

CENTER FOR DRUG EVALUATION AND RESEARCH

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

MEDICAL REVIEW(S)

Medical Officer Labeling Review

Application: sNDA 20-262/SE1-026
Sponsor: Bristol-Myers Squibb Pharmaceutical Research Institute
Drug: Paclitaxel
Proposed indication: Paclitaxel in combination with cisplatin for first-line therapy of advanced ovarian cancer
Letter Date: April 6, 1998
Review Date: April 8, 1998

The sponsor was sent a copy of labeling revisions, based on the label submitted in the sNDA; this FDA response included comments from the Medical and Biopharmaceutical reviewers, the team leaders, and Robert DeLap, M.D., Ph.D., Division Director. A teleconference was held on April 2, 1998 to discuss several issues the sponsor had with proposed FDA labeling changes. This submission contains the sponsor's proposed labeling.

Reviewer Comments:

1. Page 3. Efficacy table for the Phase 3 First-line ovarian carcinoma study:

The sponsor declined to place p-values in the Efficacy table and instead stated they would be included in the text, in order to be consistent with the rest of the labeling.

FDA: Confidence intervals should be deleted. It is not explicitly stated that only significant p-values are given; it is therefore not clear to the treating physician what is significant and what may be significant but not reported.

For this table, the p-values to be included are as follows:

Clinical response	p=0.04
Pathological response	p=0.001
Pathological complete response	p=0.20
Time to progression	p=0.0008
Survival	p=0.0002

2. Page 3, following the table:

The following sentence should be inserted after "The adverse event profile....":

3. Page 5:

The revisions are acceptable as written.

4. Page 6:

The sponsor deleted the sentence

Instead, a sentence at the end of the paragraph was inserted:

This

statement does not convey our concern that the 24 hour schedule may have greater activity than the 3 hour infusion schedule. The sponsor's statement (at the end of the paragraph) should be changed to:

5. Page 6 bottom:

The following sentence should be added after the sponsor's revised statement:

6. Page 9:

The sponsor has reworded the indication in accordance with the FDA proposal.

7. Page 11, Nursing Mothers:

The sponsor has appropriately clarified the Nursing Mothers section.

8. Page 11, Pediatric Use:

The sponsor has complied with the FDA recommendations for this section.

9. Page 13, Adverse events:

A. The medical reviewer agrees that the proposed changes in the adverse event percentages were minimal and that the original text can remain in the label.

B. Asterisks should denote comparison with $p < 0.05$ by Fishers Exact Test.

	TAXOL-Cisplatin (n=196)	Cyclophosphamide/Cis platin (n=213)
Bone marrow		
Neutropenia <2000	96	92
<500	81*	58*
Thrombocytopenia <100,000	26	36
< 50,000	10	9
Anemia <11	88	86
<8	13	9
Infections	21	15
Febrile Neutropenia	15*	4*
Hypersensitivity reactions		
All	8*	1*
Severe	3*	--*
Peripheral neuropathy		
Any	25	20
Severe	3*	--*
Nausea and vomiting		
Any	65	69
Severe	10	11
Myalgia/arthralgia		
Any	9*	2*

Severe	1	--
Diarrhea		
Any	16*	8*
Severe	4	1
Asthenia		
Any	17*	10*
Severe	1	1
Alopecia		
Any	55*	37*
Severe	6	8

* p < 0.05

10. Page 16: Hematologic

The sponsor inserted the additional information about febrile neutropenia. However, the following statement should be added:

Also, the additional information the sponsor provides about fever and infection should be identified as derived from the Taxol/cisplatin arm.

The other revisions on this page are acceptable.

11. Page 18. Gastrointestinal events:

The sponsor declined to include the FDA statement about diarrhea. This statement should be inserted.

12. Page 18. Other Clinical Events:

The sponsor's statement is

The sponsor should add:

13. Page 18. Overdosage:

The sponsor did not include the FDA statement.

This statement should remain in this section, as a reminder about the possibility of ethanol toxicity may prompt additional protective measures in the event of an overdose.

14. Page 19. Dosage and Administration:

The sponsor has altered the Dosage and Administration section. The statement

This statement pertains only to (2) in this section (i.e., dosing and administration in second-line therapy) and should be retained in this section. Second, the sponsor has omitted the second half of the

DODP statement in this sentence:

It is important to point out to clinicians that there is uncertainty about optimal administration; there is a trend towards a non-significant improvement in efficacy parameters with the 24 hour infusion. This section should remain as written by DODP.

Note to the Project Manager:

Page 14: Adverse event tables for the Phase 3 second-line ovarian cancer and breast carcinoma studies.

The sponsor should use asterisks to indicate where p is < 0.05 in these tables during the course of labeling for the non-small cell lung cancer indication.

/S/

Susan Flamm Honig, M.D.
Medical Reviewer

/S/

Grant Williams, M.D.
Team Leader

NDA 20-062
HFD 157/DV 800
DODP
/S Honig
/S Williams

MAR 11 1998

Medical Officer Labeling Review

Application: sNDA 20-262/SE1-026
Sponsor: Bristol-Myers Squibb Pharmaceutical Research Institute
Drug: Paclitaxel
Proposed Indication: Paclitaxel in combination with cisplatin for first-line therapy of advanced ovarian cancer
Letter Date: 10/7/97 ; 2/19/98 (cas edit)
Review Date: 2/26/98

As this application is an efficacy supplement, most of the label has been reviewed in the past. A recent efficacy supplement prompted re-review of the label. This review will address revisions made by the sponsor in the current application. These revisions are noted in volume 1, pages 23-41. An amendment was submitted 2/19/98 with further revisions. The following page numbers refer to the label pages in the amendment:

Page 1: Dianne Spillman, Project Manager, noted a change in wording that now reads
She will check the accuracy of this statement with the PharmTox reviewers.

Page 3: Dianne Spillman noted a discrepancy in the spelling of _____ She
will check the correct spelling with the PharmTox reviewers.

Page 3:
The sponsor's proposed revision is as follows:

The biopharmaceutical reviewer, Safaa S. Ibrahim, Ph.D., states that this revision should be deleted (review dated 2/3/98), as no data has been submitted for review. The statement should remain the same as the original statement in the current package insert:

Reviewer Note:

This comment was sent to the sponsor with the biopharmaceutical review. In a facsimile the sponsor agreed to retain the original statement.

Page 4:
A. Sponsor's proposed revision, first paragraph "...significantly longer time to progression (median 16.6 vs. 13.0 months, $p=0.0008$)...."
The data for time to progression should be changed to "(median 15.7 vs. 12.6 months, $p=0.0006$)...". This change is based on the reviewer's analysis of time to progression using corrected censoring dates.

B. The sponsor's efficacy table is as follows:

Efficacy in the Phase 3 First-line Ovarian Carcinoma Study

	Taxol/Cisplatin	Cyclophosphamide/Cisplatin
Clinical Response:	(n=113)	(n=127)
--rate (percent)	60	50
--95% Confidence Interval	(51-69)	(41-59)
Pathological Response:	(n=196)	(n=214)
--rate (percent)	34	20
--95% Confidence Interval	(28-41)	(15-26)
Time to Progression	(n=196)	(n=214)
--median (months)	16.6	13.0
--95% Confidence Interval	(14.7-19.7)	(11.5-14.7)
Survival	(n=196)	(n=214)
--median (months)	35.5	24.2
--95% Confidence Interval	(29.6-39.6)	(20.6-29.0)

The table should be corrected as follows; reviewer revisions in bold italics:

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Efficacy in the Phase 3 First-line Ovarian Carcinoma Study

	Taxol/Cisplatin	Cyclophosphamide/Cisplatin
Clinical Response: --rate (percent) --95% Confidence Interval	(n=113) 62	(n=127) 48
Pathological Response: --rate (percent) --95% Confidence Interval	(n=196) 34 (28-41)	(n=214) 20 (15-26)
Pathological <i>Complete</i> Response: --rate (percent) --95% Confidence Interval	(n=196) 21	(n=214) 16
Time to Progression --median (months) --95% Confidence Interval	(n=196) 15.7	(n=214) 12.6
Survival --median (months) --95% Confidence Interval	(n=196) 35.5 (29.6-39.6)	(n=214) 24.2 (20.6-29.0)

These revisions are based on the reviewer's analysis of clinical response and time to progression. The sponsor was informed of these differences in facsimiles dated 2/6/98 and 2/25/98. The sponsor replied on 2/25/98 to the questions about clinical response and on 3/10/98 to the questions about time to progression.

The pathologic response rate includes a combination of complete pathologic response (pCR) and microscopic residual disease. The pathologic response rate was significantly better on the paclitaxel-cisplatin arm, but there was no significant difference in pathologic complete response rate between the two arms. As the pCR has been associated with an improved outcome in ovarian cancer patients, it is important to include this parameter in this table.

We recommend that the sponsor add p-values to this table, which are more meaningful to clinicians than confidence intervals. The confidence intervals can be deleted if the sponsor chooses to save space.

Page 5: Adverse events table

A. Corrections to the stated rates

The rate of infections should be 22% for taxol/cisplatin and 16% for cyclophosphamide/cisplatin, rather than 21% and 15% respectively.

The rate of all hypersensitivity reactions on taxol/cisplatin should be 9%, rather than 8%.

The rate of any symptoms from peripheral neuropathy for taxol/cisplatin should read 26% instead of 25%.

These revisions are based on a MS Access query of the submitted database.

B. Additions

The sponsor should include the percent of patients on each arm who experienced febrile neutropenia, which was significantly different on the two treatment arms.

The sponsor should include the percent of patients on each arm who experienced arthralgia/myalgia, diarrhea, asthenia, and alopecia, other toxicities that were significantly different between the two arms.

P-values should be added to this table to indicate which toxicities were significantly different.

Although the incidence of cardiovascular events was significantly different between the two arms, this toxicity should not be included in this table. This difference is most likely due to the requirement for cardiac monitoring on the PT arm but not on the PC arm; most of the events were asymptomatic and clinically insignificant. The placement of this information in the table would not provide useful clinical information.

Page 12:

The sponsor's proposed revision is as follows:

This line should read:

Page 18: The sponsor's proposed revision is

The revision should read

Page 19: The sponsor added a sentence about the incidence of Grade IV neutropenia in ovarian cancer patients treated with PT. Additional information about febrile neutropenia should be inserted.

Page 21: The sponsor should add information about the diarrhea seen in GOG 111 to the section.

Page 22: Under the last sentence states

In GOG 111, 17% of PT patients compared to 10% of PC patients experienced asthenia. The additional information gained from the clinical trial should be discussed instead of conveying the impression that the only available information is from voluntary safety reports.

Page 23:

A. The sponsor deleted

No new data has been submitted that demonstrates the optimal regimen for paclitaxel

administration; this sentence should be retained in the labeling, slightly altered as given below.

B.
Ovarian cancer

The sponsor's proposed revision is as follows (sections revised by the reviewer are in bold print):

This section should read as follows:

For previously untreated patients, the submitted trial used Taxol in combination with cisplatin. There is no information on the efficacy of carboplatin in this patient population. Second, this trial used paclitaxel given as a 24 hour infusion. The Division has not reviewed data utilizing a 3 hour infusion.

/S/

Susan Flamm Honig, M.D.
Medical Reviewer

/S/

3/11/93

Grant Williams, M.D.
Team Leader

cc: NDA 20-262/S-026
HFD-ISO / DIV Files
/ D. Spillman
/ S. Honig
/ G. Williams

1.0 General Information

1.1 NDA Information

1.1.1 NDA 20-262/SE1-026
1.1.2 Submission Date: October 7, 1997
1.1.3 First draft: February 24, 1998
1.1.4 Completion date: March 25, 1998

1.2 Drug Name

1.2.1 Generic Name: Paclitaxel
NSC-125973; Taxol A; BMS-181339-01;
BMY-45622
1.2.2 Trade Name: Taxol
1.2.3 Chemical Name: 5 beta. 20-epoxy-1, 2 alpha. 4, 7 beta. 10
beta. 13 beta-hexahydroxytax-11-en-9-one-
4, 10-diacetate 2-benzoate 13-ester with (2R,
3S)-N-benzoyl-3

1.3 Sponsor: Bristol-Myers Squibb Pharmaceutical
Research Institute (BMS)

1.4 Pharmacologic Category: Antimicrotubule agent

1.5 Proposed Indication: Primary treatment of ovarian cancer

1.6 Dosage Form and Route of Administration:
Non-aqueous solution for dilution
IV infusion

1.7 NDA Drug Classification: Priority

1.8 Related INDs and NDAs: NDA 20-262
sNDA 20-262/S-022 (second-line treatment
of AIDS-related Kaposi's sarcoma)

INDs held by BMS: IND
IND

INDs held by IND
IND
IND
IND

IND held by

IND

INDs held by individual investigators:

1.9 Foreign Marketing:

No section included in the NDA
Paclitaxel is approved in Canada for second-
line therapy of ovarian cancer

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3.0 Material Reviewed/Clinical Data Sources/Administrative Review

3.1 Source

3.1.1 Pre-NDA and supplemental NDA submissions

The supplemental New Drug Application for paclitaxel, sNDA 20-262/SE1-026, contains 101 volumes. This review is derived from information contained in volume 1, clinical and statistical data in volumes 3-6, and case report form tabulations and data listings in volumes 7-19. Case report forms comprised volumes 20-101 and were reviewed as necessary.

Other sources of information for this review include the pre-NDA packet prepared by the sponsor and the correspondence between the FDA and BMS prior to the NDA submission. This correspondence is summarized in section 3.3, Administrative Review.

3.1.2 sNDA amendments

Several amendments were submitted to the NDA:

1. SNC-026 Letter Date 10/20/97

The sponsor submitted a written request to the Medical Research Council of the United Kingdom for interim data from the ICON 3 study. A reply from MKB Parmar, the Acting Chief Medical Statistician of the group, indicated that the MRC policy is to maintain confidentiality of all results while the trial is open to patient accrual. The Data Monitoring Committee recommended accrual of 2000 patients, which is anticipated in the spring of 1998. Results from the ICON3 study should be available in late 1998 or early 1999.

2. SE1-026 Letter Date 10/23/97

The sponsor submitted PDF files of imaged case report forms for all patients, as agreed upon by the FDA reviewers and BMS prior to the NDA submission.

3. Letter date (by facsimile) 12/4/97

The sponsor submitted a copy of the abstract submitted to the 1998 ASCO meeting updating the results of the EORTC-Canada trial (Stuart G. Bertelsen K. Mangioni C. et al. Updated analysis shows a highly significant improved overall survival for cisplatin-paclitaxel as first line treatment of advanced ovarian cancer: Mature results of the EORTC-GCCG, NOCOVA, NCIC CTG, and Scottish Intergroup trial.) They also asked whether data tapes from the EORTC-GCCG and GOG 132 studies were required for the review of the NDA. [Division response: Please send these data tapes if they become available during the review time line.]

4. Safety Update 2/3/98

The sponsor submitted the required four-month safety update, which stated that reported adverse events were similar to the incidences reported in the sNDA.

5. Labeling revisions 2/19/98

The sponsor submitted changes to the proposed labeling in the NDA submission.

3.1.3 Response to FDA requests for information

During the review process, several FDA Requests for Information were sent to the sponsor by the medical reviewer. The dates of the Response to FDA Request for Information are listed below:

Response to FDA Request for Information:

December 22, 1997

January 15, 1998

February 2, 1998

February 25, 1998

March 10, 1998

3.1.4 ODAC meeting

The questions and votes from the Oncologic Drug Advisory Committee meeting on March 20, 1998 are summarized in Appendix C.

3.1.5 sNDA summary

The pivotal trial identified by the sponsor is BMS protocol number CA139-022 (Gynecologic Oncology Group [GOG] protocol 111). This trial was a randomized comparison of cyclophosphamide and cisplatin versus paclitaxel and cisplatin as first-line therapy of patients with suboptimal Stage III and Stage IV ovarian cancer. The primary endpoints were response rate, response duration, and survival as defined in the original protocol. A subsequent amendment (less than a month after the study opened to accrual) changed the primary endpoint to progression-free survival (PFS), with survival as a secondary endpoint and response as a tertiary endpoint. This trial provides the basis for the sNDA application. A literature review of published results of prospectively randomized trials of paclitaxel in untreated ovarian cancer patients and a literature review of published results of paclitaxel therapy, either alone or in combination, in untreated patients with advanced ovarian cancer is included in the submission.

3.2 Key volume numbers

TOPIC	VOLUME	
Labeling	1	
Clinical study report, CA 139-022 (GOG 111)	3	
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Original GOG protocol	3	Page 206
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On treatment signs and symptoms	3	
Literature review, randomized studies	4-5	
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GOG-132	4	Page 199
Neijt et al	5	Page 1
du Bois et al	5	Page 48
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3.3 Administrative review

Notification of Submission Plans, June 10, 1997

Submission No. 069 to IND from the sponsor outlined the plan for the submission of data for a sNDA for approval of Taxol as first-line therapy of patients with ovarian cancer. The submission contained BMS protocol CA139-022 (GOG protocol 111), a copy of the published report of this study (McGuire WP, Hoskins WJ, Brady MF, et al. NEJM 334: 1-6, 1996), a description of the data collection, an example of a case report form, and an example of a data tabulation form. The sponsor indicated that the sNDA submission will contain a Bristol-Myers Squibb-generated study report, a Microsoft Access data tape, and SAS datasets. Hard copy data tabulations from the GOG study will be included as well.

The sponsor did not request a pre-sNDA meeting.

FDA Internal Pre-sNDA meeting.

Although the sponsor did not request a pre-sNDA meeting, the FDA reviewers met internally to ensure the completeness of the application. The following list of requirements was communicated to the sponsor:

- (1) Provide study reports from other first-line trials of paclitaxel for ovarian cancer (eg. GOG 132 presented by Muggia and the European/Canadian trial presented by Piccart at the American Society of Clinical Oncology [ASCO] meeting in 5/97)
- (2) Explain why BMS created their own database from the GOG database
- (3) Provide a description of significant differences between the BMS and GOG databases
- (4) Submit the original electronic GOG database
- (5) Include a list of patients where the BMS results for survival, time to progression, response rates, and serious adverse events were different from the GOG results
- (6) Provide the BMS case report forms for the patients listed in point 5
- (7) Provide an example of primary source data
- (8) Please give an estimate of the volume of source data forms for a given patient, since the reviewers may request copies of these forms for selected patients from the list generated in point 5
- (9) Include an electronic table in Access which documents the data (table name, field name, code, decode, label, and case report form page)
- (10) Please consider the possibility of electronic mail links for rapid communication

during the review process

Sponsor Response to FDA Requirements. July 22, 1997

The sponsor replied to each point individually:

1. The sponsor indicated that "At this time BMS does not have in its possession either the raw data nor study reports from these studies for inclusion in the application....". Instead, they planned to provide a review of all published data from randomized Phase III studies that used paclitaxel as first-line therapy for ovarian cancer and were initiated after GOG 111, and to provide the hard copies of the ASCO slide/poster presentations referred to in the FDA communication.
2. The sponsor indicated that the GOG database represented selective entry of available data. The BMS database is generated from raw data and is more complete.
3. The differences between the GOG and BMS databases are as follows:
 - The GOG generates a database with 1 record per patient with selected data; the BMS database uses multiple datasets and separate records for each treatment course, as appropriate.
 - The GOG database contains data for clinical response, surgical response, and time to progression. However, no information on individual lesion sizes is included. The BMS database contains all available tumor measurements with dates and permits calculation of response rate, time to progression, time to response, and duration of response.
 - The GOG database summarizes adverse events by the worst toxicity grade, but the categories of adverse events are limited to 12, and only events thought to be related to the study drugs are included. The BMS database reports adverse events more extensively (events/grades at each course of all documented events; multiple categories; all events, not just those related to study drugs) and includes all collected laboratory values.
4. The GOG electronic database will be included in the submission, although it has not been reviewed by BMS.
5. The requested list will be provided.
6. All BMS case report forms will be provided as electronic images only, if acceptable to the FDA.
7. and 8. The primary source data are the GOG flow sheets and case documentation. They average 50-75 pages per patient. The sponsor will include paper copies of the flow sheets, as they have not been imaged.
9. The requested table will be included.
10. The sponsor has scheduled a meeting with the appropriate FDA staff to identify and implement a secure system for electronic communication.

FDA telecon with Bristol-Myers Squibb. August 12, 1997

All of the responses to the FDA requirements were acceptable, including the proposal to submit the BMS case report forms as electronic images only, except for point 1. The telecon was held to discuss this point. Since the initial communication on July 3, the FDA staff became

aware of another large trial of paclitaxel as first-line therapy for ovarian cancer, the ICON3 (International Collaboration on Ovarian Neoplasm) study (Editorial, Lancet 349, No. 9066: 1635, June 7, 1997). To date, this trial has accrued 1254 patients, with a target accrual of 2000 patients. The FDA reviewers discussed the need to review the published literature in the context of the review of an NDA; the need for complete data was also stressed.

The agreements reached during this meeting were:

- BMS will contact the GOG and the European-Canadian study group to explore the availability of additional study information other than reprints or abstracts. This information could include statistical reports, unaudited raw data, or other available material
- BMS will contact the UK branch of its company to explore the availability of study information from the ICON3 trial
- BMS will submit the original protocols and amendments for all studies: GOG 111, GOG 132, the European-Canadian study, and ICON3

Bristol-Myers Squibb. Response to FDA Request for Information. September 12, 1997

In this communication, the sponsor agreed to provide statistical summaries and data tapes for GOG 132 and the European-Canadian study. The statistical summaries, ASCO abstracts, ASCO presentations, and study protocols will be provided in the sNDA application. When the data tapes are received from the investigators, they will be forwarded to the FDA reviewers.

The FDA agreed with the sponsor that no data listings, case report forms, or integrated summaries were necessary for these studies.

With regard to ICON3, the sponsor indicated that ICON3 "...is an ongoing study and that BMS is therefore unable to provide data from this study in the planned submission."

FDA communication to Bristol-Myers Squibb. September 22, 1997

The division stated that if an interim analysis for the ICON3 trial was conducted, the oncology reviewers would like the opportunity to evaluate the results. This information could be submitted during the course of the sNDA review.

Sponsor's Teleconference Request. February 9, 1998

The sponsor had previously indicated that it planned to have the principal investigators from the EORTC-NCI-C study and from the GOG-132 study present trial results during the sponsor's portion of the presentation. At an internal meeting, Dr. DeLap, Division Director, stated that while the sponsor could read an abstract or cite published results, data from trials not reviewed by FDA could not be presented. Dianne Spillman, Project Manager, conveyed this information to BMS during a telephone conversation. The sponsor then sent a facsimile requesting a teleconference to discuss this point. The teleconference was held and the division's position was reiterated.