# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: NDA 20449/S11

## ADMINISTRATIVE DOCUMENTS

## Item 13 -Patent/Exclusivity Information

| | | |
|---|---|---|
| 1) | Active Ingredient(s): | docetaxel |
| 2) | Strength(s): | 40 mg/ml |
| 3) | Trademark: | Taxotere® |
| 4) | Dosage Form (Route of Administration): | sterile solution |
| 5) | Application Firm Name: | Rhône-Poulenc Rorer Pharmaceuticals Inc. |
| 6) | IND Number: | [ ] |
| 7) | NDA Number: | 20-449 |
| 8) | Approval Date: | N/A |
| 9) | Exclusivity – date first ANDA could be submitted or approved and length of exclusivity period: | Pursuant to Section 505(j)(4)(D)(iii) and 505(c)(3)(D)(iii) 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 July 14, 2007<br>5,438,072, Expires November 22, 2013<br>5,403,858, Expires July 3, 2012<br>5,698,582, Expires July 3, 2012<br>5,714,512, 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 | July 14, 2007 |
| 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 | Rhône-Poulenc Rorer Pharmaceuticals Inc. |

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: Christine M. Hansen Date: 6/25/98
Name: Christine M. Hansen
Title: Patent Counsel
Rhône-Poulenc Rorer Pharmaceuticals Inc.

## 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 | Rhône-Poulenc Rorer Pharmaceuticals Inc. |

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: Christine M. Hansen Date: 6/25/98
Name: Christine M. Hansen
Title: Patent Counsel
Rhône-Poulenc Rorer Pharmaceuticals Inc.

## Item 13. Patent Information

| | | |
|---|---|---|
| 1) | Patent number | 5,403,858 |
| 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 | Rhône-Poulenc Rorer Pharmaceuticals Inc. |

The undersigned declares that Patent No. 5,403,858 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: Christine M. Hansen Date: 6/25/98
Name: Christine M. Hansen
Title: Patent Counsel
Rhône-Poulenc Rorer Pharmaceuticals Inc.

## 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 | Rhône-Poulenc Rorer Pharmaceuticals Inc. |

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: Christine M. Hansen Date: 6/25/98
Name: Christine M. Hansen
Title: Patent Counsel
Rhône-Poulenc Rorer Pharmaceuticals Inc.

## 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 | Rhône-Poulenc Rorer Pharmaceuticals Inc. |

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: Christine M. Hansen Date: 6/25/98
Name: Christine M. Hansen
Title: Patent Counsel
Rhône-Poulenc Rorer Pharmaceuticals Inc.

EXCLUSIVITY SUMMARY FOR NDA # sNDA 20449/011 SUPPL # 91

Trade Name Taxotere (docetaxel) Generic Name docetaxel

Applicant Name Rhone-Poulenc Rorer HFD # 150

Approval Date If Known 12-23-99

**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 question about the submission.

a) Is it an original NDA?

YES /___/ NO /✓/

b) Is it an effectiveness supplement?

YES /✓/ 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 /✓/ NO /___/

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

_____

_____

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

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /___/

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

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

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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 8.

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 8 (even if a study was required for the upgrade).

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

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with

hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /X/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

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

YES /___/ NO /___/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

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

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

YES /___/ NO /___/

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

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

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

YES /___/ NO /___/

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

_____

_____

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain: _____

_____

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

YES /___/ NO /___/

If yes, explain: _____

_____

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

_____

_____

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

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

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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

_____ _____

_____ _____

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

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

Investigation #1

IND # _____ YES /___/ 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 /___/

If yes, explain: _____

_____

/S/

Signature

Title: Regulatory Health Project Manager

12/16/99

Date

/S/

Signature of Office/ Division Director

12/16/99

Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

# PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

| | | | |
|---|---|---|---|
| **NDA/BLA Number:** | 20449 | **Trade Name:** | TAXOTERE (DOCETAXEL) IV 80MG/20MG |
| **Supplement Number:** | 11 | **Generic Name:** | DOCETAXEL |
| **Supplement Type:** | SE1 | **Dosage Form:** | INJ |
| **Regulatory Action:** | | **Proposed Indication:** | Second line NSCLC |

**ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?**

NO, Pediatric content not necessary because of pediatric waiver

**What are the INTENDED Pediatric Age Groups for this submission?**

____NeoNates (0-30 Days ) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

| | |
|---|---|
| **Label Adequacy** | Does Not Apply |
| **Formulation Status** | - |
| **Studies Needed** | - |
| **Study Status** | - |

**Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission?** NO

**COMMENTS:**

Pediatric Waiver Granted

Pediatric Waiver granted

**This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, ANN STATEN**

/S/ 12/10/99

Signature Date

45 Day Meeting Overview / Statistics AUG 13 1999

| | |
|---|---|
| NDA #: | 20-449 |
| Sponsor: | Rhone-Poulenc Rorer |
| Name of Drug: | Taxotere (docetaxel) for Injection Concentrate |
| Indication: | Treatment of NSCLC in patients who've been previously treated w/ platinum-based chemotherapy |
| Documents Reviewed: | volumes 1 – 5, 1 - 3 |
| Date Received: | 12/23/98, 6/23/99 |
| Medical Reviewer: | Dr. Griebel |

This supplemental NDA is comprised of 2 pivotal Phase III trials: TAX320 and TAX317. In addition, 4 supportive single agent Phase II trials (TAX270, TAX271, TAX297, SI002A) at a dose of 100mg/m$^2$ and 2 additional studies with one at a dose of 60 mg/m$^2$ (TAX241) and the other at 75 mg/m$^2$ (CHI202) were also submitted. Interim results from TAX317 were submitted in the 12/23/98 portion of this rolling submission. The SAS programs and SAS data sets for all studies are available.

TAX 320 is a multi-center, open-label, randomized parallel group Phase III study comparing docetaxel 100 mg/m$^2$ or 75 mg/m$^2$ 1 hour i.v. vs. patients receiving vinorelbine 30 mg/m$^2$ or ifosfamide 6 mg/m$^2$. The study population are those patients who have previously been treated with a platinum-based regimen. The primary efficacy endpoint is overall survival. Secondary endpoints include QOL measures, time to progression, tumor response rates (response rate, duration of response).

TAX317 is a two group, parallel, randomized study comparing docetaxel 100mg/m$^2$ (and later reduced to 75 mg/m$^2$) to best supportive care in patients previously treated with a platinum-containing regimen. The first 100 patients were randomized to receive either 100mg/m$^2$ of docetaxel or best supportive care. These results were submitted in the interim analysis. The second 104 patients were randomized to receive either 75mg/m$^2$ or best supportive care. These results have been compared separately from the first 100 patients. The primary efficacy endpoint is overall survival. The primary efficacy endpoint is overall survival. Secondary endpoints include QOL measures, time to progression, tumor response rates (response rate, duration of response).

Statistical Issues:

1. An imputation is performed when there are < 50% of missing values on a given item in a given evaluation. An overall mean is replaces the missing in such an instance.
2. The efficacy endpoint of % survival at one year was not a prespecified endpoint.
3. Censoring on the basis of subsequent therapy and the pooling of the two Taxotere treatment groups were not prespecified analyses. Pooling of dose levels is not appropriate and censoring at subsequent chemotherapy is questionable.

This supplementary NDA application is sufficiently complete for statistical review and is fileable from a statistical standpoint.

/S/

Clara Chu, Ph.D
Mathematical Statistician

CC:
HFD-150/Division File
HFD-150/Ms. Staten, CSO
HFD-150/Dr. Griebel
HFD-150/Dr. Beitz
HFD-710/Dr. Chen
HFD-710/Dr. Chi

# MEETING MINUTES

**MEETING DATE:** August 6, 1999 **TIME:** 11:30-12:30 p.m. **LOCATION:** cr-B

**IND/NDA** sNDA 20-449/011 Submission Date: June 23,1999 and June 30, 1999

**DRUG:** Taxotere (docetaxel)

**SPONSOR/APPLICANT:** Rhone-Poulenc Rorer

**TYPE of MEETING:**

1. 45-Day Filing

2. **Proposed Indication:** Taxotere 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.

**FDA PARTICIPANTS:**

| | | |
|---|---|---|
| Robert Justice, M.D. | -- | ActingDivision Director, HFD-150 |
| Julie Beitz, M.D. | -- | Acting Deputy and Medical Team Leader, HFD-150 |
| Donna Griebel, M.D. | -- | Medical Reviewer, HFD-150 |
| Gang Chen, Ph.D. | -- | Biometrics Team Leader, HFD-150 |
| John Lawrence, Ph.D. | -- | Biometrics Reviewer, HFD-710 |
| Clara Chu, Ph.D. | -- | Biometrics Reviewer, HFD-150 |
| Ann Staten | -- | Project Manager, HFD-150 |

**MEETING OBJECTIVES:**

1. To determine filing status

**DISCUSSION and DECISIONS REACHED:**

1. **FILEABILITY:** Reviewers/Team Leaders polled during meeting. NDA will be filed.

2. **POTENTIAL PROBLEMS:**

a. Medical: The sponsor will need to submit a proposed label that clearly reflects the efficacy data provided by the two phase 3 trials in second line treatment of non-small cell lung carcinoma (SE-011).

To be conveyed to sponsor:

We have done a preliminary review of the proposed labeling provided in SE011 have noted the following deficiencies:

- The labeling for second-line treatment of non-small cell lung carcinoma should include the efficacy and safety data from both pivotal phase 3 studies. As the label currently stands, the data from TAX 317 has not been provided. Please submit an updated label that includes this information.

- The Clinical Studies section of labeling should provide the efficacy and safety data that form the basis of including 60 mg/m$^2$ in the recommended dose for first and second line treatment of non-small cell lung carcinoma.

- We note in your cover letter dated 6/23/99 that accompanies SE011 that you suggest that "the optimal dose range and schedule for this patient population is 60 mg/m$^2$ to 75 mg/m$^2$ administered...." This, however, is not reflected in your proposed labeling under Dosage and Administration. Please revise accordingly.

3. **CONSULTS:**
   a. DSI (Medical): Requesting foreign sites to be audited. Specific issues to be discussed with Gus Turner. Memo drafted and given to Medical Officer.
   b. Biopharm. - Issued: looking at labeling changes. IR = recommending that RPR submit any PK info. in nsclc pts. receiving the proposed dosage regimen.

4. **ODAC DATE:** November or December. Preference is towards December meeting for both indications.

5. **TEAM GOALS:**

**To complete the priority review (2$^{nd}$ line NSCLC) first and if time permits, complete the standard review application (1$^{st}$ line) in a 6 month time frame.**

   a. Completed Reviews: Medical 11/23/99
      Statistics 11/23/99
   b. Action Package Circulated on **11-29-99**
      and to Division Director by: **December 2, 1999 for s-011;**
   c. User Fee Goal: December 23, 1999 for s-011;

6. **TEAM MEETINGS:**

| | DATE | DAY | TIME | ROOM | MEETING TYPE |
|---|---|---|---|---|---|
| a. | Sept. 21, 1999 | Tuesday | 1-2pm | WOC2-cr B | 3-Mo team for /011 (to determine labeling schedule and meetings, other issues) |
| b. | Oct 26 | Tues | 1-2 pm | ~~WOC2-cr B~~ | ~~4-mo team for /011 (if needed)~~ |
| c. | Nov. 17, 1999 | Wed. | 12-2 pm | WOC2-cr A | 5-mo team for /011/ Labeling mtg #1 |
| d. | Dec. 7, 1999 | Tuesday | 2:30 pm - 4pm | WOC2-cr B | **ODAC practice** |
| e. | 11/23/99 | TUE | REVIEWS COMPLETED : Medical & Stat | | |
| f. | ~~11/4, 11/5 or~~ 12/13, 12/14 | | ODAC MEETING | | |
| g. | Dec. 15, 1999 | Wed. | 10-11:30am | WOC2-cr B | ODAC post-mortem if needed / Labeling mtg #2 (if needed) |
| | | | | | |
| | | | | | |
| h. | Dec. 2, 1999 | Thursday | | | ACTION PACKAGE TO R Pazdur |
| i. | Dec. 9, 1999 | Thursday | ACTION PACKAGE TO TEMPLE | | |

7. **OTHER ISSUES:**
   a. Priority review clock assigned for s-011
   b. Action Letter sign-off: TBD in mini-rounds

8. **ACTION ITEMS:**

| | Who | When |
|---|---|---|
| a. Schedule of meetings/milestones | Ann | by August 20; done 8-11-99 |
| b. 45-day minutes | Ann | by August 20; done 8-11-99 |
| c. Request revised labeling | Ann | done 8-9-99 |
| d. Pediatric Waiver Letter | Ann/Julie | by 8-20-99; granted 8-10-99 |
| e. Biopharm. IR to sponsor | Ann | done 8-11-99 |
| f. DSI memo | Ann/Donna | asap |

/S/
Ann Staten, Project Manager
Minutes preparer

Concurrence Chair: /S/
Donna Griebel, M.D.
Medical Reviewer

Attachments: Medical 45 day filing review

Filing Minutes
NDA 20-449
8-6-99

Attachment

**Medical Officer 45-Day Review of NDA #20449 SE1 Nos. 11**

1. **General Information**

**SE1 No. 11 (Second line Non-Small Cell Lung Carcinoma)**

| | |
|---|---|
| Submission date: | December 23, 1998 Fast Track Submission<br>June 23, 1999 Rolling NDA Final Submission |

**(First line Non-Small Cell Lung Carcinoma)**

| | |
|---|---|
| Submission date: | June 30, 1999 |

| | |
|---|---|
| Drug Name: | Docetaxel |
| Trade Name: | Taxotere® |
| Sponsor: | Rhône Poulenc Rorer |
| Pharmacologic category: | Taxane |
| Dose/Route of Administration: | 60 - 100 mg/m$^2$ infused intravenously over 60 minutes. |

2. **Proposed Indication**

SE1 No. 11 (Second line Non-Small Cell Lung Carcinoma)

Taxotere (docetaxel) for Injection Concentrate is indicated for the treatment of patients with locally advanced or metastatic Non-Small Cell lung Cancer ***after failure of prior chemotherapy***.

DOSAGE AND ADMINISTRATION
The recommended dose of TAXOTERE is 60-100 mg/m$^2$ administered intravenously over 1 hour every 3 weeks.

(First line Non-Small Cell Lung Carcinoma)

Taxotere (docetaxel) for Injection Concentrate is indicated for the treatment of patients with *chemotherapy-naïve* locally advanced or metastatic Non-Small Cell lung Cancer.

DOSAGE AND ADMINISTRATION
The recommended dose of TAXOTERE is 60-100 mg/m$^2$ administered intravenously over 1 hour every 3 weeks.

3. **NDA Submission**

SE1 No. 11 (Second line Non-Small Cell Lung Carcinoma)

This supplement was submitted under a Fast-Track designation and was a rolling submission. The final submission, which completed the application and started the

review clock, is dated June 23, 1999. One hundred twenty-nine volumes were submitted in December 1998. Those volumes included the final study report and data from TAX 320. The June 1999 submission consisted of seven volumes containing the final study report and data from the second pivotal trial for second line treatment of non-small cell lung carcinoma, TAX 317. The data from both studies were submitted electronically. Case Report Forms from TAX 320 were submitted in volumes 68-129, and those for TAX 317 in blue volumes 14-25.

The two pivotal phase 3 randomized, controlled trials that provide the primary safety and efficacy data both enrolled participants with unresectable locally advanced or metastatic non-small cell lung carcinoma whose disease had progressed during or after treatment with platinum based chemotherapy and who had an ECOG performance status ≤ 2. Patients were stratified for best response to prior platinum therapy (progression vs. other) and ECOG status (0-1 vs. 2). The primary endpoint in both trials was median survival.

**TAX 320:** (Open label; Twenty-seven U.S. sites)
ARMS: A = Taxotere 100 mg q 21 d (N = 125)
B = Taxotere 75 mg q 21 d (N = 125)
C = Vinorelbine 30 mg/m$^2$ Days 1, 8, 15 q 21 d
*OR* Ifosfamide 2 g/m$^2$ Days 1-3 q 21 d
(N = 123)

*Reviewer Comment: Five of the 23 active sites entered 53.9% (201/373) of the patients who participated in this study. Those investigators/sites were:*

| | | | |
|---|---|---|---|
| *Frank Fossella, MD* | *US00418* | *N=53* | *(MD Anderson)* |
| *Russell Devore, MD* | *US01525* | *N=48* | *(Vanderbilt)* |
| *Ronald Neal Kerr, MD* | *US01966* | *N=42* | *(Texas Oncology)* |
| *Jeffrey Crawford, MD* | *US02002* | *N=32* | *(Duke)* |
| *Ronald Natale, MD* | *US01990* | *N=26* | *(USC/Norris)* |

*Exploratory Comparisons Among Treatment Sites – Mean Survival and Mean Censored for Further Chemotherapy Survival:*

| | *TAX 100* | | *TAX 75* | | *813* | |
|---|---|---|---|---|---|---|
| | *Survival* | *Censored* | *Survival* | *Censored* | *Survival* | *Censored* |
| *Fosella* | *244* | *210 (-14%)* | *260* | *209 (-20%)* | *288* | *162 (44%)* |
| *Devore** | *238* | *180 (-24%)* | *294* | *192 (-35%)* | *172* | *107 (-38%)* |
| *Kerr** | *133* | *115 (-14%)* | *152* | *89 (-42%)* | *170* | *109 (-36%)* |
| *Crawford* | *207* | *187 (-10%)* | *202* | *181 (-10%)* | *265* | *172 (-35%)* |
| *Natale* | *203* | *188 (-7%)* | *269* | *181 (-33%)* | *311* | *172 (-45%)* |

**TAX 317:** (Open label; 50 North American and European sites)
ARMS: A = Taxotere 75 mg* q 21 d (N = 104)
B = Best Supportive Care (N = 100)

* The study was initiated with a docetaxel dose of 100 mg/m$^2$ on November 23, 1994, but a protocol amendment (#6) issued on January 31, 1997 lowered the dose to 75 mg/m$^2$ because of higher than expected toxic death rate. Patients on active treatment at the time of the amendment underwent a dose reduction. Fifty-five of the total 104 docetaxel patients participating in this study (and 49 best supportive care patients) were entered after the protocol amendment was issued.

*Reviewer Comment: The four investigators/centers with the highest accrual were:*

| | | | |
|---|---|---|---|
| *Frances Shepherd, MD* | *CA00073* | *N=58* | *(Toronto)* |
| *Rodryg Ramlau, MD* | *PL00049* | *N=15* | *(Poland; Poznan?)* |
| *Karin Mattson, MD* | *FI00066* | *N=12* | *(Finland)* |
| *Richard Gralla, MD* | *US00174* | *N=11* | *(Oschner; LA)* |

*There were two additional investigators from Toronto who accrued patients to TAX 317:*

| | | | |
|---|---|---|---|
| *Ronald Louis Burkes, MD* | *CA00121* | *N=8* | *(Toronto)* |
| *Ronald Feld, MD* | *CA00120* | *N=2* | *(Toronto)* |

*For the purposes of a site visit, the three Toronto sites accrued 68/204 (33%) of this study's population.*

*Review Issues Raised by the Sponsor's Proposed Labeling:*

*1) Survival Claims:*

- *TAX 317 is not included in the Second Line Non-Small Cell Lung Carcinoma Data in the Proposed Efficacy section for this disease in the label.*
- *The only survival data presented is that censored for subsequent chemotherapy*
- *The only censored for subsequent chemotherapy survival data discussed in the text is the survival at one year, and the lack of significant difference in median survival is not mentioned in the text, although it is shown in the table. The table presentation of the primary endpoint of median survival is not readily understandable. There is no discussion of whether the difference in %survival at one year is significant when each docetaxel arm is compared to control (the pre-specified analysis of survival – median survival - compared each docetaxel arm to control), although the confidence intervals are provided. The only p-value provided, with a reference to "significance" was when the additional unplanned comparison of the combined docetaxel arms was made with the control in an analysis of %1-year survival.*

2) *Response:*
   - ➢ *Both ITT and evaluable analyses are presented*
   - ➢ *The N responding is prominently displayed as the response rate, instead of the percent. The percent is lower than the N responding, and this could be misleading.*
   - ➢ *A combined docetaxel treatment groups vs. the control analysis comparison is presented. This may not have been a pre-specified analysis.*

3) *TTP*
   - ➢ *Both ITT and evaluable analyses are presented*
   - ➢ *The analysis presented in the table appears to show that the only significant difference in TTP is between the docetaxel 100mg and control arm. They do a combined analysis of the two docetaxel arms vs. control that is significant, and was probably not pre-specified.*

4) *Quality of Life*
   - ➢ *The longitudinal analysis tables are presented in the label.*
   - ➢ *They claim significant differences favoring docetaxel 100mg in patient total score, observer total score, fatigue, and lung cancer symptoms. Docetaxel 75mg is not mentioned, except in a closing comment that in responders or patients with stable disease there was "a clear improvement in QoL with both D/100 and D75".*

A table summarizing the sponsor's efficacy analyses is shown below. Pre-specified endpoints are enclosed in heavy crossbars, while those analyses that were not pre-specified are enclosed in dashed crossbars.

## TAX 320

| | TAX 100 | TAX 75 | Active Control |
|---|---|---|---|
| **MEDIAN SURVIVAL** | **5.5 month** | **5.7 months** | **5.6 months** |
| **95% CI** | **4.6, 6.6** | **5.1, 7.9** | **4.3, 7.9** |
| **Separate Docetaxel Comparisons** | **Log-Rank=NS** | **Log-Rank=NS** | |
| *% 1 year Survival* | 21% | 32% | 19% |
| Separate Docetaxel Comparisons | Log-Rank = NS | Log-Rank = NS | |
| *% 1 year Survival Censoring Pt's Not Lost to follow-up* | | (lost = 10) | (lost = 5) |
| Separate Docetaxel Comparisons | | *Chi-Square p=0.046* | |
| *Median Survival Censored at* | 6.6 month | 5.8 month | 5.4 month |

| | | | |
|---|---|---|---|
| *Subsequent Chemorx* | | | |
| 95% CI | 5.0, 7.9 | 5.2, 8.0 | 4.2, 7.9 |
| Separate Docetaxel Comparisons | ? | ? | ? |
| *% 1 year Survival Censoring at Subsequent Chemorx* | 32% | 32% | 10% |
| 95% CI | 22, 43 | 20, 44 | 1, 18 |
| Separate Docetaxel Comparisons | Log-Rank P=0.13 | Log-Rank P= 0.12 | |
| | | | |
| **Response Rate (Secondary Endpoint)** | **10.5%** | **6.5%** | **0.8%** |
| 95% CI | 5.9, 17.6 | 3.0, 12.7 | 0.0, 5.2 |
| Separate Docetaxel Comparisons | **Fisher's Exact Test p=0.001** | **Fisher's Exact Test p=0.036** | |
| **Time to Progression** *Stat. Plan*:Censored at last assessment before further chemotherapy or radiotherapy *Study Report*: Censored at last assessment before further chemo, not radiotherapy AND Excluding patients without Non-small Cell Lung carcinoma | 8.4 weeks | 8.5 weeks | 7.9 weeks |
| 95% CI | 6.7, 11.0 | 6.7, 11.0 | 6.9, 11.0 |
| | | | |
| 26 week K-M % Progression | 19% | 17% | 8% |
| 95% CI | 12, 26 | 10, 24 | 3, 13 |
| Separate Docetaxel Comparisons (???for the 26 week analysis??) | **Log-Rank p=0.044** | P=0.093 | |
| | | | |
| **Duration of Response** | 32.1 weeks | 39.3 weeks | 25.6 weeks |
| Log-Rank | NS | NS | |
| **Pre-specified Secondary Quality of Life Endpoints: Changes from baseline in LCSS scores ECOG PS Body Weight** | LCSS = 84% compliance at Baseline | LCSS = 73% compliance at Baseline | LCSS = 73% compliance at Baseline |

| | | | |
|---|---|---|---|
| **Analgesic Use** | | | |
| **Separate Docetaxel Comparisons – LCSS total score ANCOVA** | 0.2<br>(NS Longitudinal)<br>(NS Pattern Mixture) | NS, NS, NS | |
| Fatigue **Separate Docetaxel Comparisons ANCOVA** | 0.03<br>(0.07, 0.06) | NS, NS, NS | |
| Symptoms **Separate Docetaxel Comparisons ANCOVA** | 0.03<br>(0.08, 0.09) | NS, NS, NS | |
| Factor 1 and Factor 1A ANCOVA | 0.02 (NS. NS)<br>0.03 (NS, NS) | NS, NS, NS<br>NS, NS, NS | |
| Observer LCSS Total Score | 0.05, 0.05, 0.05 | NS, NS, NS | |
| Observer Pain | 0.05, 0.07, 0.08 | NS, NS, NS | |
| **PS, Weight, Analgesic USE** | ???? | ???? | |

## TAX 317

| | TAX 100/75 | TAX100 | TAX 75 | BSC |
|---|---|---|---|---|
| **MEDIAN SURVIVAL**<br>**Stat Plan**- to the date of death or date of last contact if death is unknown<br>**Study Report** – censored at the date of last contact if lost to follow-up, date of *further anti-tumor therapy including chemo and surgery and immunorx.* | **7.2 months** | 5.9 months | 9.0<br>(vs. 4.6 m)<br><br>n=55 | **4.7 months**<br><br>n=49<br>(4.6 mo. for n=49) |
| **95% CI** | **5.5, 9.2** | | **5.5, 13.1** | **3.7, 6.0**<br>(3.7, 6.1 for n=49) |
| **Log Rank** | **P=0.14** | **NS** | ***P=0.016*** | |
| **Wilcoxon rank test** | **P=0.06** | | | |
| | | | | |
| % 1 year Survival | **28%** | | **40%**<br><br>(vs. 16%) | **23%**<br><br>(16% for n=49) |
| 95% CI | (19, 38) | | (26, 54) | (13, 32)<br><br>{(3, 30) for N=49} |
| P= | ?NS? | | ?? | |

| | | | | |
|---|---|---|---|---|
| **Response Rate** | **5.8%** | 6.3% | 5.5%<br>(1.4, 16.1) | |
| **Duration of Response**<br>**Stat Plan** – Censor for further chemo, radiation, and surgery<br>**Study Report** - Censored for chemo and surgery only | 26.1 weeks | 23.9 weeks<br>(n=3) | 26.1 weeks<br>(n=3) | |
| **TTP**<br>**Stat Plan** - Censored at date of last assessment prior to further therapy including chemo, immunotx, surgery, and radiation<br><br>Study Report – Censored for all of the above except radiation | **10.6 weeks** | 9.1 weeks | 12.3 weeks<br><br>n=55 | **6.7 weeks**<br><br>**n=49 for TAX 75 comparison** |
| **95% CI** | **7.6, 12.1** | | (9.0, 18.3) | **6.0,7.3**<br><br>{(6.0, 9.3) for n=49} |
| Log-Rank | **P<0.001** | 0.037 | P=0.004 | |
| | | | | |
| % 26-week non-PD | 16% | | | 5% |
| 95% CI | 8, 23 | | | 0, 10 |
| | | | | |
| Pre-specified Secondary Quality of Life Endpoints:<br>Changes from baseline in LCSS/EORTC scores<br>ECOG PS<br>Body Weight<br>Analgesic use | | | | |
| "Tumor Related Medication"<br>Incidence of administration | 62%<br>*p=0.02* | | | 77% |
| "Tumor Related Non-Pain Medication" | 30%<br>*(p<0.01)* | 31%<br>(p=0.04) | 29%<br>(p=0.06) | 49% |
| "Tumor Related Pain Medication - Morphine" | 32%<br>*p=0.01* | NS | 26%<br>P<0.01 | 49% |
| "Tumor Related Pain Medication – Non-Morphine" | 39%<br>*p=0.03* | NS | 31%<br>p<0.01 | 55% |
| | | | | |
| Radiotherapy (% patients who were treated at least | 26%<br>p=0.09 | (37%) | 16% | 37% |

| | | | | |
|---|---|---|---|---|
| once during study or follow-up) | | | *p<0.01* | (41% in the B-75) |
| | | | | |
| Mean change in PS from baseline in last PS | 0.56<br>SE=0.09<br><br>p=0.11 | 0.45<br>SE=0.14<br>NS | 0.65<br>SE=0.13<br>p<0.05 | 0.80<br>(SE=0.11)<br><br>1.09 SE+0.16 in B-57 |
| % Patients with weight loss ≥ 10% | 7%<br><br>P=0.07 | 12% | 2%<br><br>p<0.01 | 15%<br>(8% vs.D100)<br><br>(22% vs. D75) |
| QoL LCSS | 75% Baseline | | | 68% Baseline |
| EORTC | 93% | | | 89% |
| | | | | |

**Supportive Phase 2 Studies:**

There are six supportive phase 2 studies submitted in this application. Four employed a docetaxel dose of 100 mg/m$^2$. Two, CHI-202 and TAX241, utilized lower docetaxel doses – 75 mg/m$^2$ and 60 mg/m$^2$, respectively.

(First line Non-Small Cell Lung Carcinoma)

Fifty volumes were submitted. The electronic submission

This supplement was submitted June 30, 1999. Fifty volumes were submitted. The data from the pivotal study was submitted electronically. Case Report Forms from TAX 308 for patients who died and discontinued due to adverse event were submitted under Item 12, volumes 12-1 to 12-23.

There is only one phase 3 randomized, controlled trial submitted in this application that provides the primary safety and efficacy data (TAX 308) for docetaxel in the treatment of patients with unresectable locally advanced (Stage IIIb or relapsed after surgery or radiotherapy) or metastatic non-small cell lung carcinoma with no history of prior chemotherapy for their disease. The patients enrolled in this study and had an WHO performance status ≤ 2. Patients were stratified before randomization according to disease extent. Patients were recruited so that 2/3 would be treated on the docetaxel arm and 1/3 would be in the best supportive care only arm. The primary endpoint was median survival.

The trial that provides the primary safety and efficacy data is:

**TAX 308:** (Open label; 15 European sites, 1 USA, 1 Mexico)

| | | |
|---|---|---|
| ARMS: | A = Taxotere 100 mg/m$^2$ q 21 d (+ BSC) | (N = 137) |
| | B = Best Supportive Care | (N = 70) |

*Reviewer Comment: The three investigators/centers with the highest accrual were all located in Poland:*

| | | |
|---|---|---|
| *Pluzanska* | *PL00022 (Warsaw?)* | *N=46* |
| *Roskowski* | *PL00020 (Warsaw?)* | *N=43* |
| *Krzakowski* | *PL00012 (Lodz?)* | *N=37* |

*Together, these investigators accrued 61% of the patients in this study. Sixty percent of the patients these three centers accrued had stage IIIB disease (74% of the PL00022, 61% of the PL0020, and 41% of the PL00012 patients were stage IIIB).*

*Review Issues Raised by the Sponsor's Proposed Labeling:*

*5) Survival Claims:*

- *Significantly longer Overall Survival,( Does the p=0.026 in the sponsor's table refer to median survival or 1-year Survival*
- *Higher 1-year Survival*
- *They report even higher significance when censoring for subsequent chemotherapy is performed, p=0.012.*

*2) Response and TTP:*

- *They report the response rate in the ITT and "eligible and evaluable population" – 13% and 20%, respectively. (26.3% were reportedly not evaluable)*
- *They report a significantly longer time to progression, p<0.001 (Both ITT and evaluable analyses presented; only 4% were not evaluable for this endpoint.)*

*3) Other Benefits:*

- *They report "Clinical Benefit Parameters" with significant improvement include less use of radiotherapy (p<0.01), less "disease related medications other than for pain" (p<0.01), less morphinic analgesics (p<0.001), and less non-morphinic analgesics (p<0.001).*
- *They report Quality of Life "significant trends favoring docetaxel" in emotional function (p=0.01). pain (p<0.001), and dyspnea (p<0.01).*

*Additional Review Issue: The sponsor has only submitted one controlled trial for the indication of first line treatment of locally advanced or metastatic non-small cell lung carcinoma. The sponsor reports this study has demonstrated survival benefit for docetaxel when compared with best supportive care. The supportive studies are phase 2, but the sponsor has submitted two studies in second-line treatment of non-small cell lung carcinoma that they report demonstrates survival benefit associated with this stage of disease as well.*

A table summarizing the sponsor's efficacy analyses is shown below. Pre-specified endpoints are enclosed in heavy crossbars, while those analyses that were not pre-specified are enclosed in dashed crossbars.

## TAX 308 First Line

| | TAX 100 mg | BSC | |
|---|---|---|---|
| **Median Survival** | **6 months** | **5.7 months** | |
| **95% CI** | **5.0, 8.0** | **4.4, 6.8** | |
| **Log Rank** | | | |
| | | | |
| %1-year Survival?? (*in a 1/99 statistical analysis plan*) | 25 | 16 | |
| **95% CI** | 17, 32 | 7,25 | |
| **Log Rank** | P=0.026 | | |
| Censored for further chemotx: Median Survival | 6.0 months | 4.6 months | |
| 95% CI | 4.7, 8.0 | 3.9, 6.8 | |
| Log Rank | | | |
| Censored for further chemotx: % 1 year Survival | 25% | 15% | |
| | 17, 33 | 6, 25 | |
| Log Rank Test | P=0.012 | | |
| | | | |
| **TTP**<br>**Stat Plan:** to date of last evaluation before starting antitumor therapy including radiotherapy<br><br>**Study Report:** to date of last evaluation before starting surgery, immunotherapy, chemo, but excluding XRT. | **12.6 weeks** | **8.9 weeks** | |
| 95% CI | 9.9, 16.6 | 7.7, 9.7 | |
| **Log Rank Test** | **<0.001** | | |
| RESPONSE | 13.1%<br>CI = (7.5, 18.8) | | |
| Duration of Response | 37.1 weeks | | |

| | | | |
|---|---|---|---|
| | CI = (30.9, 69.9) | | |
| **Stat Plan = "Tumor Related Symptoms":**<br>**Hemoptysis**<br>**Pulmonary**<br>**Cough**<br>**Pain not related to study medication** | | | |
| **Study Report** = Clinical Benefit:<br>Usage of concurrent medications for relief of cancer related symptoms<br>Morphine<br>Non-Morphine analgesics<br>Tumor-related medications<br>Anti-infective therapy<br>Concurrent Radiotherapy<br>Dyspnea<br>Pain<br>Hemoptysis<br>Cough | | | |
| QoL - QLQ-C30 | 88% baseline | 57% baseline | |
| | Worst Score | Longitudinal | Pattern Mixture |
| Global health status | 0.09 | 0.16 | 0.13 |
| Physical Functioning | 0.08 | 0.14 | 0.22 |
| Emotional Functioning | **0.01** | **0.01** | **0.04** |
| Pain | **<0.001** | **<0.001** | **<0.001** |
| Dyspnea | **0.03** | **<0.01** | **0.02** |
| QoL – QLQ LC13 | <30% | <30% | |

**Supportive Phase 2 Studies:**

There are twelve supportive phase 2 studies submitted in this application. The docetaxel dose specified in the protocol was 100 mg/m2 in 7/12, but during the course of one of the studies it was reduced to 75 mg/m$^2$ in a protocol amendment (June 15, 1993; TAX231). Two multicenter phase 2 studies, CHI-202 and KOR302, utilized a dose of 75 mg/m$^2$, and 3 studies, all conducted in Japan (TAX241, TAX284, and TAX290) utilized a dose of 60 mg/m$^2$. Three of the twelve studies were conducted in the United States, one of which was a multi-center trial (TAX269). Five of the twelve studies were multi-center studies – TAX 269 (USA), TAX223 (EU), TAXSI002A (EU), TAX 295 (Canada), and TAX292 (Mexico).

4. **Recommended Regulatory Action:** supplemental NDA submissions (SE1 011 meet criteria for filing. The sponsor will need to submit a proposed label that clearly reflects the efficacy data provided by the two phase 3 trials in second line treatment of non-small cell lung carcinoma (SE-011).

Please convey the following comments to the sponsor:

We have done a preliminary review of the proposed labeling provided in SE011 and have noted the following deficiencies:

- The labeling for second-line treatment of non-small cell lung carcinoma should include the efficacy and safety data from both pivotal phase 3 studies. As the label currently stands, the data from TAX 317 has not been provided. Please submit an updated label that includes this information.

- The Clinical Studies section of labeling should provide the efficacy and safety data that form the basis of including 60 $mg/m^2$ in the recommended dose for first and second line treatment of non-small cell lung carcinoma.

- We note in your cover letter dated 6/23/99 that accompanies SE011 that you suggest that "the optimal dose range and schedule for this patient population is 60 $mg/m^2$ to 75 $mg/m^2$ administered...." This, however, is not reflected in your proposed labeling under Dosage and Administration. Please revise accordingly.

In addition, the Office of Post-Marketing Drug Risk Assessment has requested a review of the current label to address medication error reports received through the AERS and USP voluntary reporting systems. These errors appear to be related to the dilution instructions and the labeling of the vial overfill volumes. We are submitting these proposed changes for your concurrence.

/S/ 8/9/99
Donna J. Griebel, MD

/S/ 8/9/99
Julie Beitz, MD

cc: /

Haften

# TELECON MINUTES

**TELECON DATE:** February 20, 1998 **TIME:** 11-12:30p.m.
**LOCATION:** Conference Room B

**IND/NDA** IND [ ]

Telecon Request Submission Date: January 22, 1998
Briefing Document Submission Date: January 22, 1998
Additional Submission Dates: January 29, 1998; February 19, 1998 (fax)

**DRUG:** Taxotere (docetaxol)

**SPONSOR/APPLICANT:** Rhone-Poulenc Rorer

**TYPE of TELECON:**

1. Special Considerations

2. **Proposed Indication:** non-small cell lung cancer

**FDA PARTICIPANTS:**

Robert DeLap, M.D. Division Director
Robert Justice, M.D., Deputy Director, (Industry meeting only)
Julie Beitz, M.D., Medical Team Leader
Donna Griebel, M.D., Medical Reviewer
Tony Koutsoukos, Ph.D., Statistician, Acting Team Leader
Ning Li, Ph.D., Statistician
Ann Staten, Project Manager

**INDUSTRY PARTICIPANTS:**

Susan Coughlin, Associate Clinical Project Leader
Frank Gamza, Associate Director, Clinical Oncology
Luz Hammershaimb, M.D., Director, Clinical Research, Oncology
Yong Kim, Associate Director Biostatistics
Ann-Margaret Martin, M.A., Associate Director, Worldwide Regulatory Affairs
Barbara Rake, Senior Regulatory Affairs Specialist

**TELECON OBJECTIVES:**

1. A "Special Considerations" meeting to discuss the Statistical Analysis Plan for studies TAX317 and TAX 320. A follow-up meeting from the December 17, 1998 meeting.

**QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:**

1. Are the statistical analysis plans for the Phase 3 studies, TAX320 and TAX317 acceptable to the FDA?

FDA Response:

a. The sponsor needs to specify the primary statistical analysis of the time to event endpoints, in particular, the primary analysis of the primary endpoint. Is it going to be the logrank test or the stratified logrank test (stratified by performance status and response to prior platinum therapy)? Based on the telecon minutes of December 17, 1997, the sponsor agreed to use the stratified logrank test.

RPR Response:

The stratified logrank test will be the primary analysis, as we stated in the meeting.

FDA Response:

b. Including various prognostic factors in the Cox model could result in non-robust estimates of the treatment effect. Thus, these type of analyses should be considered exploratory. Statistical analyses looking for potential prognostic factors, like the Cox model, should not include treatment as a covariate. One could first identify prognostic factors using the masked data or the data of the control group. Then treatment could be included in the model to explore the effect of treatment to the chosen prognostic factors. The proportional hazards assumption should also be carefully checked by appropriate means.

The sponsor should provide more details about the selection procedure for prognostic factors using adjusted analyses.

RPR Response:

The Cox modeling will be carried out in a stepwise fashion as FDA commented. In the first step, without treatment in the model, the prognostic factors would be identified following the stepwise regression method with the iterations of detecting all significant factors in the model. Then, treatment would be brought in the model to determine the effect of treatment.

FDA Response:

c. For the multiple comparisons of the TAX320 study, the sponsor is going to use the Dunnett's procedure to adjust the $\alpha$ level (two comparisons: docetaxel 100

mg/m$^2$ vs control and docetaxel 75 mg/m$^2$ vs control). The Dunnett's procedure is an ANOVA based methodology for normally distributed data. How is the sponsor going to adjust the $\alpha$ level for the time to event endpoints using a logrank test?

RPR Response:

For the time to event endpoints using a logrank test, Bonferroni adjustment would be used for the two comparisons to the control.

FDA Response:

d. Quality of Life:

The sponsor should prospectively identify a small subset of questions with the most relevant components of Quality of Life (particularly those related to tumor symptoms).

In addition to the QOL analyses proposed by the sponsor, the following should be considered: Strategies for handling missing data for the analysis of repeated measurements need to be prospectively stated. Analyses utilizing "last observation carrying forwards" could be of concern since they have a high potential for bias unless data are missing at random. This is a strong assumption and needs to be verified. Multiplicity problems arise for analyses repeated at various time points. The question is can one assume that the missing mechanism is ignorable (then all data could be used in the analysis), or non-ignorable (then not all data could be used in the analysis, i.e. one could look at the time trends of the completers and the non-completers between the two treatment arms)? In either case, one has to fit an appropriate statistical model. Formal longitudinal analyses (i.e., GEE or Laird/Ware methods, etc.) may be used for determining time trends in the quality of life data. A full assessment of dropout patterns by treatment arm is an essential first step. If the dropout rate is high, analyses of the individual QOL endpoints would be more meaningful than aggregated ones.

RPR Response:

We have identified a small subset of items (two stochastically independent factors of the LCSS) via a factor analysis performed on the baseline data only (combined treatments). We expect to confirm this with the author of the LCSS. In addition to the proposed endpoint analysis, we will apply a formal longitudinal model for determining time trends. Also, a full assessment of dropout patterns by treatment group is planned.

FDA Response:

We will look at your plan once it has been submitted. So far, FDA has not been able to rely on QOL as a basis of approval in this disease. We are interested in seeing any information on improvement in symptoms (clinical benefit).

2. RPR proposes to submit four pivotal studies to demonstrate efficacy and safety of Taxotere® as second-line treatment -- one adequate and well controlled Phase 3 study (TAX320) and three Phase 2 studies: TAX270, TAX271 (previously submitted in the NDA of July 1994) and TAX297. Does the FDA agree?

FDA Response:

- Assuming sufficiently favorable results, we anticipate that this may be adequate for filing.
- For TAX317 - We would like to see the interim analysis results included in the NDA. We also want an update of survival data analysis on all patients through June 1998, which could be submitted shortly after the NDA is submitted.

3. RPR plans to maintain the dose range provided for in the breast cancer claim and will use Asian studies as additional supportive data for the lower doses (for 60mg/m$^2$, 22 patients from Japan; for 75mg/m$^2$, 10 patients from China and 125 patients from the US; for 100 mg/m$^2$, 465 patients from U.S. and Europe).
We plan to submit English translations of reports submitted to the local health agencies which were the basis for local approval. Is this acceptable to the FDA? Will you also require translated CRFs?

FDA Response:

- This may be acceptable, pending review of the application.
- For CFR's, we will need translations for patients who died within 30 days of study or dropouts due to adverse events.

RPR New Question: Wherever possible, source documents will be translated into English. Does FDA have any specific translation requirements?

FDA Response:

- CRF's must be translated in English and a statement submitted that the translation is authentic. Also, refer to 21 CFR 314.50.

CFR 314.50(f)(3) (f) Case Report Forms, (e) Additional data. - requested data to be submitted within 30 days of request to avoid a major amendment which will extend the review clock.

CFR 314.50(g)(2) (g) Other, (2) The applicant shall submit an accurate and complete English translation of each part of the application that is not in English.

RPR Response:

- RPR will provide above documents in English together with a statement attesting to the accuracy of translations.
- Source documents in the native language will be available on request.

4. RPR plans to prepare the ISS based on second-line data only. Does the FDA agree? If the FDA wishes RPR to include first-line studies to support safety (13 studies, 815 patients), will the FDA accept TSRs rather than full reports?

FDA Response:

- We would like to see the data from the first-line lung studies summarized in the ISS.

RPR Response:

- As a reminder, RPR does plan to submit first line NSCLC safety data as part of the ISS, as agreed upon. However, this summary will not include information from study TAX308. This study is a pivotal, first line trial which does not allow for interim analysis in its current design. Accordingly, we propose to supply FDA with TAX308 results at the time of our sNDA for the first line indication.

FDA Response:

- FDA agrees

5. Does the FDA want to see the safety data on second-line NSCLC also integrated with the larger global database including the breast cancer data?

FDA Response:

- We would like to see the data separately. If you are considering the possibility of providing pooled analysis in the package insert, then you should also submit the integrated analysis.

6. During the original Taxotere® NDA review and approval process, RPR was asked to provide response information from studies conducted in Japan, where the lower dose of 60 mg/m2 was used. Copies of relevant X-rays, CT scans and reports were obtained from Japan.

Does FDA foresee a similar request for the response information surrounding patients in NSCLC supportive studies TAXCHI202 (75 mg/m$^2$ dose used for this study in China) and TAX241 (60 mg/m® dose used for this study in Japan)? Please note that these studies are supportive of efficacy and safety in the second line setting RPR does not plan to include response information from the first line studies which will be submitted as additional safety support.

FDA Response:

We do not foresee such a request, however, in the course of the review it is possible that we may request some information of this type.

The telecon was concluded at 12:00 p.m.. There were no unresolved issues or discussion points.

/S/ 2/23/98

Ann Staten /Date
Project Manager
Minutes preparer

Concurrence Chair: /S/ 2/23/98

Donna Griebel, M.D./ Date
Medical Officer

Attachments: RPR fax dated 2-19-98

nrd.15<
staten

# MEETING MINUTES

**DATE:** December 22, 1998 **TIME:** 2 p.m. **LOCATION:** Conference Room G

**IND/NDA** IND ] Meeting Request/Briefing Document Submission Date:
October 7, 1998 serial no. 711 (MR)
Additional Submission Dates:
December 15, 17, and 18, 1998.

**DRUG:** Taxotere (docetaxel)

**SPONSOR/APPLICANT:** Rhone-Poulenc Rorer

**TYPE of MEETING:**

1. Pre-sNDA
2. Proposed Indication: Second-line treatment of advanced non-small cell lung cancer (NSCLC).

**FDA PARTICIPANTS:**

Robert Temple, M.D., Office Director, Office of Drug Evaluation I
Rachel Behrman, M.D., MPH, Office Deputy Director, Office of Drug Evaluation I
Robert Justice, M.D., Deputy Director
Julie Beitz, M.D., Medical Team Leader
Donna Griebel, M.D., Medical Reviewer
Gang Chen, Ph.D., Statistician, Acting Team Leader
Ning Li, Ph.D., Statistician
Ann Staten, Project Manager
Richard Schilsky, M.D., ODAC consultant

**INDUSTRY PARTICIPANTS:**

Robert Bellet, M.D., Director, Medical Affairs, Oncology
Jocelyn Berille, M.D., Associate Director, Clinical Oncology
Jean-Pierre Bizzari, M.D., Vice President, Clinical Oncology
Philip Chaikin, Pharm.D., M.D., FCP, Vice President, Clinical Research
Susan Coughlin, Ph.D., Associate Director, Clinical Oncology
Sylvain Durrleman, M.D., Worldwide Director, Biostatistics
Frank Gamza, M.D., Associate Director, Clinical Oncology
Luz Hammershaimb, M.D., Director, Clinical Oncology
Yong Kim, Ph.D., Associate Director Biostatistics
Anne-Margaret Martin, Associate Director, Worldwide Regulatory Affairs
Barbara Rake, Sr. Associate, Worldwide Regulatory Affairs, Oncology Liason
Max Talbott, Ph.D., Vice President, Worldwide Regulatory Affairs

Barbara Conley, M.D., Senior Investigator, NCI, Consultant
Richard Gralla, M.D., Alton Ochsner, Medical Foundation, Consultant
Mark Kris, M.D., Director Thoracic Oncology, MSKCC, Consultant

**MEETING OBJECTIVES:**

To discuss the development of Taxotere for second line treatment in advanced NSCLC and Rhone-Poulenc Rorer's intent to submit a sNDA.

**QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:**

1. The pivotal study TAX320 demonstrates results favoring Docetaxel over the comparator as follows:

   - Overall survival, (censored et subsequent chemotherapy) combined D100 and D75mg/m2 vs V/I with p= 0.08, Log-Rank Test
   - One year survival D100 or D75 vs. V/I p= 0.012, Chi square test.
   - Response rate(ITT) D100vsV/I p= 0.001 and D75vs V/I, p=0.036, Fisher's Exact Test.
   - Time to progression ((ITT) D100 vs. V/I, p=0.044 and D75 vs. V/I, p=0.093, Log-Rank Test.
   - Consistent QoL trends in 15 of 15 parameters in the LCSS Scale using 3 methods of analyses including two suggested in references provided by FDA after our April 30 meeting.

   Based on the above findings, RP-R believes that our claim for efficacy in this indication is supported. Assuming that these findings are confirmed by FDA review, does FDA concur?

   FDA Response:

   We still think the application is very weak and we doubt that it would be adequate to support marketing. It could be strengthened if TAX317 is completed to provide additional data at 75mg/m$^2$. The analyses in the package do not substantially alter the opinions expressed in the pre-sNDA meeting.

   Our concerns include:

   The most persuasive argument for benefit associated with Taxotere in this setting is the uncensored higher one year survival in the Taxotere 75 mg/m$^2$ treatment group (32% vs. 19% on the control arm). The longer time to progression on that arm supports the case for efficacy. Yet, all the other endpoints, including median survival and response rate in this group and the 100 mg group do not convincingly argue for meaningful benefit associated with this therapy. Even though the median TTP in the Taxotere 100 mg/m$^2$ arm was found to be statistically significantly longer, the actual

difference between this arm and the control is not meaningful – 8.4 weeks vs. 7.9 weeks. The QoL analysis does appear to demonstrate that quality of life was not negatively impacted by treatment with Taxotere as compared to vinorelbine or ifosfamide.

While the superior percentage survival at one year observed on the Taxotere 75 mg/m$^2$ arm of TAX 320 would seem to demonstrate clinically meaningful benefit, it is unclear how this should be viewed or explained in the context of no meaningful difference in TTP, a response rate of <10%, and an overall median survival that is not significantly different.

We have concerns that the analyses presented in this package were not included in the original statistical analysis plan. The efficacy endpoint of % survival at one year does not appear to have been a pre-defined endpoint. Censoring on the basis of subsequent chemotherapy and the pooling of the two Taxotere treatment groups also do not appear to have been predefined analyses. Pooling of dose levels is not appropriate and the censoring at subsequent chemotherapy is questionable. We do not think either is useful.

The interim analysis of TAX 317 is concerning in that the endpoint outcomes for the Taxotere 100 mg/m$^2$ arm are very similar to those of the TAX 320 100 mg/m$^2$ arm, and are thus far not showing superiority to best supportive care. We do recognize that this may reflect the smaller numbers on the study, but we believe these early results of TAX 317 should be considered in weighing the issues that are involved in determining whether the "benefit" described in TAX 320 is truly clinically meaningful. (TAX 317 has shown a 29% 1 year survival on the best supportive care arm, according to the April 1998 meeting package.)

2. The published literature indicates that no other agent has been well characterized to show consistent activity in this second-line setting including the agents approved for first line treatment and that physicians do treat patients in whom not only front-line but also second or third line chemotherapy have failed. Therefore there is a need for agents with well characterized and consistent effectiveness to guide therapy choices. Does FDA share this view?

   FDA Response:

   The Agency concurs that there is a need for agents that have persuasively demonstrated efficacy and safety in the setting of the second line treatment of non-small cell lung carcinoma.

3. Data in the studies to be included in the submission support a favorable benefit risk assessment. The benefits enumerated in question no.1 above are the benefits derived from Taxotere treatment and the risks associated are typical of other cytotoxics, are

manageable, and are consistent with the current labeling for the breast indication. Does FDA have any comments on this assessment?

FDA Response:

The risks summarized in the safety data of TAX 320 are those that would be expected to be associated with Taxotere. Those risks are not necessarily those that are typical of other cytotoxic agents. While the safety profile demonstrated in non-small cell lung carcinoma patients treated on TAX 320 is comparable to that associated with treatment of breast carcinoma, the risk/benefit ratio that has been observed differs substantially between these two diseases.

**ACTION ITEMS:**

1. Rhone-Poulenc Rorer will request Fast Track designation first (refer to the guidelines on Fast Track) in order to be considered for rolling submission.

2. If Fast Track designation is granted, the clock will start when TAX317 is submitted. No new ISE will be required for TAX317.

3. Rhone-Poulenc Rorer will submit the safety update report four months after submission of the TAX317 final study report.

The meeting was concluded at 3:30 p.m.. There were no unresolved issues or discussion points.

/S/ 1/7/99
Ann Staten/ Date
Project Manager
Minutes preparer

Concurrence Chair:

/S/ 1/7/99
Donna Griebel, M.D./ Date
Medical Officer

# TELECON MINUTES

**TELECON DATE:** December 17, 1997 **TIME:** 12:00 pm
**LOCATION:** Conference Room B

**IND/NDA** **IND** [ ]

Telecon Request Submission Date: November 3, 1997
Briefing Document Submission Date: November 3, 1997 (Serial no. 616)

**DRUG:** Taxotere (docetaxel)

**SPONSOR/APPLICANT:** Rhone-Poulenc Rorer

**TYPE of TELECON:**

1. Other

2. **Proposed Indication:** Non-Small Cell Lung Cancer

**FDA PARTICIPANTS:**

Robert DeLap, M.D., Division Director
Robert Justice, M.D., Deputy Director (participated in pre-meeting only)
Julie Beitz, M.D., Medical Team Leader
Donna Griebel, M.D., Medical Officer
Tony Koutsoukos, Ph.D., Statistician, Acting Team Leader
Ann Staten, Project Manager

**INDUSTRY PARTICIPANTS:**

Jocelyne Berille, Associate Clinical Project Leader
Susan Coughlin, Associate Clinical Project Leader
Sylvain Durrleman, M.D., Worldwide Director, Biostatistics
Luz Hammershaimb, M.D., Director, Clinical Research, Oncology
Yong Kim, Associate Director Biostatistics
Anne-Margaret Martin, M.A., Associate Director, Worldwide Regulatory Affairs
Robert Olivares, Associate Director Biostatistics

**BACKGROUND:** June 6, 1995 EOP2 meeting

**TELECON OBJECTIVES:**

1. To provide input and guidance relative to the further development and registration strategy of Taxotere in the NSCLC setting. (Seven questions submitted)

**QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:**

First Line Indication:
TAX308 -Multicenter, Randomized Study of Docetaxel 100mg/m2 versus BSC

1. Is BSC still acceptable as a control arm in light of the results of the meta-analysis published in the BMJ showing a significant survival gain of platinum-based regimens over BSC and the wider acceptance of combination chemotherapy as standard practice?

**FDA Response:**

- Yes, this is acceptable.

2. If the ODAC raises the trial design as an issue, will the FDA support RPR since it approved the design in 1995?

**FDA Response:**

- Yes. We will support trial design but the decision to approve for first line indication will be based on risk-benefit ratio in setting.

3. Will FDA request an interim analysis of TAX308 to support the second line indication?

**FDA Response:**

- No

Second Line Indication:
TAX317 -Multicenter, Randomized Study of Docetaxel 100mg/m2 Versus BSC

4. RPR proposes to submit an sNDA by 2Q98 based on the results of:
   1) a planned interim analysis of TAX317 in 100 patients,
   2) Phase II multicenter and single-center studies and
   3) TAX320 as supportive data.

   A conditional approval will be sought and a final approval will be contingent on submission of final results of TAX317 and TAX320.

   In light of new sNDA guidelines, is this strategy acceptable to the FDA?

**FDA Response:**

- No

  Both studies TAX317 and TAX 320, should be submitted when complete.

  We would want at least one successful, complete controlled study and an explanation for any negative results.

  TAX320, if successful, could serve as the complete, controlled study.

- This does not appear to qualify for accelerated approval. For accelerated approval, you need to establish that Taxotere either provides better response rate or similar response rate but less toxicity compared to existing active treatment.

- If TAX320 is successful in demonstrating survival benefit, it could be considered for full approval.

- For TAX317 and TAX320 - The stratified Logrank test should be used for primary analysis. The Cox test could be used as a secondary analysis.

- For TAX320, adjustments for multiple comparisons should be specified.

- If there is no significant survival benefit, there is a possibility of accelerated approval based on TAX320 if above criteria in the second bullet were met.

- For filing based on TAX320, we would need to discuss data available on TAX317 at the pre-sNDA meeting.

- Sponsor plans to submit the statistical analysis plan in early January.

TAX320 -Multicenter Randomized Study of Docetaxel 100mg/m2 versus 75mg/m2 versus investigators' choice of Vinorelbine or Ifosfamide

5. For TAX320, enrollment is closed If this is submitted as a supportive trial, do we need to amend the protocol to allow for an interim analysis?

**FDA Response:**

- see above

Proposed Combination Trial in First Line:
TAX326 -A multicenter, randomized comparison Docetaxel 75mg/m2 /Cisplatin 100mg/m2 and Docetaxel 75mg/m2/Carboplatin AUC=6 versus Vinorelbine 25mg/m2/Cisplatin 100mg/m2.

6. Is the Vinorelbine/Cisplatin combination an acceptable control arm? (You indicated in 1995 that it was.)

**FDA Response:**

- Yes, it is still acceptable. (see above re: statistical issues in question #4)
- If you are considering an interim analysis, please provide the plan.

7. Are response rates and time to progression acceptable endpoints for an interim analysis which might be the basis for an sNDA?

**FDA Response:**

- No. For first line indication, survival is the preferred primary endpoint.
- Other endpoints can be discussed further at a future conference.

**ACTION ITEMS:**

1. When you submit your statistical plan in January, request a "special considerations" teleconference meeting.

The telecon was concluded at 12:40 pm. There were no unresolved issues or discussion points.

/S/ 12/17/97

Ann Staten,
Project Manager
Minutes preparer

Concurrence Chair: /S/

Donna Griebel, M.D.
Medical Officer

## MINUTES OF MEETING

**DATE:** June 6, 1995

**PARTICIPANTS:** Rhone-Poulenc Rorer (RPR)

| | |
|---|---|
| R. Bellet, M.D. | J-P. Bizzari, M.D. |
| S. Durrleman, M.D. | M. Huber, M.D. |
| A. M. Martin | J. T. Molt, Ph.D. |
| A. Riva, M.D. | P. Santabarbara, M.D. |
| H. Burris, M.D.(con.) | M. Kris, M.D. (con.) |

NCI S. Arbuck, M.D.

FDA

| | |
|---|---|
| R. Temple, M.D., HFD-100 | P. Bunn, M.D. (by phone) |
| R. Justice, M.D., HFD-150 | J. Beitz, M.D., HFD-150 |
| L. Kaus, Ph.D., HFD-150/426 | S-J. Wang, Ph.D., HFD-713/150 |
| S. Wilson, Ph.D., HFD-713/150 | D. Pease, HFD-150 |

**SUBJECT:** EOP 2 Meeting Taxotere for First and Second Line NSCLC
IND

**BACKGROUND:** As suggested by FDA following the 12-94 ODAC meeting, RPR had requested an End-of-Phase 2 meeting for the first line and second line non-small cell lung cancer indication
Their specific questions were faxed on 6-1-95 and are attached. Outline of the proposed protocols for the Phase 3 studies (first line - TAX 308; second line - TAX317, TAX320, Taxotere vs. ifosfamide, and Taxotere high vs. low dose) were also reviewed for this meeting.

**FIRST LINE**

**QUESTION A.** Yes, this trial (starting now) is of acceptable design.

**QUESTION B.1.** Vinorelbine/cisplatin would be an acceptable comparator. However, equivalence to vinorelbine/cisplatin would take a large number of patients (> 500 per arm) to show and would not be much of a claim. Superiority would be much better and would involve fewer patients.

**QUESTION B.2.** Yes, single agent vinorelbine could be a comparator, but, again, docetaxel should beat it. A better study would be vinorelbine vs. docetaxel/vinorelbine or vinorelbine/cisplatin vs. vinorelbine/cisplatin/docetaxel.

**QUESTION B.3.** No, if the Phase 3 trials are already in progress, we would not recommend changing the comparator drugs because of positive results in the current randomized trials of paclitaxel/carboplatin.

**QUESTION B.4.** Yes, survival is acceptable as primary endpoint, with response rate, QOL, etc. secondary.

**QUESTION B.5.** Although this will be difficult to show, equivalence to vinorelbine would be acceptable, but docetaxel should be better.

**QUESTION B.6.** Yes, cooperative group studies are acceptable.

**MISCELLANEOUS:** Dr. Bunn noted his preference for 3 studies - docetaxel vs. placebo, docetaxel vs. vinorelbine, and docetaxel/ vinorelbine/cisplatin vs. vinorelbine/cisplatin.

**SECOND LINE**

**QUESTION A.** Yes, Canadian sites may be added.

**QUESTION B.1.** In study TAX320, allowing one arm to be physician choice of treatments (vinorelbine or ifosfamide, pooled) is not preferable to FDA but acceptable.

**QUESTION B.2.** Statistical design for study TAX320 is acceptable. RPR will compare separately docetaxel 100 vs. pooled treatments; if superiority is shown, they will then compare docetaxel 75 vs. pooled treatments. Study will be powered to detect a 50% increase in time to progression (120/group).

**QUESTION B.3.** For TAX320 a 50% increase in median survival is an acceptable endpoint.

**QUESTION III.** The Lung Cancer Symptom Scale is acceptable.

**MISCELLANEOUS:** RPR should continue to look at PK for predictors of problems, i.e., should be monitoring blood levels. Also, sponsor should be looking at lower doses.

cc: ORIG. IND
Div File
Attendees
DWPease/1-12-96/ .lun/R/D rev. by JBeitz/f/t 1-25-96

Questions for Non-Small Cell Lung Cancer End of Phase II meeting 4:00

I. First Line NSCLC

A. TAX 308

Is the current international phase III trial, TAX 308, which randomizes patients to either docetaxel 100 mg/m² versus best supportive care acceptable for registration in this indication?

B. Potential Studies

1. Which combination would be considered an acceptable comparator in a first line NSCLC Phase III study ? e.g.. vinorelbine/cisplatin, etoposide/cisplatin, or would the FDA prefer another combination of agents?

2. Would single agent vinorelbine be considered a suitable comparator since it is approved as a single agent in first line NSCLC ?

3. Would a positive outcome in current randomized trials of paclitaxel/carboplatin impact the evaluation of docetaxel studies?

4. Is survival acceptable as the primary endpoint of these studies with other issues such as QOL, response rate, and time to progression as secondary endpoints?

5. Would equivalence with an approved agent such as vinorelbine be acceptable for approval in this indication?

6. Would co-operative group studies be acceptable as opposed to industry studies for filing purposes ?

II. Second line NSCLC

A. TAX 317

Is the addition of Canadian sites to the previously approved study TAX 317, docetaxel vs. Best Supportive Care in second line NSCLC patients acceptable?

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-449/011

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

AUG 10 1999

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

A. STATUS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-449/S-011

Rhone-Poulenc Rorer Phamaceuticals Inc.
500 Arcola Rd., H14
Collegeville, PA 19426

JUN 25 1999

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

Dear Dr. Talbott:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Taxotere (docetaxel)

NDA Number: 20-449

Supplement Number: S-011

Date of Supplement: June 23, 1999

Date of Receipt: June 23, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on August 22,1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

(if via U.S. Postal Service)

FDA/CDER
Division of Oncology Drug
Products, HFD-150
5600 Fishers Lane
Rockville, Maryland 20857

(if via courier)

FDA/CDER
Division of Oncology Drug Products,
HFD-150
1451 Rockville Pike
Rockville, Maryland 20852

Sincerely,

/S/ 6/25/99

for Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products, HFD-150
Office of Drug Evaluation I
Center for Drug Evaluation and Research

## Item 16: Debarment Certification

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

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

# CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

*TO BE COMPLETED BY APPLICANT*

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

*Please mark the applicable checkbox.*

[X] (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f). ( Modified per Dec. 31, 1998 revised rule, see attached)

| Clinical Investigators | | |
|---|---|---|
| | See Attached List for | |
| | RP56976 V 317 | |
| | | |

[ ] (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

[ ] (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

| Philippe Maitre | V.P. Corporate Controller |
|---|---|
| Rhone-Poulenc Rorer | |
| SIGNATURE | DATE 06-12-99 |

**Paperwork Reduction Act Statement**

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

Created by Electronic Document Services/USDHHS: (301) 443-2454 EF

Rhône-Poulenc Rorer Pharmaceuticals Inc. (RPR) has determined that all patients reported on in this dossier completed study before February 2, 1999. According to the final rule on Financial Disclosure by Clinical Investigators, 21 CFR Part 54 published December 31, 1998 in the Federal Register, we certify that no investigator who treated patients on any study presented in this dossier met any of the following criteria:

- Received any compensation such as cash, stock, royalty interest, etc., which was dependent on a favorable study outcome. RPR has never issued such contracts regarding Taxotere.

- Has ownership in RPR whose value cannot be readily determined through reference to public prices. Rhône-Poulenc Rorer is a wholly owned subsidiary of Rhône-Poulenc (RP), which is a publicly traded company. Ownership of stock in RP can therefore be readily determined through reference to public prices.

- Has a proprietary interest in Taxotere such as patent, trademark, copyright or licensing agreement. RPR has cross-checked the list of potential patent owners regarding Taxotere against the list of participating clinical investigators on the attached list and found that no clinical investigators have any patent interests in Taxotere. All copyrights, trademarks and licensing agreements for Taxotere are held within RPR.