memoranda ..... N/a

- Memo from DSI regarding GLP inspection (if any) ..... N/a

- Statistical review(s) of carcinogenicity studies ..... N/a
- CAC/ECAC report ..... N/a

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
12/3/02 09:45:29 AM

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FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301)594-5742 FAX: (301) 594-0498

TO: Cheryl Anderson, Aventis
Fax: 908 304-6317

FROM: Dotti Pease, Project Manager
Phone: (301) 594-5742

Total number of pages, including cover sheet 2

Date: 10-23-02

COMMENTS: Re: Taxotere NDA 20-449/S018, attached is a comment from our statistician:

Since only one historical trial (by Wozniak et al., 1998) was appropriate for estimating the active control effect, the upper limit of the 95% confidence interval of the hazard ratio (vinorelbine+cisplatin / cisplatin) 0.86 (95% CI: 0.65-0.86) was used to estimate the active control (vinorelbine+cisplatin) effect. Assuming that non-inferiority requires the test regimens (docetaxel in combination with either cisplatin or carboplatin) to preserve at least 50% of the active control (vinorelbine+cisplatin) effect, the hazard ratio of test regimens to cisplatin required no larger than 0.927 ($= e^{0.5*ln(0.86)}$). Therefore, the hazard ratio of test regimens to the vinorelbine+cisplatin combination required no lager than 1.078 (= 0.927/0.86). That is, the

cutoff for the hazard ratio (test regimen / vinorelbine+cisplatin) in the non-inferiority test was 1.078.

The following table summarizes the results from the stratified logrank test. Based on the Hochberg procedure for multiple comparisons, the docetaxel+cisplatin combination preserved more than 50% treatment effect of the vinorelbine+cisplatin combination (adjusted p-value for non-inferiority < 0.05, the upper limit of the nominal 97.65% confidence interval was less than 1.078). It was demonstrated that the vinorelbine+cisplatin combination preserved at least 62% (= *ln* 0.910 / *ln* 0.86) of the active control (vinorelbine+cisplatin combination) effect.

Table: Reviewer's Primary Survival Analysis of Stratified Logrank Test (on All Randomized Patients)

	Comparison 1	Comparison 2
	Test Regimen A (D75+Cis) vs. Active Control (V+Cis)	Test Regimen B (D75+Cb6) vs. Active Control (V+Cis)
P-value [a]	0.122	0.657
Estimated Hazard Ratio [b]	0.884	1.036
95.3% CI [c]	(0.754, 1.036)	(0.885, 1.212)
97.65% CI [d]	**(0.737, 1.059)**	Not needed.

[a] From the superiority test "H_0: hazard ratio = 1 vs. H_1: hazard ratio ≠ 1".
[b] Hazard ratio of test treatment to the active control. A hazard ratio of less than 1 indicates that the test treatment is associated with a longer time to survival.
[c] Corresponding to a nominal significance level of 0.047.
[d] Corresponding to a nominal significance level of 0.0235.

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

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

To:	Cheryl Anderson, Aventis	**From:**	Ann Staten, Project Manager
Fax:	908-304-6317	**Fax:**	301-827-4590
Phone:	908-304-6471	**Phone:**	301-594-0490
Pages:	**1**	**Date:**	**October 10, 2002**
Re:	NDA 20-449/s-018		

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

Dear Ms. Anderson:

We have the following request:

Medical:

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.

Please let me know if there are any questions.

Sincerely,

Ann

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

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

To:	Cheryl Anderson, Aventis	**From:**	Ann Staten, Project Manager
Fax:	908-304-6317	**Fax:**	301-827-4590
Phone:	908-304-6471	**Phone:**	301-594-0490
Pages:	**1**	**Date:**	**October 10, 2002**
Re:	NDA 20-449/s-018		

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

Dear Ms. Anderson:

We have the following request:

Medical:

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

Please let me know if there are any questions.

Sincerely,

Ann

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

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

To:	Cheryl Anderson, Aventis	**From:**	Ann Staten, Project Manager
Fax:	908-304-6317	**Fax:**	301-827-4590
Phone:	908-304-6471	**Phone:**	301-594-0490
Pages:	7	**Date:**	September 24, 2002
Re:	NDA 20-449/s-018		

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

Dear Ms. Anderson:

We have the following request:

Medical:

Examination of Table 52, Section 8.2.2 of the study report for TAX326 reveals information similar to that obtained by FDA analysis for most AE's. However, for some AE's, there appear to be significant differences between sponsor and FDA analysis with respect to incidence of AE as a total or when broken down by severity of grade (for COSTART terms) or grading (for NCI terms). One difference between the sponsor's analysis and FDA approach is that we have analyzed the AE's by incidence as a maximum grade (i.e. # of patients with an AE maximum grade 1, 2, 3, 4 and total) whereas the sponsor provides incidence of grade 3/4 or severe and total. These differences in approach could account for some individual AE grade listing differences, but do not account for differences in total #'s of patients encountering a particular AE. The AE's where particularly significant discrepancies occur are listed below. The attached word document provides two tables listing the FDA analysis by NCI term and COSTART term. Please provide any insight you may have on the reason for these differences.

NCI term

weight loss
neuro-constipation
neuro-hearing

neuro-sensory
neuro-motor

COSTART term

asthenia
pain
arthralgia
constipation
hemoptysis
pleural effusion

Please let me know if there are any questions.

Sincerely,

Ann

Table 1 : AE's Reported by NCI Term, Maximum Grade, and Treatment Group

Adverse Event	Docetaxel Cisplatin N = 406	Docetaxel Carboplatin N = 401	Vinorelbine Cisplatin N = 396
Alopecia Grade			
1	104	96	102
2	199	178	64
3	3	4	0
4	0	0	0
TOTAL	306 (75%)	278 (69%)	166 (42%)
Nausea Grade			
1	120	117	102
2	131	78	134
3	38	27	65
4	2	0	1
TOTAL	291 (72%)	222 (55%)	302 (76%)
Vomiting Grade			
1	98	77	88
2	95	52	92
3	22	17	48
4	10	1	16
TOTAL	225 (55%)	147 (37%)	244 (62%)
Diarrhea Grade			
1	86	70	59
2	78	63	31
3	22	16	7
4	6	5	4
TOTAL	192 (47%)	154 (38%)	101 (26%)
Weight Loss Grade			
1	71	66	74
2	41	31	54
3	5	5	9
4	0	0	0
TOTAL	117 (29%)	102 (25%)	137 (35%)
Neuro-Constipation Grade			
1	38	49	60
2	33	22	29
3	2	1	8
4	0	1	0
TOTAL	73 (18%)	73 (18%)	97 (24%)

Stomatitis Grade			
1	53	53	45
2	35	48	35
3	8	1	5
4	0	0	0
TOTAL	96 (24%)	102 (25%)	85 (21%)
Infection Grade			
1	49	49	51
2	58	81	65
3	24	31	24
4	10	14	8
TOTAL	141 (35%)	175 (44%)	148 (37%)
Platelets Grade			
1	1	7	10
2	0	14	4
3	0	7	2
4	0	3	3
TOTAL	1	31	19
Hemoglobin Grade			
1	1	0	1
2	6	8	18
3	1	4	17
4	1	1	6
TOTAL	9	13	46
Skin Grade			
1	47	59	41
2	16	28	11
3	3	2	4
4	0	0	0
TOTAL	66 (16%)	89 (22%)	56 (14%)
Neuro-hearing Grade			
1	15	10	21
2	32	15	55
3	5	3	7
4	0	0	0
TOTAL	52 (13%)	28 (7%)	83 (21%)
Neuro-sensory Grade			
1	128	97	114
2	45	18	38
3	16	4	15

4	0	0	1
TOTAL	189 (47%)	119 (30%)	168 (42%)
Neuro-cerebellar			
Grade			
1	7	4	8
2	2	1	2
3	2	1	1
4	0	0	0
TOTAL	11 (3%)	6 (1%)	11 (3%)
Neuro-motor			
Grade			
1	34	27	22
2	31	21	27
3	13	15	21
4	1	2	1
TOTAL	79 (19%)	65 (16%)	71 (18%)

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

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

To:	Cheryl Anderson, Aventis	**From:**	Ann Staten, Project Manager
Fax:	908-304-6317	**Fax:**	301-827-4590
Phone:	908-304-6471	**Phone:**	301-594-0490
Pages:	2	**Date:**	August 26, 2002
Re:	NDA 20-449/s-018		

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

Dear Ms. Anderson:

Please refer to your sNDA submission for NSCLC. We have the following additional information request from the medical reviewer. If possible, we would like a response to question #1 by Friday.

Medical:

1. The medical reviewer's analysis of dose intensity (mg/m2/week) and relative dose intensity indicates findings similar to those presented by the sponsor in Table 49 of the study report for TAX326. However, the mean and median for cumulative dose (mg/m2) appear to be lower than those obtained by the sponsor. The medical reviewer's data was obtained by analysis of the CMDOSM2 component by treatment group and drug in the USMA dataset and is presented below. If the sponsor's analysis is based on a different approach, please clarify.

ARM	DRUG	MEAN	MEDIAN
Cis + Docetaxel	Cisplatin	242	225
	Docetaxel	242	225
Carbo + Docetaxel	Carboplatin	1230	1098
	Docetaxel	245	224
Vin + Cisplatin	Cisplatin	271	221
	Vinorelbine	201	175

2. Of the 52 patients listed in your revised Table 17 (sponsor's response to FDA inquiry) as having a change in staging from randomization, the medical reviewer has found CRF's for the following 7 patients: 11006, 21130, 11045, 11009, 22139, 11068, 12230. For the remaining 45, please indicate whether CRF's have been submitted, and if so, where can they be found in the submission. If no CRF's were submitted for the remaining 45, please submit CRF's for the following subset (paper or electronic, whichever is easier/quicker)

11075	11047	11074
21007	11067	21020
12071	12072	32022
12129	22012	32039
12163	22158	21155
12165	21059	
22016		
22025		
22053		
22270		

Please let me know if there are any questions.

Sincerely,

Ann

Fax

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

To:	Cheryl Anderson, Aventis	**From:**	Ann Staten, Project Manager
Fax:	908-304-6317	**Fax:**	301-827-4590
Phone:	908-304-6471	**Phone:**	301-594-0490
Pages:	1	**Date:**	August 15, 2002
Re:	NDA 20-449/s-018		

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

Dear Ms. Anderson:

Please refer to your sNDA submission for NSCLC. We have the following additional information request from the medical reviewer.

Medical:

> Table 23 of the Final Study Report for TAX326 reports the frequency of prior anti-cancer therapy, including lung procedures. However, no mention is made of thoracotomy or excision of lung lesion, both of which were captured in the CRF's and listed in the USURG dataset. Please justify exclusion of these from your consideration of lung procedures.

Please let me know if there are any questions.

Sincerely,

/S/

Ann

Fax

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

To:	Cheryl Anderson, Aventis	**From:**	Ann Staten, Project Manager
Fax:	908-304-6317	**Fax:**	301-827-4590
Phone:	908-304-6471	**Phone:**	301-594-0490
Pages:	2	**Date:**	August 13, 2002
Re:	NDA 20-449/s-018		

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

Dear Ms. Anderson:

Please refer to your sNDA submission for NSCLC. We have the following additional information request from the medical reviewer which we place as a fairly high priority.

Medical::

1. FDA analysis of dataset UPAT for Stage at Randomization by Treatment Group (F_DIAGEX by F_TRTGRP) reveals the following counts

Stage	Treatment Group		
	Docetaxel/Cisp	Docetaxel/Carbo	Vinorelbine/Cisp
Locally Advanced	140	129	128
Metastatic	268	278	277
Total	408	407	405

These counts are different than those found in sponsor table 19 of the final study report for TAX326, and are not entirely accounted for by the sponsor's removal of two randomized patients from the ITT population. Please clarify the reason for these discrepancies

2. Sponsor Table 17 of the final study report for TAX326 provides a listing of patients that had a change in staging from randomization. For some cases, it is not clear how the discrepancy was resolved. Furthermore, the totals for patients listed in row number 1 across the 3 treatment groups do not match the number of patient ID numbers listed in each column. Please clarify these discrepancies.

The study report states that the study was stratified by staging at randomization. Please clarify whether the discrepancies outlined in Table 17 were taken into account in the primary analysis and if so, how?

Please let me know if there are any questions.

Sincerely,

/s/

Ann

FAX

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

To: Cheryl Anderson, Aventis	**From: Ann Staten**
Fax: 908-304-6317	**Fax:** (301) 827-4590
Phone: 908-304-6471	**Phone:** (301) 594-0490
Pages, including cover sheet:	**Date: 8-16-02**

Re: sNDA 20-449/018 Taxotere

Dear Ms. Anderson,

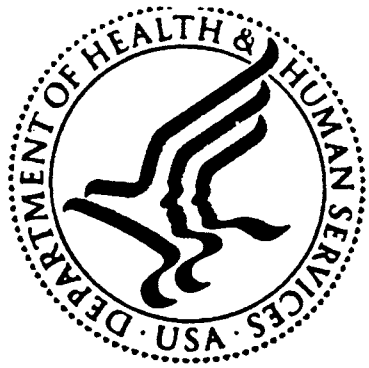
We have the following request for information.

Please provide the formula used to calculate Relative Dose Intensity (RDI) by component as presented in TAX326 Study Report Table 49, page 01-1-150.

Sincerely,

Ann Staten

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

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

To:	Cheryl Anderson, Aventis	**From:**	Ann Staten, Project Manager
Fax:	908-304-6317	**Fax:**	301-827-4590
Phone:	908-304-6471	**Phone:**	301-594-0490
Pages:	1	**Date:**	August 7, 2002
Re:	NDA 20-449/s-018		

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

Dear Ms. Anderson:

Please refer to your sNDA submission for NSCLC. We have the following additional information request from the medical reviewer which we place as a higher priority over the 8-5-02 and 8-6-02 requests.

Medical:

> It is not clear where the listing for 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.

Please let me know if there are any questions.

Sincerely,

Ann /S/

Fax

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

To:	Cheryl Anderson, Aventis	**From:**	Ann Staten, Project Manager
Fax:	908-304-6317	**Fax:**	301-827-4590
Phone:	908-304-6471	**Phone:**	301-594-0490
Pages:	1	**Date:**	August 6, 2002
Re:	NDA 20-449/s-018		

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

Dear Ms. Anderson:

Please refer to your sNDA submission for NSCLC. We have the following additional information request from the medical reviewer.

Medical:

You list a total of 1218 patients as the ITT population. However, the dataset contains information for 1220 patients who were randomized to one of 3 arms. Please identify the 2 patients (one in arm B and one in arm C) who are apparently excluded from the ITT population and clarify the rationale for their exclusion. (There is a reference on page 01-1-93 Table 5 of the TAX326 Final Study Report to an alternative diagnosis of oat cell cancer in one and pancreatic cancer in the other).

The user data set documentation guide for UPAT lists performance status as per WHO guidelines whereas the actual dataset and study report list performance status as per Karnofsky scoring. Please clarify this discrepancy.

Please let me know if there are any questions.

Sincerely,

/S/

Ann

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

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

To:	Cheryl Anderson, Aventis	**From:**	Ann Staten, Project Manager
Fax:	908-304-6317	**Fax:**	301-827-4590
Phone:	908-304-6471	**Phone:**	301-594-5770
Pages:	2	**Date:**	August 5, 2002
Re:	NDA 20-449/s-018		

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

Dear Ms. Anderson:

Please refer to your sNDA submission for NSCLC. We have the following attached information request from the medical reviewer.

Please let me know if there are any questions.

Sincerely,

/S/

Ann

The medical reviewer's analysis of the submitted dataset 'feval' reveals 32 patients who were randomized onto the trial although ultimately deemed ineligible due to violation of inclusion/exclusion criteria. The reasons for ineligibility and patient numbers are listed in Table 1 below. This is contrast to the sponsor's description of major protocol violations in section 6.1.5.5 of the final study report for TAX 326, where it is stated that 13 patients were discontinued for major protocol violations. Please clarify this discrepancy.

Table 1 : Reviewer List of Eligibility Violations

Eligibility Violation	Patient Identification Number
Serious concomitant illness	11018, 11029, 11039, 12023, 12112, 12243, 22077, 22254, 22357, 32055
Received prior/concurrent anticancer agent	11034, 22290, 31001
Previous or concurrent history of malignancy	11062, 12214, 12231, 21037
No histologically or cytologically proven NSCLC	12017, 41011
Serum creatinine > 1.65 mg/dl + clearance < 54 ml/minute	12024, 41049,
Symptomatic or history of untreated brain mets	12077, 22160, 41059, 42050
Peripheral neuropathy ≥ grade 2	12209, 22141, 21215, 22262
Total bilirubin > 1.1 x ULN	12239
Major surgical treatment within 14 days of study entry	42067
Serious complication of malignant disease	21029

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

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

To:	Marion Ceruzzi, Aventis	**From:**	Ann Staten, Project Manager
Fax:	908-304-6317	**Fax:**	301-827-4590
Phone:	908-231-5828	**Phone:**	301-594-5770
Pages:	1	**Date:**	May 28, 2002
Re:	NDA 20-449/s-018		

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

Dear Marion:

Please refer to your sNDA submission for NSCLC. We have the following request:

Please provide electronic SAS codes that produced statistical results of all efficacy endpoints.

Sincerely,

/S/

Ann

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

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

To:	Wayne F. Valley, R.Ph., Quintiles	**From:**	Ann Staten, Project Manager
Fax:	816-767-7375	**Fax:**	301-827-4590
Phone:	816-767-6466	**Phone:**	301-594-5770
Pages:	1	**Date:**	October 31, 2000

Re: IND [redacted] Taxotere – submission dated 8-2-00 (serial no. 880)

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

Wayne,

The medical and statistical reviewers have completed the review of this submission and have the following comments:

Statistical Issues:

1. In this protocol, the sponsor proposed to analyze the primary endpoint survival by making the following two comparisons: (1). Docetaxel/cisplatin to the control group, and (2) Docetaxel plus carboplatin to the control group. The sponsor proposed not to adjust α for the multiple comparisons. The primary analyses are not clear. If the sponsor will make the efficacy claim based on the summary of the two separate hypotheses tests, (i.e., the trial will be claimed as a negative trial if one of the two tests fails), no α adjustment is necessary. Otherwise, the type I error will be inflated and multiplicity should be considered.

2. The sponsor is going to use a hazard ratio of 0.75 (the lower 95% confidence limit) as the margin for "non-inferiority" or "not unacceptably worse than" the active control. This margin selection is NOT acceptable since the comparator is an active control. Using an arbitrary margin may result in an efficacy claim even when the treatment is inferior to a placebo. Certain percentage preservation of the standard therapy survival effect related to placebo should be used to determine the margin. Historical data may be needed to define the margin. Detailed statistical analysis plan should be submitted for review if the sponsor plans to claim efficacy based upon "non-inferiority". The issues regarding demonstration of non-inferiority are complex and should not be underestimated.

Please call me with any questions.

Sincerely,
/S/

cc: Orig IND [redacted]
Div File
HFD-150/Astatn/NL
/RDagher/Dbridbal