CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-262/S-026, 027, 028

ADMINISTRATIVE DOCUMENTS

MEMO TO THE FILE

sNDA #: 20-262/S-026 **DATE:** March 31, 1998

PRODUCT NAME: Taxol (paclitaxel) Injection **SPONSOR:** Bristol-Myers Squibb (BMS)

SUBJECT: Package Insert

On March 26, 1998 a second labeling meeting was held to discuss the latest package insert, submitted on February 19, 1998, for Taxol use in first-line ovarian cancer. Most of the changes proposed by the sponsor have been reviewed by the medical officer and are addressed in the reviews dated March 11, and 25, 1998 (labeling and clinical review, respectively).

Prior to the March 26, 1998 meeting, I reviewed the February 19, 1998 labeling and compared it to the final printed labeling (FPL) submitted on August 19, 1997 for the Kaposi's sarcoma efficacy supplement (S-022). The review revealed some editorial changes as well as changes not included in the original proposed labeling of October 7, 1997. Both the editorial changes and the changes not included previously are listed below for the sake of completeness.

EDITORIAL CHANGES INCLUDED IN ORIGINAL PROPOSAL (October 7, 1997 labeling)

1. In the CLINICAL STUDIES section, the sub-section and table headings for the previously approved ovarian indication is now clarified as "Second-Line" (see pp. 5-7 of the February 19, 1998 labeling).

2. In the ADVERSE REACTIONS section:

   a. The heading and the legend for the first table (page 16) have been changed as follows:

      i. There is an asterisk
      was added at the bottom of the table.

      ii. The superscripts 1 and 2 which followed the table entries

   b. The phrase has been added throughout the Hematologic and Hypersensitivity Reactions (HSRs) subsections for clarification.

CHANGES NOT INCLUDED IN ORIGINAL PROPOSAL (October 7, 1997 labeling)

The changes detailed below were not included in the October 7, 1997 labeling. However, they were submitted on November 19, and November 18, 1997 as "LABELING SUPPLEMENTS - CHANGES BEING EFFECTED" S-027 and S-028, respectively. The changes submitted in S-027 are highlighted in yellow in the attached package insert. Additionally, these changes are detailed here and were reviewed at the March 26, 1998 meeting.

In the ADVERSE REACTIONS section

1. The Respiratory subsection now includes the statement
   This statement was previously the last paragraph in the Other Clinical Events subsection.

2. The Other Clinical Events subsection contained the following changes:

a. The second paragraph was modified and the phrase in bold was added:

b. A third paragraph was added as follows:

The changes submitted in S-028 proposed changes to the DESCRIPTION, DOSAGE AND ADMINISTRATION: Stability, and HOW SUPPLIED: Storage sections. These changes are highlighted in green in the attached package insert and are currently under review by the chemistry reviewer.

The attached package insert includes the labeling changes proposed by the team members who were in attendance at the March 26, 1998 meeting. These changes have been sent to the Division Director and will be sent to the Office Director for additional comments. The team members present at the March 26, 1998 meeting agree that the attached labeling is acceptable with their concurrence below.

/S/ 3/31/98
Dianne Spillman /date
Project Manager

/S/ 3/31/98
Susan Honig, M.D. /date
Medical Reviewer

/S/ 4/3/98
Margaret Brower, Ph.D. /date
Pharmacology/Toxicology Reviewer

/S/ 4/1/98
Grant Williams, M.D. /date
Medical Team Leader

cc: NDA 20-262/S-026
HFD-150/Division File
/D.Spillman
/Action Package

a:\20262tax\se1-026\pi\980331mtf

PATENT INFORMATION CERTIFICATION

The undersigned declares that U.S. Patent No. 5,641,803 covers the use of TAXOL® (paclitaxel) for the treatment of cancer.

This product is the subject of this application for which approval is being sought:

Initial treatment of ovarian cancer in combination with a platinum compound.

Dated: September 23, 1997

Frank P. Hoffman
Associate Patent Counsel
Bristol-Myers Squibb Co.

PATENT INFORMATION CERTIFICATION

The undersigned declares that U.S. Patent No. 5,670,537 covers the use of TAXOL® (paclitaxel) for the treatment of cancer.

This product is the subject of this application for which approval is being sought:

Initial treatment of ovarian carcinoma in combination with a platinum compound.

Dated: September 30, 1997

Frank P. Hoffman
Associate Patent Counsel
Bristol-Myers Squibb Company

PATENT INFORMATION CERTIFICATION

The undersigned declares that U.S. Patent No. 4,657,927 covers the formulation and uses of PARAPLATIN® (carboplatin) for the treatment of cancer.

This product is the subject of this application for which approval is being sought:

Initial treatment of ovarian cancer in combination with TAXOL® (paclitaxel).

Dated: September 23, 1997

Frank P. Hoffman
Associate Patent Counsel
Bristol-Myers Squibb Co.

PATENT INFORMATION CERTIFICATION

The undersigned declares that U.S. Patent No. 4,140,707 covers the compound "carboplatin" PARAPLATIN® for the treatment of cancer.

This product is the subject of this application for which approval is being sought:

Initial treatment of ovarian cancer in combination with TAXOL® (paclitaxel).

Dated: September 23, 1997

Frank P. Hoffman
Associate Patent Counsel
Bristol-Myers Squibb Co.

PATENT INFORMATION CERTIFICATION

The undersigned declares that U.S. Patent No. 5,562,925 covers the use of PLATINOL® (cisplatin) for the treatment of cancer.

This product is the subject of this application for which approval is being sought:

Initial treatment of ovarian cancer in combination with TAXOL® (paclitaxel).

Dated: September 23, 1997

Frank P. Hoffman
Associate Patent Counsel
Bristol-Myers Squibb Co.

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 20-262 Supplement # 026 Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-150 Trade and generic names/dosage form: Taxol (paclitaxel) Inj Action: AP AE NA

Applicant Bristol-Myers Squibb Therapeutic Class CYTOTOXIC

Indication(s) previously approved ① SECOND-LINE TREATMENT OF ADVANCED CARCINOMA OF THE OVARY ② BREAST CANCER AFTER FAILURE OF COMBINATION CHEMOTHERAPY FOR METASTATIC DISEASE OR RELAPSE WITHIN 6 MONTHS OF ADJUVANT CHEMOTHERAPY ③ SECOND-LINE AIDS-RELATED KAPOSI'S SARCOMA

Pediatric information in labeling of approved indication(s) is adequate ✓ inadequate ___

Proposed indication in this application FIRST-LINE THERAPY IN COMBINATION WITH CISPLATIN IN ADVANCED OVARIAN CARCINOMA

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ✓No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

___Neonates (Birth-1month) ___Infants (1month-2yrs) ___Children (2-12yrs) ___Adolecents(12-16yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.

- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes ___ No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from S. Honig, M.D. (medical reviewer) (e.g., medical review, medical officer, team leader)

Signature of Preparer and Title /S/ Project Manager April 2, 1998 Date

cc: Orig NDA/BLA # 20-262/S-026
HFD-150 /Div File / D. Spellman
NDA/BLA Action Package
HFD-006/ KRoberts

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

(revised 10/20/97)

CERTIFICATION: DEBARRED PERSONS

This certifies that Bristol-Myers Squibb Company has not used in any capacity any persons identified by the United States Food and Drug Administration on the August 12, 1997 Debarment List, as well as any persons identified as being debarred in the Federal Register through August 19, 1997.

Further, we certify that Bristol-Myers Squibb Company will not use the services in any capacity of anyone debarred by the United States Food and Drug Administration.

Date: 9/23/97

Cheryl L. Anderson
Director, Worldwide Regulatory Affairs
Bristol-Myers Squibb Company
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06447-7660
(203) 284-6083

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Spillman

Food and Drug Administration
Rockville MD 20857

Date OCT 16 1997

NDA No. 20-262

d

Bristol-Myers Squibb Co.
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7600
Attention: Cheryl L. Anderson
Director

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug:	Taxol (paclitaxel) Injection
NDA Number:	20-262
Supplement Number:	S - 026
Date of Supplement:	October 7, 1997
Date of Receipt:	October 9, 1997

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research, HFD-150
Attention: Document Control Room - 17B-20
5600 Fishers Lane
Rockville, MD 20857

Chief, Project Management Staff
Division of Oncology and Pulmonary
Drug Products

TELECONFERENCE MINUTES

MEETING DATE: April 2, 1998 **TIME:** 4:30 p.m. **LOCATION:** WOC2/r 2064

NDA: 20-262/S-026 Teleconference Request Date: 4-1-98; via FAX & NC

DRUG: Taxol® (paclitaxel) Injection

SPONSOR/APPLICANT: Bristol-Myers Squibb Company (BMS)

TYPE of MEETING:

1. **Labeling**

2. **Proposed Indication:** First-line advanced ovarian carcinoma

FDA PARTICIPANTS:

Robert DeLap, M.D.., Ph.D.	--	Director, Division of Oncology Drug Products, HFD-150
Grant Williams, M.D.	--	Medical Team Leader, HFD-150/
Susan Honig, M.D.	--	Medical Reviewer, HFD-150
Dianne Spillman	--	Project Manager, HFD-150

INDUSTRY PARTICIPANTS:

Renzo Canetta, M.D.	--	Vice President, Oncology Clinical Research
Benjamain Winograd, M.D.	--	Executive Director, Oncology Clinical Research
David Tuck, M.D.	--	Associate Director, Oncology Clinical Research
Mohan Beltangady, Ph.D.	--	Director, Biostatistics & Data Management
Anthony Santopolo	--	Vice President, Worldwide Regulatory Affairs
Cheryl Anderson	--	Director, U.S. Regulatory Liaison. WWRA

BACKGROUND:

1. March 18, 1998 FAX. Medical Labeling Review.
2. March 31. 1998 FAX. HFD-150 proposed labeling for S-026 marked-up copy.
3. March 31. 1998 FAX. HFD-150 proposed labeling for S-026 clean copy.

MEETING OBJECTIVE:

To discuss issues related to the review of supplement 026..

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

NOTE: There were no questions provided for discussion in the April 1, 1998 meeting request; however. the clinical team did not feel that the submission of questions was necessary since the issues for discussion were clear.

1. **<u>'Optimal Regimen is not yet clear' Statement</u>**

BMS: (Excerpt from BMS' April 1, 1998 teleconference request).
"The original labeling proposal for sNDA 026 deleted the following statement:

Dr. Honig's March 18 faxed labeling comments stated that the subject statement should essentially remain in the product labeling because

Further comments...from your Division...have reinforced this FDA view. Although it is agreed that no further second-line ovary data has been submitted since the Agency originally mandated the inclusion of this statement (in conjunction with the approval of the three-hour infusion recommendation approval for second-line ovary), we maintain that inclusion of the statement is potentially confusing to prescribing physicians. As has been FDA's practice in recent years, the TAXOL labeling currently includes, and will continue to include, a full description of the clinical data that are considered in FDA approval decisions....

Our primary interest in further discussing this matter at this time is to better understand the FDA's position on the perceived value of the subject statement to prescribing physicians...."

- After introductions, BMS initiated the discussion for this teleconference by elaborating on their arguments for removing the statement.

FDA: The statement alluding to the 24-hour regimen should remain in the DOSAGE AND ADMINISTRATION (D&A) section of the package insert to allow physicians to choose between the two regimens. Dr. G. Williams recalled that Dr. Temple had previously proposed the phrasing since the study was not powered to determine which infusion schedule (3-hour or 24-hour) was better; however, the trend pointed to the 24-hour 175 mg/m^2 as the better regimen.

BMS: The CLINICAL STUDIES section will include information relating to the regimens that could be used. R. Canetta voiced the proposed statements to be included in this section by BMS, but maintained that the D & A section would not include the statement on optimal regimens.

FDA: We agree that the statement in the CLINICAL STUDIES section can be revised for clarity, but it would require review by the Division before it is accepted. It is clear that no one knows which regimen is better, but the fact that both the 3 and

24 hour infusion schedules have been studied in second-line ovarian cancer should be reflected in the D & A section.

BMS: BMS will submit an amendment proposing revised labeling for FDA review.

2. **Three-hour Infusion Data**

BMS: **(Excerpt from BMS' April 1, 1998 teleconference request).**
"As you are aware, during the course of the review of sNDA 026, Dr. Honig expressed great interest in receiving data from the EORTC/Intergroup three-hour infusion study....a large proportion of prescribing physicians currently administer TAXOL in the first-line ovarian setting using the three-hour infusion....we are most interested in discussing the timing for and content of a submission of data from the EORTC/Intergroup trial to support inclusion of the three-hour data in the TAXOL package insert."

FDA: BMS should submit the original protocol, a study report, the EORTC electronic data (including raw survival data and patient demographics), toxicity information with a focus on differences seen in this patient population (e.g., neurotoxicity and febrile neutropenia), and dosing information with cyclophosphamide.

BMS is not expected to recreate the EORTC database as was done for the first-line ovarian cancer supplement 026. However, the Division encourages BMS to conduct spot checks of the database then forward the database to the Division

BMS should focus on survival, dosing, and demographics. There should be less concern about other aspects of the study. Safety would be of interest to the Division especially if BMS were planning to make promotional statements.

If EORTC did not collect dosing data, BMS should inform the FDA as soon as possible.

BMS: EORTC of Canada does collect individual dosing information, but it is unclear whether the Scottish or Scandinavian groups of EORTC did the same.

How much detail does the Division want to see in the study report?

FDA: The study report should include whatever analyses EORTC had conducted including information on EORTC procedures and quality control responses.

BMS: The Division has already received EORTC raw safety data in the Taxol/cisplatin regimen but it is in a different indication (NSCLC, S-024).

FDA: BMS should provide a summary of the results of this data. Also, it is not useful to have a pre-sNDA meeting since BMS does a good job of documenting the information needed for review. Information on response rates and time to progression is not needed either since the Division will focus on survival and toxicity.

BMS: Which CRFs will the Division require for deaths and discontinuations?

FDA: BMS should follow the requirements in the regulations regarding CRF submission; however, if this results in extensive effort on BMS' part, this issue may be revisited.

BMS: BMS will have the raw data from the EORTC study after ASCO 1998.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

There were no unresolved issues requiring further discussion.

ACTION ITEMS:

	Item	Responsible Person	Due Date	Completion Date
1.	Propose revisions to draft package insert.	C. Anderson, BMS	ASAP	✓ 4-7-98
2.	Review revisions to draft package insert.	Review Team, FDA	ASAP	

The teleconference concluded at approximately 4:50 p.m..

/S/

Dianne Spillman /date
Project Manager/Minutes preparer

4/7/98

Concurrence Chair: /S/

Susan Honig, M.D. /date
Clinical Reviewer

4/8/98

ATTACHMENT (BMS 4-1-98 FAX; 3 pages)

cc: Original NDA 20-262 / S-026
HFD-150/Div.Files

electronic cc: S.Honig
G.Williams
R.DeLap
D.Pease
L.Vaccari
D.Spillman

F/T by: dds/4-7-98
a:\20262tax.bms\se1-026\mtgs\minutes\980402l-tcm

MEETING MINUTES = LABELING (LA): Clinical teleconference

TELECONFERENCE MINUTES

MEETING DATE: February 11, 1998 **TIME:** 10:00 a.m. **LOCATION:** WOC2/r 2063

NDA: 20-262/S-026 Teleconference Request Date: 2-9-98

DRUG: Taxol® (paclitaxel) Injection

SPONSOR/APPLICANT: Bristol-Myers Squibb Company

TYPE of MEETING:

1. **Other:** Clinical - ODAC presentation

2. **Proposed Indication:** First-line ovary

FDA PARTICIPANTS:

Robert DeLap, M.D., Ph.D.	–	Director, Division of Oncology Drug Products, HFD-150
Grant Williams, M.D.	–	Medical Team Leader, HFD-150
Susan Honig, M.D.	–	Medical Reviewer, HFD-150
Dianne Spillman	–	Project Manager, HFD-150
Lynn VanUmmersen, M.D.	–	Oncology Fellow, HFD-150
Leslie Vaccari	–	Special Assistant, HFD-150

INDUSTRY PARTICIPANTS:

Renzo Canetta, M.D.	–	Vice President, Oncology Clinical Research
Benjamin Winograd, M.D.	–	Executive Director, Oncology Clinical Research
David Tuck, M.D.	–	Associate Director, Oncology Clinical
Mohan Beltangady, Ph.D.	–	Director, Biostatistics & Data Management
Cheryl Anderson	–	Director, U.S. Regulatory Liaison, WWRA

BACKGROUND:

1. January 21, 1998 BMS FAX re: ODAC presentation.
2. February 6, 1998 FDA call to BMS re: ODAC presentation.
3. February 9, 1998 BMS teleconference request.
4. February 10, 1998 FDA call to BMS re: need for teleconference request.
5. February 10, 1998 BMS call to FDA requesting teleconference be scheduled.

MEETING OBJECTIVE:

To reach mutual agreement on the manner in which the publicly presented results from the phase 3 studies GOG-132 (Muggia) & EORTC (Piccart) are presented to ODAC.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. **<u>First-line Ovarian ODAC presentation.</u>**

BMS: BMS' ODAC presentation will concentrate on the presentation of data from GOG-111; however, BMS would like to present data from the other two trials (GOG-132 & EORTC) that have been completed and were presented at ASCO last year. The expectation is that the results of GOG-111 will provide the basis for labeling and approval of Taxol in first-line ovarian cancer, but that the GOG-132 and EORTC studies would confirm the results of GOG-111. As such, BMS should be allowed to include two 10 minute presentations by the investigators of the GOG-132 & EORTC studies since BMS does not have access to the data.

BMS does not intend to present data from the carboplatin/Taxol studies since the data from these studies are not mature.

FDA: The Division also expects that labeling changes and a decision on this sNDA would be based only on study GOG-111.

Division policy has been to only allow a presentation of studies that have been submitted to the NDA and reviewed by Division personnel. For any application, it is important to acknowledge the existence of other studies during a presentation overview; however, these other studies should not be presented separately from the pivotal study or studies.

An applicant's presentation should reflect the information submitted in the NDA. Other studies should not be given more prominence than they were given in the NDA. It is inappropriate to have a separate presentation that provides the details of studies not reviewed by the Division, since it may influence ODAC deliberations and decisions. In the past, applicants have presented data not reviewed by the Division. This has been problematic because when the results were actually reviewed by the Division, the outcome has been different than originally presented to the Committee.

BMS: Information about GOG-132 & EORTC will be provided in the background document and will include a disclaimer that the data from these studies have not been reviewed by BMS or the FDA.

FDA: The extent of the information should only be what was publicly available (i.e., the abstract and ASCO slides from 1997 and the ASCO abstract from 1998 submitted to the NDA).

FDA: Will BMS staff present the other studies during the overview portion or will another presenter, not intimately involved in the studies, present the information?

BMS: This can not be determined yet since BMS must find another presenter.

FDA: Who will present GOG-111 data?

BMS: BMS staff will present this study.

FDA: We suggest including the other studies (GOG-132 & EORTC) in the BMS presentation with a comment that investigators from those studies are available to answer any questions from the Committee.

BMS is allotted one hour to present to ODAC; this includes any presentations by patient advocates.

2. **NSCLC ODAC presentation.**

BMS: BMS asked about the possibility of extending the time allotted for the presentation of the three trials submitted to support the use of Taxol in NSCLC (NDA 20-262/S-024). The presentation would likely not be longer than 90 minutes.

FDA: A longer presentation may not be to BMS' advantage especially when this issue is scheduled for the second afternoon of a two day meeting.

BMS can submit a proposed agenda for the NSCLC presentation, with the times for each agenda item, for FDA review and comment. Following internal team discussions, the FDA will determine whether it is appropriate to extend the time allotted for BMS' NSCLC presentation.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

1. Agenda and time allotted for the Taxol NSCLC ODAC presentation.

ACTION ITEMS:

	Item	Responsible Person	Due Date	Completion Date
1.	Provide agenda & times for each agenda item for the NSCLC ODAC presentation.	BMS: C.Anderson	ASAP	✓ 3-3-98
2.	Review agenda. Determine whether to extend BMS presentation time.	FDA: I.Chico/G.Williams R.Justice/R.DeLap,	ASAP	✓ 3-4-98
3.	Relay team decision on NSCLC ODAC to BMS.	D.Spillman, FDA	ASAP	✓ 3-4-98

The teleconference concluded at approximately 10:20 a.m.

ADDENDUM TO MINUTES:

2-13-98 C. Anderson of BMS called to verify whether the Division would allow BMS to include the final survival curves for the EORTC study in the literature overview section of their ODAC package. These survival curves are to be presented at the 1998 ASCO meeting. Some BMS teleconference participants understood that the survival curves could be included if BMS preceded the literature discussion of the studies with a statement that the data has not been submitted to the FDA for review.

2-13-98 After discussing the above issue internally, D. Spillman (Project Manager, FDA) called BMS and spoke with S. Behling since C. Anderson was unavailable. The Division determined that the survival curves should not be included in BMS' ODAC background package; however, BMS may have overheads available to show the committee should questions arise regarding survival in the EORTC study.

/S/ 4/1/98
Dianne Spillman /date
Project Manager/Minutes preparer

Concurrence Chair: /S/ 4/2/98
Susan Honig, M.D. /date
Clinical Reviewer

cc: Original NDA 20-262 / S-026
HFD-150/Div.Files

electronic cc: HFD-150/S.Honig/rev. 2-12-98
/G.Williams
/R.DeLap
/D.Pease
/L.Vaccari
/D.Spillman/draft: 2-12-98

F/T by: dds/4-1-98
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MEETING MINUTES = OTHER (O): Clinical teleconference

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-262/S-026, 027, 028

CORRESPONDENCE

Bristol-Myers Squibb
Pharmaceutical Research Institute
Richard L. Gelb Center for Pharmaceutical Research and Development
5 Research Parkway P.O. Box 300 Wallingford, CT 06492-7660

April 7, 1998

NDA SUPPL AMEND
SE1-026
(PL)

NDA 20-262 - TAXOL® (paclitaxel)
sNDA 026 - First-Line Ovary

AMENDMENT

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:

Provided in this submission is the WordPerfect version of the proposed labeling which was sent to your Division yesterday for pending sNDA 026. Also included herein is the document on diskette. Although this WordPerfect version has been checked against the version submitted yesterday, the 'official' labeling proposal should be considered to be that which should have been received in your Division on this date.

As usual, any questions or comments should be relayed to the undersigned.

Sincerely,

Cheryl L. Anderson
Director, U.S. Liaison

/pk
Enclosure

Finally, the March 4th request posed by Pharmacology Review Staff concerning the incorporation of available overdosing information into the product labeling will be addressed in written correspondence to this application in the near future.

Sincerely,

Cheryl L. Anderson
Director, U.S. Liaison

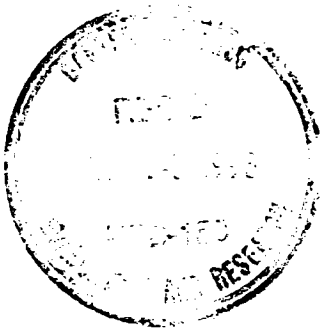
Attachments
Desk copies: D. Spillman (2)
S. Honig

Bristol-Myers Squibb
Pharmaceutical Research Institute

Richard L. Gelb Center for Pharmaceutical Research and Development

Amendment to:
sNDA 026 - First-line Ovary
NDA #20-262 TAXOL® (paclitaxel)

March 12, 1998



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

Dear Dr. DeLap:

In response to Dr. Honig's request earlier this week, we have requested that Dr. Piccart provide information on cross-over therapy in the EORTC study. At that time that meaningful information is provided to the Company concerning this matter we will forward it to Dr. Honig via fax. We do not anticipate that any such information would be incorporated into the ODAC presentation of data from the subject study, and plan to hold any such information which we receive from Dr. Piccart in reserve so that it may be used to respond to any relevant questions from ODAC members.

Finally, on March 4th we received a request, (in conjunction with both sNDA 026 and pending sNDA 024), that available information on 'overdosing' be provided such that the TAXOL labeling can be updated. The information which was submitted within the NDA was felt by both BMS and FDA Review Staff to support the labeling statements about 'overdosing' at the time of the initial NDA approval; no new clinical or animal data has become available which would add to the current labeling information on anticipated signs and symptoms associated with what might be construed to be 'overdosing' with paclitaxel, and no further information is available on appropriate 'antidotes'. For the information of Review Staff, included in this submission are the postmarketing surveillance reports for possible 'overdose' available to BMS.

Sincerely,

Cheryl L. Anderson
Director, U.S. Liaison

Desk copies: D. Spillman (2)

0000003

T46661 To MO (SHL)
D/C to BP4 (SI)
3/17/98

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

Amendment to:
sNDA #20-262/S-026 (First Line Ovarian Cancer)
TAXOL® (paclitaxel) INJECTION

March 10, 1998

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

Dear Dr. DeLap:

Provided in this amendment are responses to the February 26th and March 4th questions received from Dr. Honig on sNDA 026. (The requests of February 26th concern differences between Dr. Honig's and BMS' assessment of dates of progression; the March 4th request was for the results of the nodal biopsy for patient

At this time we would also like to formally respond to two of the three March 4th questions received from Biopharmaceutics and Pharmacology Review Staff through Ms. Spillman on the subject application. Provided below are those questions (in italics) followed by responses.

1. Please submit the study report/results of the effect of hepatic dysfunction on paclitaxel disposition to the Agency for review.

2. The revised labeling statement on page 3:

should remain the same as the original statement in current package insert:

It is agreed that the subject 'original statement' within the current package insert will remain unchanged in conjunction with sNDA 026. For information on the status of studies in which the effect of hepatic dysfunction on paclitaxel disposition has been studied, please refer to the latest NDA Annual Report for NDA 20-262, (dated February 26th). Further, FDA Review Staff should be aware that, in anticipation of labeling changes in conjunction with this Phase IV committment, a meeting will likely be requested in the near future.

Bristol-Myers Squibb
Pharmaceutical Research Institute

Richard L. Gelb Center for Pharmaceutical Research and Development

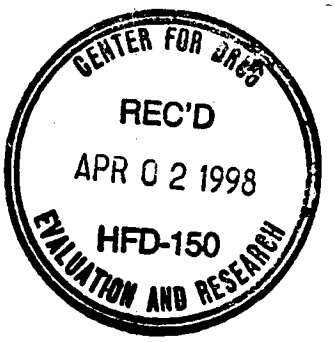
5 Research Parkway P.O. Box 5100 Wallingford, CT 06492-7660

TAXOL® (paclitaxel) - NDA 20-262
sNDA 026, First-line Ovary

AMENDMENT
-Request for Teleconference

April 1, 1998

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



Dear Dr. DeLap:

Significant issues have surfaced in conjunction with the review activities on sNDA 026 which seem to warrant some discussion. To address two of these issues, a brief teleconference is requested for sometime on Thursday, April 2, or Friday, April 3, involving you and the Medical Review Staff. The matters which would be the subject of the requested discussion are described below.

'Optimal regimen is not yet clear' Statement

The original labeling proposal for sNDA 026 deleted the following statement:

Dr. Honig's March 18 faxed labeling comments stated that the subject statement should essentially remain in the product labeling because

Further comments yesterday from your Division relating to this matter have reinforced this FDA view. Although it is agreed that no further second-line ovary data has been submitted since the Agency originally mandated the inclusion of this statement (in conjunction with the approval of the three-hour infusion recommendation approval for second-line ovary), we maintain that inclusion of the statement is potentially confusing to prescribing physicians. As has been FDA's practice in recent years, the TAXOL labeling currently includes, and will continue to include, a full description of the clinical data that are considered in FDA approval decisions; this practice appropriately allows physicians to make informed decisions about the manner in which the drug can be safely administered.

Our primary interest in further discussing this matter at this time is to better understand the FDA's position on the perceived value of the subject statement to prescribing physicians. This information will be of particular interest in light of our recent review of the product labels for other cytotoxics approved by FDA within the past decade which revealed that those product labels do not include similiar caveats about the adequacy of currently available information to support the labeled dosing recommendations (despite the absence of studies which might elucidate the 'optimal regimens').

Three-hour Infusion Data

As you are aware, during the course of the review of sNDA 026, Dr. Honig expressed great interest in receiving data from the EORTC/Intergroup three-hour infusion study. We were unable to respond to this request within the review clock for sNDA 026, and we were frankly frustrated by our inability to do so. We are very much aware, through marketing research, that a large proportion of prescribing physicians currently administer TAXOL in the first-line ovarian setting using the three-hour infusion. To ensure that the approved TAXOL labeling is both as informative and relevant to actual use as possible, we are most interested in discussing the timing for and content of a submission of data from the EORTC/Intergroup trial to support inclusion of the three-hour data in the TAXOL package insert.

Sincerely,

Cheryl L. Anderson
Director, U.S. Liaison

Desk Copies: D. Spillman (2)
Dr. Honig (1)

Bristol-Myers Squibb
Pharmaceutical Research Institute

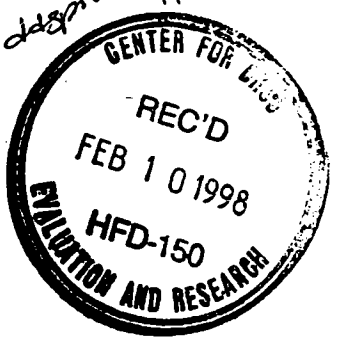
Richard L. Gelb Center for Pharmaceutical Research and Development

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

TAXOL® (paclitaxel) - NDA 20-262
sNDA 026 - First-line ovary

Re: TELECONFERENCE REQUEST

See 2/11/98 meeting minutes dispute 4/2/98



February 9, 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:

Further to my conversation with Ms. Spillman on Friday the 6th, please consider this to be a formal request for a teleconference concerning presentations to ODAC at the scheduled March meeting for sNDA 026. The objective of this discussion is to reach mutual agreement on the manner in which the publicly presented results from Phase III studies GOG-132 (Muggia) and EORTC (Piccart) are presented to ODAC.

Although datatapes from the two subject studies have not been made available by study investigators, it must be recognized that the study results have very likely been considered in the treatment community's assessment of 'standard of care' for this disease setting. (We understand that this is the reason for Dr. Honig's stated interest in datatapes from the subject studies and share in her interest in these data.) We propose to allow Drs. Muggia and Piccart to make very brief presentations for the two subject studies, preceded with a statement from BMS clarifying that raw data from the studies has not been submitted for FDA review.

The requested teleconference should take approximately 30 minutes. We respectfully request your direct involvement in the discussion, as well as that of Drs. Williams and Honig. The attendees from BMS will likely include Drs. Canetta, Winograd, Tuck and myself. I will follow up on arrangements with Ms. Spillman.

Sincerely,

Cheryl L. Anderson
Director, U.S. Liaison
Worldwide Regulatory Affairs

/ks

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

NDA 20-262, TAXOL® (paclitaxel) Injection

October 7, 1997

Dr. 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
Rockvill, MD 20852-1448

Dear Dr. DeLap:

Submitted herewith is a Supplementary New Drug Application for TAXOL in the first-line treatment of advanced carcinoma of the ovary. As discussed over recent months, this application includes data from the completed study GOG-111, (CA139-022), the results of which show significantly improved survival for the combination of TAXOL/cisplatin over cyclophosphamide/ cisplatin in the same disease setting. As also discussed, this application includes, (as a part of a comprehensive literature review), all information currently available to The Bristol-Myers Squibb Company from other TAXOL randomized studies which have been/are being conducted in this disease setting.

The content of this submission reflects those commitments made to your Division in written correspondence dated July 22nd with regard to the presentation of data from study CA139-022. (However, imaged case report forms from this study will be submitted within two weeks, as agreed with Ms. Spillman recently.) Of particular note, the application includes the requested list highlighting cases where the BMS results are different from GOG's results for survival, time to progression, and response; (this list may be found in volume 15, on pages 292 through 320). As you are aware, Review Staff has expressed an interest in receiving data from two additional randomized studies which were presented at this year's ASCO meeting, (GOG-132 and an EORTC study) and BMS personnel has requested and obtained statistical reports from the investigators for the two cited 'completed' studies and these documents are included in this submission. Data tapes for these studies have also been requested by Company personnel. Further, an inquiry will be made to the investigators for the cited ongoing study concerning the availability of any 'interim analyses'.

Any comments or questions that may relate to this application may be relayed to the undersigned at (203) 284-6083. We look forward to working closely with Review Staff on their review of this application and will endeavor to respond to any inquiries as quickly as possible.

Cheryl L. Anderson, Director
Worldwide Regulatory Affairs

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

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: December 31, 1992
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314).*

NAME OF APPLICANT
Bristol-Myers Squibb Company

DATE OF SUBMISSION
OCT 7 1997

ADDRESS *(Number, Street, City, State and Zip Code)*
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7600

TELEPHONE NO. *(Include Area Code)*
(203) 284-6083

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)
20-262

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*
Paclitaxel

PROPRIETARY NAME *(If any)*
TAXOL® (paclitaxel) Injection

CODE NAME *(If any)*
NSC-125973; Taxol A; BMS-181339-01; BMY-45622

CHEMICAL NAME
5β, 20-epoxy-1,2α,4,7β,10β,13β-hexahydroxytax-11-en-9-one-4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Nonaqueous solution for dilution	IV infusion	30 mg/5 ml vials

PROPOSED INDICATIONS FOR USE
Primary treatment of ovarian cancer

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part*
Bristol-Myers Squibb IND

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) *(21 CFR 314.55)*

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☒ SUPPLEMENTAL APPLICATION
☐ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION *(e.g., Part 314.70(b)(2)(iv))*

PROPOSED MARKETING STATUS *(Check one)*

X APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT *(OTC)*

~~Use lower case Xs to indicate choices~~

CONTENTS OF APPLICATION

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

X	1. Index
X	2. Summary (21 CFR 314.50(c))
X	3. Chemistry, manufacturing, and control section (21 CFR 314.50(d)(1))
	4. a. Samples (21 CFR 314.50(e)(1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50(e)(2)(i))
X	c. Labeling (21 CFR 314.50(e)(2)(ii))
	i. draft labeling *(4 copies)*
	ii. final printed labeling *(12 copies)*
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50(d)(2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50(d)(3))
	7. Microbiology section (21 CFR 314.50(d)(4))
X	8. Clinical data section (21 CFR 314.50(d)(5))
	9. Safety update report (21 CFR 314.50(d)(5)(vi)(b))
X	10. Statistical section (21 CFR 314.50(d)(6))
X	11. Case report tabulations (21 CFR 314.50(f)(1))
X	12. Case report forms (21 CFR 314.50(f)(1))
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
X	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355(b)(2) or (j)(2)(A))
X	15. OTHER *(Specify)* Certification of Debarred Persons

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Cheryl L. Anderson, Director Worldwide Regulatory Affairs	Cheryl L. Anderson	10/7/97

ADDRESS *(Street, City, State, Zip Code)*	TELEPHONE NO. *(Include Area Code)*
5 Research Parkway P.O. Box 5100 Wallingford, CT 06492-7600	**(203) 284-6083**

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

FORM FDA 356h (6/92)