

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-262/S-024

CORRESPONDENCE

Bristol-Myers Squibb
Pharmaceutical Research Institute
Richard L. Gelb Center for Pharmaceutical Research and Development
5 Research Parkway P.O. Box 5100 Wallingford, CT 06492-7660

ORIGINAL

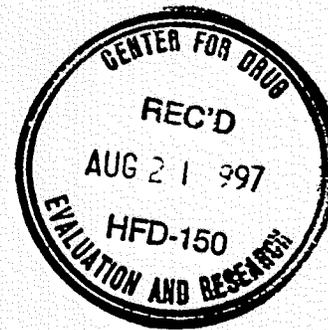
NDA SUPPL AMEND

(SNC TO S-024)

AMENDMENT TO S-024 (NSCLC):
NDA #20-262 TAXOL® (paclitaxel) INJECTION

August 19, 1997

Robert DeLap, M.D., Ph.D., Director
Division of Oncology Drug Products-HFD-150
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852-1448



Dear Dr. DeLap:

In reference to our supplemental new drug application for TAXOL® (paclitaxel) for the treatment of advanced NSCLC (S-024), we are herewith providing the relevant patent certification.

If you have any questions or concerns with regard to this submission, please contact the undersigned at 203-284-7593 or Ms. Cheryl Anderson, Director, at 203-284-6083.

Sincerely,

Susan H. Behling, Associate Director
Worldwide Regulatory Affairs

/ks
Enclosure

**Bristol-Myers Squibb
Pharmaceutical Research Institute**

Richard L. Gelb Center for Pharmaceutical Research and Development

5 Research Parkway P.O. Box 5100 Wallingford, CT 06492-7660

TAXOL NDA #20-262- S-024

MEETING REQUEST

Robert DeLap, M.D., Ph.D., Director
Division of Oncology Drug Products, HFD-150
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852 -1448

May 5, 1998



Dear Dr. DeLap:

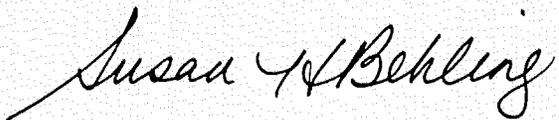
In reference to our pending SNDA for TAXOL in advanced NSCLC, and in follow-up to the March 20, 1998 ODAC discussions, Bristol-Myers Squibb Company would like an opportunity to meet with you and Oncology Division review staff to discuss revisions to our proposed labeling. In particular, we wish to add to our labeling proposal the results of the second 3-hour infusion study of TAXOL followed by cisplatin in NSCLC (Study CA139-208), as these data were not available at the time of our initial submission. We believe that the results of this study should be described in the package insert along with the results of the EORTC trial (CA139-103) and study CA139-165, and that the recommended dose and schedule should reflect the regimens used in these studies. Proposed labeling statements, along with a list of specific questions for discussion, are provided herewith.

We believe that the findings in the TAXOL-containing arms in the EORTC study and in study CA139-208 are consistent with those observed in the ECOG trial (CA139-165). Furthermore, the recently completed (March, 1998) final survival analysis of study CA139-224 (which compared single-agent TAXOL given over 3 hours versus best supportive care) shows a significant advantage for TAXOL in this disease setting. These results further support the evidence of the efficacy of the 3-hour infusion of TAXOL followed by cisplatin in NSCLC and we would like to discuss the Division's willingness to consider these survival data in conjunction with the review of this SNDA. A brief summary of these results is provided herein for your consideration.



Revised proposals for the 'INDICATIONS' and 'DOSAGE AND ADMINISTRATION' sections of the package insert are also provided herewith. I will be in contact with Ms. Spillman to establish a mutually agreeable meeting date. If you have any questions or concerns please do not hesitate to call me at 203-284-7593.

Sincerely,



Susan H. Behling
Director, Oncology U.S. Liaison
Worldwide Regulatory Affairs

Desk Copy: Dianne Spillman, CSO
Isagami Chico, M.D., Medical Officer
Robert DeLap, M.D., Director
Grant Williams, M.D., Group Leader

Bristol-Myers Squibb
Pharmaceutical Research Institute

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Richard L. Gelb Center for Pharmaceutical Research and Development

5 Research Parkway P.O. Box 5100 Wallingford, CT 06492-7660

TAXOL® (paclitaxel) - NDA 20-262
sNDA 024 - NSCLC

REQUEST FOR TELECONFERENCE

March 13, 1998

Robert DeLap, M.D., Ph.D., Director
Division of Oncologic Drug Products, HFD 150
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852-1448



Dear Dr. DeLap:

Our statisticians would like to discuss with the FDA statistical reviewers the GEE-based analyses on the FACT-L QOL scores for the CA139-165 trial prior to the scheduled ODAC next week. While we examined the change in lung cancer score (LCS) using the Wei-Lachin nonparametric stochastic ordering test, the agency statisticians have analyzed the data using the GEE linear model approach.

For the LCS analyses, however, the agency statisticians conclude that the drop-out bias is ignorable (page 11 of the statistical review). Thus, we are surprised to see that the treatment comparisons yield a $p=0.242$ using the parametric model-based approach while we obtain $p=0.027$ based on the nonparametric tests. Additional analyses show that the GEE-based slope estimates and the comparative p -values may be very sensitive to the model specification.

We would like to have a telephone conversation with Drs. Smith and Koutsoukos as early as possible and discuss some of these findings in order to elucidate the source of such different conclusions.

As usual, I may be contacted at (203) 284-6083.

Sincerely

Handwritten signature of Cheryl L. Anderson.

Cheryl L. Anderson
Director, U.S. Liaison

Desk copies: D. Spillman (3)

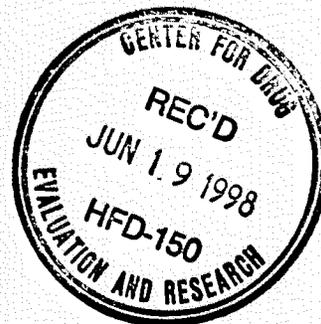


Bristol-Myers Squibb
Pharmaceutical Research Institute
Richard L. Gelb Center for Pharmaceutical Research and Development
5 Research Parkway P.O. Box 5100 Wallingford, CT 06492-7660

TAXOL NDA #20-262 S-024 (NSCLC)

June 18, 1998

Robert L. Justice, M.D., Acting Director
Division of Oncology Drug Products, HFD-150
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852-1448



Dear Dr. Justice:

In response to the Division's labeling proposal for the use of TAXOL in combination with cisplatin in patients with non-small cell lung cancer (NSCLC) which we received on May 27, 1998, enclosed please find a BMS counterproposal. A WordPerfect 6.1 version of the proposal with the changes incorporated is also included as a hardcopy and on diskette.

While the majority of the changes recommended by the Division have been accepted and incorporated into this proposal (in particular, we agree to accept the Division's recommendation for the 'DOSAGE AND ADMINISTRATION' section), some changes to the following sections are proposed:

CLINICAL STUDIES:

We have included p-values in the efficacy tables where appropriate but we do not agree that it is appropriate to also include asterisks denoting the significant differences. In addition, given the bifactorial design of the Phase 3 second-line ovary study, inclusion of p-values in the existing table would be inappropriate; however, the p-values for the appropriate comparisons in study CA139-015 are described in the text.

In the description of the results of the ECOG study, we believe that it appropriate to include mention of the significant outcome in the pooled analysis of the survival results. These results were very convincing to the ODAC and seem most relevant for inclusion in the package insert.

Editorial changes to the statement regarding the quality of life results in the ECOG study are proposed.

We acknowledge that the Division has requested a statement in the 'Clinical Studies' section regarding the adverse event comparisons in the ECOG study. However, to be consistent with the



remainder of our insert, such statements have been incorporated into the 'ADVERSE REACTIONS' section of the insert, along with the AE table. References to the 'ADVERSE REACTIONS' section have been incorporated throughout the 'Clinical Studies' section.

INDICATIONS:

We request that the wording for the indication in NSCLC patients include the phrase as this correctly represents the population of patients evaluated in the ECOG study.

ADVERSE REACTIONS

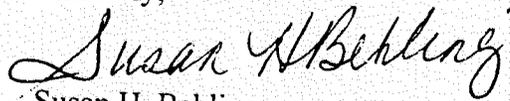
Given that safety data of TAXOL administered in combination with cisplatin is now available from 4 clinical studies which have been reviewed by the Division (GOG 111, ECOG, EORTC and study CA139-208), we propose the inclusion of adverse event incidences from a new pooled analysis to the table previously entitled "Summary of Adverse Events in 812 Patients with Solid Tumors Receiving Single-Agent TAXOL". The data used to generate this proposed change have been previously submitted and are summarized in the attached table. (Please note that transfusion information for GOG-111, while not specifically described in the report of that study, were included in the database and can be found in data listing number 39 of S-026.)

Although we agree that the 'DOSAGE AND ADMINISTRATION' recommendation for the treatment of patients with NSCLC will not include the 3 hour infusion of TAXOL at this time, we believe that the safety information from the 3 hour infusion studies in NSCLC should be described in the package insert in the public's best interest as it is often used in this manner. This is not inconsistent with labeling practices in disease settings outside of the oncology setting (e.g. BusPar®, Serzone®). Therefore, this proposal incorporates the adverse events from both the EORTC NSCLC study and study CA139-208 in the table, along with relevant changes to the text.

The left column of the side-by-side version of this labeling proposal represents the final package insert for S-024, consistent with the April 9, 1998 approval letter. Certain editorial changes (update to the OSHA handling practice reference and reference statements to the 'ADVERSE REACTIONS' section of the labeling within the 'Clinical Studies' section for consistency) have been incorporated.

Please call me at 203-677-7593 if you have any questions or concerns with this proposal.

Sincerely,



Susan H. Behling,
Director, U.S. Liaison
Worldwide Regulatory Affairs

Desk Copy: Dianne Spillman, CSO (with diskette)

Attachment

Bristol-Myers Squibb
Pharmaceutical Research Institute

Richard L. Gelb Center for Pharmaceutical Research and Development

5 Research Parkway P.O. Box 5100 Wallingford, CT 06492-7660

DUPLICATE

Amendment to:

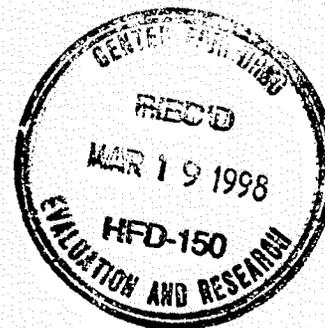
sNDA #20-262/S-024 (Non-Small Cell Lung Cancer)

TAXOL® (paclitaxel) INJECTION

March 18, 1998

SUPPL NEW CORRESP

SEI-024 (XR)



Robert DeLap, M.D., Ph.D., Director
Division of Oncologic Drug Products, HFD 150
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852-1448

Dear Dr. DeLap:

In reference to our supplemental new drug application for TAXOL® (paclitaxel) for the treatment of advanced non-small cell lung cancer (S-024), we are herewith providing a revised patent certification.

If you have any questions, please contact the undersigned at (203) 284-7593.

Sincerely,

A handwritten signature in cursive script that reads "Susan H. Behling".

Susan H. Behling
Associate Director, U.S. Liaison
Worldwide Regulatory Affairs

/pk
Enclosure