CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number:NDA 8-453/S-001-004, S-006-012

Trade Name: ANECTINE INJECTION

Generic Name:(succinylcholine chloride)

Sponsor: Burroughs Wellcome Company

Approval Date:June 22, 1973

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA8-453/S-001-004, S-006-012

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				X
Approvable Letter			X	
Final Printed Labeling	X			
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI			X	
Pharmacology Review(s)			X	
Statistical Review(s)			X	
Microbiology Review(s)	X			
Clinical Pharmacology Biopharmaceutics Review(s)			X	
Bioequivalence Review(s)			X	
Administrative Document(s)	X			
Correspondence			X	

NDA 8-453/S-001,002

JUN 22 1973

AF 13-316

Burroughs Wellcome Company
Attention: D. A. Knight
3030 Cornwallis Road
Research Triangle Park,
North Carolina 27709

Gentlemen:

We acknowledge the receipt on March 2, 1973 of your communication dated February 27, 1973 regarding your supplemental new drug application of October 19, 1970 and February 2, 1971 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Anectine (succinylcholone chloride) Injection.

We also acknowledge receipt of your additional communication dated March 1, 1972.

The supplemental application provides for updating manufacturing information and labeling indication as required by the Federal Register Notice of August 26, 1970.

We have completed the review of this supplemental application, and it is approved. This action approves your application, as supplemented, on the basis of effectiveness of the drug as well as safety. The enclosures summarize the conditions relating to the approval of this application.

Sincerely yours,

cc: ATL-DO
OSE (BD-100)
DMD (BD-120)
DOC (BD-106)
IAS (BD-244)
JPurvis/6/8/73/ep/6/12/73

APPROVAL

George F. Leong, Ph.D.
Acting Director
Office of Scientific Evaluation
Bureau of Drugs

Enclosures:

Records and Reports Requirements(Reg.130.13)
Conditions of Approval of NDA

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION: BD-120

2. NDA NUMBER: 8-453

3. NAME AND ADDRESS OF APPLICANT *(City and State)*
Burroughs Wellcome
Research Triangle Park, N.C. 27709

4. DATE NDA APPROVED:

5. IF PRIOR TO OCT 10, 1962, DATE APPROVED FOR EFFICACY
August 14, 1952

6. NAME OF DRUG
Anectine

7. NONPROPRIETARY NAME
succinylochlone chloride

8. SUPPLEMENT

NUMBER	DATE
001	10/19/72
002	2/2/71

9. PURPOSE OF SUPPLEMENT
To provide updated manufacturing information as required by F.R. Notice of August 26, 1970

10. AMENDMENT DATE(s)
6/1/71 7/20/72
3/1/72 10/11/72
3/16/73 2/27/73

11. OTHER DATE *(Report, etc.)*

12. PHARMACOLOGICAL CATEGORY
Neuromuscular blocking agent

13. AF NUMBER
13-316

14. DOSAGE FORM
Injection

15. HOW DISPENSED
[X] Rx [ ] OTC

16. RELATED IND/NDA/MF(s)

17. POTENCY(ies)
2% and 500 mg/unit 100 mg./unit

18. NAS/NRC
[ ] UNDER REVIEW [X] REVIEWED

19. CHEMICAL NAME
Suxamethonium chloride

20. RECORDS AND REPORTS

CURRENT		REVIEWED	
[ ] YES	[ ] NO	[ ] YES	[ ] NO

21. CHEMICAL FORMULA

22. REMARKS
1. The assay submitted for methyl paraben in the dosage form is satisfactory
2. The microbiologist believes the preservative system is adequate provided normal precautions of aseptic procedure is observed during usage of multidose containers
3. Lot #2 - p-185 was miscalculated by company. Recalculation now shows potency % Succinylcholine chloride anhydrous now satisfactory.

23. CONCLUSIONS
Issue approval letter

24. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Robert N. Huckins	Robert N. Huckins	6/4/73

DISTRIBUTION [ ] ORIGINAL JACKET [ ] DUPLICATE JACKET [ ] REVIEWER

BD-100 BD-120 BD-120/RNHuckins/6/4/73 dea

NDA 8-453
Supp. #S-001, S-002
and unnumbered supplement
dated 2/27/73

May 30, 1973

MICROBIOLOGICAL REVIEW NOTES

Remarks:

These supplements did not provide any change in use of preservatives.

The firm has supplied data to demonstrate that the methylparaben present is compatible with the other ingredients in that it causes marked reduction in vegetative bacterial yeast and fungal challenges.

Conclusions:

The effectiveness of the preservative system is believed adequate provided normal precautions of aseptic procedure is observed during usage of the multidose containers.

Richard Norton

cc:
Orig. NDA
Dup. NDA
BD-100
BD-140
~~BD-400~~ BD120
BD-430
BD-145
BD-140/RNorton/5/30/73
yy/typed final: 5/30/73

NDA 13-453/S-001, S-002
AP 13-316

NOV 21 1972

Burroughs Wellcome Company
Attention: D. A. Knight
3030 Cornwallis Road
Research Triangle Park, North Carolina 27709

Gentlemen:

We acknowledge the receipt on October 16, 1972 of your communication dated October 11, 1972 regarding your supplemental new drug application of October 19, 1970 and February 2, 1971 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Anectine (succinylcholine chloride) Injection.

The supplemental application provides for updating manufacturing information as required by Federal Register Notice of August 26, 1970.

We have completed our review of this supplemental application. However, before we are able to reach a final conclusion the following additional information is necessary:

Please submit information to assure the sterility of the multiple dose vials is maintained during the actual period of use of the vials. It is necessary that an analytical procedure for methylparaben be submitted to the Administration in order to confirm that the potency of the methylparaben does not decrease below the labeled quantity during the stability studies.

We have reservations concerning the stability data submitted for Anectine Injection over the 24 month storage period. We note that Anectine Injection Lot #2-P-165 is below the accepted potency of % of label amount of succinylcholine chloride after 24 months of storage at 10°C. Potency data should be reported as percent of label amount of anhydrous succinylcholine chloride.

Please submit the above information promptly.

Sincerely yours,

Elmer A. Gardner, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Scientific Evaluation
Bureau of Drugs

cc: ATL-DO
OSE (BD-100)
DMD (BD-120)
Med (BD-106)
IAS (BD-242)
RHHuckins/11/10/72/esr/11/16/72
R/D init. by: RShultz/11/10/72

REV/NF

BD-120

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION: BD-120

2. NDA NUMBER: 8-453

3. NAME AND ADDRESS OF APPLICANT (City and State)
Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, N. C. 27709

4. DATE NDA APPROVED:

5. IF PRIOR TO OCT. 10, 1962, DATE APPROVED FOR EFFICACY
August 14, 1952

6. NAME OF DRUG: Anectine

7. NONPROPRIETARY NAME: succinylcholine chloride

8. SUPPLEMENT

NUMBER	DATE
001	10/19/70
002	2/2/71

9. PURPOSE OF SUPPLEMENT
To provide updated manufacturing information as required by F. R. Notice of August 26, 1970.

10. AMENDMENT DATE
6/1/71 7/20/72
3/1/72 10/11/72
3/16/72

11. OTHER DATE (Report, etc.)

12. PHARMACOLOGICAL CATEGORY
Neuromuscular blocking agent

13. AF NUMBER
13-316

16. RELATED IND/NDA/NF(s)

14. DOSAGE FORM
Injection

15. HOW DISPENSED
[XX] Rx [ ] OTC

17. POTENCY(ies) 2% and 500 mg/unit
1000 mg/unit

18. NAS/NRC
[ ] UNDER REVIEW [X] REVIEWED
FR 8/26/70

19. CHEMICAL NAME
Suxamethonium chloride

20. RECORDS AND REPORTS

CURRENT		REVIEWED	
[ ] YES	[ ] NO	[ ] YES	[ ] NO

21. CHEMICAL FORMULA

22. REMARKS
Letter from Burroughs Wellcome Co. contained following:
(1) It was not necessary to submit assay for methyl paraben as Company depends on other controls. GMP regulations are all that is necessary; unsatisfactory response.
(2) All tests are performed according to USP on drugs and dosage forms except in case of anectine Flopack 500 mg and 1000 mg where all USP tests are performed on bulk powder not on repacked package.
(3) Succinylcholine dichloride dihydrate USP calculated on anhydrous basis used in all formulations.

23. CONCLUSIONS
Issue Rev./WF. letter requesting the following:
(1) Information to assure the sterility of the multiple dose vials is maintained during the actual period of use of the vials. It is necessary that an analytical procedure be submitted for methyl paraben.
(2) Anectine Injection Lot #2-p-185 is below accepted potency after 24 months of storage. Potency data should be reported as percent of label amount of anhydrous succinycholine chloride.

24. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Robert N. Huckins		November 10, 1972

DISTRIBUTION [ ] ORIGINAL JACKET [ ] DUPLICATE JACKET [ ] REVIEWER

SEP 26 1972

NDA 8-453/S-001, S-002
AF 13-316

Burroughs-Wellcome Company
Attention: D. A. Knight
3030 Cornwallis Road
Research Triangle Park, North Carolina 27709

Gentlemen:

We acknowledge the receipt on July 24, 1972 of your communication dated July 20, 1972 regarding your supplemental new drug application of October 19, 1970 and February 2, 1971 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Anectine (succinylcholine chloride) Injection.

The supplemental application provides for updating manufacturing information as required by Federal Register Notice of August 26, 1970.

We have completed our review of this supplemental application. However, before we are able to reach a final conclusion the following additional information is necessary:

1. An assay for methyl paraben in the dosage form since all ingredients listed quantitatively on the label should have an analytical procedure to confirm the correct composition.

2. All tests for succinylcholine chloride included in the current NF should be performed on all lots of the bulk new drug substance and also for all lots of the final dosage form.

3. The information in your submission indicates that the succinylcholine chloride dehydrate salt is used in your formulations. If this is true, it should be designated as such in your composition statement and in the batch formula.

Please submit the above information promptly.

We will continue to reserve comment on the proposed labels and other labeling until the application is completed by submission of the above information.

Sincerely yours,

Elmer A. Gardner, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Scientific Evaluation
Bureau of Drugs

cc: ALT-DO
OSE (BD-100)
DND (BD-120)
Med (BD-106)
IAS (BD-242)
RHuckins/8/18/72/ajk/8/30/73/8/30/72/9/25/72

R/D init. by: RShultz/8/18/72

REV/M.F.

SUMMARY OF SUPPLEMENT.

NDA # 8-453.

9/13/72

Original approval date: 14 August 1952.

Trade name: Anectine.

Generic name: succinylcholine chloride.

Category of Drug: Anesthetic adjunct. Depolarizing neuromuscular blocking agent.

Date of Supplement: 1 March 1972.

Reason for Supplement: Final printed labeling.

Material reviewed: The supplement.

Summary: Final printed labeling has been submitted which is the same as the draft labeling submitted on 1 June 1971, and approved in a letter dated 21 July 1971. This package insert contains excellent and thorough prescribing for succinylcholine chloride. This is not surprising since Burroughs-Wellcome is the original clinical developer of succinylcholine chloride, and many of their current employees (including Dr. William P. Colvin) participated in this development.

Recommendation: This supplement, containing final printed labeling, is approved.

David L. Scally, M.D.

Division of Neuropharmacological Drug Products.
Office of Scientific Evaluation.
Bureau of Drugs.
Food and Drug Administration.
Department of Health, Education, and Welfare.

13 September 1972.

Orig Dup BD-100 BD-120 BD-120/DLScally

CHEM...'S VIEW
(If necessary, continue any on 8" x 10½" paper. Key continuation to ...m by number.)

1. ORGANIZATION: BD-120

2. NDA NUMBER: 8-453

3. NAME AND ADDRESS OF APPLICANT (City and State)
Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, N. C. 27709

4. DATE NDA APPROVED: Aug. 14, 1952

5. IF PRIOR TO OCT 10, 1962, DATE APPROVED FOR EFFICACY:

6. NAME OF DRUG: Anectine

7. NONPROPRIETARY NAME: Succinylcholine chloride

8. SUPPLEMENT

NUMBER	DATE
001	10/19/70
002	2/2/71

9. PURPOSE OF SUPPLEMENT
To provide updating manufacturing information as required by F. R. notice of August 26, 1970

10. AMENDMENT DATE(s)
6/1/71 7/20/72
3/1/72
3/16/72

11. OTHER DATE (Report, etc.)

12. PHARMACOLOGICAL CATEGORY
Neuromuscular blocking agent

13. AF NUMBER: 13-316

16. RELATED IND/NDA/MF(s)

14. DOSAGE FORM: Injectable

15. HOW DISPENSED
☒ Rx ☐ OTC

17. POTENCY(ies): 2%

18. NAS/NRC
☐ UNDER REVIEW ☒ REVIEWED
F. R. 8/26/70

19. CHEMICAL NAME: Suxamethonium chloride

20. RECORDS AND REPORTS

CURRENT		REVIEWED	
☐ YES	☐ NO	☐ YES	☐ NO

21. CHEMICAL FORMULA

22. REMARKS
Stability data satisfactory to justify a two year expiration date. M.O. has approve packet insert and labels. Updated manufacturing information needs the following additional information: 1. An assay for methyl paraben in final dosage form. 2. All tests for N.D.S. included in current NF should be performed on all lots of bulk N.D.S. and for final dosage form. 3. Clearification whether anhydrous or dihydrate used in composition and batch formula. If dihydrate used should be designated as such.

23. CONCLUSIONS
Issue Rev./wf letter requesting above information

24. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Robert N. Huckins		Aug. 18, 1972

DISTRIBUTION ☐ ORIGINAL JACKET ☐ DUPLICATE JACKET ☐ REVIEWER

FDH FORM 2266 (10/68) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED. 1

BD-120

BD 120

1 MAY 1972

NDA 8-453

Burroughs Wellcome Co.
Attention: D. A. Knight
3030 Cornwallis Road
Research Triangle Park,
North Carolina 27709

Dear Mr. Knight:

Your correspondence of March 16, 1972 is acknowledged in which you submitted twelve copies of your current vial and carton labeling for Anectine Injection.

We remind you that our letter of May 6, 1971 has not been answered in regard to current manufacturing information as required by the Federal Register Notice of August 25, 1970. The section referred to is XI (1) and (2). A copy of the notice is enclosed for your information.

We are reserving comment on the proposed labels and other labeling until the application is completed in other respects.

A prompt reply to this request will be appreciated.

Sincerely yours,

Elmer A. Gardner, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Scientific Evaluation
Bureau of Drugs

Enclosure

ATL-DO
Orig Dup
BD-1 BD-242 BD-22
BD-100/BD-120
BD-120/RNHuckins/3/29/72
init:RCShultz/3/30/72/cm/4/25/72

CHEMIST'S REVIEW
(If necessary, continue any item on "½" paper. Key continuation to item no.)

1. ORGANIZATION: BD-120

NDA NUMBER: 8-453

3. NAME AND ADDRESS OF APPLICANT (City and State)
Burroughs - Wellcome Co.
Research Triangle Park, North Carolina

4. DATE NDA APPROVED:

5. IF PRIOR TO OCT 10, 1962, DATE APPROVED FOR EFFICACY
August 14, 1952

6. NAME OF DRUG
Anectine

7. NONPROPRIETARY NAME
Succinylcholine chloride

8. SUPPLEMENT

NUMBER	DATE
001	10/19/70
002	2/ 2/71

9. PURPOSE OF SUPPLEMENT
Revised Labeling

10. AMENDMENT DATE(s)
6/ 1/71
3/ 1/72
3/16/72

11. OTHER DATE (Report, etc.)

12. PHARMACOLOGICAL CATEGORY
Neuromuscular blocking agent

13. AF NUMBER
13-316

16. RELATED IND/NDA/MF(s)

14. DOSAGE FORM
Injectable

15. HOW DISPENSED
[X] Rx [ ] OTC

17. POTENCY(ies)
2%, 5% and 10%

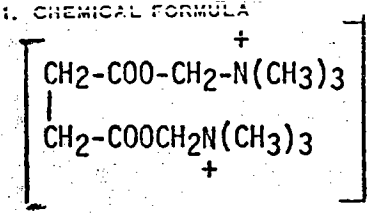
18. NAS/NRC
[ ] UNDER REVIEW [X] REVIEWED FR 8/26/70

19. CHEMICAL NAME
Suxamethonium chloride

20. RECORDS AND REPORTS

CURRENT	REVIEWED
[ ] YES [ ] NO	[ ] YES [ ] NO

21. CHEMICAL FORMULA



22. REMARKS
Our letter of May 6, 1971 has not been answered in regard to current manufacturing information as required by the FR Notice of August 26, 1970. This was included in letter to be issued below.

23. CONCLUSIONS.
Issue Rev/WF letter

24. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Robert N. Huckins		April 25, 1972

DISTRIBUTION [ ] ORIGINAL JACKET [X] DUPLICATE JACKET [ ] REVIEWER

FDH FORM 2266 (10/68) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

BD-120 init:RCShultz

BD-22 File

NDA 8-453

orig.
3/9/72

MEMORANDUM OF TELEPHONE CONVERSATION

Between:

Robert N. Huckins

and

Donald A. Knight Burroughs Wellcome Co.

Mr. Knight was informed that no current carton or immediate container labeling was submitted with their March 1, 1972 amendment. The last set of labels for the cartons and immediate containers were submitted in July 28, 1955. It was suggested that these labels be submitted as a supplement amendment. He agreed to do this.

Robert N. Huckins

cc:
(Orig. Dup. Trip.)
BD-100 BD-120 BD-22
BD-120/RNHuckins/3/9/72
R/D Init: RCSmith/3/9/72
T/Trip/3/10/72

NDA 8-453/S-001, S-002
AF

JUL 21 1971

Burroughs Wellcome & Company,
(U.S.A.), Incorporated
Attention: Dr. W. P. Colvin
3030 Cornwallis Road
Research Triangle Park, North Carolina 27709

Gentlemen:

Reference is made to your communication dated June 1, 1971, regarding your supplemental new drug application of February 2, 1971, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Anectine (succinylcholine chloride) Injection.

The supplemental application provides for revised labeling.

Changes of the kind which you have proposed are permitted by regulation to be made in advance of approval of the supplement.

The changes should be put into effect at the earliest possible time, preferably within 30 days. Please submit twelve copies of the final printed labeling as soon as available, and a statement of the date when the revised labeling is placed in use.

Yours truly,

Marvin Saife, M.D.
Deputy Director for Medical Affairs
Office of Scientific Evaluation
Bureau of Drugs

cc:
ATL-DO
OSE (BD-100)
DMD (BD-120)
Med (BD-22)
IAS (BD-242)
RSSilk 7/8/71/vs/7/15/71
R/D init. by: RShultz 7/9/71,
LGeismar 7/13/71

REVIEW DEFERRED

SUMMARY OF NDA OR SUMMARY OF SUPPLEMENT/////////.

Orig
Def
BD-100
BD-120

DATE SUMMARY COMPLETED: 2 July 1971.

NDA#: 8-453. Burroughs Wellcome & Co. (USA) Inc.

ORIGINAL APPROVAL DATE: 14 Aug 52. Revised 20 Aug 52.
Declared not a new drug on 1 Aug 55.

NAME OF DRUG: Trade- Anectine.

BD-120 (Delete)
R/D BD120
(Sandy)

Generic- succinylcholine chloride.

Structural formula (if indicated)- Not indicated.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

2% solution for I.M. and I.V. injection.
5% and 10% solution and sterile powder for preparation of dilute solutions for intravenous drip.

CATEGORY OR USE OF DRUG:

Neuromuscular blocking agent.

DATE OF SUPPLEMENT(S)////////////

1 Jun 71. Resubmission. NDA Suppl Amendment.

REASON FOR SUPPLEMENT(S)////////////

Labeling revision.

MATERIAL REVIEWED:

This submission.

Summary of 11 Mar 71.

Letter to B&W from Marvin Seife, M.D. dated 6 May 71.

SUMMARY:

This resubmission incorporates the suggestions contained in the 6 May 71 letter of Marvin Seife, M.D.

A final printed labeling is expected, when it is printed, if this is approved.

REVIEW OF THE LABELING:

This revision incorporates all necessary dispensing information on succinylcholine chloride. This includes all recent knowledge about toxicity in certain disease states; some of this work was supported by the sponsor. Burroughs Wellcome & Co. were active clinical developers of succinylcholine.

RECOMMENDATION:

This labeling supplement is approvable.

David L. Scally, M.D. B.D. 120.
Division of Neuropharmacological Drug Products.
Office of Scientific Evaluation.
Bureau of Drugs.
Food and Drug Administration.
Department of Health, Education, and Welfare, U.S.P.

Odate 07-08-71.

NDA 8-453/S-001, S-002

MAY 6 1971

AF 13-316

Burroughs Wellcome & Company, Inc.
Attention: Dr. W. P. Colvin
3030 Cornwallis Road
Research Triangle Park, North Carolina 27709

Gentlemen:

Reference is made to your supplemental new drug application of February 2, 1971 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Anectine (succinylcholine chloride).

We also acknowledge receipt of your additional communication dated October 19, 1970.

The supplemental application provides for revised labeling.

It is understood from the telephone discussion on January 29, 1971 between your representative Dr. W. P. Colvin and Dr. D. L. Scally of this Administration that only the first WARNING will be capitalized and placed in a box.

Changes of the kind which you have proposed are permitted by regulation to be made prior to approval of a supplement provided the conditions set forth in section 130.9(e) are met. The supplement fails to comply with those conditions in that final printed labeling has not been submitted.

We also note that the current manufacturing information as required by the Federal Register Notice of August 26, 1970 has not been received. The information should follow the outline as described in 21 CFR 130.4(f) a copy of which is enclosed for your use.

Since it is desirable that changes of this kind be put into effect at the earliest possible time, we request that you promptly submit the information indicated above.

Yours truly,

Marvin Seife, M.D.
Acting Director
Office of Scientific Evaluation
Bureau of Drugs

Enclosure

cc:
BLT-DO
OSE (BD-100)
OND (BD-120)
Med (BD-22)
IAS (BD-242)
WSKletch 4/14/71:mb 4/15/71
R/D init. by Scally Shultz, Geismar 4/15/71

REV. DEF.

CHEMIST REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION: OSE

2. NDA NUMBER: 8-453

3. NAME AND ADDRESS OF APPLICANT (City and State): Burroughs Wellcome & Co. Inc Research Triangle Park N.C. 27709

4. DATE NDA APPROVED:

5. IF PRIOR TO OCT 10, 1962, DATE APPROVED FOR EFFICACY:

6. NAME OF DRUG: Anectine

7. NONPROPRIETARY NAME: succinylcholine

8. SUPPLEMENT

NUMBER	DATE
001	10/19/70
002	3/2/71

9. PURPOSE OF SUPPLEMENT: revised labeling

10. AMENDMENT DATE(s):

11. OTHER DATE (Report, etc.):

12. PHARMACOLOGICAL CATEGORY: Neuromuscular blocking agent

13. AF NUMBER: 13-316

16. RELATED IND/NDA/MF(s):

14. DOSAGE FORM: Injectable

15. HOW DISPENSED: ☒ Rx ☐ OTC

17. POTENCY(ies): 2% 5% & 10%

18. NAS/NRC: FR 8/26/70 ☐ UNDER REVIEW ☒ REVIEWED

19. CHEMICAL NAME:

20. RECORDS AND REPORTS

CURRENT		REVIEWED	
☐ YES	☐ NO	☐ YES	☐ NO

21. CHEMICAL FORMULA:

22. REMARKS: Revised re FR of 8/26/70 See MOR dated 3/11/71 DR Scally Controls have not been updated as requested in F.R.

23. CONCLUSIONS: Review deferred ~~approvable~~ Recommend letter issue requesting FPL & updating information as per 130.4(F)(1)(4)(3)

4/1/71

24. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
		4/1/71

DISTRIBUTION ☐ ORIGINAL JACKET ☐ DUPLICATE JACKET ☐ REVIEWER BD-128

FDH FORM 2266 (10/68) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED. 1

NDA 6931/S-002
NDA 8453/S-003

APR 2 4 1975

Burroughs Wellcome Company
Attention: D. A. Knight
3030 Cornwallis Road
Research Triangle Park, N. C. 27709

Gentlemen:

Reference is made to your Supplemental New Drug Applications of March 10, 1975, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Syncurine (decamethonium bromide) Injection (NDA 6931) and for Anectine (succinylcholine chloride) Injection (NDA 8453).

The supplemental applications provide for the use of Limulus Amebocyte Lysate Test for pyrogens in Water for Injection.

The applications are incomplete under Section 505(b)(1) and (4) of the Act in that it fails to contain full reports of adequate tests by all methods reasonably applicable to demonstrate whether or not the Limulus Amebocyte Lysate Test performs effectively as an in vitro indicator of the presence of endotoxins, and of the development of standards designed to insure the continued safety, purity, and potency of this product. In this regard, we have the following comments:

(1) We refer you to the January 12, 1973 and September 18, 1973 FEDERAL REGISTER statements regarding "Biological Products" and "Limulus Amebocyte Lysate," respectively.

(2) The applications submitted provide the the use of the LAL Test as a final pyrogen test rather than as an in-process test, since the rabbit test is not performed on the finished drug. As a result, the Limulus Test is not exempt from the license requirements stated under Section 351 of the Public Health Services Act, and the 21 CFR 273 regulations pertaining to the propagation or manufacture, and preparation of such products.

Since the supplemental applications are incomplete under Section 505(b)(1) and (4) of the Act, they may not be filed as applications provided for in Section 505(b).

Sincerely yours,

Margaret A. Clark, M.D.
Acting Director
Division of Surgical-Dental
Drug Products
Bureau of Drugs

cc: NDA 6931/S-002; 8453/S-003
HFD-160
HFD-108
R/D SKoch (HFD-160) 4/9/75
R/D init. by RJerussi - 4/18/75
MClark - 4/18/75
INCOMPLETE
Final typed by sm - 4/22/75

APR 2 1975

CHEMIST REVIEW (If necessary, continue item on 8½" x 10½" paper. Key continuation item by number.)

1. ORGANIZATION: HFD-160

2. NDA NUMBER: 6931 / 8453

3. NAME AND ADDRESS OF APPLICANT (City and State)
Burroughs Wellcome Co.
Research Triangle Park, N.C. 27709

4. DATE NDA APPROVED: 7-15-49 / 8-14-52

5. IF PRIOR TO OCT 10, 1962, DATE APPROVED FOR EFFICACY: 6-22-73

6. NAME OF DRUG
Tubocurine
Anectine

7. NONPROPRIETARY NAME
decamethonium bromide
succinylcholine chloride

8. SUPPLEMENT
NUMBER: 5002, 5003
DATE: 3-10-75

9. PURPOSE OF SUPPLEMENT
provides for use of the Limulus Amebocyte Lysate test for pyrogens in Water for Injection.

10. AMENDMENT DATE(s)

11. OTHER DATE (Report, etc.)

12. PHARMACOLOGICAL CATEGORY
skeletal muscle relaxant

13. AF NUMBER: 13-316

16. RELATED IND/NDA/MF(s)

14. DOSAGE FORM
sterile soln.

15. HOW DISPENSED
☑ Rx ☐ OTC

17. POTENCY(ies)
1mg/ml 20mg/ml.

18. DRUG REQUIRES
☐ NDA ☐ ANDA

19. CHEMICAL NAME

20. RECORDS AND REPORTS

CURRENT		REVIEWED	
☑ YES	☐ NO	☐ YES	☐ NO

21. CHEMICAL FORMULA
FR notices on LAL 1-12-73, 9-18-73
Dec MEMO with Don Knight, B-W Co. dated 4-2-75, in which firm was informed this LAL test cannot be implemented under 314.8(d).

22. REMARKS
these drugs do not contain a test for pyrogens on their finished drug specification sheets (ref. 5/23/73 spec sheet 6931; 1/15/73 specs 8453); the distilled water pyrogen test is these NOT an in-process test. the 1-12-73 FR statement states LAL test cannot yet be used as the final pyrogen test. Determination made by the Commissioner that this test be marketed only under section 351 of PHS Act & section 505 of FFDC Act (FR of 9-18-73) – license request.

23. CONCLUSIONS
Incomplete letter under section 505(6)(1) and (4)

ATL-DO
cc: ~~NDAs 6931~~/8453 Orig.
HFD-160, HFD-102 (C. Kumkumian)
R/D S. Koch 4/10/75
R/D Init. R.A. Jerussi 4/17/75
Finalxerox PD 4/18/75

RAJ 4/17/75

24. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
S. KOCH		4-10-75

DISTRIBUTION ☐ ORIGINAL JACKET ☐ DUPLICATE JACKET ☐ REVIEWER

FORM FDH 2266 (11/73) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED. 1

NDA 8-453/S-004

DEC 05 1975

Burroughs Wellcome Co.
Attention: D. A. Knight
3030 Cornwallis Road
Research Triangle Park, North Carolina 27709

Gentlemen:

Reference is made to your communication of November 6, 1975 (received November 10, 1975) pertaining to your new drug application for Anectine (succinylcholine chloride) Injection, NDA 8-453. This communication has been classified as a supplemental new drug application under section 314.8(d).

The supplemental application provides for a revised package insert.

Changes of the kind which you have described may be made in advance of the approval of the supplement provided the conditions set forth in section 314.8(e) are met. We wish to point out that your submission did not follow the provisions of 314.8(e) in that we did not receive a supplement marked "Special new drug application supplement - Changes being effected" and that the supplement was not submitted promptly at the time the change was made effective. Please amend your NDA properly in the future when making changes under section 314.8(d).

In regard to the date the change was effective, we would appreciate an explanation of the discrepancy between the date printed on the package insert, January 1975, and the date you indicated the change was effective, June 1975.

We have completed our review of this supplemental application and it is approved. Our letter of August 20, 1952 detailed the conditions relating to the approval of this application.

Sincerely yours,

Margaret A. Clark, M.D.
Director
Division of Surgical-Dental Drug Products
Bureau of Drugs

cc: ATL-DO
NDA 8-453/S-004 Orig.
HFD-616
HFL-10
HFD-160
HFD-160/Document Room
R/D by: GBoyer 11/24/75
R/D Init. by: CMHealey Jr. 11/25/75
FKuerer 11/26/75
RAJerussi 11/26/75
MClark MD 11/26/75
Final typed by: pk 11/28/75

APPROVAL

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

160

NDA NUMBER: 8-453

DATE APPROVAL LETTER ISSUED: DEC 05 1975

TO: Press Relations Staff *(PA-40)*

FROM:
- [X] Bureau of Drugs
- [ ] Bureau of Veterinary Medicine

ATTENTION

Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

TYPE OF APPLICATION
- [ ] ORIGINAL NDA
- [X] SUPPLEMENT TO NDA
- [ ] ABBREVIATED ORIGINAL NDA
- [ ] SUPPLEMENT TO ANDA

CATEGORY
- [X] HUMAN
- [ ] VETERINAR

TRADE NAME *(or other designated name)* AND ESTABLISHED OR NONPROPRIETARY NAME *(if any)* OF DRUG

Anectine(succinylcholine chloride) Injection

DOSAGE FORM: Injectable

HOW DISPENSED
- [X] RX
- [ ] OTC

ACTIVE INGREDIENT(S) *(as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.)*

succinylcholine chloride

NAME OF APPLICANT *(Include City and State)*

Burroughs Wellcome Co.
Attn: D. A. Knight
3030 Cornwallis Road
Research Triangle Park, N.C. 27709

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

revised Precaution section of package insert

FORM PREPARED BY

NAME: Gary Boyer

DATE: 11/25/75

FORM APPROVED BY

NAME: [signature]

DATE: 12/2/75

NOV 18 1975

MEDICAL OFFICER'S REVIEW OF SUPPLEMENT

NDA 8-453/S004

DATE COMPLETED: November 17, 1975

Burroughs Wellcome Co.
3030 Cornwallis Rd.
Research Triangle Park
North Carolina

ORIGINAL APPROVAL DATE: 8/14/52

NAME OF DRUG: Tarade: Anectine
Generic: Succinylcholine

CATEGORY OF DRUG: Neuromuscular blocking agent.

DATE OF SUBMISSION: November 6, 1975

TYPE OF SUBMISSION: Supplement filed in accord with Section 314.8(d)(1) for revised labeling.

CLINICAL EVALUATION: The sponsor informs us that they have revised the package insert and put the revised insert into use effective June 1975. The revisions include:

1. To add the phrase "those receiving quinidine" to the first sentence of the second paragraph of the Precaution section.

2. In the same section edrophonium has been deleted from the second sentence of the fourth paragraph.

3. A new paragraph has been added to the Precautions section which describes malignant hyperthermia.

It should be noted that this revised package insert is dated January 1975 Futher, in the annual report dated 9/24/75 the revised insert is submitted and presumably was in effect at that time.

CONCLUSIONS: The revisions made in this package insert are medically acceptable; however, the exact date that this went into effect is uncertain as the insert is dated January 1975 and at this time the sponsor tells us it went into effect in June of 1975. Also, regardless of whether it went into effect in January or June of 1975, the sponsor should have notified us much more expeditiously.

RECOMMENDATIONS: Mr. Clarence Nealey, Supervisory Consumer Safety Officer, and Dr. Robert Jerussi, Supervisory Chemist, should review the appropriateness of this submission under these circumstances.

cc: NDA 8-453/S004
HFD-108, HFD-160
MClark,M.D.:HFD-160:11/17/75
Final typed from tape nm 11/19/75
Doc.Rm.-160

Margaret A. Clark, M.D.

a rate of from 0.5 mg (0.5 cc) to 10 mg (10 cc) per minute to obtain the desired amount of relaxation. The amount required per minute will depend upon the individual response as well as the degree of relaxation required. In the experience of Foldes, the average rate is 2.5 mg per minute. In the series reported by Little, Hampton and Grosskreutz, an average dose of 4.3 mg per minute was used. The 0.2% solution may be especially useful in those cases where it is desired to avoid overburdening the circulation with a large volume of fluid, e.g., cardiac cases. In any case, the rate of administration will be varied from time to time. The degree of relaxation can be regulated to the needs of the surgeon by adjusting the drip. Only freshly prepared solutions of succinylcholine should be used.

Intermittent intravenous injections of succinylcholine may also be used to provide muscular relaxation for long procedures. An initial intravenous injection of 20 to 80 mg may be given initially followed at appropriate intervals by further injections of 3 to 5 mg to maintain the degree of relaxation required.

The intravenous dose of succinylcholine for infants and children is 1.0 to 2.0 mg per kg.

Intramuscular Use: Succinylcholine may be given intramuscularly to infants, older children or adults when a suitable vein is inaccessible. A dose of up to 2.5 mg per kg may be given, but not more than 150 mg total dose should be given.

MANAGEMENT OF ADVERSE REACTIONS: Apnea or prolonged muscle paralysis should be treated with controlled respiration.

The use of neostigmine to reverse a non-depolarization block is a medical decision which must be made upon the basis of the individual clinical pharmacology and the experience and judgment of the clinician. When neostigmine is used atropine should also be administered.

Bibliography Available on Request

HOW SUPPLIED:

For immediate injection of single doses for short procedures:
ANECTINE brand SUCCINYLCHOLINE CHLORIDE INJECTION

20 mg in each cc (expressed as anhydrous succinylcholine chloride)
Multiple-dose vials of 10 cc — for intravenous injection
ANECTINE Injection is a sterile solution made isotonic with sodium chloride, pH adjusted with hydrochloric acid and preserved with methylparaben 0.1%.

Also Available:

For preparation of intravenous drip solutions only:

ANECTINE brand SUCCINYLCHOLINE CHLORIDE (expressed as anhydrous succinylcholine chloride)

*FLO-PACK®, 500 mg Sterile Powder. For preparation of dilute solutions for intravenous drip only.

HIGH POTENCY ANECTINE brand SUCCINYLCHOLINE CHLORIDE (expressed as anhydrous succinylcholine chloride)

*FLO-PACK®, 1000 mg Sterile Powder. For preparation of dilute solutions for intravenous drip only.

*U.S. Patent Nos. 2,957,501 - 2,957,609

BURROUGHS WELLCOME CO.
Research Triangle Park, N.C. 27709
Printed in U.S.A. Jan 1975 411012

411012

APPROVED DEC 05 1975

Wellcome

ANECTINE® brand SUCCINYLCHOLINE CHLORIDE

This drug should be used only by individuals familiar with its actions, characteristics and hazards.

DESCRIPTION: Anectine brand Succinylcholine Chloride is an ultra short-acting depolarizing type muscle relaxant. Chemically it is a di-quaternary base consisting of the di-chloride salt of the dicholine ester of succinic acid. It is a white, odorless, slightly bitter powder and very soluble in water. The drug is unstable with alkaline solutions, but relatively stable in acid solutions depending upon the concentration of the solution and the storage temperature. While solutions of succinylcholine chloride are sterilized by autoclaving, they should, nevertheless, be stored under refrigeration to preserve their potency.

ACTIONS: Anectine brand Succinylcholine Chloride causes skeletal muscle paralysis by blocking neural transmission at the myoneural junction. It competes with acetylcholine for the cholinergic receptors of the motor end plate. Like acetylcholine, bond with these receptors produces a depolarization followed by an initial transient muscle contraction often visible as fasciculations. Neuromuscular transmission then becomes inhibited and remains so as long as there is an adequate concentration of succinylcholine at the receptor sites. The neuromuscular block so achieved produces a flaccid paralysis of skeletal muscles. Succinylcholine is dissipated through the enzymatic action of pseudocholinesterase at such a rate that the effect of a single paralyzing dose of the drug generally disappears within 8 to 10 minutes. When a single effective dose of the drug is given intravenously, muscular relaxation occurs within a minute, persists for about 2 minutes and returns to normal within 8 to 10 minutes. If a paralyzing dose is given intramuscularly, the onset of action may be delayed for 2 to 3 minutes. When given by intravenous drip, a predetermined degree of muscular relaxation can be closely approximated by adjusting the rate of flow of the infusion.

An important difference between succinylcholine and tubocurarine is that the former is not generally antagonized by anticholinesterases. On the contrary, such drugs as physostigmine, neostigmine and procaine usually prolong the action of succinylcholine. This would support the theory that succinylcholine is hydrolyzed by cholinesterases and that interference with this enzyme action results in persistence of activity of the drug. Succinylcholine is rapidly hydrolyzed by pseudocholinesterase to succinylmonocholine (a weak non-depolarizing type of muscle relaxant), and then more slowly to the normal metabolites succinic acid and choline. However, about 10% of the drug is excreted unchanged in the urine. The drug's action may be additionally altered by acetylcholine, dehydration, hypothermia, electrolyte imbalance, certain antibiotics, some carcinomas, procaine-type local anesthetics or the administration of other non-depolarizing or depolarizing muscle relaxants.

The drug has no known effect on consciousness, the pain threshold or cerebration. It should, therefore, be used only during adequate anesthesia.

The paralysis following the administration of succinylcholine is generally initially selective and usually appears in the following muscles consecutively: levator muscles of the eyelids, muscles of mastication, limb muscles, abdominal muscles, muscles of the glottis and finally intercostal muscles and the diaphragm. The drug has no direct effect on the myocardium. Initially a transient bradycardia accompanied by hypotension, arrhythmias and even a sinus arrest may occur during endotracheal intubation due to an increase in vagal tone. This is noted particularly in children and is more apparent with repetitive injections than following continuous intravenous drip administration. These effects are enhanced by cyclopropane and halothane and are inhibited by thiopental and atropine. Later the drug may cause tachycardia and hypertension as a result of an asphyxial pressor response and mild sympathetic ganglion stimulation.

Succinylcholine causes a slight, transient increase in intraocular pressure. The effect is seen immediately after its injection and during the fasciculation phase. It appears to be the result of brief contraction of the extraocular muscles. This suggests that the drug should not be used when open eye injury is present and should be used with caution, if at all, in intraocular surgery. The opinion is expressed that the effect is probably not sufficient to contraindicate the drug in general surgery or electroshock therapy for patients with glaucoma or in patients undergoing eye surgery under general anesthesia.

Succinylcholine has no direct effect on the uterus or other smooth muscles. The drug is highly ionized and has a low lipid solubility; therefore, it will not cross the placenta readily. Further, the enzymatic destruction of succinylcholine is an important factor in controlling the concentration gradient. Infants are relatively more resistant to depolarizing relaxants than adults.

Tachyphylaxis may occur after repeated doses of succinylcholine.

NOTE: On rare occasions when succinylcholine is given over a long period of time, the characteristic depolarization block of the myoneural junction changes to a non-depolarizing block resulting in prolonged respiratory depression or apnea similar to the blockade caused by tubocurarine. Under those circumstances small repeated doses of prostigmine may shorten the action of succinylcholine.

INDICATIONS: Succinylcholine chloride is indicated as an adjunct to anesthesia to induce skeletal muscle relaxation. It may be employed to reduce the intensity of muscle contractions of pharmacologically or electrically induced convulsions.

CONTRAINDICATIONS: Succinylcholine is contraindicated for persons with a known hypersensitivity to the drug.

WARNINGS:

WARNING: Succinylcholine should be used only by those skilled in the management of artificial respiration and only when facilities are instantly available for endotracheal intubation and for providing adequate ventilation of the patient, including the administration of oxygen under positive pressure and the elimination of carbon dioxide. The clinician must be prepared to assist or to control respiration.

Succinylcholine should not be mixed with short-acting barbiturates in the same syringe, or administered simultaneously during intravenous infusion through the same needle. Solutions of succinylcholine have an acid pH whereas those of barbiturates are alkaline in reaction. Depending upon the resultant pH of a mixture of solutions of these drugs, either free barbituric acid may be precipitated or succinylcholine hydrolyzed.

Usage in Pregnancy: The safe use of succinylcholine has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

PRECAUTIONS: Low levels of, or abnormal variants of plasma cholinesterase may be associated with prolonged respiratory depression or apnea following the use of succinylcholine. Low levels of plasma cholinesterase may occur in patients with severe liver disease or cirrhosis, severe anemia, malnutrition, severe dehydration, changes in body temperature, exposure to neurotoxic insecticides or those receiving antimalarial drugs. Succinylcholine should be administered with extreme care to such patients and dosage should be minimal. If low plasma cholinesterase activity is suspected, a small test dose of from 5 to 10 mg of succinylcholine may be administered, or relaxation may be produced by the cautious administration of a 0.1% solution of the drug by intravenous drip. Drugs which either inhibit plasma cholinesterase, such as neostigmine or phospholine iodide, or compete with succinylcholine for the enzyme, as does intravenous procaine, should not be given concurrently with succinylcholine.

Succinylcholine should be administered with great caution to patients with severe burns, those recovering from severe trauma, those suffering from electrolyte imbalance, those receiving quinidine, those who have been digitalized recently or who may have digitalis toxicity as serious cardiac arrhythmias or cardiac arrest may result. Great caution should be observed also in patients with

pre-existing hyperkalemia or who are paraplegic, have suffered spinal neuraxis injury, or have degenerative or dystrophic neuromuscular disease, as such patients tend to become severely hyperkalemic when succinylcholine is given.

When succinylcholine is given over a prolonged period of time, the characteristic depolarization block of the myoneural junction may change to a non-depolarizing block which results in prolonged respiratory depression or apnea. Under such circumstances, small repeated doses of neostigmine may possibly act as an antagonist. A peripheral nerve stimulator (e.g. the Wellcome Peripheral Nerve Stimulator) may be used to ascertain the type of neuromuscular blockade. If a depolarization block is present both fast (tetanic) and slow (twitch) rates of nerve stimulation are well sustained, and post-tetanic facilitation is absent. If a non-depolarizing block is present there is post-tetanic facilitation and "fade" of successive stimuli on both fast (tetanic) and slow (twitch) rates of nerve stimulation.

Succinylchloride should be used with caution during ocular surgery and in patients with glaucoma. The drug should be employed with caution in patients with fractures or muscle spasm as the muscle fasciculations may cause additional trauma. Muscle fasciculations and hyperkalemia may be reduced by administering a small dose of a non-depolarizing relaxant. If other relaxants are to be used during the same procedure, the possibility of a synergistic or antagonistic effect should be considered.

During the past few years, reports have called attention to a fulminant syndrome, malignant hyperthermia, observed during anesthesia. Its etiology is not fully understood. Malignant hyperthermia occurs in genetically prone individuals of all ages and both sexes receiving potent anesthetics such as halothane, methoxyfluothane, cyclopropane and diethyl ether. It appears to develop irrespective of the concomitant use of a muscle relaxant, but may be triggered by succinylcholine. Because of the seriousness of this syndrome and the need for early effective treatment of the patient, it is suggested that the continuous monitoring of the temperature will serve as an aid to the early recognition of malignant hyperthermia.

ADVERSE REACTIONS: Adverse reactions consist primarily of an extension of the drug's pharmacological actions. Profound and prolonged muscle relaxation may occur, resulting in respiratory depression to the point of apnea. Hypersensitivity to the drug may exist in rare instances.

The following adverse reactions have been reported: bradycardia, tachycardia, hypertension, hypotension, arrhythmias, cardiac arrest, prolonged respiratory depression or apnea, hyperthermia, increased intraocular pressure, muscle fasciculation, postoperative muscle pain, myoglobinemia and excessive salivation.

DOSAGE AND ADMINISTRATION: The dosage of succinylcholine is essentially individualized and its administration should always be determined by the clinician after careful assessment of the patient.

To avoid distress to the patient, succinylcholine should be administered only after unconsciousness has been induced.

FOR SHORT SURGICAL PROCEDURES: The average dose for relaxation of short duration is 40 mg (2.0 cc) Anectine brand Succinylcholine Chloride Injection given intravenously. The optimum dose will vary among individuals and may vary from 20 to 30 mg for adults (1.0 to 4.0 cc). Following administration of doses in this range, relaxation develops in about 1 minute; maximum muscular paralysis may persist for about 2 minutes, after which recovery rapidly takes place within 8 to 10 minutes. However, very large doses may result in more prolonged apnea. An initial test dose of 10 mg (0.5 cc) may be used to determine the sensitivity of the patient and the individual recovery time from the drug.

FOR LONG SURGICAL PROCEDURES: The dosage of succinylcholine chloride administered by infusion depends upon the duration of the surgical procedure and the need for muscle relaxation. The average rate of administration for continuous intravenous infusion is 2.5 mg per minute for adult patients. Solutions containing from 0.1% to 0.2% (1 to 2 mg per cc) succinylcholine chloride have commonly been used for continuous intravenous drip. Solutions of 0.1% or 0.2% may conveniently be prepared by adding 1 g succinylcholine chloride (the contents of one 10 cc ampul containing 100 mg per cc or of one Anectine brand Succinylcholine Chloride Sterile Powder Flo-Pack unit containing 1 g) respectively to 1,000 or 500 cc of sterile solution such as sterile 5% dextrose solution or sterile isotonic saline or lactate solution. The more dilute solution (0.1% or 1 mg per cc) is probably preferable from the standpoint of ease of control of the rate of administration of the drug and hence, of relaxation. This intravenous drip solution containing 1 mg per cc may be administered at

NDA 8453/S-006

Burroughs Wellcome Co.
Attention: D. A. Knight
3030 Cornwallis Road
Research Triangle Park, NC 27709

MAR 30 1978

Gentlemen:

We acknowledge the receipt on February 8 and March 1, 1978 of your communications dated February 2 and March 1, 1978 regarding your supplemental new drug application of December 7, 1977 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Anectine (succinylcholine chloride) Injection.

The supplemental application provides for to be an alternate supplier of the active ingredient succinylcholine chloride.

We have completed the review of this supplemental application as amended and it is approved. Our letter of June 22, 1973 detailed the conditions relating to the approval of this application.

Sincerely yours,

Philip G. Walters, M.D.
Acting Director
Division of Surgical-Dental
Drug Products
Bureau of Drugs

APPROVAL

cc: NDA 8453/S-006
~~HFD-160~~
~~HFD-616~~
Doc.Room/HFD-160
R/D SKoch 3/17/78
R/D Init. RAJerussi 3/24/78
R/D Init. PGWalters 3/30/78
ft pd 3/30/78

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER: 3/S-006

DATE APPROVAL LETTER ISSUED: MAR 30 1978

TO: Press Relations Staff *(PA-40)*

FROM:
- [X] Bureau of Drugs
- [ ] Bureau of Veterinary Medicine

ATTENTION

Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

TYPE OF APPLICATION
- [ ] ORIGINAL NDA
- [X] SUPPLEMENT TO NDA
- [ ] ABBREVIATED ORIGINAL NDA
- [ ] SUPPLEMENT TO ANDA

CATEGORY
- [X] HUMAN
- [ ] VETERINARY

TRADE NAME *(or other designated name)* AND ESTABLISHED OR NONPROPRIETARY NAME *(if any)* OF DRUG

Anectine (succinylcholine chloride) Injection

DOSAGE FORM

HOW DISPENSED
- [XX] RX
- [ ] OTC

ACTIVE INGREDIENT(S) *(as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.)*

succinylcholine choride 20 mg/ml

NAME OF APPLICANT *(include City and State)*

Burroughs Wellcome Co.
Research Triangle Park, NC 27709

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

skeletal muscle relaxant

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

manufacturing revision

FORM PREPARED BY

NAME

DATE: 3-24-78

FORM APPROVED BY

NAME

DATE: 3-30-78

Form FD 1642 (4/73) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

CHEMI' REVIEW
(If necessary, continue Item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATIO' HFD-160

2. NDA NUMBER 8453

3. NAME AND ADDRESS OF APPLICANT (City and State)
Burroughs Wellcome Co.
Research Triangle Park, N.C. 27709

4. AF NUMBER 13-316

5. SUPPLEMENT (S)

NUMBER(S)	DATE(S)
S-006	12-7-77

6. NAME OF DRUG
Anectine Injection

7. NONPROPRIETARY NAME
succinylcholine chloride injection (SCC)

8. SUPPLEMENT(S) PROVIDES FOR:
as an alternate.
supplier of the active ingredient-succinylcholine chloride.
Periodic report

9. AMENDMENTS AND OTHER (Reports, etc.) DATES
2-2-78
3-1-78
9-13-77 R-11

10. PHARMACOLOGICAL CATEGORY
muscle relaxant

11. HOW DISPENSED
☑ Rx ☐ OTC

12. RELATED IND/NDA/DMF(S)

13. DOSAGE FORM (S)
sterile solution & powder

14. POTENCY (Iso)
20 mg/ml

15. CHEMICAL NAME AND STRUCTURE
Insert in R-11 dated 7-75.

16. RECORDS AND REPORTS
CURRENT ☑ YES ☐ NO
REVIEWED ☑ YES ☐ NO

17. COMMENTS
Spoke with HFD-322 (W. Brown) 3/16/78; a 7/20-21/76 inspection of plant was satisfactory on CGMP compliance, and will be basis for favorable action on this request. Processing of this supplement will not await receipt of written word from HFD-322.
The 2/2-78 amendment renews processing of raw material active ingredient on receipt at B-W from includes a statement from dated 1-24-78 confirming supplied material to be in compliance with USP XIX specs, and provides revised specifications & test sheets for SCC. The Specifications & Sampling Inst. (item # 24959-60) are dated 2-24-78 (acc 3/1-78 S/A), and the Testing Instn are dated 2/23-77. Revisions: particulate matter limits*, microbial count procedure, and pH limits 4.0-5.0 from 3.5-4.5 (on 5% soln). General method for the determination of particulate matter (GM 04-17 dated 12-8-76) includes.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend S006 Approval
No Reply manufacturing & controls, R-11

cc: NDA 8453/S-006
HFD-160, Doc. Room/HFD-160
R/D SKoch 3/16/78
R/D Init. RAJerussi 3/24/78
fx pd 3/30/78

*nmt 100 particles ≥ 50 mcg/10 grams.

RAJ 3/24/78

MAR 30 1978

19. REVIEWER
NAME
SIGNATURE
DATE COMPLETED 3-16-78

DISTRIBUTION ☐ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE

FORM FDH 2266 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

NDA 8-453/S-007

MAY 22 1985

Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, NC 27709

Attention: Donald A. Knight

Gentlemen:

Please refer to your supplemental new drug application dated July 23, 1979 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Anectine (succinylcholine chloride) Injection, USP and Sterile Powder Flo-Pack.

We also acknowledge your additional correspondence dated February 26, 1980, January 19, 1982, January 27, 1983 and August 30, 1984 amending the application.

This supplement (S-007) provides for a revision in the multiple dose vial formulation to include % excess of and sterilization of the Flo-Pack.

We have completed our review of this supplemental application and it is approved. Our letter of June 22, 1973, detailed the conditions relating to the approval of this application.

Sincerely yours,

Patricia H. Russell, M.D.
Acting Director
Division of Surgical-Dental
Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

cc: ATL-DO (HFR-4100)
NDA 8-453
HFN-160
HFN-83
Doc. Room 160
R/D: JPHannan 5/17/85
R/D init by PHRussell 5/20/85, GBoyer 5/20/85, PHCooney 5/20/85
FT td W1810Y 5/21/85

APPROVAL

Microbiologist's

~~CHEMIST'S~~ REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION: HFN-160

NDA NUMBER: 8-453

4. AF NUMBER:

3. NAME AND ADDRESS OF APPLICANT (City and State)
Burroughs Wellcome Co.
Research Triangle Park, NC 27709

5. SUPPLEMENT (S)

NUMBER(S)	DATE(S)
S-007 RS	8/30/84

6. NAME OF DRUG: Anectine Injection and Flo-Pack

7. NONPROPRIETARY NAME: succinylcholine chloride

8. SUPPLEMENT(S) PROVIDES FOR:
Revision in the multiple dose vial formulation to include a % excess & and & Flo-Pack.

9. AMENDMENTS AND OTHER (Reports, etc.) DATES

10. PHARMACOLOGICAL CATEGORY: muscle Relaxant

11. HOW DISPENSED: ☒ RX ☐ OTC

12. RELATED IND/NDA/DMF(S)
8-453/S-007 7/23/79
S-453/S-007 RS 2/26/80
8-453/S-007 RS 1/31/82
8-453/S-007 RS 1/27/83

13. DOSAGE FORM (S): Sterile Powder or solution for Injection

14. POTENCY (Iso)

15. CHEMICAL NAME AND STRUCTURE

16. RECORDS AND REPORTS
CURRENT: ☐ YES ☐ NO
REVIEWED: ☐ YES ☐ NO

cc: NDA 8-453
HFN 160, Doc Room 160
R/D PCooney, 9/28/84
R/D init. by CPHoiberg, 10/1/84&PGW/PHR, 10/1/84

17. COMMENTS

See attached Review Notes.

OCT 0 4 1984

18. CONCLUSIONS AND RECOMMENDATIONS

Approve the supplement for sterilization of Flo-Pack using the hr cycle. Sterility assurance level = 10^{-3}.

PGW/PHR 10-1-84

19. REVIEWER

NAME:

SIGNATURE: 10/1/84

DATE COMPLETED: 9/28/84

DISTRIBUTION: ☐ ORIGINAL JACKET ☒ REVIEWER ☐ DIVISION FILE

FORM FDA 2266 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

E. Review Notes

The path of submission and resubmission of this supplement has been lengthy. Provided below is a brief history, particularly of the submission as it pertains to sterilization of the Flo-Pack.

The Burroughs Wellcome Annual Report #12, dated November 28, 1978, mentioned several manufacturing changes related to these products, including sterilization of the Flo-Pack product. The process described is essentially analgous to an process since there is an sterilization.

The Administration responded in a letter dated March 12, 1979 in which it was stated that some of the manufacturing and control changes would require submission of a supplemental new drug application. Questions were posed concerning the sterilization.

NDA 8-453/S-007, dated July 23, 1979, was submitted in response by Burroughs-Wellcome. The cycle was briefly described and it was stated that the other components of the Flo-Pack are sterilized in the same cycle.

The Administration's response was a letter dated November 2, 1979 in which further requests were made including microbiological data to support the efficacy of the cycle and the procedures used to monitor production cycles.

Burroughs Wellcome then resubmitted the application (NDA 8-453/S-007 RS, February 26, 1980). The cycle description was essentially 12 hr., 0% relative humidity, 130°F, and 30.7 psi of 83/12 . A microbiological study was supplied indicating a sterility assurance level of 10^{-6}.

Review of the resubmission(#1) indicated that it was again insufficient. The Administration's letter of November 21, 1970 asked for further information including clarification of qualification studies, validation data generated in production vessels, qualification data for closure componentry, bioburden limits, concentration of for production cycles, and monitoring procedures for production cycles.

The company resubmitted the supplement which was dated Jan. 19, 1982. The information submitted was again deemed insufficient and the administration again asked for clarification in a letter dated June 12, 1982.

Burroughs Wellcome responded with yet another resubmission dated Jan. 27, 1983, and the Administration responded with further questions in a letter dated June 6, 1984. The response to those questions is the subject of this review, NDA-8-453/S-007RS, August 30, 1984.

It should be noted that the quality of the submissions responding to the Administration's letters is poor in the opinion of this reviewer. This supplement, in particular that portion dealing with the sterilization of the Flo-Pack, has had a long and arduous history (since July 23, 1979). It should further be pointed out that it seems the company has been marketing the drug using the process since that time without an approved supplement (as indicated from distribution data in annual reports).

Since the Flo-Pack is after sterilization, the expected sterility assurance level for this drug would be 10^{-3}. The data submitted over the long history of this supplement indicate that the cycle is sufficient to ensure such a level of sterility. End-product sterility testing which is required for release of lots gives further evidence at the 10^{-3} level. It is for these reasons that the supplement is now recommended for approval of the hour sterilization cycle of the Flo-Pack.

Peter H. Cooney, Ph.D.
9/28/84

FT-jb,W3065P,D0061P,10/2/84

NDA 8453/S-007

Division of Surgical-Dental Drug Products
Microbiologist's Review No. 1
October 25, 1979

A.1. NDA: 8453/S-007
Applicant: Burroughs Wellcome Co.
Research Triangle Park, NC 27709
AF#: 13-316

2. Product Name: Anectine(R) Injection
Anectine(R) Flo-pack
Nonproprietary: Succinylcholine chloride

3. Dosage Form: Sterile solution with powder, 10cc vial (20 mg/ml). Rx.

4. Pharmacological Category: Skeletal muscle relaxant

B.1. Initial Submission: July 23, 1979. Subject of this Review.

2. Amendments: N/A.

C. Remarks:

1. The submission responds to the Administration's letter of March 12, 1979, which addressed Annual Report No. 12 dated November 28, 1978. Review chemist requested a supplement to provide for changes in formulation and manufacturing procedures.

2. Supplement provides for (1) a % excess of in the compounding of the 20 mg/ml MDV dosage form and (2) sterilization of the Flo-Pack bottles and package with

D. Conclusions:
Request that applicant address the following: (1) Rationale for terminal heat process applied to 20 mg/ml vial. (2) Microbiological data to support efficacy of cycle and procedures used to monitor production cycles.

Vivjan Greenman

NDA 8453/S-007
HFD-160
R/D VGreenman 10/25/79
R/D Init RAJerussi 10/27/79; JPMann 10/29/79
Doc Room 160
ft mv 10/31/79

NOV 02 1979

NDA 8453
HFD-160
R/D SKoch 9/20/79
R/D Init RAJerussi 10/3/79; JPMann 10/29/79
fx 10/30/79 Doc Room 160

CHEMIST REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION	2. NDA NUMBER
HFD-160	8453

3. NAME AND ADDRESS OF APPLICANT (City and State)	4. AF NUMBER
Burroughs Wellcome Co. Research Triangle Park, N.C. 27709	13-316

5. SUPPLEMENT (S) NUMBER(S)	5. SUPPLEMENT (S) DATE(S)
S-007	7/23/79

6. NAME OF DRUG	7. NONPROPRIETARY NAME
Anectine Injection	succinylcholine chloride

8. SUPPLEMENT(S) PROVIDES FOR:
revised MDV formulation to provide for 5% xs of
In addition, the
sterilization of the filled Flo-Pack bottle, is described.
this submission in response to our 3-12-79 supplement
request ltr generated by changes described in 2-12 (11-28-78).

9. AMENDMENTS AND OTHER (Reports, etc.) DATES

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF(S)
skeletal muscle relaxant	☒ RX ☐ OTC	

13. DOSAGE FORM (S)	14. POTENCY (Ies)
sterile soln	20 mg/ml

15. CHEMICAL NAME AND STRUCTURE
Specs & Sample Inst. + Test Inst. on Sterile Flo-Pack powder
500mg & 1000 mg. issue date = 6-21-79.

16. RECORDS AND REPORTS
CURRENT ☒ YES ☐ NO
REVIEWED ☒ YES ☐ NO

17. COMMENTS
The formulation change due to low potency at time of
manufacture averaging 94% label. Placed into effect 5-31-78.
Information on sterilization of filled Flo-Pack bottles: usual 88°/12
min exposure time 12 hrs /130°F followed by 5 vacuum cycles + hold
period. Acceptance limit for residual said to be 10 ppm,
but Spec Sheet states residue level of not to 10 ppm "for information only,
not required for approval."
First 20mg/ml vial sterilization step has not been dropped as implied in periodic
report. However, rationale of 104.4°C/35 min cycle not clear.
The nitrogen & pH Tests on succinylcholine chloride raw material have been
deleted because the perchloric acid titration assay and free acid test perform
same function.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend Revised/waiting Final letter requesting addnl info on
(1) process & residue specs (2) rationale for terminal 20 mg/ml vial
sterilization step (3) tests conducted on finished Flo-Pack vial. See attached
draft letter.
This supplement should be reviewed by V. Grenmarr as microbiologist prior to
letter issue. NOV 02 1979

RCJ 10/3/79 JPM 10/29/79

19.
NAME — REVIEWER SIGNATURE — DATE COMPLETED 9-20-79

DISTRIBUTION ☐ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE

FORM FDH 2244 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED. 1

NDA 8453/S-008

Burroughs Wellcome Co.
Attention: D.A. Knight
3030 Cornwallis Road
Research Triangle Park, N.C. 27709

NOV 21 1980

Gentlemen:

Please refer to your supplemental new drug application of February 26, 1980 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Anectine Injection

The supplemental application provides for revision in the manufacturing procedure to delete the

We have completed the review of this supplemental application and it is approved. Our letter of June 22, 1973 detailed the conditions relating to the approval of this application.

Sincerely yours,

James P. Mann, M.D.
Director
Division of Surgical-Dental
Drug Products
Bureau of Drugs

APPROVAL

cc: NDA 8453/S-008
ATL-DO (HFD-4100)
HFD-160
HFD-616
HFD-160/V.Greenman, SKoch
R/D by JMSinger(HFD-160)11/13/80
R/D Init. by GBoyer 11/13/80, CRodriguez 11/14/80 & JPMann 11/14/80
Final Typed by JK 11/20/80
Doc. Rm. 160

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION: HFD-160

2. NDA NUMBER: 8453

3. NAME AND ADDRESS OF APPLICANT (City and State)
Burroughs Wellcome Co
Research Triangle Park, NC 27709

4. AF NUMBER: 13-316

5. SUPPLEMENT (S)

NUMBER(S)	DATE
5-007	2/26
5-008	2/26

6. NAME OF DRUG: Anectine Injection

7. NONPROPRIETARY NAME: succinylcholine chloride inj

8. SUPPLEMENT(S) PROVIDES FOR:
5007 → revised MDV formulation to provide for % - XS of
In addition, the sterilization of the filled Flo-Pack bottles is described. This submission is submitted in response to our 11-2-79 R/WF letter (S-007)
S-008 provides for deletion of 20 mg/ml MDV terminal sterilization

9. AMENDMENTS AND OTHER (Reports, etc.) DATES

10. PHARMACOLOGICAL CATEGORY: skeletal muscle relaxant

11. HOW DISPENSED: ☒ RX ☐ OTC

12. RELATED IND/NDA/DMF

13. DOSAGE FORM (S): sterile solution

14. POTENCY (ies): 20 mg/ml

15. CHEMICAL NAME AND STRUCTURE
see 9-20-79 Chem Review

16. RECORDS AND REPORTS
CURRENT ☐ YES ☐ NO
REVIEWED ☐ YES ☐ NO

17. COMMENTS
Firm requests permission to drop final procedure of 20 mg/ml MDV. See S-008.
Regarding sterilization residues, firm says release specs for those Anectine dosage forms so sterilized are 10 ppm Et_2O, 50 ppm and 500 ppm. Batches are held in quarantine until lab analysis indicates levels "meet" specs. The sterilization cycle is described as 0% RH/130°F over 12 hrs with steel 58/12 mix. This aspect should be investigated further and may be made the subject of an inquiry separate from provision of stability loss in potency during manuf. procedure (ca. 94% label) promote use of XS. "
Assay, ID tests A, B, C to be performed on sterile powder Flo-Pack filled vials together with Completeness of Solution test (USP). No spec sheets submitted. S008 revised manuf. procedure submitted. Sterility test results also included. The HFD-322 satisf. CGMP response dated 5-6-80.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approval S007. However, microbiologist should review the 2/26/80 submission insofar as effectiveness of cycle is concerned. Any further inquiry in this regard may be included in S007 approval letter. The manuf. & controls on S008 adequate; microbiologist should review sterility test results.

19. REVIEWER
NAME: H
SIGNATURE
DATE COMPLETED: 7-3-80

cc: NDA 8543
HFD-160
R/D by: SKoch (HFD-160) 7/3/80
Init by: IOneson 7//780
Doc. Room 160
Xeroxed 7/7/80 sm

JUL 08 1980

Microbiologist's

~~CHEMISTRY~~ REVIEW 1 of 2

(If necessary, continue any item on 8½" x 10½" paper. Key continuations to item by number.)

1. ORGANIZATION	2. NDA NUMBER
HFD-120	8453

3. NAME AND ADDRESS OF APPLICANT (City and State)	4. AF NUMBER
Burroughs Wellcome Co. Research Triangle Park, N.C. 27709	13-316

6. NAME OF DRUG	7. NONPROPRIETARY NAME	5. SUPPLEMENT(S) NUMBER(S)	DATE(S)
Anectine Injection	Succinylcholine chloride injection	S-007 RS	7/26/80
		S-008	7/26/80

8. SUPPLEMENT(S) PROVIDES FOR:

(S-007) 1. A % TECESS OF dosage form and bottles and package. FOR 20mg/ml MDV "Sterilization of FLO-PAK (Recvd. 7/3/80)

(S-008) 2. Deletion of TERMINAL sterilization cycle for 20mg/ml MDV dosage form.

9. AMENDMENTS AND OTHER (Reports, etc.) DATES

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF(S)
	☐ RX ☐ OTC	

13. DOSAGE FORM (S)	14. POTENCY (Iec)

15. CHEMICAL NAME AND STRUCTURE

16. RECORDS AND REPORTS

CURRENT ☐ YES ☐ NO

REVIEWED ☐ YES ☐ NO

17. COMMENTS

1. The resubmission for S-007 provides additional information as requested in our letter of November 2, 1979,

2. Item #4 in our letter of November 2, 1979 clarification of terminal heat process for 20mg/ml vial has been addressed. S-008 provides for deletion of this sterilization cycle. Sterility test data on 9 lots show no growth from 690 samples tested prior to terminal heat cycle.

Validation of the terminal heat cycle was performed. Data and information submitted are incomplete, but no further requests are indicated since this cycle has been deleted.

3. Efficacy of the cycle and a description of the process are provided but the information is inadequate. See Reviewer Notes on page 3.

18. CONCLUSIONS AND RECOMMENDATIONS

1. Recommend approval of S-008, deletion of terminal heat cycle.

2. Recommend Reviewed/Waiting Firm Letter for S-007.

NOV 12 1980 10-31-80

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
		10-30-80

DISTRIBUTION ☐ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE

FORM FDH 2265 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

cc: NDA 8453; HFD-160; R/D VGreenman 10/30/80
Init IOneson 10/31/80; Xer. 11/3/80; Doc. Rm. 160.

NDA 8-453/S-009

DEC 22 1981

Burroughs Wellcome Co.
Attention: George M. Lyon, Jr., M.D.
3030 Cornwallis Road
Research Triangle Park, NC 27709

Gentlemen:

Please refer to your supplemental new drug application of July 23, 1980 submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Anectine Injection and Flo-Pack. This supplemental application was resubmitted on June 23, 1981.

We acknowledge receipt on October 23, 1981 of your communication dated October 20, 1981 enclosing final printed labeling.

The supplemental application provides for revised labeling.

We have completed the review of this supplemental application and it is approved. Our letter of June 22, 1973 detailed the conditions relating to the approval of this application.

At the next printing, the labeling should be revised to state that the recommended pediatric doses are for endotracheal intubation.

Please submit one market package of the drug labeled in accord with this supplement when available.

Sincerely yours,

James P. Mann, MD
Director
Division of Surgical-Dental
Drug Products
Bureau of Drugs

ATL-DO (HFR-4100)
NDA 8-453/S-009
HFD-160
HFD-180
HFD-100
HFD-616
HFD-160 CRodriguez, DShah
R/D JMSinger HFD-160 11/17/81
R/D init. by: GBoyer 11/17/81; CRSinopoli 11/18/81; CRodriguez 11/18/81;
JPMann 11/19/81
FT OLA WO490N A0018N 9/11/81
Doc Room 160

APPROVAL

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION: HFD-160 (IDE)

2. NDA NUMBER: 8-453

3. NAME AND ADDRESS OF APPLICANT *(City and State)*: Burroughs Wellcome Co
Research Triangle Park, N C 27709

4. DATE NDA APPROVED: 8/20/82

5. IF PRIOR TO OCT 10, 1962, DATE APPROVED FOR EFFICACY:

6. NAME OF DRUG: Anectine injection
Anectine Sterile Powder

7. NONPROPRIETARY NAME: Succinylcholine Chloride

8. SUPPLEMENT NUMBER: 009- DATE: 10/20/81

9. PURPOSE OF SUPPLEMENT:
revised labeling-
NDA 8-453
HFD-160 Doc Room 160
R/D DShah HFD-160 11/10/81
R/D Init CSinopoli 11/12/81

10. AMENDMENT DATE(s):
Recd by chem

11. OTHER DATE *(Report, etc.)*:

12. PHARMACOLOGICAL CATEGORY: Depolarizing neuromuscular blocking drug

13. AF NUMBER:

14. DOSAGE FORM: Sterile solution, Powder

15. HOW DISPENSED: ☒ Rx ☐ OTC

16. RELATED IND/NDA/MF(s):
Received by Chem
11/10/81

17. POTENCY(ies): 20 mg/ml

18. DRUG REQUIRES: ☒ NDA ☐ ANDA

19. CHEMICAL NAME: Succinylcholine chloride

20. RECORDS AND REPORTS

CURRENT		REVIEWED	
☒ YES	☐ NO	☐ YES	☐ NO

~~21. CHEMICAL FORMULA~~

The firm has submitted the Final printed Package inserts

22. REMARKS

The labeling has been revised in accord with the comments contained in the division letter of 6th august- "No chemistry" supplement remains approvable.

23. CONCLUSIONS

(1) The supplement should be approved
(2) Please refer to the M.O review

CRS 11-12-81

NOV 17 1981

24. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
	Ph D	11/10/81

DISTRIBUTION: ☐ ORIGINAL JACKET ☐ DUPLICATE JACKET ☐ REVIEWER

FORM FDH 2266 (11/73) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED. 1

Nda 8-453/S-009FP

Medical Officer's Review

Date Completed: November 5, 1981

Original Approval Date: 8/20/52

Name of Sponsor: BurroughsWellcome Co.
3030 Cornwallis Road
Research Tirangle Park, N.C. 27709

Date of Submission: October 20, 1981

Date Received: October 23, 1981

Name of Drug: Trade: Anectine Injection, USP
Anectine Sterile Powder Flo-Pack

Generic; Succinylcholine chloride

Category (Use) of Drug: Depolarizing neuromuscular blocking drug

Dosage Forms and Routes of Administration: Solution of 20 mg/ml in multiple dose vials of 10 ml and powder, 500 and 1000 mg in Flo-Pack vials for dilution for intravenous or intramuscular administration

Type of Submission: Supplement to approved NDA covering revised labeling in conformance with 21 CFR 201.57, Federal Register notice of May 16, 1980 and in response to Agency letter of August 6, 1981

Material Reviewed

The submission consists of covering letter from George M, Lyon, Jr., M.D., Director, Drug Regulatory Affairs, and the agreed upon revisions in labeling (prescribing information) in final printed form.

Summary and Conclusions

The labeling incorporates those changes transmitted in letter of August 6, 1981 and is essentially that which will be promulgated through labeling guidelines for neuromuscular blocking agents and should be approved.

In reviewing the section on Dosage Administration both in this labeling and that in proposed guidelines, it is noted that the pediatric dosages are not indicated as those suitable for endotracheal intubation. At the next printing of this labeling, this should be inserted and will be brought to the attention of HFD-177 by the reviewer.

Recommendations

Labeling as submitted should be approved; however at the next printing, the recommended pediatric doses should specify that these are for endotracheal intubation.

11/5/81

Patricia H. Russell, M.D.

11/6/81

NDA 8-453
HFD-160 HFD-180
R/DPHRussell(HFD-160)11/5/8
Init by:CRodriguez 11/5/81
JPMann 11/6/81
doc. rm. 160

NOV 10 1981

doses in this range, relaxation develops in about 1 minute; maximum muscular paralysis may persist for about 2 minutes, after which recovery takes place within 4 to 6 minutes. However, very large doses may result in more prolonged apnea. An initial test dose of 0.1 mg/kg (~0.5 ml) may be used to determine the sensitivity of the patient and the individual recovery time.

FOR LONG SURGICAL PROCEDURES: The dosage of succinylcholine administered by infusion depends upon the duration of the surgical procedure and the need for muscle relaxation. The average rate for an adult ranges between 2.5 and 4.3 mg per minute.

Solutions containing from 0.1% to 0.2% (1 to 2 mg per ml) succinylcholine have commonly been used for continuous intravenous drip. Solutions of 0.1% or 0.2% may conveniently be prepared by adding 1 g succinylcholine (the contents of one Anectine Sterile Powder Flo-Pack unit containing 1 g succinylcholine chloride) respectively to 1,000 or 500 ml of sterile solution, such as sterile 5% dextrose solution or sterile isotonic saline solution. The more dilute solution (0.1% or 1 mg per ml) is probably preferable from the standpoint of ease of control of the rate of administration of the drug and, hence, of relaxation. This intravenous drip solution containing 1 mg per ml may be administered at a rate of 0.5 mg (0.5 ml) to 10 mg (10 ml) per minute to obtain the required amount of relaxation. The amount required per minute will depend upon the individual response as well as the degree of relaxation required. The 0.2% solution may be especially useful in those cases where it is desired to avoid overburdening the circulation with a large volume of fluid. It is recommended that neuromuscular function be carefully monitored with a peripheral nerve stimulator when using succinylcholine by infusion in order to avoid overdose, detect development of Phase II block, follow its rate of recovery, and assess the effects of reversing agents.

Solutions of succinylcholine must be used within 24 hours after preparation. Discard unused solutions.

Intermittent intravenous injections of succinylcholine may also be used to provide muscle relaxation for long procedures. An intravenous injection of 0.3 to 1.1 mg/kg may be given initially, followed, at appropriate intervals, by further injections of 0.04 to 0.07 mg/kg to maintain the degree of relaxation required.

The intravenous dose of succinylcholine is 2 mg/kg for infants and small children. For older children and adolescents the dose is 1 mg/kg.

Intramuscular Use: If necessary, succinylcholine may be given intramuscularly to infants, older children or adults when a suitable vein is inaccessible. A dose of up to 3 to 4 mg/kg may be given, but not more than 150 mg total dose should be administered by this route. The onset of effect of succinylcholine given intramuscularly is usually observed in about 2 to 3 minutes.

HOW SUPPLIED: For immediate injection of single doses for short procedures:
Anectine® Injection, 20 mg succinylcholine chloride in each ml.
Multiple-dose vials of 10 ml.
Box of 12 vials, NDC-0081-0071-95.
Store in refrigerator at 2°-8°C (36°-46°F). The multi-dose vials are stable for up to 14 days at room temperature without significant loss of potency.

For preparation of intravenous drip solutions only:

Anectine® Flo-Pack®, 500 mg sterile succinylcholine chloride powder.
Box of 12 vials, NDC-0081-0085-15.

Anectine® Flo-Pack®, 1000 mg sterile succinylcholine chloride powder.
Box of 12 vials, NDC-0081-0086-15.

Anectine Flo-Pack does not require refrigeration. Solutions of succinylcholine must be used within 24 hours after preparation. Discard unused solutions.

BURROUGHS WELLCOME CO.
Research Triangle Park, NC 27709
Printed in U.S.A.

September 1981

411005

NFD 160

8-453

411005

APPROVED DEC 22 1981

Wellcome

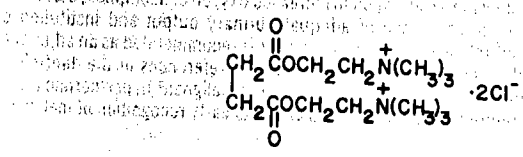
ANECTINE® (SUCCINYLCHOLINE CHLORIDE) INJECTION, USP
ANECTINE® (SUCCINYLCHOLINE CHLORIDE) Sterile POWDER FLO-PACK®

This drug should be used only by individuals familiar with its actions, characteristics and hazards.

DESCRIPTION: Anectine (succinylcholine chloride) is an ultra short-acting depolarizing-type, skeletal muscle relaxant for intravenous administration.

Succinylcholine chloride is a white, odorless, slightly bitter powder and very soluble in water. The drug is unstable in alkaline solutions but relatively stable in acid solutions, depending upon the concentration of the solution and the storage temperature. Solutions of succinylcholine chloride should be stored under refrigeration to preserve potency. Anectine Injection is a sterile solution for intravenous injection, containing 20 mg succinylcholine chloride in each ml and made isotonic with sodium chloride. The pH is adjusted to 3.5 with hydrochloric acid. Methylparaben (0.1%) is added as a preservative. Anectine® Flo-Pack is a sterile powder, containing either 500 mg or 1000 mg of succinylcholine chloride in each vial.

The chemical name for succinylcholine chloride is 2,2'-[(1,4-Dioxo-1,4-butanediyl) bis(oxy)]bis[N,N,N-trimethylethanaminium]dichloride, and the structural formula is:



CLINICAL PHARMACOLOGY: Succinylcholine is a depolarizing skeletal muscle relaxant. As does acetylcholine, it combines with the cholinergic receptors of the motor end plate to produce depolarization. This depolarization may be observed as fasciculations. Subsequent neuromuscular transmission is inhibited so long as adequate concentration of succinylcholine remains at the receptor site. Onset of flaccid paralysis is rapid (less than one minute after intravenous administration), and with single administration lasts approximately 4-6 minutes.

Succinylcholine is rapidly hydrolyzed by plasma pseudocholinesterase to succinylmonocholine (which possesses nondepolarizing muscle relaxant properties) and then more slowly to succinic acid and choline. About 10% of the drug is excreted unchanged in the urine. The paralysis following administration of succinylcholine is selective, initially involving consecutively the levator muscles of the face, muscles of the glottis and finally the intercostals and the diaphragm and all other skeletal muscles.

Succinylcholine has no direct action on the uterus or other smooth muscle structures. Because it is highly ionized and has low fat solubility, it does not readily cross the placenta.

Tachyphylaxis occurs with repeated administration.

When succinylcholine is given over a prolonged period of time, the characteristic depolarizing neuromuscular block (Phase I block) may change to a block with characteristics superficially resembling a non-depolarizing block (Phase II block). This may be associated with prolonged respiratory depression or apnea in patients who manifest the transition to Phase II block. When this diagnosis is confirmed by peripheral nerve stimulation, it may be reversed with anticholinesterase drugs such as neostigmine (See Precautions).

While succinylcholine has no direct effect on the myocardium, changes in rhythm may result from vagal stimulation, such as may result from surgical procedures (particularly in children) or from potassium-mediated alterations in electrical conductivity. These effects are enhanced by cyclopropane and halogenated anesthetics.

Succinylcholine causes a slight, transient increase in intraocular pressure immediately after its injection and during the fasciculation phase, and slight increases may persist after onset of complete paralysis. This suggests that the drug should not be used in the presence of open eye injuries.

Succinylcholine has no effect on consciousness, pain threshold or cerebration. It should be used only with adequate anesthesia.

INDICATIONS AND USAGE: Succinylcholine chloride is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Succinylcholine is contraindicated for persons with genetically determined disorders of plasma pseudocholinesterase, personal or familial history of malignant hyperthermia, myopathies associated with elevated creatine phosphokinase (CPK) values, known hypersensitivity to the drug, acute narrow angle glaucoma, and penetrating eye injuries.

WARNINGS: Succinylcholine should be used only by those skilled in the management of artificial respiration and only when facilities are instantly available for endotracheal intubation and for providing adequate ventilation of the patient, including the administration of oxygen under positive pressure and the elimination of carbon dioxide. The clinician must be prepared to assist or control respiration.

Succinylcholine should not be mixed with short-acting barbiturates in the same syringe or administered simultaneously during intravenous infusion through the same needle. Solutions of succinylcholine have an acid pH, whereas those of barbiturates are alkaline. Depending upon the resultant pH of a mixture of solutions of these drugs, either free barbituric acid may be precipitated or succinylcholine hydrolyzed.

Succinylcholine administration has been associated with acute onset of fulminant hypermetabolism of skeletal muscle known as malignant hyperthermic crisis. This frequently presents as intractable spasm of the jaw muscles which may progress to generalized rigidity, increased oxygen demand, tachycardia, tachypnea and profound hyperpyrexia. Successful outcome depends on recognition of early signs, such as jaw muscle spasm, lack of laryngeal relaxation or generalized rigidity to initial administration of succinylcholine for endotracheal intubation, or failure of tachycardia to respond to deepening anesthesia. Skin mottling, rising temperature and coagulopathies occur late in the course of the hypermetabolic process. Recognition of the syndrome is a signal for discontinuance of anesthesia, attention to increased oxygen consumption, correction of metabolic acidosis, support of circulation, assurance of adequate urinary output and institution of measures to control rising temperature. Dantrolene sodium, intravenously, is recommended as an adjunct to supportive measures in the management of this problem. Consult literature references or the dantrolene prescribing information for additional information about the management of malignant hyperthermic crisis. Routine, continuous monitoring of temperature is recommended as an aid to early recognition of malignant hyperthermia.

PRECAUTIONS:

General: Low levels or abnormal variants of pseudocholinesterase may be associated with prolonged respiratory depression or apnea following the use of succinylcholine. Low levels of pseudocholinesterase may occur in patients with the following conditions: burns, severe liver disease or cirrhosis, cancer, severe anemia, pregnancy, malnutrition, severe dehydration, collagen diseases, myxedema, and abnormal body temperature. Also, exposure to neurotoxic insecticides, antimalarial or anti-cancer drugs, monoamine oxidase inhibitors, contraceptive pills, pancuronium, chlorpromazine, ecothiopate iodide, or neostigmine may result in low levels of pseudocholinesterase. Succinylcholine should be administered with extreme care to such patients. If low pseudocholinesterase activity is suspected, a small test dose of from 5 to 10 mg of succinylcholine may be administered, or relaxation may be produced by the cautious administration of a 0.1% solution of the drug by intravenous drip. Apnea or prolonged muscle paralysis should be treated with controlled respiration.

Succinylcholine should be administered with great caution to patients recovering from severe trauma, those suffering from electrolyte imbalance, those receiving quinidine, and those who have been digitalized recently or who may have digitalis toxicity, because in these circumstances it may induce serious cardiac arrhythmias or cardiac arrest. Great caution should be observed also in patients with pre-existing hyperkalemia, those who are paraplegic, or have suffered extensive or severe burns, extensive denervation of skeletal muscle due to disease or injury of the central nervous system, or have degenerative or dystrophic neuromuscular disease, because such patients tend to become severely hyperkalemic when given succinylcholine.

When succinylcholine is given over a prolonged period of time, the characteristic depolarization block of the myoneural junction (Phase I block) may change to a block with characteristics superficially resembling a non-depolarizing block (Phase II block). Prolonged respiratory depression or apnea may be observed in patients manifesting this transition to Phase II block. The transition from Phase I to Phase II block has been reported in 7 of 7 patients studied under halothane anesthesia after an accumulated dose of 2 to 4 mg/kg succinylcholine (administered in repeated, divided doses). The onset of Phase II block coincided with the onset of tachyphylaxis and prolongation of spontaneous recovery. In another study, using balanced anesthesia (N_2O/O_2/narcotic-thiopental) and succinylcholine infusion, the transition was less abrupt, with

ANECTINE® (Succinylcholine Chloride) INJECTION, USP
ANECTINE® (Succinylcholine Chloride) Sterile POWDER FLO-PACK®

great individual variability in the dose of succinylcholine required to produce Phase II block. Of 32 patients studied, 24 developed Phase II block. Tachyphylaxis was not associated with the transition to Phase II block, and 50% of the patients who developed Phase II block experienced prolonged recovery.

When Phase II block is suspected in cases of prolonged neuromuscular blockade, positive diagnosis should be made by peripheral nerve stimulation, prior to administration of any anticholinesterase drug. Reversal of Phase II block is a medical decision which must be made upon the basis of the individual clinical pharmacology and the experience and judgment of the physician. The presence of Phase II block is indicated by fade of responses to successive stimuli (preferably "train of four"). The use of anticholinesterase drugs to reverse Phase II block should be accompanied by appropriate doses of atropine to prevent disturbances of cardiac rhythm. After adequate reversal of Phase II block with an anticholinesterase agent, the patient should be continually observed for at least 1 hour for signs of return of muscle relaxation. Reversal should not be attempted unless: (1) a peripheral nerve stimulator is used to determine the presence of Phase II block (since anti-cholinesterase agents will potentiate succinylcholine-induced Phase I block), and (2) spontaneous recovery of muscle twitch has been observed for at least 20 minutes and has reached a plateau with further recovery proceeding slowly; this delay is to ensure complete hydrolysis of succinylcholine by pseudocholinesterase prior to administration of the anticholinesterase agent. Should the type of block be misdiagnosed, depolarization of the type initially induced by succinylcholine, that is depolarizing block, will be prolonged by an anticholinesterase agent.

Succinylcholine should be used with caution, if at all, during ocular surgery and in patients with glaucoma. The drug should be employed with caution in patients with fractures or muscle spasm because the initial muscle fasciculations may cause additional trauma.

Neuromuscular blockade may be prolonged in patients with hypokalemia or hypocalcemia.

Drug Interactions: Drugs which may enhance the neuromuscular blocking action of succinylcholine include: phenelzine, promazine, oxytocin, aprotinin, certain nonpenicillin antibiotics, quinidine, β-adrenergic blockers, procainamide, lidocaine, trimethaphen, lithium carbonate, magnesium salts, quinine, chloroquin, propanidid, diethylether, and isoflurane.

If other relaxants are to be used during the same procedure, the possibility of a synergistic or antagonistic effect should be considered.

Pregnancy: **Teratogenic Effects:** Pregnancy Category C.
Animal reproduction studies have not been conducted with succinylcholine chloride. It is also not known whether succinylcholine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Succinylcholine should be given to a pregnant woman only if clearly needed.

Nonteratogenic Effects: Pseudocholinesterase levels are decreased by approximately 24% during pregnancy and for several days postpartum. Therefore, a higher proportion of patients may be expected to show sensitivity (prolonged apnea) to succinylcholine when pregnant than when nonpregnant.

Labor and Delivery: Succinylcholine is commonly used to provide muscle relaxation during delivery by caesarean section. While small amounts of succinylcholine are known to cross the placental barrier, under normal conditions the quantity of drug that enters fetal circulation after a single dose of 1 mg/kg to the mother will not endanger the fetus. However, since the amount of drug that crosses the placental barrier is dependent on the concentration gradient between the maternal and fetal circulations, residual neuromuscular blockade (apnea and flaccidity) may occur in the neonate after repeated high doses to, or in the presence of, atypical pseudocholinesterase in the mother.

ADVERSE REACTIONS: Adverse reactions consist primarily of an extension of the drug's pharmacological actions. It causes profound muscle relaxation resulting in respiratory depression to the point of apnea; this effect may be prolonged. Hypersensitivity to the drug may exist in rare instances. The following additional adverse reactions have been reported: cardiac arrest, malignant hyperthermia, arrhythmias, bradycardia, tachycardia, hypertension, hypotension, hyperkalemia, prolonged respiratory depression or apnea, increased intraocular pressure, muscle fasciculation, postoperative muscle pain, myoglobinemia, excessive salivation, and rash.

DOSAGE AND ADMINISTRATION: The dosage of succinylcholine is essentially individualized and its administration should always be determined by the clinician after careful assessment of the patient. To avoid distress to the patient, succinylcholine should not be administered before unconsciousness has been induced. Succinylcholine should not be mixed with short-acting barbiturates in the same syringe or administered simultaneously during intravenous infusion through the same needle.

FOR SHORT SURGICAL PROCEDURES: The average dose for relaxation of short duration is 0.6 mg/kg (~2.0 ml) Anectine (succinylcholine chloride) Injection given intravenously. The optimum dose will vary among individuals and may be from 0.3 to 1.1 mg/kg for adults (1.0 to 4.0 ml). Following administration of

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION: HFD NDE, DSDDP 160

2. NDA NUMBER: 8-453

3. NAME AND ADDRESS OF APPLICANT *(City and State)*
Burroughs Wellcome Co
Research Triangle Park
North Carolina 27709

4. AF NUMBER: 13-316

5. SUPPLEMENT (S)

NUMBER(S)	DATE(S)
S-009	7/23/80

6. NAME OF DRUG: Anectine Injection and Flo-Pack

7. NONPROPRIETARY NAME: Succinylcholine chloride

8. SUPPLEMENT(S) PROVIDES FOR:
the addition of a statement to the "management of Adverse Reactions"

9. AMENDMENTS AND OTHER *(Reports, etc.)* DATES

10. PHARMACOLOGICAL CATEGORY: depolarizing type muscle relaxant

11. HOW DISPENSED: ☒ RX ☐ OTC

12. RELATED IND/NDA/DMF(S)

13. DOSAGE FORM (S): Intravenous injection & intravenous drip

14. POTENCY *(Iso)*: 20 mg/ml for injection 500mg Sterile Powder

15. CHEMICAL NAME AND STRUCTURE
dichloride salt of the dicholine ester of Succinic acid.

16. RECORDS AND REPORTS
CURRENT ☐ YES ☐ NO
REVIEWED ☐ YES ☐ NO

17. COMMENTS

No changes are involved as far as manuf. and controls are concerned. Please refer to the M.O's review.

cc: NDA 8453
HFD-160
R/D by: DShah (HFD-160) 9/5/80
Init by: IOneson 9/5/80
Doc. Room 160
Zeroxed 9/9/80 sm

SEP 11 1980

18. CONCLUSIONS AND RECOMMENDATIONS

No reply for Chemistry.
Please refer to the M.O's review

Sd 9-5-80

19. REVIEWER

NAME | SIGNATURE | DATE COMPLETED: 9/5/80

DISTRIBUTION ☐ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE

FORM FDH 2266 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

NDA 8-453

MEDICAL OFFICER'S REVIEW

Date Completed: October 21, 1980

Original Approval Date: 8/20/52

Name of Sponsor: Burroughs Wellcome Company
3030 Cornwallis Road
Research Triangle Park, N.C. 27709

Name of Drug: Trade: Anectine
Generic: Succinylcholine chloride

Type of Submission: Final Printed Labeling

Date of Submission: July 23, 1980

Date Received: July 28, 1980

Material Reviewed: Covering Letter signed by D.A. Knight, Associate Director, Drug Regulatory Affairs, rationale for revision of package insert, bibliography covering use of Dantroline Sodium in the management of malignant hypothermia.

Summary:

It is noted that the sponsor sought to include this information in the prescribing information for the subject product as a means of providing information for safer use of succinylcholine; however there are other changes needed to update the prescribing information in keeping with presently accepted standards requested for similar drugs considered as anesthetic adjuncts. In keeping with this needed information for safe administration of the product, the following should be incorporated in a letter to the sponsor requesting revision of the prescribing information for this product.

1. The official name of the product, "succinylcholine chloride injection, USP should appear on the package insert.

2. The "Description" section should include the structural formula of the active ingredient, succinylcholine chloride.

3. The "Description" section should provide the pH of the solution and the name of any additives used to adjust to the final pH.

4. The first paragraph of the "Actions" section is poorly organized and worded. Dissipated is hardly an exact description of the metabolism of the drug. The information in the first and second paragraphs should be revised and consolidated to more concisely present information relevant to safe administration. The following may be used as a guide to this revision:

> "Succinylcholine is a depolarizing skeletal muscle relaxant. Like acetylcholine it combines with the cholinergic receptors of the motor endplate to produce depolarization. This depolarization may be observed as fasiculations. Subsequent neuromuscular transmission is inhibited so long as adequate concentration of succinylcholine remains at the receptor site. Onset of flaccid paralysis is rapid, (less than

one minute after intravenous administration), and with single administration lasts approximately 4-6 minutes (if the sponsor can substantiate the longer duration claimed with his product, he may do so).

Succinylcholine is rapidly hydrolyzed by plasma pseudocholinesterase to succinyl monocholine (which possesses nondepolarizing muscle relaxant properties) and then more slowly to succinic acid and choline. About 10% of the drug is excreted unchanged in the urine. The paralysis following administration of succinylcholine is selective, initially involving consecutively the levator muscles of the eyelids, muscles of mastication, limb muscles, abdominal muscles, muscles of the glottis and finally the intercostals and the diaphragm.

Onset and duration of action may be altered by the use of other medications such as anticholinesterases, depolarizing or nondepolarizing muscle relaxants, dehydration, electrolyte imbalance, certain non-penicillin antiobiotics, procaine type local anesthetics. Neuromuscular blockage with succinylcholine is potentiated by quinine, magnesium salts and prolonged by hypokalemia or hypocalcemia.

Succinylcholine has no direct action on the uterus or other smooth muscle structures. Because it is highly ionized and has low fat solubility it does not readily cross the placenta.

Tachyphylaxis occurs with repeated administration. When succinylcholine is given over a prolonged period of time, the characteristic depolarizing neuromuscular block may change to a non-depolarizing block similar to that seen with tubocurarine. When this diagnosis is confirmed by peripheral nerve stimulation, it may be reversed with cholinergic drugs such as physostigmine.

While succinylcholine has no direct effect on myocardium, changes in rhythm may result from vagal stimulation or potassium mediated alterations in electrical conductivity. These effects are enhanced by cyclopropane and halogenated anesthetics.

Slight increases in intraocular pressure may persist after onset of complete paralysis. This suggests that the drug should not be used in open eye injuries.

Succinylcholine has no effect on consciousness, pain threshold or cerebration. It should be used only with adequate anesthesia."

5. The "Indications" section might be expanded as follows:

"Succinylcholine is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation, to provide skeletal muscle relaxation during surgery or mechanical ventilation and to reduce the intensity of muscle contractions associated with pharmacologically or electrically induced convulsions."

6. In light of present understanding, the "Contraindications" section should be expanded as follows:

"Succinylcholine is contraindicated in patients with known hypersenativity to the drug, genetically determined disorders of plasma pseudocholinesterase and myopathies associated with elevated CPK values."

7. "Usage in Pregnancy" should be removed from the "Warnings" section and placed in Precautions. The drug should be classified Category B for usage in pregnancy and an additional paragraph on appropriate usage in Labor and Delivery should be added to this section.

8. Because of the seriousness of the fulminant hypermetabolic process which may be triggered by succinycholine and the urgent need to recognize the problem early to avert a fatal outcome, the statement on malignant hyperthermia should be removed to the Adverse Reactions section and more specific information provided as follows:

"Succinylcholine administration has been associated with acute onset of fulminant hypermetabolism of skeletal muscle known as malignant hyperthermic crisis. This frequently presents as intractable spasm of the jaw muscles which may progress to generalized rigidity, increased oxygen demand, tachycardia, tachypnea and profound hyperpyrexia. Successful outcome depends on recognition of early signs such as inappropriate response to initial administration of succinycholine for endotracheal intubation or failure of tachycardia to respond to deepening anesthesia. Skin mottling, rising temperature and coagulopathies occur late in the course of the hypermetabolic process. Confirmation of the diagnosis requires discontinuance of anesthesia, attention to increase oxygen consumption, correction of metabolic acidosis, support of circulation, assurance of adequate urinary output and institution of measures to control rising temperature. Dantrolene sodium intravenous is recommended as an adjunct to supportive measures in the management of this problem. Consult literature references or the Dantrolene prescribing information for additional information about the management of malinant hyperthermic crisis."

9. "Dosage and Administration" should be given in mg/kg with milliter doses provided in parentheses. A more positive statement relating to discarding unused solutions should be incorporated in this section.

10. A statement describing use of peripheral nerve stimulator in monitoring neuromuscular blockade as a means of preventing overdosage would be appropriate.

11. The final paragraph of the "Mangment of Adverse Reactions" section should be rewritten as follows:

Positive diagnosis of nondepoparizing block should be made by peripheral nerve stimulator prior to administration of cholinergic drugs when this is suspected in cases of prolonged neuromuscular blockade. To prevent disturbances of cardiac rhythm, the use of these drugs should be accompanied by appropriate doses of atropine.

12. "The How" supplied section should provide a table of available products to include any additives such as preservatives or hydrochloric acid.

13. A statement that the product is restricted to prescription use should be incorporated as well as a statement to the effect that the products carry an expiration date.

Conclusions and Recommendations:

The above recommendations should be incorporated in a letter to the sponsor and revised labeling requested.

Patricia H. Russell, M.D.

cc: NDA 8-453
HFD-160
HFD-180
R/D by PHRussell(HFD-160)10/21/80
R/D Init. by CRodriguez 10/22/80 & JPMann 10/22/80
Final Typed by JK 11/10/80
Doc. Rm. 160

NOV 12 1980

cc: NDA 8453
HFD-160
R/D by: DShah (HFD-160) 9/25/80
Init by: IOneson 9/25/80
Doc. Room 160

CHEMIST'S REVIEW
(If necessary, continue any item on 8½" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION: HFD 160, DSDDP, NDE

2. NDA NUMBER: S-453

3. NAME AND ADDRESS OF APPLICANT (City and State):
Burroughs Wellcome Co
Research Triangle Park
N.C. 27709

4. AF NUMBER: 13-316

5. SUPPLEMENT (S)

NUMBER(S)	DATE(S)
S-010	8/8/80

6. NAME OF DRUG: Anectine injection

7. NONPROPRIETARY NAME: Succinylcholine Chloride Inj.

8. SUPPLEMENT(S) PROVIDES FOR:
the change in bottle neck diameter and stopper diameter

9. AMENDMENTS AND OTHER (Reports, etc.) DATES

10. PHARMACOLOGICAL CATEGORY: Skeletal Muscle relaxant

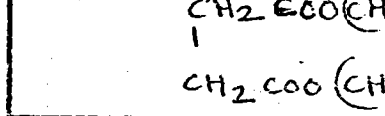
11. HOW DISPENSED: ☒ RX ☐ OTC

12. RELATED IND/NDA/DMF(S)

13. DOSAGE FORM (S): Sterile solution

14. POTENCY (ies): 20 mg/ml

15. CHEMICAL NAME AND STRUCTURE



16. RECORDS AND REPORTS

CURRENT: ☒ YES ☐ NO

REVIEWED: ☒ YES ☐ NO

17. COMMENTS
In this supplement, the firm has submitted the data to support the change in bottle neck diameter and stopper diameter to minimize potential chipping of glass during the filling operation. The firm has included the proposed and current packaging specifications and stability commitment. The firm's stability protocol should also include the following. ① Under Physical testing (a) check for particulates (b) visual examination of stopper and color of the solution ② Stability testing should be carried out at 3, 6, 12, 18, and 24 mos. The firm is measuring hydrolysis products at various intervals. There is no upper limit for these degradation product. The firm should be asked to establish upper limits for this test.

18. CONCLUSIONS AND RECOMMENDATIONS

SEP 29 1980

18. — Supplement is not approvable. See the chemist's letter to the applicant. per w/f 9-25-80

19. REVIEWER

NAME: I

SIGNATURE:

DATE COMPLETED: 9/25/80

DISTRIBUTION: ☐ ORIGINAL JACKET ☒ REVIEWER ☐ DIVISION FILE

PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

CHEMIST'S REVIEW
(If necessary, continue any item on 8½" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION: HFD NDE, DSDRF 160

2. NDA NUMBER: 8-453

3. NAME AND ADDRESS OF APPLICANT *(City and State)*: Burroughs Wellcome Co Research Triangle Park, N.C. 27709

4. AF NUMBER: 13-316

5. SUPPLEMENT (S)

NUMBER(S)	DATE(S)
S-010	8/8/80

6. NAME OF DRUG: Anectine injection

7. NONPROPRIETARY NAME: Succinylcholine Chloride injection

8. SUPPLEMENT(S) PROVIDES FOR: Change in bottle neck diameter and stopper diameter

9. AMENDMENTS AND OTHER *(Reports, etc.)* DATES: COORS/12/8/80

10. PHARMACOLOGICAL CATEGORY:

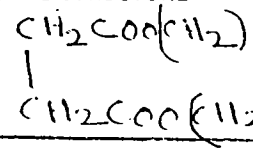
11. HOW DISPENSED: ☑ RX ☐ OTC

12. RELATED IND/NDA/DMF(S): Received by Chemist 1/21/81

13. DOSAGE FORM (S): Skeletal muscle relaxant

14. POTENCY *(Iso)*: 20mg/ml

15. CHEMICAL NAME AND STRUCTURE



16. RECORDS AND REPORTS

CURRENT: ☑ YES ☐ NO

REVIEWED: ☑ YES ☐ NO

17. COMMENTS

The firm has responded to the division's letter of September 29, 1980. The firm has upgraded it's protocol to include storing of samples of first three production batches with new stoppers in inverted position for stability study. The firm will include visual examination of stopper, color, particulates at 3, 6, 12, 18 and 24 mos. The firm has recently submitted a stability indicating HPLC assay to the USP and agency. The method will be used to monitor degradation in stability samples.

18. CONCLUSIONS AND RECOMMENDATIONS

Supplement is approvable. Please refer to the chemists portion of a letter to the applicant

FEB 12 1981

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
		2/9/81

NDA 8-453
HFD-160
R/D DShah RFD-160 2/9/81
R/D Init RONeson 2/9/81 doc room 160 final xeroxed mw 2/11/81

NDA 8-453/S-011

MAY 15 1981

Burroughs Wellcome Co.
Attention: Mr. D. A. Knight
3030 Cornwallis Road
Research Triangle Park, NC 27709

Gentlemen:

We acknowledge the receipt on December 16, 1980 of your communication dated December 11, 1980 regarding your supplemental new drug application of October 20, 1980 submitted pursuant to section 505(b) of the Federal,Food, Drug, and Cosmetic Act for Anectine Flo Pack and Injection (Succinylcholine Chloride).

The supplemental application as amended provides for a revision in the assay procedure from a volumetric determination to a stability indicating procedure.

We have completed the review of this supplemental application as amended and it is approved. Our letter of June 22, 1973 detailed the conditions relating to the approval of this application.

Sincerely yours,

James P. Mann, M.D.
Director
Division of Surgical-Dental
Drug Products
Bureau of Drugs

APPROVAL
NDA 8-453
ATL-DO (HFR-4100)
HFD-160, HFD-616
R/D DShah HFD-160 5/11/81
R/D Init IOneson 5/12/81; JPMann 5/13/81
doc room 160
final typed mw 5/14/81

CHEMIST'S REVIEW
(If necessary, continue on plain 8½" x 11" paper. Key continuation to item by number.)

1. ORGANIZATION: HFD-160

2. NDA NUMBER: 8-453 / S-011

3. NAME AND ADDRESS OF APPLICANT (City and State)
Burroughs Wellcome Co
Research Triangle Park, N. C. 27709

4. AP NUMBER:

5. SUPPLEMENT(S)

NUMBER(S)	DATE(S)
S-011	10/20/80

6. NAME OF DRUG: Anectine® 5ml Pack

7. NONPROPRIETARY NAME: Succinylcholine chloride

8. SUPPLEMENT(S) PROVIDES FOR:
revision in the assay procedure from a volumetric determination to a stability indicating procedure

9. AMENDMENTS AND OTHER (Reports, etc.) DATES
Amend - 12/11/80

10. PHARMACOLOGICAL CATEGORY: Skeletal Muscle relaxant

11. HOW DISPENSED: ☑ Rx ☐ OTC

12. RELATED IND/NDA/DMF(S)
Repeal from Ethicon Lab.

13. DOSAGE FORM(S): Sterile Solution and Powder

14. POTENCY (Tablets)
20 mg/cc injection
500 mg and 1000 mg powder

15. CHEMICAL NAME AND STRUCTURE
NDA 8-453
HFD-160
R/D DShah HFD-160 5/11/81
R/D Init IOneson 5/12/81; JPMann 5/13/81
doc room 160
final copied mw 5/14/81

16. RECORDS AND REPORTS
CURRENT: ☑ YES ☐ NO
REVIEWED: ☑ YES ☐ NO

17. COMMENTS
Attached with this are the results from Atlanta Regional Laboratory. Results are unsatisfactory the analysist have two minor comments. These comments will not be included in the letter to the firm.
The firm has included a system suitability test. The method validation request was sent to HFD-160 on 12/17/80. Results were received on 5/11/81 and with modern autoinjector the reproducibility could be within 1%. So I donot agree with the comments of the analyst

18. CONCLUSIONS AND RECOMMENDATIONS
Supplement should be approved. Please refer to the chemists letter to the applicant

MAY 15 1981

19. REVIEWER
NAME:
SIGNATURE:
DATE COMPLETED: 5/11/81

DISTRIBUTION: ORIGINAL JACKET / REVIEWER / DIVISION FILE

FORM FDA 2301 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED

IND/NDA 8-453 DATE November 13, 1980

IND/NDA 8-453
Review and Evaluation of Pharmacology and Toxicology Data

SPONSOR/APPLICANT: Burroughs Wellcome Co.

DRUG: Anectine (succinylcholine chloride)

CATEGORY: Ultra Short-Acting Depolarizing Type Muscle Relaxant

TYPE OF SUBMISSION/DATE: Supplement (11) - October 20, 1980

EVALUATION: This supplement provides for a revision in the assay procedure from a volumetric determination to a stability-indicating procedure.

ACTION INDICATED: This supplement is approvable from the standpoint of pharmacology.

Clyde G. Oberlander
Pharmacologist

NOV 25 1980

DISTRIBUTION: Routine NDA

cc: NDA 8-453; HFD-160; HFD-180;
R/D COberlander 11/13/80; Init JKInscoe 11/13/80;
Xer 11/24/80; Doc.Rm.160,

NDA 8-453/S-012

Burroughs Wellcome Co.
Attn: Mr. D. A. Knight
3030 Cornwallis Road
Research Triangle Park, NC 27709

FEB 11 1982

Gentlemen:

We acknowledge the receipt on November 13, 1981 and January 25, 1982 of your communications dated November 10, 1981 and January 22, 1982 regarding your supplemental new drug application of October 30, 1981 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cos Cosmetic Act for Anectine(R) (succinylcholine chloride) Injection, 20 mg/ml.

The supplemental application as amended provides for a change in the rubber stopper from the
and vials.

We have completed the review of this supplemental application as amended and it is approved. Our letter of June 22, 1973 detailed the conditions relating to the approval of this application.

Sincerely yours,

James P. Mann, M.D.
Director
Division of Surgical-Dental
Drug Products
Bureau of Drugs

NDA 8-453
ATL-DO HFR-4100
HFD-160, HFD-616
R/D DShah HFD-160 2/3/82 DShah 2/11/82
R/D Init CSinopoli 2/3/82; JPMann 2/4/82
doc room 160
final typed mw 2/10/82 CRA 2/10/82

APPROVAL

CHEMIST'S REVIEW
(If necessary, continue any item on 8½" x 10½" paper. Key continuation to item number.)

1. ORGANIZATION: HFD-160

2. NDA NUMBER: 8-452

3. NAME AND ADDRESS OF APPLICANT (City and State)
Burroughs Wellcome Co
Research Triangle Park, NC 27709

4. AF NUMBER

5. SUPPLEMENT (S)

NUMBER(S)	DATE(S)
012	10/30/81

6. NAME OF DRUG: Anectine injection

7. NONPROPRIETARY NAME: Succinylcholine chloride

8. SUPPLEMENT(S) PROVIDES FOR:
a Change in the rubber stopper from the to the for sterilization

9. AMENDMENTS AND OTHER (Reports, etc.) DATES
11/22/82
(updated stability data) 11/10/82

10. PHARMACOLOGICAL CATEGORY: Skeletal muscle relaxant

11. HOW DISPENSED: ☒ Rx ☐ OTC

12. RELATED IND/NDA/DMF(S)
Received by chemist 11/13/81

13. DOSAGE FORM (S): Sterile Solution

14. POTENCY (Iles): 20 mg/ml

DMF -

15. RECORDS AND REPORTS
CURRENT: ☒ YES ☐ NO
REVIEWED: ☒ YES ☐ NO

17. COMMENTS
Please refer to the attached pages.

The company has annaced its decision to discontinue currently used stopper due to molding difficulties -
current expiration dating period - 18 mos
(Stored at 35°F - 46°F)

18. CONCLUSIONS AND RECOMMENDATIONS
FEB 11 1982
The supplement should be approved
Please refer to the Chemists portion of a letter to the applicant
CA 2/3/82

19. REVIEWER
NAME
SIGNATURE
DATE COMPLETED: 2/3/82

DISTRIBUTION: ☐ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE

FORM FDH 2266 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

1

2/4/82

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number:NDA 20-262/S-026, 027, 028

Trade Name: Taxol Injection, 30mg/5 mL & 100 mg/16.7 mL

Generic Name:(paclitaxel)

Sponsor: Bristol-Myers Squibb Pharmaceutical Research Institute

Approval Date: April 9, 1998

Indication: S-026 provides for the use of Toxal as first-line therapy for the treatment of advanced carcinoma of the ovary in combination with cisplatin. S-027 provides labeling changes to the ADVERSE REACTIONS section, and S-028 provides labeling changes to the DESCRIPTION, DOSAGE AND ADMINISTRATION; Stability, HOW SUPPLIED; Storage sections.

CENTER FOR DRUG EVALUATION AND RESEARCH

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

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				X
Approvable Letter			X	
Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI	X			
Pharmacology Review(s)	X			
Statistical Review(s)	X			
Microbiology Review(s)	X			
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)			X	
Administrative Document(s)	X			
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20-262/S-026, 027, 028

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-262 / S-026, S-027, S-028

Bristol-Myers Squibb Pharmaceutical Research Institute
5 Research Parkway - P.O. Box 5100
Wallingford, CT 06492-7660

APR - 9 1998

Attention: Cheryl L. Anderson
Director, Worldwide Regulatory Affairs

Dear Ms. Anderson:

Please refer to your supplemental new drug applications dated October 7, November 19 and 18, 1997, received October 9, November 20 and 21, 1997, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Taxol (paclitaxel) Injection, 30 mg/5 mL and 100 mg/16.7 mL.

We acknowledge receipt of your submissions and correspondences to S-026 dated October 20, 23, and 27, December 22, 1997, January 15, February 2, 3, 9, 19, and 25, March 10, and 12, and April 1 and 6, 1998. We also acknowledge receipt of your amendment dated January 9, 1998, containing final printed labeling (FPL), for supplemental applications S-027 and S-028 and the correspondence to S-027 dated January 13, 1998. We note that the submissions to S-027 and S-028 have been superseded by the February 19, 1998 submission to S-026. Therefore, the submissions to S-027 and S-028 will not be reviewed, but they will be retained in our files.

The User Fee goal dates for these applications are April 9, May 20 and 21, 1998.

Supplemental application S-026 provides for the use of Taxol as first-line therapy for the treatment of advanced carcinoma of the ovary in combination with cisplatin. Supplemental application S-027 provides labeling changes to the ADVERSE REACTIONS section, and supplemental application S-028 provides labeling changes to the DESCRIPTION, DOSAGE AND ADMINISTRATION: Stability, HOW SUPPLIED: Storage sections.

We have completed the review of these supplemental applications, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed modified draft labeling. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed modified draft labeling.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED

LABELING" for approved supplemental NDAs 20-262 / S-026, S-027, S-028. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Oncology Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising
and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Dianne Spillman, Project Manager, at (301) 594-5746.

Sincerely yours,

/S/ 4-9-98

Robert J. DeLap, M.D., Ph.D.
Director
Division of Oncology Drug Proucts
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE

cc:
Original NDA 20-262
HFD-150/Div. files (with labeling)
HFD-150/CSO/D.Spillman (with labeling)
HFD-150/S.Honig (with labeling)
/G.Williams (with labeling)
/J.Jee (with labeling)
/R.Wood (with labeling)
/M.Brower (with labeling)
/P.Andrews (with labeling)
/M.Takeuchi (with labeling)
/A.Koutsoukos (with labeling)
/S.Ibrahim (with labeling)
/A.Rahman (with labeling)
/L.Vaccari (with labeling)
/D.Pease (with labeling)
/R.DeLap (with labeling)
HFD-002/ORM (with labeling)
HFD-101/Office Director (with labeling)
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.
HFI-20/Press Office (with labeling)
HFD-021/ACS (with labeling)

Drafted by: dds\3-30-98
Initialed by: S.Honig\4-2-98
G.Williams\4-2-98
J.Jee\4-2-98
R.Wood\4-2-98
M.Brower\4-3-98
P.Andrews\4-2-98
M.Takeuchi\4-2-98
A.Koutsoukos\4-2-98
S.Ibrahim\4-7-98
A.Rahman\4-7-98
D.Pease\4-2-98
F/T by: dds\4-7-98

a:\20262tax\se1-026\reg-ltrs\s026-ap-ltr

APPROVAL (AP) **S-026**

ACK/RET (AR) **S-027, S-028**

CENTER FOR DRUG EVALUATION AND RESEARCH

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

MEDICAL REVIEW(S)

APR - 9 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: 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/Cisplatin (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	22	15
Febrile Neutropenia	15*	4*
Hypersensitivity reactions		
All	8*	
Severe	3*	1*
		--*
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

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

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

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 ***Complete*** 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/

3/11/98

Grant Williams, M.D
Team Leader

cc: NDA 20-262/S-026
HFD-150 / Div Files
/D. Spillman
/S. Honig
/G. Williams

Medical Officer NDA Review: Paclitaxel (Taxol) MAR 25 1998
March 25, 1998

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

2.0 Table of Contents

TOPIC **Page Number**

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 20-101and 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	
Explanation of patient code numbers	3	Page 58
Original GOG protocol	3	Page 206
Blank case report forms	3	
Randomization logs	3	

On treatment signs and symptoms	3	
Literature review, randomized studies	4-5	
EORTC study	4	Page 56
GOG-132	4	Page 199
Neijt et al	5	Page 1
du Bois et al	5	Page 48
ICON3	5	Page 147
Literature review, nonrandomized studies	6	
List of differences between BMS and GOG results	15	

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, 199-

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, 199-

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.

4.0 Chemistry/Manufacturing Controls

Paclitaxel is a marketed drug; the chemistry and manufacturing controls have been previously reviewed and approved. The sponsor submitted an Environmental Assessment, which will be reviewed by the Chemistry Reviewer, Josephine Jee, Ph.D.

5.0 Animal Pharmacology/Toxicology

Paclitaxel is a marketed drug; the preclinical pharmacology has been previously reviewed by Margaret Brower, Ph.D. and approved.

6.0 Human Pharmacology, Pharmacokinetics, Pharmacodynamics

Paclitaxel is a marketed drug: the clinical pharmacology has been previously reviewed by Margaret Brower, Ph.D. and approved.

7.0 Relevant Human Experience/Literature Review

Because the sponsor submitted a published literature review as part of the application, the reviewer's literature review and discussion in the context of the NDA will be presented in section 11.0.

8.0 Summary of Clinical Studies

8.1 Pivotal trials

The sponsor submitted one pivotal trial in this sNDA: CA 139-022 or GOG 111. This study was a prospective multicenter randomized trial of cyclophosphamide and cisplatin versus paclitaxel and cisplatin as first-line therapy of advanced stage ovarian cancer. This trial is reviewed in detail.

The sponsor describes the generation of the database for this study. The GOG required the submission of a series of reporting forms, GOG internal forms, documents from patient records, and representative pathology and cytology slides that were centrally reviewed. Data was extracted from these records in order to generate the GOG database. The contents of the GOG database are as follows:

Patient demographics
Patient pre-treatment characteristics
Surgical measurements from initial and second-look laparotomies

Dosing data per course
Clinical and pathologic response with dates
Date of clinical recurrence
Date of death or last known follow up
Worst on-study toxicity as CTC grade for 18 toxicity groupings
GOG evaluation of patient eligibility, response, protocol violations

This data was transferred to BMS. The sponsor then created its own database from the source documents to include all available information. Examples of additional data included in the BMS database are all adverse events (the GOG database included only AEs felt by the investigators to be related to study drug) and all tumor assessments (the GOG required only 1-2 measurable indicator lesions). The sponsor expanded the limited number of GOG adverse event categories in order to allow better assessment of events such as infection, febrile episodes, cardiovascular events, peripheral neuropathy, arthralgia/myalgia, and gastrointestinal events.

BMS performed an audit of documents on randomly selected patients. The records of 97 patients treated at 19 different sites were examined and were used to create a database with the same structure as the BMS database. The database created on the 97 patients from documents derived from the study sites was compared to the database generated from the GOG database for the same 97 patients. The comparison of the audited and GOG databases will be discussed in the Efficacy section, section 9.5. Where a discrepancy in pathology review between the study site and the GOG existed, the central GOG review was used.

8.2 Supportive trials

Supportive information for this application includes a literature review of both randomized and non-randomized trials of paclitaxel as first-line therapy in ovarian cancer. These studies are listed in the following tables and the relevant trials are reviewed in section 11.0.

Table 1. Summary of published randomized trials of paclitaxel as first-line therapy for ovarian cancer.

Study Number	Institution/ Group	Therapy	Taxol Dose and Schedule	Number of patients	Efficacy
CA 139-209	EORTC/ Intergroup	PT v. PC	175 mg/m^2 over 3 hours	680	*PFS*: 16.6 v. 12 months *OS*: 35 v. 25 months* *cResponse*: 57% v. 43% *pCR*: 3% v. 0%
CA 139-057	GOG-132	PT v. T v. P	135 mg/m^2 over 24 hours with P; 200 mg/m^2 over 24 hours as single agent	648	*PFS*: 14.1 v. 11.4 v. 16.4 months *OS*: 26.6 v. 26.0 v. 30.2 months *cResponse*: 67.2% v. 42.0% v. 67.2% *pCR*: 22% v. 6% v. 14.5%
CISCATAX.18	Neijt (Dutch/ Danish/ Swiss)	T/CBDCA v. PT	175 mg/m^2 over 3 hours in both arms	211	NA
	duBois (AGO)	T/CBDCA v. PT	185 mg/m^2 over 3 hours (both arms)	660	NA
ICON3	Medical Research Council	T/CBDCA v. CBDCA or CAP	175 mg/m^2 over 3 hours	2000	NA

cResponse= clinical partial and complete response in the subset of patients with measurable disease
pCR = pathologic complete response (on the subset of patients with a clinical CR who underwent second-look laparotomy)
PT= cisplatin and paclitaxel: PC=cisplatin and cyclophosphamide: T=paclitaxel: P=cisplatin: CBDCA=carboplatin
* ASCO 1998 abstract

Table 2. Published non-randomized trials of paclitaxel as first-line therapy for ovarian cancer (cited by BMS). [Table adapted from sponsor's tables 1 and 6, volume 6, pps. 39, 44]

Study Number	Institution	Ovarian pts/ Total pts	FIGO Stage II/III/IV	Debulking: optimal/ suboptimal/ none	Response rate: All pts/Eval. Pts (ovarian pts)
			Taxol Alone		
CA 139-093*	NorthWest Thames	33/33	--/--/33	--/--/33	36%/48%
CA 139-090*	Scandinavian	27/27	--/27/--	--/27/--	52%/61%
			Taxol/Cisplatin		
CA 139-010	Johns Hopkins (sequential use)	6/44	--/6 (III + IV)	--/6/--	83%/100%
CA 139-070	NCIC-CTG	29/29	4/21/3	11/16/2	31%/82%
	Cleveland Clinic	19/35	19 (advanced)	--/--/--	NA (pilot for toxicity)
			Taxol/Carboplatin		
CA 139-073 GOG 9202	Fox Chase	39/39	39 (advanced)	--/--/--	46%/75%
CA 139-099	ECC Amsterdam	36/36	-- 24/12	--/--/--	53%/70%
CA 139-238*	Newcastle	11/11	4/6/1	7/4/--	27%/75%
CA 139-178*	Inst. Roussy	40/40	--/40 (III + IV)	--/--/--	NA
CA 139-179*	KAO Germany	14/14	14 (advanced)	--/--/--	NA
23-93.015*	KAO Germany	15/15	15 (advanced)	--/--/--	NA
CA 139-091	Velindre H.	30/30	30 (advanced)	--/--/--	53%/73%
36-93.031	U. Milan	27/27	--/25/2	13/14/--	63%/81%
36-93.017*	S. Orsola H.	9/9	--/9 (III + IV)	--/--/--	NA
Baker-Norton	M.D.	14/14	--/--/--	--/--/--	NA

Study Number	Institution	Ovarian pts/ Total pts	FIGO Stage II/III/IV	Debulking: optimal/ suboptimal/ none	Response rate: All pts/Eval. Pts (ovarian pts)
Three Drugs					
CA 139-061	NCI-Med. Branch	13/13	1/5/6	3/9/--	69%/75%
	Salpetriere	14/14	--/10/4	--/6/8	64%/82%
B-W/ Amgen	M.D. Anderson	23/26	23 (advanced)	--/23/--	65%/88%
High Dose					
CA 139-146	U. North Carolina	2/26	--/2/--	--/2/--	100%/100%
CA 139-121	Memorial	16/16	1/11/4	6/10/--	81%/100%

* Accrual continuing and or interim analysis on a patient subset

8.3 Ongoing trials

Ongoing studies in ovarian cancer, including trials sponsored by BMS and investigator-initiated trials, are summarized in the following table:

Redacted 1

pages of trade secret and/or confidential commercial information

9.0 CA139-022/GOG 111: Phase III randomized study of cyclophosphamide and cisplatin versus Taxol and cisplatin in patients with suboptimal Stage III and Stage IV epithelial ovarian carcinoma

Trial Accrual Dates: April 13, 1990 to March 2, 1992
Data Cutoff: March 30, 1995

9.1 Rationale and objectives

Ovarian carcinoma is diagnosed in 26,800 women in the United States yearly, with a similar incidence in other countries around the world (Parker SL, Tong T, Bolden BA, Wingo PA. CA:Cancer J. for Clin. 47[1]: 5-27, 1997). The disease is usually diagnosed at an advanced stage, and few women are cured despite the high activity of platinum-based regimens. Standard therapy has consisted of either cisplatin or carboplatin in combination with cyclophosphamide. Although initial response rates are 60-70%, responses are not durable. The median survival of these advanced stage patients is 18-24 months, and the 5-year survival is 10-20%. The activity of paclitaxel in ovarian cancer led to its approval by the FDA for use in patients who had failed first-line or subsequent chemotherapy for the treatment of metastatic carcinoma of the ovary.

Preclinical evidence of synergy between paclitaxel and cisplatin, evidence of non-overlapping toxicity seen in pilot clinical trials, paclitaxel's novel mechanism of action (microtubule stabilization) and the activity seen with this compound in pre-treated ovarian cancer patients led to the current study, which tested this combination as first-line therapy of advanced stage ovarian cancer.

The objectives of this trial were:

- To determine response rate, response duration, and survival in suboptimal Stage III and Stage IV ovarian cancer treated with two different platinum-based combination chemotherapy regimens [amended less than a month after the study opened to determine progression-free survival as the primary endpoint, survival as the secondary endpoint, and response as the tertiary endpoint]
- To evaluate the relative activity of a new combination, cisplatin/taxol, as compared to the standard regimen, cisplatin/cyclophosphamide
- To further evaluate the toxicities of the new combination of cisplatin/taxol in this larger patient population
- To compare the relative toxicities of the two regimens
- To compare the therapeutic index of the two regimens

Reviewer Comment:

1. Endpoints should be prospectively defined. However, the change in the primary endpoint with recalculation of the sample size at a time point when few patients had been entered on trial should not affect the results. A MS Access query indicated that 9 patients had been entered on study at the time the amendment was made.

9.2 Design

This trial was a randomized controlled multicenter open-label Phase III trial in chemotherapy-naive suboptimal Stage III and Stage IV ovarian cancer patients who had undergone optimal surgery for ovarian cancer. The study was conducted by the GOG in 86 hospitals affiliated with its member institutions in the United States. Patients were stratified by measurable or non-measurable disease and then randomized to receive either cisplatin/paclitaxel (PT) or cisplatin/cyclophosphamide (PC). Randomization was performed centrally by the GOG office and was balanced within and across GOG centers. The regimens were as follows:

Cisplatin 75 mg/m^2 IV at 1 mg/minute Day 1
Cyclophosphamide 750 mg/m^2 IV bolus Day 1 The drugs may be given together

OR

Paclitaxel 135 mg/m^2 as a 24 hour continuous infusion Day 1
Cisplatin 75 mg/m^2 IV Day 2

Both regimens were given every 21 days for a total of 6 cycles.

Patients randomized to receive PT were premedicated with dexamethasone 20 mg po 14 and 7 hours prior to the paclitaxel infusion, benadryl 50 mg IV 30 minutes prior to paclitaxel, and ranitidine or its generic equivalent 50 mg IV 30 minutes prior to paclitaxel. The dexamethasone was given IV in patients with active emesis from bowel dysfunction. The paclitaxel was mixed in 4 aliquots, each administered over 6 hours for stability reasons. Patients had continuous cardiac monitoring during the taxol infusion, which could be discontinued after 2 cycles if no cardiac toxicity was observed; the protocol was later amended to require cardiac monitoring for all cycles based on reports of ventricular tachycardia.

All patients had a baseline postoperative abdominal-pelvic CT scan prior to study entry; patients with measurable disease were restaged every 2 cycles. Patients with a complete clinical response at the conclusion of their assigned therapy and all patients with non-measurable disease were required to undergo a second-look laparotomy within 8 weeks of the last cycle of chemotherapy. The protocol was later amended to exempt patients with CA-125 values of greater than 100 from the second-look laparotomy. Patients were required to complete a 21 item self-report questionnaire and a 5 item nurse-administered neurologic assessment prior to the first cycle and 4-6 weeks after the last cycle of therapy. As noted below, the time points for these assessments were changed in protocol amendments. A summary of all the required study parameters is attached in Appendix A.

Dose reductions in cisplatin were not permitted. Renal or neurologic toxicity mandated a treatment delay, but not a dose reduction. Cyclophosphamide or paclitaxel could be dose-reduced to 500 or 110 mg/m^2 respectively for grade 4 nadir hematologic toxicity (except grade 4 anemia). In the subsequent cycles, the drugs were given at the starting dose unless there was persistent grade 3-4 adverse effects. Paclitaxel was discontinued for AV block but not for asymptomatic sinus bradycardia.

Patients were removed from study for :

- Grade IV hematologic toxicity requiring a treatment delay of > 6 weeks
- Persistent creatinine elevation ≥ 2.0 mg/dl for more than 6 weeks
- Grade IV non-hematologic toxicity requiring a treatment delay of > 6 weeks
- Grade III-IV peripheral neuropathy requiring a treatment delay of > 6 weeks

The protocol was amended 15 times, including 1 amendment made prior to patient accrual and 1 amendment for closure of accrual, with multiple changes per amendment. Most of the amendments corrected typographical and grammatical errors or clarified statements in the consent form. The changes are summarized below:

April 11, 1990	Correction of typographical errors (prior to patient accrual)
April 20, 1990	Clarification of one sentence in the consent form
May 11, 1990	1. Patients with non-measurable disease and a CA-125 > 100 despite a complete clinical response were not required to undergo a second-look

	laparotomy. 2. An audiogram was required pre-treatment. 3. The statistical section was changed. The primary endpoint was altered from frequency and duration of complete response to progression-free interval. Response was listed as the third endpoint. The median time to progression with a cisplatin-based regimen was assumed to be 10.3 months for women with measurable disease and 14.4 months for women with non-measurable disease. Median survival estimates were unchanged from those in the original protocol. A clinically significant difference was considered to be an increase in the TTP by 40% or more. A sample size of 360 patients was calculated to provide an 84.6% chance of detecting a treatment effect of this magnitude. The new calculations provided an 82.7% chance of detecting a 40% increase in the median survival after 24 months of follow up, and an 80% chance to detect a 19% increase in complete responses due to taxol. Plans for an interim analysis were also outlined: the analysis will be performed when there are 50 failures in the PC group, expected after 2/3 of the sample size is accrued. If the progression-free interval is greater among PC patients, the study would be stopped early, with a loss in power of 3%. If the progression-free interval is greater among PT patients with a p=0.005, the study will be stopped early with an increase in type I error of 0.5%. 4. Solution preparation standards were updated.
August 24, 1990	1. The ovarian cancer surgical procedure and second-look laparotomy sections were revised. 2. Taxol drug stability data were updated. 3. A postoperative abdominal CT scan was not required if the measurable disease was present outside the abdomen, pelvis, or retroperitoneum. 3. Cytology slides from malignant pleural effusions were required for submission.
January 4, 1991	The Neurologic Assessment procedure was limited to 6 study sites.
February 8, 1991	All patients randomized to PT were required to undergo cardiac monitoring on all cycles because of reports of ventricular tachycardia.
April 5, 1991	1. Two additional study sites were added to the Neurologic Assessment list. 2. Additional timepoints were added for the Neurologic Assessment: prior to cycle 3 and after a negative second-look laparotomy. 3. Patients with non-measurable disease were required to undergo a postoperative pelvic examination and abdominal CT scan.

June 10, 1991	Demographic data was collected with the Neurologic Assessment.
July 29, 1991	Holter monitoring was instituted for a subset of patients, 70 on each arm.
August 9, 1991	A ninth site was added for Neurologic Assessment.
September 27, 1991	These changes were retrospective to July 29, 1991. Neurologic Assessments were added at the 3 and 6 month follow up visits.
February 21, 1992	Protocol closed to accrual as of March 2, 1992.
May 22, 1992	Taxol stability data were updated.
November 25, 1992	A study pathologist was named as a principal investigator.
June 3, 1994	Paclitaxel information was updated and new information about adverse events was added to the consent form.

Reviewer Comment:

1. The trial was open-label. However, conducting a double-blinded study with these drugs was not possible because of the complexity of the ancillary procedures required. For example, patients on PC would have been required to undergo a prolonged hospitalization, taken either the same paclitaxel premedication or placebo premedication, etc. This approach was not feasible or ethical.

2. Stratification was performed for measurable versus evaluable disease and by GOG center but not for other factors. This approach is reasonable: there is little prognostic difference between suboptimal Stage III and Stage IV patients, and all patients were required to have good performance status, the most important prognostic factor. Stratification by measurability of disease allowed calculation of response rates. Stratification by GOG center was designed to maximize the comparability of results across the country. One potential drawback: each center was frequently comprised of a main hospital and several smaller hospitals. Thus, there may have been intracenter variations in treatment according to subcenter. However, the large number of hospitals (86) precluded further stratification. Randomization should offset any bias.

3. The nurse-administered assessment evaluated neurotoxicity alone. As defined in the original protocol, the 21 item self-administered inventory was designed to measure neurotoxicity, but the first 8 questions could address either peripheral neuropathy or general quality of life issues. The quality of life measures are limited by the non-blinded nature of the study. In addition, the time points initially chosen were baseline and the conclusion of chemotherapy. The endpoint will cause bias in the results, since patients who complete 6 cycles of chemotherapy with a partial or complete response are likely to have significantly different results than patients who stopped therapy because of progressive disease or chemotherapy-related toxicity. The choice of an intermediate endpoint, such as after cycle 4, would give a more accurate comparison of the two groups. The addition of the cycle 3 time point as well as the timepoints during follow-

up addressed this limitation. However, because of the timing of the amendments, these data will be limited by missing timepoints and the limited number of sampled sites.

4. Stringent criteria to maintain dosing were included in the protocol.

5. The addition of increased cardiac monitoring allowed for a better delineation of paclitaxel-related arrhythmia; the voluntary Holter monitoring in both treatment arms allows a comparison to untreated patients with comparable medical problems. The requirement for monitoring during all paclitaxel cycles was due to literature reports of ventricular arrhythmias. A MS Access query of cardiovascular adverse events revealed premature ventricular contractions: 1 patient had an asymptomatic 4-beat run of ventricular tachycardia. No significant occurrences of ventricular tachycardia were noted.

6. Although CA-125 has not been accepted as a surrogate marker of patient benefit, an elevated value is likely to be associated with persistent disease. It is appropriate to spare these patients the morbidity of the second-look laparotomy procedure.

7. The statistical section was changed early in the course of the study, less than a month after the study opened to accrual. The endpoint was changed from response rate to time to progression, an endpoint associated with patient benefit. The trial retained the statistical power to detect a meaningful difference in response, TOP, and survival. This amendment should not influence the outcome of the study. A MS Access query was performed to ascertain the number of patients entered on study prior to the statistical amendment. Between 4/13/90 and 5/11/90, 9 patients were entered on study and began treatment. This small number is unlikely to introduce bias.

9.3 Eligibility, enrollment, and demographic/baseline characteristics

9.3.1 Inclusion/exclusion criteria

9.3.1.a Inclusion criteria

- Patients with established ovarian epithelial cancer, suboptimal (> 1cm in diameter) Stage III and Stage IV. All patients must have optimal surgery for ovarian cancer, with at least an exploratory laparotomy and appropriate tissue submitted for histologic examination. A TAH/BSO should be performed when appropriate
- One of the following pathologic subtypes: serous, mucinous, clear cell, or endometrioid adenocarcinoma, undifferentiated carcinoma, mixed epithelial carcinoma
- Measurable or non-measurable disease, but patients with measurable disease are preferred. To qualify as measurable disease, lesions must measure at least 3 cm on CT; patients are required to have restaging every 2 cycles
- Must have cytologic confirmation that a pleural effusion is malignant, if entry is based on this site
- Must be entered within 6 weeks of staging surgery
- Adequate bone marrow, renal, and hepatic function
- GOG PS 0, 1, 2 [Reviewer note: GOG PS = ECOG PS]

9.3.1.b Exclusion criteria

- Borderline carcinoma, "probably malignant", or a pathologic subtype not listed above
- Optimally debulked Stage III patients
- Previous cancer chemotherapy of any type or radiation therapy
- Septicemia, severe infection, acute hepatitis, or severe gastrointestinal bleeding
- History of cardiac arrhythmia or patients on anti-arrhythmic medication
- Inability to complete the study or the required follow up
- Unclassified cases of ovarian cancer (unable to verify tumor arising from ovarian tissue)
- Prior history of malignancy other than non-melanoma skin cancer

9.3.2 Enrollment, removal from study, protocol violations

9.3.2.a Enrollment

Four hundred ten patients were randomized on study, 196 to PT and 214 to PC. Two hundred forty patients had measurable disease, 113 on PT and 127 on PC. Twenty-one of these patients were inevaluable, 11 on PT and 10 on PC, for the following reasons: 6 patients on each arm had the wrong primary, 5 patients (randomization not given: completed therapy but had inadequate tumor evaluations performed, and 4 patients requested to go off study prior to completing therapy (randomization not given: . Of the 177 with non-measurable disease, 87 were randomized to receive PT and 90 to receive PC.

Several patients were incorrectly stratified: 1 patient on each arm was incorrectly stratified as measurable disease; 4 patients on PC and 5 patients on PT were incorrectly stratified as non-measurable disease. The sponsor noted that 113 patients on PT actually had measurable disease, as did 127 patients on PC. One patient on the PC arm never received treatment she died of a postoperative pulmonary embolus prior to cycle 1.

Reviewer Comment:

1. There are unequal numbers of patients on the two treatment arms. Randomization logs were available for 43 of the 86 hospitals and probably represent the 43 official GOG centers, each with several subsites. The sponsor was asked to clarify this point. In a Response to FDA Request for Information (RFRI) dated 12/22/97, the sponsor confirmed that patients were stratified by GOG center, not by subcenter. Patients were randomized consecutively by center, regardless of the subcenter that contributed the patient. On FDA review, the logs were filled in correctly, in chronologic order, without skipping assignments, and without gaps. The imbalance is probably due to the stratification for measurable and non-measurable disease and because some centers accrued only 1 or 2 patients. For example, of the 43 logs provided, 5 centers entered patients with measurable disease only and 4 centers entered patients with non-measurable disease only. Eleven centers entered 2 patients each, and 24 centers entered 1 patient each.

2. The number of patients incorrectly stratified totaled 11, representing 3% of the study population. The errors were equally distributed between the two arms and should not affect the outcome of the study.

3. The sponsor corrects the number of patients with measurable disease and uses actual,

not randomized, measurability in the response analyses. As randomized, 109 patients on PT and 124 patients on PC were considered to have measurable disease. Although not a true intent-to-treat analysis, this correction is acceptable.

4. The number of inevaluable patients with measurable disease is 21/240, or 8.8%. This rate is acceptable for a study of this design in this disease. Again, inevaluable patients were equally distributed between the two arms.

5. The sponsor indicates that 5 patients were inevaluable on the measurable disease stratum because they had inadequate tumor evaluations performed. These patients, according to review of their case report forms, had a baseline CT scan and had no further radiographic evaluations. All 5 underwent a second-look laparotomy. Thus, these patients were inevaluable for clinical response, but should be evaluable for pathologic response, time to progression, and survival.

9.3.2.b Removal from study

Patients were removed from study for the reasons summarized in the following table:

Table 4. Removal from study (modified from sponsor table 23, volume 3, page 87)

Reason off study	**Number of patients (%)**		
	Cisplatin/Taxol	Cisplatin/Cyclophos-phamide	Total
Completed treatment	168 (86)	165 (77)	333 (81)
Drug-related toxicity:	11 (6)	15 (7)	26 (6)
Renal	2	4	6
Ototoxicity	--	5	5
Hypersensitivity	5	--	5
Hematologic	--	4	4
Polyneuropathy	1	--	1
Emesis	--	1	1
Seizures	--	1	1
Cardiac	1	--	1
Cutaneous	1	--	1
Infection	1	--	1
Disease progression	5 (3)	20 (9)	25 (6)
Death:	6 (3)	5 (2)	11 (3)
Disease progression	2	--	2
Treatment complication	1	3	4
Intercurrent disease	3	2	5
Patient request	4 (2)	7 (3)	11 (3)
Wrong primary tumor	1 (1)	1 (<1)	2 (<2)
Never treated	--	1 (<1)	1 (<1)
Cerebrovascular accident	1 (1)	--	1 (<1)

Reviewer Comment:

1. There are no drug discontinuations for hypersensitivity to cisplatin listed here. However, in sponsor Table 18, volume 3, page 81, one patient experienced a hypersensitivity reaction to cisplatin on the sixth and final cycle, with premature discontinuation of therapy.

2. Patient developed heart block during cycle 6 after 4.5 hours of the taxol infusion. This patient received the full dose of cisplatin and was considered to have completed therapy, according to the sponsor. This patient is not the patient reported as off-study for cardiac adverse event. The patient removed for cardiac reasons was patient who had ECG changes consistent with silent ischemia.

3. The narratives for the patients removed from study were reviewed. Although patient (PC) is listed as removed from study due to renal toxicity, the narrative reports only a grade 1 creatinine elevation at study discontinuation. Her concomitant problems included grade IV leukopenia and granulocytopenia, grade III nausea and vomiting, grade III symptomatic pericardial effusion, grade II bilateral pleural effusions, thrombocytopenia (grade not given), and grade I hypokalemia. None of her toxicities met the off-study criteria, although it is appropriate from a clinical standpoint to remove her because of multiple severe toxicities. With significant pericardial and pleural effusions, the patient may have had progressive disease. There is no significant difference in the incidence of renal toxicity (any or severe) between the two arms, even after removal of this patient.

4. The cutaneous toxicity consisted of Stevens-Johnson syndrome secondary to vancomycin in a patient treated with PT who developed neutropenic sepsis. The sponsor has conservatively attributed it to study therapy, although it was probably due to antibiotic therapy.

5. The patient removed due to neurotoxicity had grade II neurotoxicity recorded. Grade III or greater neurotoxicity was required for removal from study.

9.3.2.c Protocol violations

Three hundred seventy patients were eligible. Forty patients did not meet all of the eligibility criteria, and were equally distributed between the two arms (20 on PT and 20 on PC). These violations are as follows:

Table 5. Summary of major and minor protocol violations (modified from sponsor table 7, volume 3, page 67 and Table 10, page 70)

Protocol Violation	Number of patients, Cisplatin-taxol	Number of patients, Cisplatin-cyclophosphamide
Major violations:		
Diagnosis other than ovarian cancer	8	10
History prior malignancy		2 (breast)
Optimally debulked	1	
Wrong stage	1 (stage IB)	
Minor violations:		
No baseline AST	5	3
No baseline bilirubin	2	1
No baseline platelet count	0	1
Elevated AST	4	3
Elevated creatinine	1	1
Low white blood cell count	0	1
Low platelet count	1	0
Wrong cell type:	Total = 8	Total = 10
Ovarian--low malignant potential	1	1
Unknown primary	3	4
Primary peritoneal	1	2
Gastrointestinal	2	1
Endometrial/ovarian	1	1
Endometrial	0	1

Reviewer Comment:

1. Because of the equal distribution of the protocol violations, both major and minor, between the two arms, the study results are unlikely to be significantly affected.

2. Other protocol violations include some of the removal-from-study decisions; one example is given in Reviewer Comments 3 and 5 following section 9.3.2.b. Some patients were removed by investigators who believed it was in the patient's best interest rather than according to study criteria. However, the number of patients removed in this fashion was small, affected both arms, and is unlikely to significantly affect the study results.

9.3.3 Patient demographics and baseline characteristics; tumor characteristics

9.3.3.a Patient characteristics

The median age in each arm was 59 years. Eighty-four percent of patients had a performance status of 0 or 1; 16% had a PS of 2. There was no significant difference in the distribution of performance status between arms. The extent of pretreatment procedures was comparable in the two treatment arms.

No patient had received prior hormonal therapy, radiation therapy, or chemotherapy for cancer treatment. All patients had undergone at least 1 laparotomy prior to protocol entry. Forty-one patients had been optimally debulked (6 randomized to PT, 8 randomized to PC with no residual tumor; 15 and 12 respectively with <1cm residual tumor). All of these optimally debulked patients, except the one noted in the protocol violations, had Stage IV disease. There was no significant difference in the amount of residual tumor between the two arms.

In terms of laboratory tests, 48% of patients in each arm had grade 1-2 anemia at baseline, probably due to extent of disease and prior surgery. Hematology parameters were balanced between the two arms. Forty-three percent of patients on each arm had at least 1 abnormal liver function test at baseline, most commonly an elevated alkaline phosphatase (34% PT, 37% PC). The majority of the elevations were grade 1 and were not significantly different between the two arms. Five percent of PT patients and 6% of PC patients had grade 1 creatinine elevations and 1% in each arm had grade 2 creatinine elevations. Again, these differences were not significant.

9.3.3.b Tumor characteristics

Sixty-six percent of patients had Stage III disease and 34% had Stage IV disease. The diagnosis of ovarian carcinoma was confirmed on central pathology review in 96% of patients; serous adenocarcinoma was the most common type, representing 74% of PT patients and 64% of PC patients (p=0.025). The other cell types were evenly distributed between the two arms, as was the distribution of histologic grade.

9.3.3.c Extent and type of disease

Two hundred forty patients had measurable disease, 113 on PT and 127 on PC; 170 had non-measurable disease (83 on PT and 87 on PC). The most common sites of disease in the patients with measurable disease, considering all measurable and non-measurable lesions, were the pelvis (103 patients, 43%), the abdomen (81 patients, 34%), pleural effusions (62 patients,

26%), liver (51 patients; 21%), ascites (49 patients, 20%), lymph nodes (40 patients, 17%), lung (18 patients, 8%), skin/soft tissue/other (11 patients, 5%), and bone (2 patients, 1%). The distribution of disease sites was comparable in the two treatment arms. A median of 1 measurable site per patient was identified for evaluation of tumor response. This lesion measured 2-5 cm in size in 65% of patients with measurable disease (61% PT, 68% PC). Twenty-six percent of these patients had a lesion between 5 and 10 cm (28% PT, 24% PC), and 3% of patients had a lesion greater than 10 cm (2% PT, 4% PC). There was no significant difference in the number or size of indicator lesions between the two chemotherapy arms. A CT scan was used to assess response in 70% of patients with measurable disease; physical examination was used alone in 16% of patients, a different imaging modality in 3%, and the procedure used was not reported in 11% of patients. Again, these differences in method of assessment were not significantly different between the two arms.

Reviewer Comment:

1. The sponsor lists the actual measurability of the patients, rather than their randomized (intent-to-treat) status. The randomized numbers were 109 patients with measurable disease on PT and 124 on PC.

2. There were more patients with the serous cell type on PT than on PC. However, histologic subtype is not a significant prognostic factor, and this imbalance should not affect the study outcome. [Reference: Ozols RF, Rubin SC, Dembo AJ, and Robboy S. Epithelial Ovarian Cancer. In Hoskins WJ, Perez CA, Young RC (eds): Principles and Practice of Gynecologic Oncology, page 748. Philadelphia, J.B. Lippincott, 1992.] Also, this factor was not identified in adjusted analyses by the FDA statistician as a significant prognostic factor.

9.3.4 On-study therapy

One patient randomized to PC died prior to treatment. A total of 1074 cycles of PT were given to 196 patients; 1145 cycles of PC were administered to 213 patients. The range of cycles per patient was one to 6; the median number of courses in each arm was 6. In the PT arm, 85.7% of patients received 6 cycles; in the PC arm, 77.9% received the planned 6 cycles.

9.3.4.a Dose reductions

There was a significant difference in the incidence of dose reductions between the two arms: 27% incidence of dose-reduction overall for paclitaxel and 21% for cyclophosphamide ($p=0.003$). The predominant reason for dose reduction in both arms was hematologic toxicity: 275 of the 288 paclitaxel dose reductions, and 238 of the 244 cyclophosphamide dose reductions. In the PT arm, 5 patients had dose reductions in paclitaxel because of hypersensitivity reactions, 1 because of cardiac arrhythmia, 5 because of physician decision, and 2 because of dosing error. In the PC arm, 6 patients had dose reductions because of a dosing error. The need for dose-reductions increased with the number of cycles: on course 1, 3% of patients received a decreased dose of paclitaxel and <1% received a decreased dose of cyclophosphamide. At cycle 6, these values were 39% and 30% respectively.

The protocol did not permit dose-reductions for cisplatin, only treatment delays.

However, 10 patients on PT received 12 cycles of chemotherapy with a reduced dose of cisplatin. The reasons for dose reduction included a hypersensitivity reaction (1 cycle), 5 cycles in which cisplatin was not given because of removal from study for a paclitaxel hypersensitivity reaction, 2 cycles for neurotoxicity, 3 cycles because of a dosing error, and 1 cycle in which no documentation could be found that cisplatin was administered. On the PC arm, 13 cycles in 9 patients were given with reduced doses of cisplatin. The reasons for dose reduction included grade 4 neutropenia (1 cycle, in which both cyclophosphamide and cisplatin were reduced), neurotoxicity in 2 cycles, ototoxicity in 1 cycle, a dosing error in 4 cycles, and no explanation in 5 cycles.

9.3.4.b Treatment delays

All cycles after cycle 1 were analyzed for delays in study therapy and included 878 cycles of PT and 932 cycles of PC. Treatment delays occurred in 21% of courses of PT compared to 55% of courses of PC ($p < 0.001$). The median number of days to the next course was 21 days for PT compared to 28 days for PC ($p<0.001$). Fewer than 5% of PT cycles were delayed more than 7 days, compared to 13% for PC. The reason for treatment delay in the PC arm was delayed hematologic recovery in 356 of the 932 cycles (38%), compared to 41 of 878 cycles delayed for hematologic parameters in the PT arm (5%).

9.3.4.c Dose-intensity

Dose-intensity was calculated for each study drug individually as the cumulative dose in mg/m^2 given to each patient divided by the duration of treatment in weeks. The treatment duration was defined as the day of first study therapy to 3 weeks after the last study therapy. The relative dose intensity was the received dose intensity divided by the scheduled or planned dose-intensity in $mg\ m^2/wk$ multiplied by 100. Patients were also grouped by their relative dose-intensity as having received <80, 80-90, or > 90% of the planned dose intensity. The results are summarized in the following table:

Table 6. Dose-intensity (sponsor table 22, volume 3, page 86)

	ARM A (N=196)		ARM B (N= 213)	
	Paclitaxel	Cisplatin	Cyclophosphamide	Cisplatin
Cumulative dose per patient (mg/m^2):				
Median	756	448	4212	448
Range				
Planned dose intensity ($mg/m^2/wk$)	45	25	250	25
Delivered dose intensity ($mg/m^2/wk$)				
Median	41	24	204	21
Range				
Relative dose intensity--% of scheduled dose [no.pts (%)]				
≥ 90%	102 (52)	142 (72)	70 (33)	88 (41)
80-90%	64 (33)	40 (20)	51 (24)	65 (31)
< 80%	30 (15)	14 (7)	92 (43)	60 (28)

The difference between the delivered dose-intensity of paclitaxel on the PT arm and the delivered dose-intensity of cyclophosphamide on the PC arm was statistically significant, with a p value of <0.001. The delivered dose-intensity of cisplatin on the two arms was also significantly different ($p < 0.001$): patients received a higher dose-intensity of cisplatin on the PT arm than on the PC arm.

Reviewer Comment:

Dose-intensity (DI) has been shown preclinically and retrospectively to be important in the treatment of ovarian cancer. Dose-intensity is calculated as the dose per unit time; therefore.

both total dose and treatment interval are important determinants of DI. While the incidence of dose reductions is significantly greater for PT than PC (27% compared to 21%), the absolute difference clinically is small (6%). Similarly, reductions in cisplatin dose were similar in the two arms. In contrast, more than twice as many courses of PC were delayed compared to PT. Consistent one-week delays may affect efficacy. In addition, lengthening the course of therapy by 1 week per cycle may have an adverse effect on quality of life. These data demonstrate a higher dose intensity for both paclitaxel and cisplatin on the PT arm, and lower dose intensity for both cyclophosphamide and cisplatin on the PC arm.

9.3.5 Subsequent therapy

The majority of patients received subsequent therapy, including chemotherapy, radiation therapy, immunotherapy, and hormonal therapy. Eighty percent of patients treated with PT received subsequent therapy, as did 73% of the PC patients. There was no significant difference between the two groups in the number of patients who received any of these modalities, nor in the number of subsequent regimens. Patients treated initially with PC were most likely to receive paclitaxel as subsequent therapy (38% of the patients on this arm); other common drugs included carboplatin, cisplatin, and altretamine. Paclitaxel was used as second-line therapy in 19 of these patients. On the PT arm, patients most commonly received carboplatin (47%), followed by cyclophosphamide, altretamine, and cisplatin. Forty-three patients on the PT arm received a second paclitaxel-containing regimen; 14 of these received it as second-line therapy.

Reviewer Comment:

A significant percentage of patients on PC received paclitaxel after disease progression, although only 9% received paclitaxel as second line therapy. Despite a 38% cross-over rate, a significant survival advantage for PT was observed.

9.4 Endpoints/statistical considerations

9.4.1 Endpoints

The endpoints included objective response in patients with measurable disease. Response was defined differently than in most oncology trials:

Complete clinical response:	Disappearance of all gross disease for 3 weeks
Partial response:	50% or greater reduction in the product obtained from measurement of each lesions for at least 3 weeks
Progressive disease:	50% or greater increase in the product from any lesion documented within 6 weeks of study entry or the appearance of any new lesion within 8 weeks of entry into study

The following parameter was used to define pathologic response:

Complete pathologic response:	Pathologic confirmation of complete response at second-look laparotomy

The sponsor added the following categories:

Microscopic disease only:	Absence of all gross residual disease at second-look surgery, but positive blind biopsies
Residual disease:	Gross residual disease at second-look surgery

The protocol did not further specify other definitions or other response parameters. In the analysis, the sponsor added the following points.

Tumor markers, such as CA-125, were not used to assess response. The GOG response criteria were followed; however, the response data in this application reflect the judgement of BMS physicians, not the GOG assessment.

The sponsor included the following categories for patients with measurable disease:

Inevaluable:	Patients who did not have ovarian cancer as determined by the GOG review
	Patients who did not have reassessment of tumor lesions which were measurable at baseline
Early death or early toxicity:	Patients who died on study prior to reassessment of tumor lesions
	Patients who went off study due to serious AE related to study therapy prior to reassessment of tumor lesions

The sponsor added the following categories for patients with non-measurable disease:

Never treated:	Patients who were randomized but never treated
Wrong primary:	Patients who were randomized but determined on GOG central review to have the wrong primary tumor or cell type
Early death or early toxicity:	Patients who died on study prior to the third course
	Patients who went off study due to serious AE related to study therapy prior to the third course
Progressive disease:	Patients with new lesions or clear progression prior to the third course
No measurable disease:	Patients with non-measurable disease who received at least 3 cycles of therapy

Patients were assigned to these categories; if more than one applied, the first on the above list was used.

The sponsor added the following category to the pathologic assessment of response:

Unevaluable:	Patients who did not have ovarian cancer

The sponsor added the following categories for patients who did not undergo second-look laparotomy:

Wrong primary:	Patients who were randomized but determined on GOG central review to have the wrong primary tumor or cell type
Death/toxicity:	Patients who died prior to surgery or were removed from study due to toxicity (whether drug-related or not)
Contraindicated:	Patients with a medical contraindication to surgery
Refused:	Patients who met the criteria for second-look surgery but refused
Not reported:	Patients with no explanation why second-look surgery was not performed
Persistent disease:	Clinical evidence of persistent or progressive disease or persistent elevation of CA-125 after completion of study therapy

Again, patients were assigned to one category in a hierarchical fashion.

Although not included in the original protocol, the sponsor calculated the following parameters:

- Duration of clinical response (duration of CR + PR and duration of CR)

Method 1. From the day of first study drug administration until the date clinical progression was noted. Duration of CR was calculated from the day of the CR. Patients who did not progress were censored at their last date of follow up. Patients who died of disease and for whom a progression date was not available were considered to have progressed on the date of their death.

Method 2. Patients were censored at the time of any therapy which was initiated prior to clinical evidence of recurrence or progression. Examples of this therapy included intensification or consolidation therapy after second-look surgery, second-line therapy based on elevated CA-125 alone, or evidence of persistent but not progressive disease at second-look. Patients who did not relapse prior to this analysis were censored at the date of last follow-up.

- Duration of pathological response

This parameter was calculated for patients with a pathologic CR (pCR) and microscopic residual disease (micro) as well as for patients with pCR. The same two methods were used.

- Time to clinical response

This parameter was calculated for CR and PR as the length of time from the first day of treatment until documentation of the best clinical response.

Other prospectively defined endpoints included survival, defined as the length of life from study entry to death; for living patients, from study entry to date of last contact. Progression-free interval was defined in the protocol as date from study entry to the date of reappearance or increasing parameters of disease or to date of last contact. The sponsor calculated this parameter with two methods:

Method 1. Day of randomization until the date clinical evidence of recurrent or progressive disease was first reported. Patients who did not progress were censored at the last date of follow up. Patients who died of disease without a date of progression were considered to have progressed on the day of death.

Method 2. Patients were censored at the time of any therapy following removal from the study but prior to clinical evidence of recurrence or progression.

Finally, the sponsor generated a new parameter, time to worsening of performance status. This endpoint was calculated from the day of randomization until the date of the first worsening in performance status or death on study. All treated patients with assessment at baseline and at "the same time on study" were included.

The neurologic assessments were grouped in the following time categories:

Baseline: Forms completed prior to the first course of therapy
On study: Forms completed prior to course 4, 5, or 6 or at off-study. If more than 1 form per patient was available, the worst evaluation was used
Three months: Forms completed after second-look surgery or 3 months off-treatment
Six months: Forms completed 6 months off-treatment

The analysis of these forms is described in the Efficacy section.

The minimum length of trial to evaluate response was defined as receiving 1 course of therapy and living 3 weeks for a repeat measurement to be performed. The minimum length of trial to evaluate toxicity was defined as receiving 1 course of therapy and receiving any follow-up information for observation of toxicity.

Reviewer Comment:

1. The response criteria are more liberal than the standard oncology criteria: responses need to be maintained for 3 weeks, not 4; 50% increase in disease rather than 25% constitutes progression. However, a one-week difference between duration of CR or PR is unlikely to make a difference, particularly since clinical CRs were required to have pathologic confirmation. Because ovarian cancer is frequently difficult to measure or evaluate on scans, the requirement for 50% increase in disease ensured that patients were not deprived of potentially beneficial therapy.

2. The differences in the GOG and the sponsor's assessment of response will be discussed in the Efficacy section (9.5).

3. Pathologic complete response appears to be the best predictor for long-term disease-free survival. Patients with microscopic residual disease (as opposed to bulk residual disease) have a high rate of relapse. The value of this assessment as an endpoint is unclear. However,

clinically, it permits selection of patients for additional therapy.

4. It is reasonable to categorize patients who did not have ovarian cancer or who did not have reassessment of tumor lesions as inevaluable, but it is important to recognize that the "gold standard" analysis is intent-to-treat. Also, the 5 patients with measurable disease who did not undergo repeat CT evaluation did undergo second-look laparotomy; these patients can still be considered evaluable for pathologic response, time to progression, and survival.

5. Patients with "early death or toxicity", whether with measurable or non-measurable disease, should still be considered in the calculation of progressive disease, if there is evidence of progression at the time they went off study. The sponsor's hierarchy does not include these patients in a PD assessment.

However, an Access query indicates that only two patients developed progressive disease prior to cycle 3. Both had progression shortly after cycle 3 and were taken off study.

6. All patients entered on the trial should be evaluable for toxicity, not only patients who received 1 course of therapy and had follow-up.

7. The sponsor added multiple response parameters calculated by several methods in a post-hoc fashion. This analysis may be biased. The sponsor also classified patients who died of disease without a date of progression as progressing on the date of their death. This method will likely significantly overestimate time to progression in these patients.

8. Two methods were used to calculate response duration and time to progression. The first method uses the conventional method (from the date of first study drug administration until documentation of progressive disease). The second censors patients at the time a new therapy is instituted, prior to objective documentation of progression. This method is not conventionally used. However, because some patients were given consolidation therapy or treated on the basis of rising CA-125 values, this method may decrease the likelihood that a benefit that resulted from a new therapy is mistakenly attributed to the study therapy.

9. The sponsor indicated that patients with a baseline PS assessment and a repeat assessment at "the same time on study" were included. I believe there is a misprint--any patient with 2 PS evaluations was considered, not a population with a baseline PS and a second PS all on the same visit date.

10. Neurologic assessments from cycles 4-6 and off-study were grouped together. Because patients go off-study for different reasons (toxicity versus response), a better analysis might have grouped assessments from cycles 4-5 and separated forms from cycle 6 and off-study timepoints.

11. Although the GOG protocol states that progressive disease was defined in part by the appearance of any new lesion "within 8 weeks of entry into the study", this line is a missprint. A new lesion at any time constituted progressive disease, as confirmed by the sponsor.

9.4.2 Statistical considerations

In the initial protocol, the following calculations were made. Approximately half the patients were anticipated to have measurable disease. Based on data from prior GOG studies, the complete response rate for PC was estimated to be 30%. An improvement of 20% in the complete response rate was deemed to be clinically significant. In order to demonstrate this

benefit, a sample size of 84 evaluable patients with measurable disease per arm was calculated, which would necessitate a total of 336 patients in the trial. The sample size should provide 80% power to detect a 20% difference in the complete response rate with the probability of a type I error at 0.05. It was then estimated that the median survival for PC was 18.5 months for patients with non-measurable disease and 22.5 months for patients with measurable disease. In order to detect a 50% decrease in death rates, follow up for 1 year after study closure was necessary; the sample size allowed an 87% chance of detecting an improvement of this magnitude.

As noted in section 9.2, the statistical section was modified. The primary endpoint was altered from frequency and duration of complete response to progression-free interval. Response was listed as the third endpoint. The median time to progression with a cisplatin-based regimen was assumed to be 10.3 months for women with measurable disease and 14.4 months for women with non-measurable disease. Median survival estimates were unchanged from those in the original protocol. A clinically significant difference was considered to be an increase in the TOP by 40% or more. A sample size of 360 patients was calculated to provide an 84.6% chance of detecting a treatment effect of this magnitude. The new calculations provided an 82.7% chance of detecting a 40% increase in the median survival after 24 months of follow up, and an 80% chance to detect a 19% increase in complete responses due to taxol. Plans for an interim analysis were also outlined: the analysis would be performed when there were 50 failures in the PC group, expected after 2/3 of the sample size is accrued. If the progression-free interval was greater among PC patients, the study would be stopped early, with a loss in power of 3%. If the progression-free interval was greater among PT patients with a p=0.005, the study would be stopped early with an increase in type I error of 0.5%.

Analysis of pretreatment characteristics was performed using Fisher's Exact Test. For ordered or numeric measures, the Kruskal-Wallis test was used. Fisher's Exact Test was also used to compare dose-intensity calculations, the number of patients who received subsequent therapy, and the clinical response rates in the two treatment arms. The Kruskal-Wallis test was used to evaluate the treatment difference in number of subsequent drug regimens and the number of days between courses. The pathologic response rates were compared using the Cochran-Mantel-Haenszel test adjusted for the randomized strata.

An analysis of treatment effect on response rate was performed after adjustment for baseline prognostic factors in a two-stage logistic regression model. The following factors were considered in the initial stage:

Residual tumor diameter	(≤ 5 cm versus > 5 cm)
Stage	(III versus IV)
Age	(≤ median versus > median)
Site accrual	(0-9 patients versus 10+ patients)
Histologic grade	(1-2 versus 3)
Performance status	(0-1 versus 2)
Liver function tests	(None abnormal versus any abnormal)

In order to remain in the model, a significance level of 0.10 was required in the forward stepwise option. The second stage of the model evaluated the response rate in a logistic

regression model including the factors selected in the first stage, the treatment arm, and the stratum (measurable or non-measurable). For clinical response, stratum was omitted as this parameter was only evaluated in patients with measurable disease. P-values for each potential prognostic factor were calculated for the unadjusted and adjusted analyses. The final model included p values and the odds ratio with 95% confidence intervals.

Time to clinical response was described with summary statistics; the Kruskal-Wallis test was used to assess treatment differences.

Survival was calculated with Method 1 and Method 2 described in section 9.4.1 above and was plotted with Kaplan-Meier curves. The method of Brookmeyer and Crowley was used to calculate the 95% confidence intervals. The logrank test was used to compare treatments stratified by measurable and non-measurable disease.

Adjusted analyses of time to progression and survival were performed using the same forward stepwise Cox regression described for response rate with the same baseline prognostic factors. The forward stepwise model was used to select significant factors; in the final model, these factors were included with treatment arm and stratum. Each potential prognostic factor was tested for its effect on the time to event (adjusted and unadjusted) and the median time to event.

Worsening of performance status, calculated by days from baseline and number of cycles of chemotherapy, was evaluated with Kaplan-Meier curves. Patients who had a recorded baseline PS and also a second PS recorded on study or who died on study were included in this analysis.

Neurologic parameters were assessed with descriptive statistics.

Safety analyses were performed on patients who received at least one dose of study medication. Results were tabulated by frequency by treatment arm on cycle 1 and by worst on-study grade. Incidence rates of major toxicities were calculated and also broken down by grade. Differences in the incidence of events and in the incidence of severe events between treatment arms were evaluated with Fisher's Exact Test.

Reviewer Comment:

1. The analysis stratified by measurability, as specified in the initial protocol document, is considered as the primary analysis by the FDA reviewers. We also rely on an unstratified analysis for TTP and survival. The results of the logistic regression analyses will be reviewed, but are considered as supportive analyses.

2. Ninety-five percent of patients in this trial fit the criteria for inclusion in analysis of time to worsening of PS. However, this analysis will be difficult to interpret, since the timepoints of assessment will differ from patient to patient. Some patients may have had reassessment of PS when they completed all study therapy with a clinical response; others may have been reassessed at the time of progressive disease or removal from study for toxicity, which will bias the assessment.

3. The prognostic factors included in the model are all recognized factors for ovarian cancer except for baseline liver function tests. The reviewer performed a comprehensive MedLine search and reviewed major oncology and gynecologic oncology textbooks and did not find this feature mentioned. In addition, the liver function abnormalities noted in this study were primarily CTC grade 1 and of questionable clinical relevance. The FDA statistician, Massa

Takeuchi, Ph.D. re-ran the program without this factor; results are noted in the Efficacy sections. However, the unadjusted analysis is considered the primary analysis.

9.5 Efficacy analysis

9.5.1 Response

9.5.1.a Clinical response

Two hundred forty patients had measurable disease, 113 randomized to PT and 127 randomized to PC. A total of 21 patients were inevaluable; the reasons are listed in section 9.3.2.a. The sponsor reported response data for all patients, both evaluable and inevaluable, with measurable disease. The response data may be summarized as follows:

Table 7. Complete and partial response rates for GOG 111

Response	Cisplatin-Taxol	Cisplatin-Cyclophosphamide	P-value
Complete response	40/113 (35%)	32/127 (25%)	0.092
Partial response	28/113 (25%)	32/127 (25%)	
Overall response	68/113 (60%)	64/127 (50%)	0.153

If one considers only the 219 evaluable patients (102 on PT and 117 on PC), the complete response rates were 39% and 27% respectively; overall response rates were 67% and 55%. Neither of these differences was statistically significant.

Reviewer Comment:

1. Clinical response rates as reported by the sponsor were not significantly different between the two treatment arms, whether all patients with measurable disease were used or only evaluable measurable patients.

2. The reviewer performed a series of MS Access queries to verify response. All 240 patients with measurable disease were included. The definitions of complete and partial response in the protocol were used, as well as the requirement for a confirmatory measurement. The reviewer accepted evidence of response from a second-look laparotomy as well as subsequent radiographic studies or physical examination as confirmation of response.

Eighty-seven patients had a verified non-surgical response based on the Access algorithm developed by Grant Williams, M.D., Team Leader: 40 on PC and 47 on PT. An additional 21 patients had a negative second-look laparotomy to confirm response: 9 on PC and 12 on PT. The total number of responders based on this preliminary assessment is therefore 49 on PC and 59 on PT, for a total of 108 of 240. On comparing the lists of BMS responders and FDA responders, 4 patients on PC and one patient on PT were noted to have responses documented in the case report forms, although they did not appear on the

list generated by the algorithm. The number of responders by arm is therefore 53 on PC and 60 on PT.

The following patients had discordant results between the FDA and the BMS evaluation:

Table 8. FDA Responders not listed as BMS responders

Patient ID	Treatment Arm	Tumor Evaluation Description	FDA
	PC	Incomplete follow-up; not all lesions assessed	No response
	PC	PR documented at C3 and C5 (excluded because of wrong primary)	PR
	PT	cCR confirmed by CT and by 2nd look lap (excluded because of wrong primary)	CR
	PT	PR confirmed by 4 measurements (excluded because of wrong primary)	PR
	PT	Lesion measured at baseline by CT (area 20 cm^2); PR by PE at C2, C3, C6 and PR documented by 2nd-look lap	PR

The sponsor indicated in the study report that an intent-to-treat analysis of all patients entered on study with measurable disease (240 patients) was performed. Thus, data from patients with the wrong primary should have been analyzed for response. The patient with incomplete follow-up was removed from the list of FDA responders, leaving 52 responders on PC and 60 on PT, or 112 of 240.

The patients with discordant assessments between BMS and the FDA were then reviewed. These results are summarized below.

Table 9. BMS responders not listed as FDA responders: PC arm

Pt No	Tumor Evaluation Description	FDA Judgement
	3 lesions at baseline; 1 measured only at C1,3	Incomplete F/U No response
	1 measurable lesion: area of 12 at C0 to area of 9 at C5	No response
	CR confirmed by PE on review of CRF	Agree with CR
	3 baseline lesions: 1 measured only at baseline, 1 with a single measurement indicating a decrease in size	Incomplete F/U No response
	CR confirmed by PE on review of CRF	Agree with CR
	No second confirmation of CR	No response
	CR confirmed by 2 different modalities (sono, then CT)	Agree with CR
	4 measurable lesions at baseline: 1 measured only at baseline, 1 with 1 measurement after baseline at C4 but not at C6 2 evaluable lesions at baseline: 1 not evaluated again, 1 evaluated at C3 but not confirmed with 2nd measure	Incomplete F/U No response
	No second confirmation of PR	No response
	No second confirmation of CR	No response
	No second confirmation of PR	No response
	No second radiographic confirmation of CR, but pathologic confirmation of PR at second-look laparotomy	Agree with PR
	1 measurable lesion at baseline with no change at C2; no other measurements	No response

Based on this review, 4 additional responders were added to the PC arm, for a total of 56.

Table 10. BMS responders not listed as FDA responders: PT arm

Patient ID	Tumor Evaluation Description	FDA Judgement
	2 meas.lesions at baseline; no PR at C4; PR at end-of-treatment without confirmation No confirmation of resolution of effusion	No response
	1 meas. lesion at baseline; no change at C2; absent C4; no confirmation of response	No response
	Cul-de-sac lesion measurable by PE at baseline; no other measurements recorded. At 2nd-look lap. 0.2 cm disease resected.	Agree with PR
	Meas. lesion at baseline decreased by PE; at C5, new cul-de-sac lesion noted (0.5 cm); decreased at C6 (0.3 cm) and gone at end-of-treatment. At second-look lap. no residual disease in these areas	Agree with PR
	2 meas. lesions and 1 eval. at baseline; incomplete follow-up on the 2 meas. lesions (1 meas. at C3; the other at end-of-treatment); no f/u of eval	Incomplete follow-up; no response
	Baseline meas. lesion absent by PE at C4; no confirmatory exams. 2nd-look lap neg in pelvis	Agree with CR
	No confirmatory measurement of PR (C1,3 only)	No response
	Ratio of area at C3 to baseline=.54; ratio at C5 to baseline = .21	Agree with PR
	PR at C5, but no confirmation; evaluable lesion not evaluated after baseline	No response
	Subhepatic lesion meas. only at baseline; residual .3 cm disease in "abdomen" at 2nd look lap	Incomplete follow-up; no response
	No CT confirmation of CR, but 2nd-look lap negative in that region	Agree with CR
	Baseline lesion not re-measured, but 2nd-look lap showed PR in that area. Bilat pleural effusions increased at C2 and not re-checked	No response; ? progression based on non-evaluable sites

Based on this review, an additional 4 responders were added to the PT arm for a total of 64 (Pt based on subsequent information from the sponsor was already counted on the basis of second-look laparotomy results).

The sponsor was sent the following questions (facsimile 2/6/98); they responded with a submission dated 2/25/98 (not sent by facsmile). The questions are in italics; the sponsor's answers are listed below each question:

(1) If all 240 patients with measurable disease were included in the analysis, why were patients not considered to be responders?

These 3 patients had the wrong primary tumor; although included in the denominator, the sponsor did not consider them to be responders.

Reviewer Comment:

Pt Listed in the CRF as Stage IVA suboptimally resected papillary serous cystadenoma of the ovary; listed as eligible by the GOG reviewer

Pt Primary peritoneal carcinoma

Pt Deemed "wrong primary" because primary ovarian tissue was not biopsied. Operative report indicates that a "massive" unresectable tumor was found which involved all pelvic structures in an indistinguishable mass, with a large omental cake and disease above the liver and ascites. The ascitic fluid and an omental biopsy showed papillary adenocarcinoma with psammoma bodies.

Because all three patients have ovarian cancer as encountered in clinical practice, the reviewer feels it is appropriate to include them in both the numerator and denominator for response.

(2) Patient had a PR confirmed on serial physical examinations. Why does BMS not consider this patient to be a responder?

The sponsor indicated that the patient had the wrong primary, and was not considered as a responder.

Reviewer Comment:

This patients was called the wrong primary by the GOG reviewer because the outside surface of the ovaries was involved, but not the cortex.

The operative note describes tumor throughout the abdomen, involving the peritoneal surface, cul-de-sac, omentum, surface of the colon and appendix, liver, bladder, and ovaries. At the local hospital, 95% of the tumor in the ovaries was described as located on the surface; 5% consisted of microscopic cortical involvement.

Again, this patient clinically had ovarian cancer; the reviewer includes her in both the numerator and denominator for response.

(3) Please review Tables 9 and 10. Can you clarify why BMS considers these patients as responders?

For 9 patients in these tables, there was no disagreement between BMS and FDA.

For 3 patients, BMS agreed with the FDA's assessment of no response:

PC arm:

For 13 patients, BMS feels the clinical evidence supports the assessment of response. Additional narratives were included for review.

Reviewer Comment:

PC arm:

002-018: Lesion 1, measured only at C1 and C3, in question. Baseline size = 4.5 x 7 cm; C3 size = 3.5 x 3.5. No further CT measurements. Sponsor submitted follow-up note from the investigator, who stated that reevaluation showed C3 measurements of 9.0 x 7.0; C5 8.0 x 6.0; end-of-study 7.0 x 5.5. The investigator called the patient a PR. The reviewer reiterates that the inconsistent measurements call into question whether this lesion progressed or not.

Additional physican examinations document the disappearance of the pelvic mass. The reviewer agrees with BMS' assessment of a PR.

One baseline lesion was not measured again; BMS provided 4 additional physical examinations that document disappearance of this lesion. The Medical Treatment Reporting Forms indicate that 2 CT scans showed diminution of the liver lesions. The third area, enlarged lymph node, was not followed by the GOG as an indicator lesion. No CT scans mention this area. BMS calls this patient a PR; the reviewer agrees.

BMS provides a note from the investigator indicating that a CT scan from 4/3/92 (after treatment ended) shows continued improvement in the two baseline lesions in question, providing the confirmatory evaluation. The splenic and other lymph nodes mentioned as baseline were not followed by the GOG; no scans mention increase in the size of these areas. BMS calls this patient a PR; the reviewer agrees.

BMS indicates that on a follow-up form, a CT was performed and showed stable disease; no measurements given. BMS calls this patient a PR; the reviewer agrees.

Additional physical examination findings from the GOG flow sheets are provided to show absence of the measurable lesion. BMS calls this patient a CR; the reviewer agrees.

PT arm:

The GOG follow-up form shows a confirmatory CT. The pleural effusion is not evaluated further, but no mention of an effusion is made, even when the patient subsequently relapsed in the pelvis. BMS calls this patient a PR; the reviewer agrees.

The sponsor states that a confirmatory CT scan was performed 12/18/91 and showed residual pelvic lymph nodes. The patient was admitted for biopsy of these nodes, which were reportedly negative. The follow-up form from the GOG investigator shows that a CT was scheduled. The first page of a discharge summary indicates that the patient was admitted for a biopsy, but no results are given. Subsequent GOG follow-up sheets have a check-mark indicating that the patient is disease-free. No specific documentation is provided.

The reviewer feels that this information is suggestive, but the specifics are lacking. The sponsor was asked to provide the results of the nodal biopsy. The pathology report was sent on 3/10/98 and stated that the aspirate was inadequate for diagnosis. The reviewer therefore did not classify this patient as a responder.

This patient had two measurable lesions at baseline: a cul-de-sac lesion and a right upper lobe lesion. The cul-de-sac lesion measured 8 x 10 cm at baseline, 6 x 8 cm on 11/22/91, and 4 x 5 cm on 12/12/91. The right upper lobe lesion measured 2 x 3 cm at baseline, was absent on 11/22/91, and measured 3 x 1 cm on 3/23/92. The sponsor includes a GOG follow-up form dated 3/1/92, where a pelvic exam was within normal limits. This information confirms the resolution of the cul-de-sac mass. A chest X-ray dated 3/1/92 was marked "abnormal--no change". The sponsor states that this X-ray result supports the complete resolution of the mass. In addition, a pleural effusion was present at baseline. The only additional assessment of the effusion comes from the chest X-ray 3/1/92 was abnormal but without change. The sponsor calls this patient a PR; the reviewer agrees.

The sponsor submitted a GOG follow-up sheet indicating that a second CT now showed a CR. Because a third CT was not performed to document the CR, the patient was deemed a PR by the sponsor; the reviewer agrees.

A pleural effusion was listed as an evaluable lesion at baseline but was not examined further. The sponsor states that the effusion was cytologically negative for malignancy and was therefore not followed. The vaginal apex lesion shrank by 50% on 5/5/92 and was absent on 5/28/92. BMS states that confirmation of the PR was obtained, but not of the CR; the reviewer agrees.

BMS agrees that there is not enough follow-up to document a CR. However, they state the subhepatic lesion was absent at second-look laparotomy and that the presence of a small amount of residual disease should support an assessment of PR. The reviewer agrees--initial lesion size was 2.5 x 2.0 cm and the only residual disease at second-look surgery was 0.3 cm in size.

The FDA reviewer did not assess this patient as a responder because of probable progression based on an increasing pleural effusion. The Medical Treatment Reporting Forms for cycles 4 and 5 note normal chest X-ray results. This information supports an assessment of PR.

(4) The most recent BMS communication (2/2/97, pages 4-5) indicates that confirmation of response was strictly adhered to, and implies that results from a second-look laparotomy were not used to confirm responses. If this statement is correct, then please consider the following list of patients:

**also listed in Tables 9 and 10 above*

These patients had responses confirmed by a negative second-look laparotomy, but did not have documentation of response confirmation by non-surgical means on the case report forms. In a few instances for example), additional tumor measurements were hand-written on the BMS Summary form at the end of the case report form, raising questions about the adequacy of the data. In one instance (patient not only were additional measurements hand-written on the summary form but additional non-evaluable sites were added.

If BMS did not accept second-look laparotomy results as the confirmation of a response, please explain why these patients are considered to be responders.

The sponsor noted that BMS did accept second-look laparotomy results as the confirmation of a response.

3. As a result of the first FDA analysis, the FDA assessment of response shows an overall response rate of 60/113 (53%) for PT and a response rate of 60/127 (47%) for PC. These response rates are lower than those calculated by the sponsor. However, there is no statistically significant difference between the 2 arms, in accordance with the sponsor's statement in the study report.

4. Based on BMS' reply, the FDA assessment of response shows an overall response rate of 70/113 (62%) for PT (CR 40/113 or 35%; PR 30/113 or 27%) and a response rate of 61/127 (48%) for PC (CR 30/127 or 24%; PR 31/127 or 24%).

The sponsor noted a response rate of 68/113 or 60% for PT. The FDA analysis adds 3 patients to the sponsor's calculation (pts excluded because of wrong primary: disagreement between FDA and BMS) and subtracts 1 (pt , inadequate documentation: disagreement between FDA and BMS; sponsor asked to provide additional

documentation).

The sponsor noted a response rate of 64/127 or 50% for PC. The FDA analysis adds one patient to the sponsor's calculation of PC response rate (excluded because of wrong primary: disagreement between FDA and BMS) and subtracts 4 (pt : disagreement between FDA and BMS; and pts : BMS agrees with FDA assessment).

The FDA analysis results in a statistically significant response rate between PT and PC with a p-value of 0.04. The CR rate is at the border of significance, with a p-value of 0.048 with Fisher's exact test and 0.06 with Chi-square and a Yates correction factor. An overall difference in the response assessments of 5 patients changes the result from insignificant to statistically significantly different. These results are probably reflective of the difficulties in assessing response in the ovarian cancer population.

9.5.1.b Response by pre-treatment characteristics

The sponsor identified 7 baseline prognostic factors that might influence outcome. These factors included age, performance status, stage, residual tumor diameter, histologic grade, cell type, and baseline liver function tests. None of the first 6 factors correlated with clinical response. For the 7th factor, response rates in each arm were higher for patients with any abnormal liver function test compared to normal liver function tests (69% versus 53% PT; 54% versus 47% PC). However, the sponsor notes that most patients with abnormal liver function tests had grade 1 elevations of alkaline phosphatase, and that there is no clear pathophysiologic explanation for this observation.

Reviewer Comment:

1. The inclusion of liver function tests in a multivariate analysis is not justified (see Reviewer Comment after section 9.4.2): there is no literature that supports this factor as a prognostic or predictive indicator. Given the fact that the abnormalities were clinically insignificant, the inclusion of abnormal LFTs is questionable.

2. Cell type was included, although there is no clear published data that suggest that the serous subtype conveys a different prognosis. It is reasonable to test whether adjusting for this imbalance alters the results, but should be considered an exploratory analysis only.

3. No baseline patient characteristics were found to be predictive of response.

9.5.1.c Logistic regression for clinical response

The sponsor identified a different set of 7 factors that might influence the likelihood of response. These factors included residual tumor diameter ($\leq$ 5 cm v. > 5 cm), age, stage, performance status, site accrual (less than 10 v. 10 or more patients), histologic grade, and liver function. Fisher's exact test was used to assess the significance of these factors. None were significant except liver function, which yielded a p-value of 0.091. This factor was retained in the stepwise procedure and in the final regression analysis was tested with treatment arm. Neither factor was significant in the final model.

Reviewer Comment:

1. The literature does not support the use of liver function abnormalities in this model. Only 38 patients had elevations of CTC grade 2 or 3, further diminishing the clinical relevance of this factor.

9.5.1.d Time to clinical response

The median time to clinical response was 7.9 weeks for PT compared to 8.6 weeks for PC, not significantly different. For complete responders, the median time to the observation of response was 9.0 weeks for PT and 9.6 weeks for PC (p=0.444).

9.5.1.e Duration of response

At the time of analysis, 55 of the 68 responders to PT (81%) and 56 of the 64 responders to PC (88%) had clinical evidence of progression or recurrence. The median duration of clinical response as calculated in Method 1 (see section 9.4.1, Endpoints) was 15.8 months for PT compared to 16.4 months for patients on PC (p=0.249). These values were 14.9 months and 15.7 months for complete responders, respectively (p=0.779). When Method 2 was used, the duration of response was 21.9 months for PT and 13.8 months for PC, not significantly different (p=0.209). Using Method 2 to calculate duration of complete response gave values of 19.8 months for PT and 12.9 months for PC (p=0.260).

Reviewer Comment:

1. Two methods were used to calculate duration of response. Method 1 is the conventional method; Method 2 attempted to account for the effect of cross-over therapy. Method 2 is likely to induce bias, as patients on PC were more likely to subsequently receive paclitaxel. The response duration for PC was shortened as a result. Method 1 is preferable. However, both methods showed a non-significant difference in response duration between the two arms.

2. Regardless of the methodology used, there were no significant differences in the clinical response rate, time to response, or duration of response between the two arms. No baseline or prognostic factors predictive of a response to therapy could be identified.

3. A MedLine search indicates that the clinical complete and overall response rates for the cisplatin-cyclophosphamide arm are comparable to those reported in the literature for this combination.

9.5.1.f Pathologic response

A total of 341 patients were considered to be evaluable for pathologic response. These characteristics are summarized below:

Table 11. Evaluability for pathologic response (modified from sponsor's table 28, volume 3, page 101)

	Cisplatin-Taxol	Cisplatin-Cyclophosphamide
Evaluable:	n=163	n=178
Second-look laparotomy	122	109
Clinically persistent disease	28	53
Early death/toxicity	13	16
Inevaluable:	n=33	n=36
Wrong primary (surgery performed)	6	3
Refused surgery	20	24
Wrong primary (no surgery)	2	7
Surgery contraindicated	4	1
Reason not given	1	1

Pathologic findings for all patients (evaluable and inevaluable) are summarized in the following table:

Table 12. Pathologic response (modified from sponsor's table 28, volume 3, page 101)

Response	Cisplatin-Taxol	Cisplatin-Cyclophosphamide	P-value
Complete pathologic response	42/196 (21%)	35/214 (16%)	0.196
Microscopic residual disease	25/196 (13%)	8/214 (4%)	
Overall pathologic response rate	67/196 (34%)	43/214 (20%)	0.001

If only evaluable patients are considered, the pathologic complete response rate for PT was 26% and 20% for PC (p=0.191). If the pathologic complete response rate plus microscopic residual disease rate is calculated for evaluable patients only, the response rate was 67/163 or 41% for PT

compared to 43/178 or 24% for PC (p=0.001). If these rates are calculated for the entire randomized population, the complete pathologic response rates are 21% (42/196) for PT and 16% (35/214) for PC (p=0.196); overall response rate for the entire population is 34% (67/196) for PT and 20% (43/214) for PC (p=0.001).

Reviewer Comment:

1. The pathologic complete response rate was not significantly different between the evaluable patients nor in the entire randomized population. The pathologic response rates become significant only when microscopic residual disease is included in the definition of response.

2. An Access query to verify the reported pathologic response rates showed 46 pathologic CR for PT and 40 for PC, compared to 42 and 35 respectively as noted in the Study Report. The Access query also showed microscopic residual disease at laparotomy in 27 PT patients and 10 PC patients, compared to 25 and 8 in the Study Report. The sponsor was asked to clarify this point (2/4/98 by facsimile). In a submission dated 2/25/98, the sponsor noted that the fields used in the Access database contained data from investigators and did not always match the central GOG assessment, which was considered as the final interpretation.

9.5.1.g Pathologic response by pretreatment characteristics

The same set of 7 baseline characteristics used to analyze clinical response were applied to pathologic response analysis. Age, performance status, size of residual disease at laparotomy, histologic grade, cell type, and baseline liver function tests were not associated with pathologic response. The stage of disease was significant only for the PT arm: Stage IIIB patients treated with PT had a pathologic response rate of 40% compared to a pathologic response rate of 20% for patients with Stage IV disease. On the PC arm, these response rates were 19% and 22% respectively.

Reviewer Comment:

1. The same comments made earlier about the use of cell type and baseline liver function tests apply here.

2. This exploratory analysis suggests that PT offers an advantage over PC in Stage III patients. This hypothesis will require prospective testing in an independent data set.

9.5.1.h Logistic regression for pathologic response

The 7 factors used in the logistic regression for clinical response as well as stratum were applied in this analysis. Patients with Stage III disease were more likely to respond than patients with Stage IV disease (30% versus 21%). No other factor was significant. This factor was retained at the end of the stepwise selection and was tested with treatment arm and stratum in the final model. In this model, treatment with PT was the only factor significantly associated with pathologic response (p=0.002).

9.5.1.i Duration of pathologic response

The duration of overall pathologic response (complete or microscopic residual) was 28.5

months in the PT arm and 17.5 months in the PC arm. For complete pathologic responders, these values were 32.2 months and 16.5 months respectively when calculated by Method 1. Method 2 yielded a duration of overall pathologic response of 33.0 months for PT and 16.5 months for PC (p=0.167); the numbers for pathologic complete response were 32.9 months compared to 21.2 months. None of these calculated durations was statistically significantly different between the two arms.

Reviewer Comment:

1. Pathologic complete response rate and duration of pathologic response were not significantly different between the two arms. The pathologic response rate was significantly different only when both a complete response and microscopic residual disease were considered.

2. Multivariate analysis suggests that PT may offer an advantage in Stage III disease relative to Stage IV disease. However, this hypothesis requires independent confirmation. If true, it is not clear whether paclitaxel itself offers an advantage in earlier stage disease or whether the higher dose-intensity of cisplatin achieved in this combination offers the advantage.

9.5.2 Time to progression

9.5.2.a Unadjusted analysis

At the analysis time point, 163 of the 196 PT patients had progressive disease (83%) and 191 of the 214 PC patients had progressed (89%). The time to progression was 16.6 months for PT patients and 13.0 months for PC patients (p= 0.0008). This difference is equivalent to a 30% reduction in the risk of tumor progression for PT patients (relative risk 0.698).

Because the protocol did not prohibit maintenance therapy prior to clinical evidence of progression, time to analysis was also calculated with Method 2, where patients were censored at the time of subsequent therapy if this therapy was given prior to clinical progression. In this method, 90 additional PT patients and 93 additional PC patients were censored. In this method, time to progression was 16.6 months for PT and 13.4 months for PC (p=0.016; relative risk 0.686).

Reviewer Comment:

1. Regardless of the method used, treatment with PT resulted in a significantly longer time to progression.

2. The median time to progression observed for the PC arm is comparable to those cited in the literature.

3. This finding represents significant clinical benefit.

4. The reviewer performed an analysis to confirm the reported differences in time to progression. The submitted database did not allow calculation of a progression date from other events for the majority of patients. For example, an Access query using Grant William's algorithm identified patients with a 50% increase in tumor size. However, tumor measurements were only included for the timeframe of chemotherapy administration, and only 11 patients had progression of existing lesions while on treatment according to the algorithm. In response to an FDA Request for Information (1/15/98), BMS supplied a list of progression dates or censoring

dates for each patient (2/2/98). The GOG case report forms were then reviewed for each patient. The BMS case report forms were used as a secondary source, because they contained follow-up information in less detail than the GOG forms. The progression dates were confirmed from the CRF. Dates generated from the PD algorithm were used in preference to those recorded by the sponsor, if a discrepancy existed.

In order to establish a censoring date (ie, patient alive or dead but without documented progression), the following rules were used by the reviewer:

- The censoring date was the last date the patient was examined, not the last date the GOG form was written or the last date of phone contact
- For patients without any documentation of progression, a second analysis was run with a progression date established by a CA-125 > 100 and significantly increased relative to the end-of-treatment value

The following tables were generated:

Table 13. Patients with progressive disease: Discrepancies in date of PD between BMS and FDA

Pt ID	BMS date	FDA date	FDA interpretation of CRF
	6/28/91	10/8/91	Increased disease at second-look laparotomy not documented on on-therapy measurements
	6/3/92	8/28/91	50% increase in disease per algorithm
	2/24/94	2/1/94	Pt called PD because of CA-125, but it increased 2/1/94, not 2/24/91
	2/15/92	12/15/92	Cannot find any data from 2/15/92; CRF lists 12/15/92 as progression date
	2/5/93	8/12/93	CT on 8/12/93 is the first evidence of PD I can find
	6/16/92	9/22/92	September CT scan shows PD; June CT scan read as stable disease
	9/29/92	6/22/92	50% increase in disease per algorithm
	2/15/93	11/26/91	50% increase in disease per algorithm
	9/22/92	4/21/92	CT with progressive disease

Table 14. Patients without progression per sponsor, but PD per FDA

Pt ID	BMS date	FDA date	FDA interpretation of CRF
	6/20/93	6/8/92	CRF states increased disease on physical exam
	4/20/93	7/1/92	CRF states increased disease on physical exam
	7/22/91	6/3/91	CRF states increased disease on physical exam
	10/15/93	10/15/93	Phone report from outside MD stated PD*
	3/2/95	12/2/94	Paracentesis of 8 liters required#
	5/31/94	1/31/91	PD by CT scan
	8/19/91	6/5/91	Increased ascites by PE; none at second-look lap
	12/2/91	5/6/91	CT by local MD showed progression
	4/15/92	1/15/92	Clinical deterioration per local MD report
	2/9/93	9/5/91	Positive biopsy of pelvic mass that increased in size
	12/9/91	11/14/91	New intra-abdominal carcinomatosis at second-look lap
	8/25/94	2/22/94	CT scan showed PD
	9/23/94	6/10/94	CT showed PD
	11/23/94	11/23/94	PE shows new abnormality
	10/20/92	7/30/92	PE shows new vaginal mass (last exam date before death)

Superscripts indicate an additional entry for the same patient in Table 16.

Table 15. Patients without progression: Discrepancies in censoring date between BMS and FDA

Pt ID	BMS date	FDA date	FDA interpretation of CRF
	10/15/91	5/13/91	5/13/91 last documented exam; sponsor's date is a phone report of death from a social worker
	7/9/91	4/15/91	4/15/91 last documented exam; admitted in extremis 7/5/91 with death 7/9/91
	10/24/94	7/13/92	7/13/92 last documented exam; sponsor's date reflects that the patient was alive, but no other information was given
	2/6/95	10/13/93	10/13/93 last documented exam; sponsor's date is a report that a pharmacist filled a prescription for her
	11/6/92	8/25/92	Last documented exam; sponsor's date is a call from the family reporting her death[$]
	4/29/92	5/21/91	Last documented exam; pt then refused f/u. Sponsor's date is a phone report of death
	3/14/92	1/13/92	1/13/92 was date of last exam; sponsor's date is death in hospice[@].
	11/20/92	7/22/92	Last exam date; sponsor has date of death per nursing home
	3/2/95	2/27/95	Last exam date; sponsor has phone report
	2/17/92	11/4/91	Last exam date; sponsor has date of death (DOD) from outside MD from bowel obstruction
	3/1/95	1/13/95	Last exam date; sponsor has DOD from leukemia
	6/24/94	12/7/92	Last exam date; sponsor has DOD from phone call from family, but patient had been lost to follow-up with no intervening exams
	1/22/94	10/21/93	Last exam; sponsor has phone DOD
	4/4/93	3/10/92	Last exam; sponsor has DOD from tumor registry; pt felt to have colon cancer, not ovarian cancer
	6/13/94	5/10/94	Last exam date; sponsor has phone report of

Pt ID	BMS date	FDA date	FDA interpretation of CRF
	11/4/91	3/6/91	Last exam date; sponsor has family phone report of death
	12/20/93	8/1/94	Last MD report 8/1/94; sponsor's date is a phone call^
	1/15/94	8/11/93	Last exam; sponsor's date is DOD from medical records
	12/13/94	5/25/94	Last exam; sponsor's date is phone call from son that patient is
	9/15/91	5/27/91	Last exam date; patient then refused f/u. Sponsor has phone report of death
	9/15/92	5/5/92	Last exam date; sponsor's date is DOD in hospice
	5/6/94	10/5/90	Last exam date; no contact with patient afterwards.
	6/25/93	2/19/93	Last exam date; sponsor's date is DOD from LMD
	9/15/92	5/28/92	Last exam date; sponsor's date is phone DOD
	8/16/94	4/7/94	Last exam date; sponsor's date is phone call from pt
	5/25/92	3/12/92	Last exam date; sponsor's date is phone DOD+
	8/7/92	4/7/92	Last exam date; sponsor has the date from a form indicating the patient has been lost to follow up
	2/28/93	11/11/92	Last exam date; sponsor has DOD
	2/10/92	8/27/91	Last exam; sponsor has DOD
	8/1/92	5/13/92	Last exam date; sponsor has DOD
	11/2/94	10/21/91	Last exam date; pt lost to follow up; sponsor has phone report
	11/16/94	4/25/94	Last exam date; sponsor has date of a call from a neighbor indicating that patient is well
	3/9/95	6/15/94	Last exam; sponsor's date is from a form indicating phone contact with the patient 2/95

Pt ID	BMS date	FDA date	FDA interpretation of CRF
	10/17/94	4/18/94	Last exam; I cannot find any data corresponding to the date listed by the sponsor
	4/29/93	9/28/92	Last exam; sponsor's date is phone report of DOD
	10/23/92	1/28/92	Last exam; sponsor has DOD
	1/24/92	11/13/91	Last exam; sponsor has DOD
	2/4/92	1/6/92	Last exam; sponsor has DOD
	8/29/94	12/9/93	Last exam; sponsor has phone call from pt
	11/4/94	9/23/94	Last exam; sponsor has phone report
	8/15/92	4/3/92	Last exam date; sponsor has DOD
	11/7/91	9/24/91	Last exam date; sponsor has DOD

Table 16. Patients without progression, but with significant rises in CA-125

Pt ID	BMS date	FDA date	FDA interpretation of CRF
	7/28/95	12/21/93	12/21/93 CA-125 = 212
	10/15/93	12/29/92	CRF states PD; CA-125 was <10; rose to 415, then 1115*
	9/28/94	7/10/93	CA-125 from <7 to 300; stable PE and CT
	3/2/95	11/15/93	CA-125 8298#
	11/6/92	5/28/92	CA-125 from 182 to 390; 8/25/92 = 1860$
	3/14/92	1/13/92	Off study for treatment complications with CA-125 2021 on 10/25/91; CA-125 = 11,100 on 1/13/92@
	12/8/93	1/22/93	CA-125 increased to >100 (no value given) and chemo changed; 10/22/93, CA-125 = 1323
	6/13/94	3/26/93	CA-125 increased to 140!
	9/21/94	3/17/94	CA-125 219 3/17/94
	12/20/93	11/15/93	CA-125 increased to 181^
	8/16/94	4/7/94	Exam/scan negative; CA-125 830
	5/25/92	12/31/91	CA-125 from WNL to 172+
	5/21/92	3/3/92	CA-125 from 1240 to 4520

The above tables were sent to the sponsor for comment on 2/25/98. Specific comments were requested for Tables 13-15; Table 16 was intended as exploratory only.

An analysis of time to progression was first run using the BMS dates and status in JMP. This analysis yielded a TTP of 16.6 months for PT and 13.0 months for PC with a p value of 0.0006. These results correspond to those in the study report.

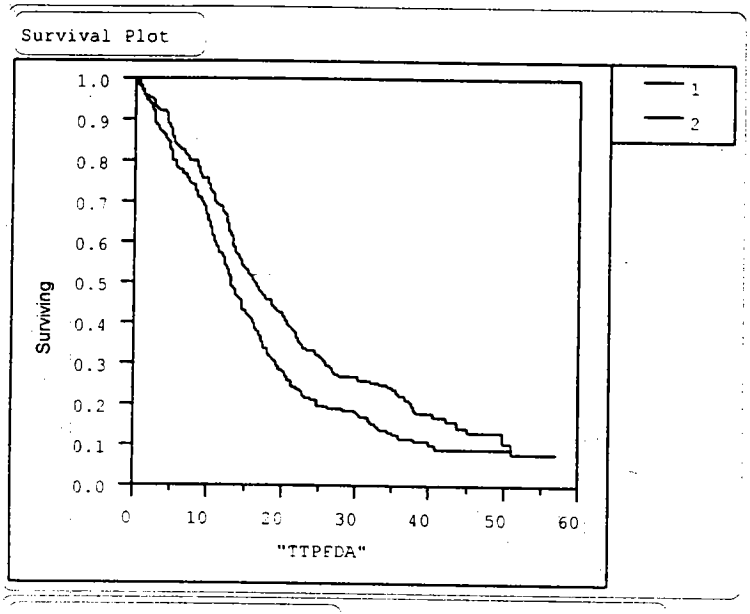
A second analysis was performed using FDA-generated information from tables 13-15 (see below for corrections to data based on sponsor's reply). Median TTP was 16.8 months for PT compared to 13.4 months for PC (p=0.006). The curve generated from JMP appears below:

Figure 1. Kaplan-Meier plot of time to progression, FDA analysis

Product-Limit Survival Estimates

Time Variable: "TTPFDA"

Censoring Variable: "DODPstat"



Tests Between Groups

Test	Chi-Square	DF	Prob>ChiSq
Log-Rank	7.5304	1	0.0061
Wilcoxon	7.5383	1	0.0061

1

2

Combined

A third analysis was run using progression dates generated from the CA-125 values in table 16, for patients without objective evidence of progression. Time to progression for PC patients was 12.6, compared to 15.5 months for patients treated with PT (p=0.006). This analysis was intended to be an exploratory analysis only. Tumor marker levels are not a proven surrogate endpoint; although rising CA-125 values are probably associated with subsequent relapse/progression, the time lag can be substantial and the value of treating an asymptomatic patient with a rising marker has not been demonstrated.

The sponsor sent a facsimile 3/10/98 that addressed the TTP questions. Tables 13 and 14 were reviewed in detail. Table 15 was not reviewed on a case-by-case basis, as BMS used different rules for assessing progression than the reviewer. These results are summarized below:

Table 13:

Pt	
	BMS agrees with the FDA reviewer
	The FDA reviewer mistakenly wrote "8/28/91" as the progression date; the correct date is 4/22/92. The sponsor prefers the date of 8/28/91, which is the date of exam under anesthesia with biopsy. The reviewer assesses progression on 4/22/92, when physican examination (used to follow the patient throughout the study) documented a 4-fold increase in tumor area.
	BMS agrees with the FDA reviewer
	BMS agrees with the FDA reviewer
	BMS supplied a follow-up form that supports their progression date; FDA reviewer agrees with BMS
	BMS agrees with the FDA reviewer
	The FDA-generated algorithm documented a 50% increase in disease on 6/22/92. However, the disease was initially measured on CT with an end-of-treatment CT that documented significant shrinkage. Interim measurements were based on physical examination and were less accurate, leading to the apparent increase in lesion size. The FDA reviewer agrees with the sponsor
	The FDA-generated algorithm documented a 50% increase in disease on 11/26/91; however, BMS notes that a nodal area increased in size from .7 x .7 cm to 1 x 1 cm as measured on a CT scan. This increase was not classified as PD. FDA reviewer agrees with BMS
	BMS agrees with the FDA reviewer

Table 14:

	BMS agrees with the FDA reviewer
	BMS states that an abnormality on exam was detected 7/1/92, but they do not accept this finding as evidence of progression. They censored the patient for progression on 4/20/93, the date of death. However, the only notes in the record are from these two dates. The note from 7/1/92 indicates that an evaluation was in progress for the PE abnormality. The FDA reviewer, in the absence of other information, assesses progression on 7/1/92, the date a change in the PE was noted by the patient's doctor.
	On 6/3/91, the physician noted "rectal shelf fullness suspicious for recurrence." On that date, the patient had a CA-125 level that increased from 161.8 on 4/18/91 to 2417. The patient was begun on hormonal therapy for recurrence. The FDA reviewer assesses progression on 6/3/91 and not on 7/22/91, which is the next available information and documents the date of death.
	Dates were the same, but sponsor and FDA disagreed about whether or not this patient progressed. The sponsor included her as an event on this date.
	BMS agrees with the FDA reviewer

The FDA assessed progression on 1/31/91 on the basis of increased lung lesions, not pelvic adenopathy. However, on review of the CRF, the lung lesion is measured at 1.5 x 1.5 cm throughout the course of treatment, even though the investigator's note indicated an increase. The sponsor stated that review of the CRF indicates PD on 10/8/91, not 5/31/94; the FDA reviewer agrees with this date.
BMS does not accept "increased abdominal tension attributed to ascitic fluid" as evidence of progression. As the patient had no ascites at second-look laparotomy, the FDA reviewer assesses progression on this date.
The text of the follow-up sheet from 6/4/91 indicates "residual" disease on the CT; the CT is coded as a 3 (abnormal with a change) in the evaluation section of this sheet; and no evidence of recurrence/progression is checked. The data on this sheet are internally inconsistent. The sponsor's assessment of progression on the date of death is accepted.
FDA reviewer agrees with BMS; clinical detioration may have been due to concomittant therapy rather than disease
BMS agrees with the FDA reviewer
BMS agrees with the FDA reviewer
BMS agrees with the FDA reviewer
BMS agrees with the FDA reviewer
The dates are the same. However, the FDA assesses progression on this date based on a change in physical examination described as "vague fullness and thickening...", coded as "abnormal/change" on the follow-up sheet.
FDA reviewer agrees with BMS--reference to vaginal mass based on history, not on exam

For Table 15, the sponsor and the FDA reviewer used different censoring rules. The FDA reviewer's progression dates ranged from 3 days to 3.6 years shorter than the sponsor's and in one case was 7.5 months later than the sponsor's assessed date. The mean difference in date was 7 months. Of the 42 patients listed in Table 15, only 12 had progression dates that differed by less than 3.5 months, the absolute difference in TTP between the two treatment arms demonstrated in GOG 111. It is important to assess whether differences in assessment of TTP can eliminate the advantage seen for PT over PC. Whether the FDA dates or the sponsor's dates are used, the difference persists, supporting the efficacy of cisplatin and paclitaxel over that of cisplatin and cyclophosphamide in the first-line treatment of ovarian cancer.

When TTP was re-run using data corrected from the correspondance with BMS, the following results were obtained: median TTP for PC was 13.4 months; median TTP for PT was 16.8 months; p-value 0.006.

These analyses demonstrate time to progression that is comparable to those submitted in the sponsor's report; in all cases TTP with PT is statistically significantly superior to TTP with PC. The absolute difference between treatment arms is 3.4 months in the FDA analysis, compared to 3.6 months with the sponsor's analysis. This difference remains clinically

significant. The results are robust and demonstrate clinical benefit with PT.

9.5.2.b Cox regression analysis for time to progression

The 7 pretreatment patient characteristics used in the analyses of clinical and pathologic responses and stratum were applied to time to progression. None were significant except stratum. Patients with non-measurable disease had a significantly longer time to progression than patients with measurable disease (16.4 months compared to 13.4 months; p=0.009). This factor and treatment arm were included in the final Cox regression analysis. Both patients with non-measurable disease and patients treated with PT had a significantly reduced risk of disease progression. The relative risk for non-measurable patients was 0.768 (p=0.015) and for PT patients was 0.704 (p=0.001). The median TOP for patients with non-measurable disease treated with PT was 21.3 months, compared to 13.9 months in similar patients treated with PC. For patients with measurable disease, TOP was 14.6 months for PT and 12.0 months for PC (p=0.05).

Cell type was included in this model, despite the lack of evidence for its importance as a prognostic factor, because the incidence of serous adenocarcinoma was imbalanced between the two arms. This factor was not selected in the model and had a minimal impact on the risks presented per the sponsor.

Reviewer Comment:

1. The same comments about the choice of pretreatment variables apply here. The FDA statistical reviewer re-ran the Cox regression analysis without liver function tests included as a potential variable. The results were not different from those described above.

2. Patients with non-measurable disease are likely to have a longer time to progression because of the difficulty of assessing intra-abdominal tumor in ovarian cancer.

3. The subset analysis by stratum supports the advantage for PT seen in the analysis of all randomized patients.

9.5.3 Survival

9.5.3.a Unadjusted analysis

At the analysis time point, 114 of the 196 PT patients had died (58%) compared to 154 of the 214 PC patients (71%). Follow-up time ranged from 28.6-57.2 months for the PT arm and from 9.9 to 56.6 months for the PC arm. In the first 18 months of follow-up, 3 patients on PC were lost to follow-up and were censored from the analysis

The median survival for PT patients was 35.5 months compared to 24.2 months for PC patients (p=0.0002). The calculated relative risk was 0.635 (95% CI 0.497, 0.811), indicating a 36% reduced risk of mortality with PT therapy. By Cox analysis, residual tumor diameter was significant in its impact on survival. After adjustment for this factor, there remained a statistically significant effect of paclitaxel-based therapy.

Reviewer Comment:

1. The survival was significantly better for PT patients than for PC patients. The median survival observed in the PC arm is comparable to that reported in the literature for this combination.

2. The dates of death listed in the database (table "DEATH") were included in the FDA audit. These dates of death were then used in a MS Access query to calculate survival times. The survival times calculated for each patient correlated within 1 day for all 410 patients enrolled in the trial. These calculated survival times (in days) were then exported to JMP and a Kaplan-Meier analysis was performed. The results of this analysis are presented below. Median survival for the PC arm (Arm 1) was 735 days or 24.2 months; median survival for the PT arm (Arm 2) was 1079 days or 35.5 months (see Appendix B for data listings used to derive median survival). The difference was statistically significant with p=0.0002 by the log-rank method or p=0.0003 by the Wilcoxon method. These results are identical to those calculated by the sponsor.

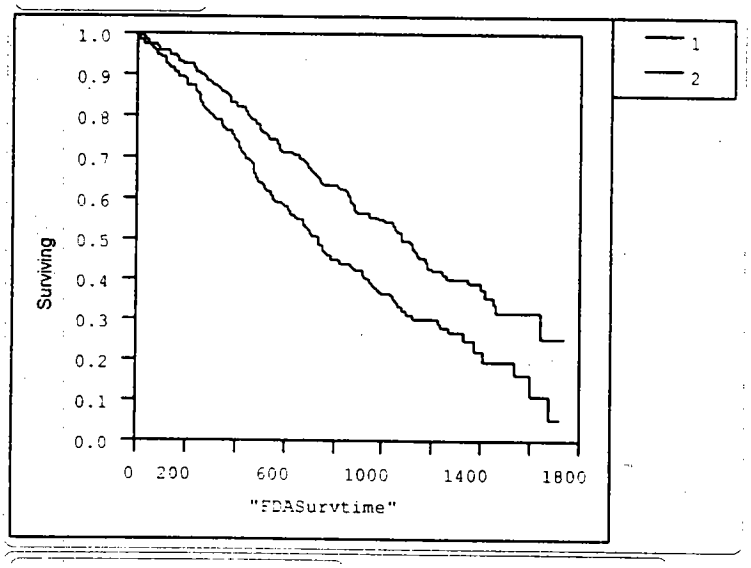
Figure 2. Kaplan-Meier plot of survival, FDA analysis

Product-Limit Survival Estimates

Time Variable: "FDASurvtime"

Censoring Variable: "FDAStatus"

Survival Plot



Tests Between Groups

Test	Chi-Square	DF	Prob>ChiSq
Log-Rank	13.9455	1	0.0002
Wilcoxon	13.0290	1	0.0003

1

2

Combined

9.5.3.b Cox regression analysis for survival

The 7 pretreatment characteristics used to analyze pathologic and clinical response and time to progression were applied to survival. None were significant except small residual diameter ($\leq$ 5 cm) after staging surgery, which was related to survival (p=0.007). In the final Cox regression analysis, this factor was retained with treatment arm and stratum. Both residual tumor diameter and treatment with PT were significant in determining survival. Patients treated with PT had a RR of 0.627 (95% CI 0.491, 0.801); patients with small residual tumor diameter had a RR of 0.682 (95% CI 0.522, 0.891). Patients with small residual disease treated with PT had a median survival of 37.9 months, compared to a median survival of 17.8 months in patients with small residual disease treated with PC (p=0.074). Because of the baseline imbalance in the incidence of serous adenocarcinoma, this factor was tested and was not found to significantly alter the results.

Reviewer Comments:

1. The same comments about the choice of prognostic factors apply here. The FDA statistical reviewer re-ran the Cox regression analysis without liver function tests as a baseline variable; the results were unchanged and remained significant in favor of PT.

2. Treatment with PT was associated with a statistically significant and clinically impressive improvement in overall survival.

9.5.4 Time to worsening of performance status

Performance status was assessed at each visit and was used as an indication of the quality of life of the patients on study. One hundred eighty-eight of the 196 patients on PT had both a baseline PS score and at least one follow-up PS score recorded on study, and 203 of the 214 PC patients had this data recorded. On the PT arm, 37 of the 188 had a lower PS on study compared to baseline; on the PC arm, 30 of the 203 patients had a lower PS on study compared to baseline. The time to worsening of PS on each arm was calculated and was not significantly different between the two arms (p=0.060). Because there was a significant difference in treatment delays between the two arms, the number of courses to worsening of PS was calculated and was again not significantly different (p=0.231).

Reviewer Comment:

1. Ninety-six and 95% of the patients on PT and PC respectively had baseline and repeat measures of PS assessed. However, only a small percentage had deterioration in their PS during the course of the study. It is unlikely that this measure is sensitive enough to pick up QOL changes in the specified study population.

9.6 Safety analysis

9.6.1 Adverse events

Four hundred nine patients were evaluable for safety; one patient died prior to receiving any therapy. Twenty-seven patients were discontinued from the study for adverse events: 12 patients on PT and 15 on PC.

Myelotoxicity was common in both arms of the trial. The percent of patients with leukopenia was the same in both arms (82%), as was the percent of patients with individual grades of leukopenia, including severe (grade 3-4) leukopenia.

The most common observed adverse event was neutropenia. Neutropenia was most commonly severe, but of short duration; the sponsor stated that the neutropenia was without clinical consequences. The following table summarizes the incidence and type of this adverse event:

Table 17. Type and incidence of neutropenia (worst course); % (n) (data derived from sponsor table 39, volume 3, page 123; sponsor table 42, volume 3, page 126; sponsor table 43, volume 3, page 126).

Type of Neutropenia	Cisplatin-Taxol N=190	Cisplatin-Cyclophosphamide N=205	P-value
Any	96% patients	92%	0.146
CTC Grade III-IV	92% (175)	80% (163)	0.001
Grade III	11% (21)	22% (45)	
Grade IV	81% (154)	58% (118)	
Infections: Number of patients with infections Number of episodes	 41 patients 54	 32 patients 46	0.123
Febrile neutropenia	35 courses/1074 courses (3.3%)	9 courses/ 1145 (0.8%)	< 0.001

Other myelosuppressive toxicities are summarized in the following table and are expressed in terms of the worst course:

Table 18. Myelosuppression (data derived from sponsor table 40, volume 3, page 124; sponsor table 41, volume 3, page 125)

Adverse myelosuppressive event	Cisplatin-Taxol	Cisplatin-Cyclophosphamide	P-value
Anemia:	n=188	n=207	
Any	88% (165)	86% (178)	0.656
Grade III-IV	13% (24)	9% (19)	0.263
Grade III	10% (18)	8% (16)	
Grade IV	3% (6)	1% (3)	
Anemia (baseline Hb normal):	n=91	n=102	
Any	88% (80)	83% (85)	0.417
Grade III-IV	13% (12)	3% (3)	0.013
Grade III	9% (8)	2% (2)	
Grade IV	4% (4)	1% (1)	
Thrombocytopenia:			
Any	26% (49)	30% (62)	0.434
Grade III-IV	10% (18)	9% (19)	1.000
Grade III	5% (9)	5% (11)	---
Grade IV	5% (9)	4% (8)	---

Thrombocytopenia and anemia were not significantly different between the two arms. However, 49% of the patients in each treatment arm had abnormal baseline hemoglobin values, most likely due to surgery. When the subgroup with normal baseline hemoglobin values was examined, there was a statistically significantly greater incidence of severe anemia in the PT arm. The sponsor suggests that this effect is due to the higher dose-intensity of cisplatin achieved in this arm.

Table 19. Adverse events (worst course) (data from sponsor tables 44-49, p. 129-133, and sponsor table 50, page 135, all in volume 3).

Adverse event	Cisplatin-Taxol	Cisplatin-Cyclophosphamide	P-value
Peripheral neuropathy: Any Grade III-IV	 26% (49) 3% (5)	 20% (43) 0 (0)	 0.286 0.025
Ototoxicity: Any Grade III-IV	 6% (11) 0 (0)	 10% (22) 2% (4)	 0.102 0.124
Arthralgia/myalgia: Any Grade III (no grade IV)	 10% (18) 1% (1)	 2% (4) 0 (0)	 0.002 0.479
Hypersensitivity: Any Grade III-IV	 9% (15) 3% (5)	 <2% (3) 0 (0)	 0.003 0.025
Nausea/vomiting (g.3-4):	10% (19)	11% (23)	0.747
Diarrhea: Any Grade III-IV	 17% (32) 4% (7)	 8% (16) 1% (2)	 0.008 0.094
Liver function tests: Alkaline phosphatase Any Grade III-IV AST Any Grade III-IV Bilirubin Any Grade III-IV	 36% (66) 1% (1) 18% (33) 0 (0) 2% (2) 1% (1)	 33% (67) 1% (3) 13% (26) 0 (0) 1% (2) 0 (0)	 0.668 0.625 0.203 1.000 0.478
Cardiovascular events Any Grade III-IV	 28% (53) 5% (10)	 7% (14) 3% (5)	 0.001 0.188
Creatinine: Any elevation Grade III-IV	 40% (74) 2% (3)	 46% (95) 2% (4)	 0.221 1.000

Adverse event	Cisplatin-Taxol	Cisplatin-Cyclophosphamide	P-value
Alopecia	55% (107)	37% (79)	0.001
Asthenia	17% (33)	10% (21)	0.041

Cardiovascular events were more common in patients on the PT arm (53 patients, or 28%) than in patients on the PC arm (14 patients, or <7%). Grade 3-4 events occurred in 5% of PT patients and <3% of PC patients. The difference in incidence of cardiovascular events is attributed by the sponsor to the requirement for cardiac monitoring in patients who received paclitaxel.

Reviewer Comment:

1. There was a 6.5% discontinuation rate for adverse events. This rate is consistent with the type of therapy and the patient population.

2. The PT arm was associated with a significantly greater incidence of grade III-IV neutropenia than the PC arm (92% v. 80%); however, it should be noted that the rate of neutropenia with PC remains high. Although the sponsor stated the neutropenia was "without clinical consequences" (section 8/10, volume 1, page 122), there was a significantly greater incidence of febrile neutropenia with PT than with PC; it occurred in 35 courses compared to 9 courses. However, only 3 patients (0.7%) in the study died of sepsis, and all received PC (see Reviewer Comments 2 and 3 after section 9.6.3). These data suggest that the neutropenia is unlikely to be associated with irreversible morbidity. Patients presumably were hospitalized for febrile neutropenia, which may decrease the quality of life. However, more PT cycles were delivered on time, indicating that the neutropenia, whether associated with fever or not, was unlikely to interfere with the scheduled administration of drug. The decreased quality of life associated with hospitalization for febrile neutropenia must be weighed against the decreased quality of life that may be associated with treatment delays and a longer period of chemotherapy treatment with PC.

3. The sponsor notes that severe anemia was more likely in patients treated with PT who had a normal baseline hemoglobin; however, the number of patients in this subgroup analysis is small.

4. The majority of detectable cardiovascular events on the PT arm consisted of bradycardia, tachycardia, hypotension, an abnormal ECG, ventricular extrasystoles, unspecified arrhythmia, hypertension, syncope, and atrial fibrillation. While it is likely that monitoring on the PT arm detected more events, it is also likely that paclitaxel was responsible for some or all of the observed events. Bradycardia, for example, is a well-reported side effect of paclitaxel. What is more relevant, however, is how many events were symptomatic. Since most of the events were grade 2 or less, there does not appear to be a clinically meaningful difference in cardiovascular events between the two arms.

5. Other adverse events that were significantly different between the two arms included severe peripheral neuropathy, arthralgia/myalgia, hypersensitivity reactions, diarrhea, and

alopecia. All of the observed events are consistent with the labeled toxicities of paclitaxel; none represent new findings.

6. The reviewer ran multiple MS Access queries and verified the incidence and severity of the adverse events. These queries generally yielded the same results as those reported by the sponsor. In the few cases where the numbers were not the same, they differed by 2-3 patients/events, not a significant difference. The Adverse Event category of "Other" was also reviewed to assess whether significant events had been mistakenly assigned to this category. No mistaken attributions were identified; the majority of events in this category consisted of fatigue. Finally, a query for the incidence of bowel obstruction was run; 4 patients on PC and 2 patients on PT experienced this complication. Bowel obstruction was uncommon and is more likely related to the underlying illness than to the drug therapy.

6. Overall, the significant benefit conveyed by PT therapy outweighs the increased toxicity of this combination.

9.6.2 Neurologic assessment

The Neurologic Assessment was performed on a subset of patients at 9 designated sites. The assessment consisted of 2 parts, the patient self-report form and the nurse-administered questionnaire. The patient self-report form consisted of 21 questions; the first 8 asked general status questions and the rest referred specifically to neurologic signs and symptoms. The response options for questions 1-19 were "not at all", "a little", "quite a bit", and "very much." For the analysis, these responses were coded from "0" (not at all) to "3" (very much). Question 15 ("When holding an object in your hand, are you able to feel its shape?") was scored as "0" (very much) to "3" (not at all) to make these scores consistent numerically with the other questions. Questions 20 and 21 were graphical ("...draw a tight spiral"; "shade in all the places ...where you have...numbness") and were not analyzed.

The second part of the assessment consisted of a 5 question nurse-administered questionnaire. Question 1 was not analyzed, as this question measured the time it took a patient to button a shirt, but did not provide a uniform number of buttons or a uniform button size. In question 2, patients were asked to identify a nickel among a dime, a penny, a paper clip, and a key in a paper bag and were timed. The question was scored on the "time to identify nickel" and on whether or not the patient could identify the nickel. Questions 3-5 used a yes-no format ("Can the patient stand steadily with her feet together with her eyes closed?"; position sense testing in the hand and then in the feet).

Seventy-six patients completed both a baseline and a follow-up neurologic assessment during the course of study, 42 on PT and 34 on PC. The data were collected from 8 different GOG sites and comprised 23-88% of the study population at the respective sites.

For the patient self-assessment, mean total scores with standard deviation were plotted for each arm for baseline values compared to on study, off study, 3 month follow up and 6 month follow up time points. The sponsor analyzed patients with paired data for the two arms at the above timepoints. The number of patients compared was 34 PT/30 PC for baseline/on study; 36 and 22 respectively for baseline/off study; 9 and 11 respectively for baseline/3 month follow up; and 4 and 2 respectively for baseline/6 month follow up. Patients on PT had an elevated mean

total score versus baseline at all time points. There appeared to be a trend towards higher scores in the PT arm compared to the PC arm. However, because this data was derived from a subset of patients with a non-validated instrument, no formal comparison was performed.

In the nurse-administered questionnaire, questions 2-5 showed no difference between the two treatment groups and no difference between baseline assessment and on-study timepoints. The time to identify a nickel was analyzed in the same paired comparison at the same timepoints as for the patient-administered questionnaire. The numbers of patients included were 26 PT/22PC for baseline/on study; 23/14 respectively for baseline/off study; 7/6 respectively for baseline-3 month follow up; and 3/1 respectively for baseline/6 month follow up. There was a trend for an increased time requirement in the PT arm at all timepoints compared to baseline, and an increased time compared to PC. Again, no formal comparison was made.

Reviewer Comment:

1. Nine centers were designated for neurologic testing, but data are reported from only 8 sites. A Request for Information was sent to the sponsor regarding the 9th site. The sponsor noted that the ninth center designated for neurologic testing accrued a total of 3 patients to GOG 111, but received its designation after 1 patient was already on study. Of the two potentially eligible patients, neither had an assessment performed. No data were excluded from analysis.

2. The percent of patients recruited from the designated sites varies widely. A Request for Information was sent to the sponsor asking whether this phenomenon was due to lack of recruitment, or to the time differences in the designation of specific sites. The sponsor replied that the percentages listed in the study report referred to patients who had both a baseline and a follow-up assessment and could be analyzed. The percentage of patients with at least one assessment was higher. Although reasons for non-participation in the neurologic assessment were not listed, the timing of the designation of a study site was a factor.

3. There is a large amount of missing data for both the patient-administered and the nurse-administered questionnaires, as demonstrated by the numbers of patients included in the paired timepoints. The missing data weakens the analysis. The sponsor's descriptive analysis rather than a quantitative analysis is appropriate.

4. Although these data are of poor quality, they suggest that PT was associated with a higher incidence of clinically evident neuropathy, consistent with the formal CTC reporting in section 9.6.1.

9.6.3 Mortality

Ten patients died within 30 days of the last study dose: 6 on PT and 4 on PC. Three deaths were attributed to treatment-related complications, 3 to intercurrent problems, and 4 to progressive disease. The deaths are summarized in the following table:

Table 20. Mortality within 30 days of study treatment (modified from sponsor table 52, volume 3, page 150).

General Cause of Death	Specific Cause of Death	Patient Number	Treatment Arm
Treatment-related complications	Myocardial infarction		Paclitaxel
	Cardiac arrest		Cyclophosphamide
	Sepsis		Cyclophosphamide
Intercurrent problems	Pulmonary embolus		Paclitaxel
	Perforated gastric ulcer		Paclitaxel
	Myocardial infarction		Cyclophosphamide
Disease progression			Paclitaxel
			Paclitaxel
			Paclitaxel
			Cyclophosphamide

Reviewer Comment:

1. Comments from review of the narratives on patients who died of treatment-related complications:

Patient (PT) died of an MI which, on review of the narrative, may have been related to the surgical procedure as well as to the drug therapy. The patient had a history of hypertension and cardiovascular disease and expired 14 days post-operatively and 6 days after cycle 1.

Patient (PC), listed as cardiac arrest, died while septic; blood cultures grew coagulase-negative staph and Candida.

2. Comments from review of the narratives on patients who died of intercurrent problems:

Patient (PT) died of a perforated gastric ulcer after 4 cycles of therapy. It is possible that this complication was related to steroid premedication for paclitaxel. The patient did not receive any concomitant medications, according to a review of the case report form and of the "Concurrent medication" table in the submitted database.

3. Comments from review of the narratives on patients who died of progressive disease:

Patient (PT) suffered an anterior wall MI in the recovery room after her staging laparotomy. Nineteen days later, she began study therapy. At baseline she had bilateral pleural effusions and required oxygen therapy. Treatment was complicated by CHF which responded to therapy. She subsequently died 11 days after cycle 1 with continued effusions and a

low oxygen saturation. It is difficult to assess whether she died of progressive disease or cardiac complications.

Patient (PC) had her death attributed to progressive disease. However, the narrative indicates that she had febrile neutropenia with blood cultures positive for Staph. aureus. Her death is more likely a treatment-related complication.

4. Overall, the number of deaths on or within 30 days of study drug is small, representing 2.4% of the study population. The combination of cisplatin and paclitaxel does not appear to cause excess mortality compared to the standard-therapy arm.

5. Review of the case report forms showed that patient subsequently died of leukemia. While she does not fit the category of death within 30 days, this event should be mentioned. She was randomized to cisplatin and cyclophosphamide and refused further therapy after 3 cycles. She was then treated with carboplatin and cyclophosphamide, carboplatin/cyclophosphamide/etoposide, and hexamethylmelamine. She did not receive paclitaxel; the leukemia is not related to the drug submitted in this sNDA.

9.7 Sponsor's audit results

Audited data were collected on site for 97 patients accrued at 19 of the 86 participating centers; these data were compared to the data transcribed from the GOG primary documents for these same patients. These results are referred to as the "audited database" and the "transcribed database" respectively.

Reviewer Comment:

These results were used for quality control only. All efficacy analyses were performed by the sponsor using the transcribed database (Response to FRFI 12/22/97, BMS).

9.7.1 Study drug audit results

No differences in treatment delays, drug discontinuations, or drug interruptions were identified. Only 1 patient was found to have a dose reduction recorded differently in the audited and transcribed databases. Patient received cyclophosphamide at 750 mg/m^2 for cycles 1-3, with a dose reduction to 500 mg/m^2 for cycles 4-6. The transcribed database listed the dose reduction at cycle 2 instead of cycle 4. No other discrepancies in dose reduction were found.

9.7.2 Efficacy data audit results

9.7.2.a Survival

Survival status and date of death or last follow up were confirmed for 95 of the 97 patients (98%). For 15 patients, additional follow up was obtained. For 6 patients, additional follow up and a later date of death, after database closure, was obtained. For 2 patients (2%), the actual date of death in the audited database differed from the transcribed date by 1 and 2 days respectively. This information is summarized in the following table.

Table 21. Sponsor table 54, volume 3, pages 165-168

Table 54

Survival Dates: Transcription Versus Audit

Patient #	Arm	Transcribed Database		Audited Database		Comments
		Last Alive	Status	Last Alive	Status	
	TAXOL/Cisp	28JUL94	Alive			Confirmed
	Cyclo/Cisp	09NOV92	Dead			Confirmed
	Cyclo/Cisp	05DEC94	Alive			Confirmed
	Cyclo/Cisp	23JAN95	Alive	9OCT95	Alive	Additional follow-up
	Cyclo/Cisp	06MAR93	Dead			Confirmed
	Cyclo/Cisp	06AUG92	Dead			Confirmed
	TAXOL/Cisp	05MAR93	Dead			Confirmed
	TAXOL/Cisp	04NOV92	Dead			Confirmed
	TAXOL/Cisp	21NOV94	Alive	03MAY95	Alive	Additional follow-up
	TAXOL/Cisp	28SEP94	Alive			Confirmed
	TAXOL/Cisp	09AUG94	Alive			Confirmed
	TAXOL/Cisp	13DEC94	Alive	25JUL95	Alive	Additional follow-up
	Cyclo/Cisp	31OCT94	Alive			Confirmed
	Cyclo/Cisp	01AUG94	Alive	15DEC94	Alive	Additional follow-up
	Cyclo/Cisp	20DEC91	Dead			Confirmed
	TAXOL/Cisp	27FEB91	Dead			Confirmed
	Cyclo/Cisp	14DEC93	Dead	16DEC93	Dead	Change in death date (2 days)
	Cyclo/Cisp	23SEP94	Alive			Confirmed
	Cyclo/Cisp	30MAY92	Dead			Confirmed
	TAXOL/Cisp	29APR92	Dead			Confirmed
	TAXOL/Cisp	15MAY92*	Dead			Confirmed
	Cyclo/Cisp	13JUL91	Dead			Confirmed
	Cyclo/Cisp	14MAR92	Dead			Confirmed
	Cyclo/Cisp	19AUG91	Dead			Confirmed
	Cyclo/Cisp	14MAY91	Dead			Confirmed
	TAXOL/Cisp	14FEB95	Alive	26AUG95	Dead	Additional follow-up and date of death
	Cyclo/Cisp	02MAR95	Alive	22AUG95	Alive	Additional follow-up
	Cyclo/Cisp	02SEP93	Dead			Confirmed

Table continues on next page

Table 54

Survival Dates: Transcription Versus Audit

Patient #	Arm	Transcribed Database		Audited Database		Comments
		Last Alive	Status	Last Alive	Status	
Table 54 continued						
	TAXOL/Cisp	16DEC94	Alive			Confirmed
	Cyclo/Cisp	11FEB94	Dead	12FEB94	Dead	Change in death date (1 day)
	Cyclo/Cisp	15NOV92	Dead			Confirmed
	TAXOL/Cisp	13JUN94	Dead			Confirmed
	TAXOL/Cisp	08MAR93	Dead			Confirmed
	TAXOL/Cisp	12JUN94	Dead			Confirmed
	Cyclo/Cisp	19DEC94	Alive	28SEP95	Alive	Additional follow-up
	Cyclo/Cisp	07DEC93	Dead			Confirmed
	Cyclo/Cisp	15JAN94	Dead			Confirmed
	Cyclo/Cisp	02DEC92	Dead			Confirmed
	Cyclo/Cisp	23SEP94	Dead			Confirmed
	TAXOL/Cisp	21DEC91	Dead			Confirmed
	TAXOL/Cisp	18JAN95	Alive			Confirmed
	Cyclo/Cisp	15OCT92	Dead			Confirmed
	TAXOL/Cisp	06MAY94	Alive			Confirmed
	TAXOL/Cisp	01AUG94	Alive	27SEP94	Dead	Additional follow-up and date of death
	TAXOL/Cisp	11FEB91	Dead			Confirmed
	Cyclo/Cisp	13FEB95	Alive			Confirmed
	TAXOL/Cisp	20JUN94	Alive	31JUL95	Alive	Additional follow-up
	TAXOL/Cisp	14JUL94	Alive	15SEP94	Dead	Additional follow-up and date of death
	Cyclo/Cisp	27MAY94	Dead			Confirmed
	TAXOL/Cisp	16AUG91	Dead			Confirmed
	TAXOL/Cisp	05FEB93	Dead			Confirmed
	Cyclo/Cisp	18JAN93	Dead			Confirmed
	TAXOL/Cisp	16AUG94	Alive	01NOV94	Dead	Additional follow-up and date of death
	TAXOL/Cisp	20SEP90	Dead			Confirmed

Table continues on next page

Table 54

Survival Dates: Transcription Versus Audit

Patient #	Arm	Transcribed Database		Audited Database		Comments
		Last Alive	Status	Last Alive	Status	
Table 54 continued						
	Cyclo/Cisp	30MAR92	Dead			Confirmed
	TAXOL/Cisp	23MAR94	Dead			Confirmed
	Cyclo/Cisp	21MAY92	Dead			Confirmed
	TAXOL/Cisp	29JAN92	Dead			Confirmed
	TAXOL/Cisp	24OCT94	Alive	21APR95	Alive	Additional follow-up
	TAXOL/Cisp	12SEP90	Dead			Confirmed
	TAXOL/Cisp	03NOV94	Alive			Confirmed
	Cyclo/Cisp	01AUG92	Dead			Confirmed
	TAXOL/Cisp	15FEB95	Alive	28SEP95	Dead	Additional follow-up and date of death
	Cyclo/Cisp	01NOV91	Alive	15MAY95	Alive	Additional follow-up
	TAXOL/Cisp	02NOV94	Alive	20OCT95	Alive	Additional follow-up
	Cyclo/Cisp	16NOV94	Alive	11SEP95	Alive	Additional follow-up
	TAXOL/Cisp	17OCT94	Alive			Confirmed
	TAXOL/Cisp	29NOV94	Alive			Confirmed
	Cyclo/Cisp	29NOV94	Alive			Confirmed
	Cyclo/Cisp	12FEB92	Dead			Confirmed
	Cyclo/Cisp	30AUG94	Alive			Confirmed
	Cyclo/Cisp	09NOV91	Dead			Confirmed
	TAXOL/Cisp	01SEP94	Dead			Confirmed
	Cyclo/Cisp	24JUL94	Dead			Confirmed
	TAXOL/Cisp	06SEP94	Alive	10JAN95	Alive	Additional follow-up
	TAXOL/Cisp	15MAY92*	Dead			Confirmed
	TAXOL/Cisp	04OCT90	Dead			Confirmed
	Cyclo/Cisp	29APR91	Dead			Confirmed
	Cyclo/Cisp	21MAY93	Dead			Confirmed
	TAXOL/Cisp	24SEP93	Dead			Confirmed
	TAXOL/Cisp	04SEP92	Dead			Confirmed
	TAXOL/Cisp	30JUL93	Dead			Confirmed

Table continues on next page

Table 54

Survival Dates: Transcription Versus Audit

Patient #	Arm	Transcribed Database		Audited Database		Comments
		Last Alive	Status	Last Alive	Status	
Table 54 continued						
	Cyclo/Cisp	07NOV94	Alive	05JUN95	Alive	Additional follow-up
	Cyclo/Cisp	29JAN93	Dead			Confirmed
	TAXOL/Cisp	26JUL93	Dead			Confirmed
	TAXOL/Cisp	05OCT94	Alive			Confirmed
	Cyclo/Cisp	23DEC90	Dead			Confirmed
	TAXOL/Cisp	11MAR94	Dead			Confirmed
	TAXOL/Cisp	19OCT91	Dead			Confirmed
	TAXOL/Cisp	18JAN95	Alive	27JUL95	Dead	Additional follow-up and date of death
	Cyclo/Cisp	04DEC91	Dead			Confirmed
	Cyclo/Cisp	24AUG94	Alive	25APR95	Alive	Additional follow-up
	TAXOL/Cisp	04NOV94	Alive	10MAR95	Alive	Additional follow-up
	Cyclo/Cisp	18JUL93	Dead			Confirmed
	Cyclo/Cisp	27OCT94	Dead			Confirmed
	Cyclo/Cisp	19DEC92	Dead			Confirmed
	TAXOL/Cisp	29NOV92	Dead			Confirmed

* *15 inputted for day of month: actual day unknown*

Reviewer Comment:

1. Information on 13 PT and 8 PC patients was obtained that changed the date of last follow-up or status. Of the 13 PT patients, 6 had died with 2-9 months of additional follow-up. The other 7 were confirmed as alive with an additional 4-13 months of follow-up. The 8 PC patients were confirmed as alive with follow-up ranging from 3 months to 2 years 7 months. Most of the additional follow-up and change in status occurred after the data cut-off point of March 30, 1995. In 5 patients, information was available prior to the cut-off that was not reported in the transcribed database. One patient received PC; her status remained alive, but with 4 additional months of follow up (The other 4 received PT: one remained alive with 4 additional months of follow-up; the other 3 had died prior to the data cut-off. Overall, the number of patients with a change in status is low.

2. The change in the transcribed dates of death for the two patients treated with PC is insignificant, as they were by only 1 and 2 days.

3. Overall, the transcribed database has acceptable accuracy.

9.7.2.b Response data

There were no changes in pathologic documentation of response. For clinical response, 8 patients had their status changed. Two patients on PT and 1 patient on PC were upgraded from non-response to a partial response because of additional tumor measurements found at the audit. Four patients treated with PT who were called a CR in the transcribed database did not have confirmation that all non-measurable baseline lesions were absent. Finally, 1 patient on the PC arm did not have baseline measurable disease that could be confirmed, and she was reassessed as non-measurable. These results are summarized below.

Table 22. Clinical Response: Transcription versus audit (sponsor table 55, volume 3, page 169).

Patient #	Arm	Transcribed Database	Audited Database	Comments
	PC	SD	PR	Additional measurements found
	PT	CR	PR	Non-measurable baseline lesions not reassessed
	PT	Non-measurable	PR	Additional measurements found
	PC	SD	Non-measurable	No measurements found
	PT	CR	PR	Non-measurable baseline lesions not confirmed absent
	PT	Unevaluable	PR	Additional measurements found
	PT	CR	PR	Non-measurable baseline lesions not confirmed absent
	PT	CR	Unevaluable	Non-measurable baseline lesions not confirmed absent

Reviewer Comment:

1. Four patients were upgraded to a CR on the PT arm in the transcribed database, compared to the audited database. However, response rate, while of interest, was not the primary efficacy endpoint. These discrepancies in response will not affect time to progression or survival analyses.

2. The transcribed database differs from the audited database by 8 patients, or 8% (8 of 97). Because of the difficulty of measuring ovarian cancer in general and because of inter-observer variations in assessment, it is not surprising that the response data showed more discordance between the 2 databases than survival.

9.7.2.c Safety data audit results

Overall, there were few significant changes in the safety profiles after the audit. The

sponsor provides details in volume 3, pages 170-181. The differences will be listed in summary form in this review:

Myelotoxicity:
1 patient on PT was found to have grade III leukopenia
1 patient on PC was found not to have grade III leukopenia
Worst-course grade IV neutropenia decreased from 85 to 83% on PT and increased from 65% to 70% for PC
1 additional patient on PC had grade IV thrombocytopenia
3 patients on PC had grade IV anemia (none recorded in transcribed database)

Infections:
Additional mild/moderate infections found in source records--
PT: infections increased from 6 to 20 episodes in 261 cycles
PC: infections increased from 11 to 20 episodes in 249 cycles

No change in grade III-IV infections
Generally skin infections, URI

Fever:
PT: additional 16 cycles with fever
PC: additional 13 cycles with fever

Febrile neutropenia:
PT: additional 11 cycles with febrile neutropenia
PC: additional 6 cycles with febrile neutropenia

Cardiovascular:
PT: 20 additional patients with a cardiovascular event
PC: 5 additional patients with a cardiovascular event
All grade 1-2; included tachycardia (13--10 PT, 3 PC), hypertension (7--5 PT, 2 PC), bradycardia (7--6 PT, 1 PC)), abnormal ECG (3--2 PT, 1 PC), and hypotension (3--PT)

Neurotoxicity:
PT: 9 additional patients with peripheral neuropathy (grade I or unspecified)
PC: 12 additional patients with peripheral neuropathy (3 with grade II)

Ototoxicity:
PT: increase from 3 to 11 patients (grade II or unspecified)
PC: increase from 5 to 11 patients (less than grade III)
Events included hearing loss, tinnitus

Arthralgia/myalgia:
PT: 10 additional patients with this event for a total of 14
PC: 10 additional patients with this event for a total of 10
Transcribed database had no grade III/IV events; audited database showed 1 patient in each arm with grade III arthralgia/myalgia

Hypersensitivity: PT: 2 additional patients identified
PC: 2 additional patients identified
No additional grade III/IV events found

Gastrointestinal: PT: 3 additional patients with grade III nausea/vomiting
PC: 1 additional patient with grade IV nausea/vomiting
1 additional patient with grade III diarrhea
Changes in symptoms:

Nausea/vomiting:	PT: from 71% to 92%
	PC: from 60% to 87%
Diarrhea:	PT: from 8% to 37%
	PC: from 10% to 23%
Anorexia:	PT: from 12% to 37%
	PC: from 8% to 27%

Liver function: No significant changes

Renal function: PT: 1 patient found with grade III creatinine

Reviewer Comment:

1. The audited database shows differences in toxicity assessments compared to the transcribed database, but most of the changes consisted of mild to moderate side effects and were similar for both arms. The incidence of febrile neutropenia and peripheral neuropathy may be underestimated by the transcribed database in both arms, but the relative incidences are likely to be unchanged.

9.8 Subset Analysis by Age and Race

9.8.1 Pretreatment characteristics

Pretreatment characteristics on both arms were well-balanced by race and age with two exceptions. Patients on the PT arm who were younger than age 65 were more likely to have a better performance status (PS 0 for 43% of patients < 65) than older patients (PS 0 in 24%); younger patients on this arm were also more likely to have serous adenocarcinoma (78%) than older patients (68%).

Reviewer Comment:

1. Performance status rather than age is the significant prognostic factor, and the distribution of PS (in contrast to the occurrence of PS 0 specifically) was well-balanced between the two treatment arms, both overall and by age.

2. Pathologic subtype is not a recognized prognostic factor and was not significant in the sponsor's exploratory analyses. This difference should not have influenced outcome in this subgroup.

9.8.2 Survival analysis

The median survival with PT in patients younger than age 65 was 38.8 months, compared with 24.9 months in older patients. The median survival with PC was comparable in younger patients (23.2 months) and older patients (24.8 months). These data with 95% confidence intervals are presented in the following table:

Table 23. Survival by age (sponsor table 68, volume 3, page 184).

	Cisplatin-paclitaxel		Cisplatin-cyclophosphamide	
	< 65 (n=134)	≥ 65 (n=62)	< 65 (n=155)	≥ 65 (n=59)
Median (months)	38.8	24.9	24.8	23.2
95% CI	35.4-48.0	16.5-34.3	20.6-30.4	16.3-31.5

The median survival with PT was longer in white or other non-black race patients (36.7 and 37.0 months respectively) compared with black patients (23.8 months). Similar findings occurred in the PC arm: median survival for whites, 24.8 months; other non-black, 40.8 months; black, 15.8 months. There were few black or other race patients included in the study, which make it difficult to interpret these findings. The following table summarizes the data.

Table 24. Survival by Race (sponsor table 69, volume 3, page 184)

	Cisplatin-Paclitaxel			Cisplatin-Cyclophosphamide		
	White (n=178)	Black (n=14)	Other (n=4)	White (n=187)	Black (n=19)	Other (n=8)
Median (months)	36.7	23.8	37.0	24.8	15.8	40.8
95% CI	29.6-41.5	21.8-37.5	1.0-37.0	21.5	12.8-28.5	8.7-NR

Reviewer Comment:

The sponsor performed the required analyses by age and race. Survival was comparable between the two age groups for PC. PT improved survival in younger women but not older women; PT produced survivals comparable to PC in this age group. Given the small numbers of patients, it is not possible to evaluate the clinical significance of these findings. It would be of interest to evaluate survival by age in other large trials of paclitaxel-cisplatin combinations in order to determine whether this difference persists.

9.8.3 Safety analysis by subset

9.8.3.a Safety by age

The incidence of leukopenia and neutropenia were similar in both age groups. Younger patients treated with PT more likely to have severe neutropenia than older patients treated with PT; older patients treated with PC were more likely to have severe leukopenia and neutropenia than younger patients on that arm. The incidence of thrombocytopenia, anemia, and infection was more frequent in patients aged 65 or older in either arm.

Among non-hematologic toxicities, hypersensitivity reactions were more common in older women treated with PT. Older patients on both arms had a higher incidence of cardiovascular events, peripheral neuropathy, and diarrhea. Nausea and vomiting were less common in older women treated with either regimen. Ototoxicity was more frequent and more severe in older patients treated with PC compared to the other groups. Patients younger than age 65 treated with PT had more alopecia and arthralgia/myalgia than the other treatment groups. Laboratory abnormalities were generally similar between older and younger patients in either treatment group.

Reviewer Comment:

1. Non-hematologic toxicity, ototoxicity, and peripheral neuropathy were more common in older women, consistent with neurologic changes observed with aging.

2. Some of the differential toxicity might have been due to differences in dose intensity. At the reviewer's request, the sponsor provided a dose-intensity analysis by age, summarized in the following table:

Table 25 (sponsor's Attachment 5, RFRI, 12/22/97). Dose intensity (DI) analyzed by age

	Arm A				Arm B			
	< 65 years		> 65 years		< 65 years		> 65 years	
	Taxol (n=134)	Cisplatin (n=134)	Taxol (n=62)	Cisplatin (n=62)	CTX (n=154)	Cisplatin (n=154)	CTX (n=59)	Cisplatin (n=59)
Median cumulative dose/patient ($mg/m^{2)}$	771	447	737	449	4229	448	4099	448
Median DI (mg/m^2/week)	41	24	41	24	205	21	204	21
Relative DI (% pts): % scheduled dose								
>90	54	73	48	71	33	42	32	41
80-90	43	22	34	18	22	28	29	39
>80	19	5	18	11	45	31	39	22

This analysis demonstrates that dose-intensity was comparable between the two age groups, and that dose-intensity was higher with PT than with PC, regardless of age. The observed differences in toxicity patterns are probably due to age differences or small sample sizes rather than to differences in the amount of drug delivered.

9.8.3.b Safety by race

The small number of patients included in the "other" category precluded an analysis of this group compared to white or black patients for toxicity parameters. Overall, any grade of hematologic toxicity was comparable in black and white patients. Grade III-IV hematologic toxicity was less common in blacks than in whites in both treatment arms. Rates of infection were comparable for blacks and whites.

White patients treated with PT had a higher incidence of hypersensitivity reactions than black patients. Ototoxicity was more common in white patients; severe ototoxicity occurred only in white patients treated with PC. White patients treated with PC had more alopecia than all other groups. Patients treated with PT had more asthenia than patients treated with PC; among the PT patients, the incidence was similar in black and white patients. Among PC patients, asthenia was more common in whites than blacks. White patients treated with PT had the

highest incidence of arthralgia/myalgia. Other toxicities were comparable between the races. Laboratory testing demonstrated more liver function abnormalities among white patients; creatinine elevations were more common in black patients.

Reviewer Comment:

This analysis is required in an NDA. However, the small number of non-white patients and the small number of events within each group does not allow meaningful clinical conclusions to be drawn from this data. Overall, there are no obvious differences in safety profile or outcome related to age or race.

9.9 Sponsor summary and conclusions

The GOG 111 study was the first prospective randomized controlled trial of paclitaxel and cisplatin conducted as initial therapy for advanced ovarian cancer. Paclitaxel produced superior pathologic response rates, improved time to progression, and prolonged survival compared to standard therapy. An increase in survival of 11.3 months with Taxol represents a significant improvement over standard therapy and demonstration of clinical benefit. Administration of paclitaxel did not interfere with cisplatin dosing and in fact led to improved dose-intensity. The sponsor also notes that the median survival on the cisplatin-cyclophosphamide arm is consistent with prior published reports; thus, the observed benefit with PT is not due to unexpectedly poor performance of the control arm.

The safety profile of paclitaxel has been documented in both clinical trials and post-marketing use of this drug. The predominant side effect was neutropenia which did not interfere with the timing of dose administration. A greater incidence of anemia and severe peripheral neuropathy was seen with paclitaxel, possibly due to the increased dose intensity with the study combination. The incidence of severe cardiac events was similar in the two arms. Fever, alopecia, asthenia, arthralgia/myalgia, and allergic reactions were more common with paclitaxel. Severe events were rare and occurred with the same frequency on both arms. The numbers of patients who discontinued therapy because of adverse events and patients who died on study were comparable in the two arms.

This study used a 24 hour infusion of paclitaxel because of the timing of the initiation of this study in the development of paclitaxel. A 3 hour infusion might cause less neutropenia but may cause more neurotoxicity.

The sponsor created its own database for analysis. The discrepancies between the GOG database and the BMS database can be summarized as follows: BMS analyzed all randomized patients, while the GOG excluded 24 eligible patients from analysis; and BMS applied WHO criteria for confirmation of clinical response, resulting in a non-significant difference in clinical response, while the GOG reported a superior clinical response rate for the PT arm. Other efficacy and safety results were consistent between the 2 databases. The audit of the primary records showed some discrepancies, but these discrepancies were primarily minor differences that did not impact on the study conclusions.

A review of the literature (section 11.0), particularly a review of the EORTC Intergroup study, supports the findings of GOG 111. The measured TTP in both arms of the Intergroup

study was concordant with that measured in GOG 111; response rates were also comparable. Thus, there is additional published data corroborating the results of the pivotal trial.

Overall, the combination of cisplatin and paclitaxel was more toxic than cisplatin and cyclophosphamide, but resulted in a significant survival advantage for PT. Continued research to define the optimal use of paclitaxel is ongoing. Paclitaxel at a dose of 135 mg/m^2 over 24 hours in conjunction with cisplatin 75 mg/m^2 should be approved for the primary treatment of patients with advanced ovarian carcinoma.

9.10 Reviewer summary and conclusions

GOG 111 was a prospective randomized controlled trial of paclitaxel and cisplatin compared to cyclophosphamide and cisplatin as first line therapy for advanced ovarian cancer. The populations were well-balanced. Progression-free survival was the primary endpoint; survival was the secondary endpoint. The PT arm resulted in a statistically significant prolongation of PFS by 3.6 months and a significant prolongation of OS by 11.3 months. These differences are clinically significant as well and are of striking clinical benefit. No significant differences in clinical response were seen. Overall pathologic response was significantly better with PT, although there was no significant difference in the rate of complete pathologic CR with PT. These results are summarized below:

Table 26. Overall summary of sponsor's results for GOG 111

Efficacy Parameter	Cisplatin-paclitaxel	Cisplatin-cyclophosphamide	p-value
Clinical complete response	40/113 (35%)	32/127 (25%)	0.092
Clinical partial response	28/113 (25%)	32/127 (25%)	
Overall clinical response	68/113 (60%)	64/127 (50%)	0.153
Complete pathologic response	42/196 (21%)	35/214 (16%)	0.196
Microscopic residual disease	25/196 (13%)	8/214 (4%)	
Overall pathologic response rate	67/196 (34%)	43/214 (20%)	0.001
Median progression free survival	16.6 months	13.0 months	0.0008
Median survival	35.5 months	24.2 months	0.0002

It is paradoxical that PT improved PFS and OS without changing the rate of response. However, there was a trend to improved response with PT upon review of the actual response

rates. In addition, it is difficult to fully assess response in ovarian cancer patients because of the intra-abdominal growth pattern of this tumor and concomittant difficulties in accurate serial imaging of tumor masses. Finally, the number of pathologic complete responses was low, decreasing the chance of detecting a significant difference in outcome.

The toxicity of the PT regimen was greater, due either to the side effects of the drugs themselves or to the improved dose-intensity achieved with this regimen compared to PC. The adverse events were consistent with those described in the label for paclitaxel. Despite the increased toxicity, treatment-related mortality on the two arms was comparable.

Overall, this study demonstrates the efficacy of cisplatin and paclitaxel as first-line therapy of ovarian cancer. The striking clinical benefits observed in this study outweigh the increased but reversible toxicity associated with PT, in the opinion of the reviewer.

10.0 Comparison of the Study Report and Published Reports of GOG 111

The GOG 111 study results were presented by McGuire at the American Society of Clinical Oncology meetings in 1993 and 1995 and were published in abstract form in the Proceedings of these meetings (Proc. ASCO 12: page 255, abstract 808, 1993; Proc. ASCO 14: page 275, abstract 771, 1995). The results were published in complete form in a peer-reviewed journal in 1996 (McGuire WP, Hoskins WJ, Brady MF, et al. New Eng. J. Med. 334: 1-6, 1996). The differences and additions between the study report from the sponsor and the published report will be outlined.

Methods:

In the published article, the authors listed additional off-study criteria:

- Cardiac events, with the exception of sinus bradycardia, were reported to the study chairman and were considered a cause for discontinuing therapy
- Severe allergic reaction to paclitaxel

These criteria were not explicitly mentioned in the protocol document.

Reviewer Comment:

Review of the material submitted in the NDA indicates that only 1 patient was removed from study for a cardiac event. Although not explicitly mentioned in the protocol, it is reasonable and medically advisable to remove patients from study for severe allergic reactions to paclitaxel.

Patient evaluability:

As the sponsor noted in the study report, McGuire and colleagues analyzed 386 patients who fulfilled all eligibility criteria. Twenty-four patients were excluded.

Reviewer Comment:

The sponsor states in the NDA that 370 patients were fully eligible. The protocol violations are listed in Table 5. The article by McGuire and colleagues gives the following reasons for ineligibility:

3	Inappropriate stage	(2 per sponsor)
13	Wrong primary	(16 per sponsor)
3	Wrong cell type	(2 per sponsor)
4	History of cancer	(2 per sponsor)
1	Wrong type of surgery	(0 per sponsor)

Despite the differences in assessment of eligibility, the appropriate analysis is the intent-to-treat analysis, which includes all randomized patients. The intent-to-treat analysis was performed by the sponsor but not by the GOG authors.

Dosing:

Eighty-seven percent (160/184)of women randomized to PT completed the planned course of therapy compared to 78% (158/202) of women on PC. Nine women (5%) on PT and 23 (11%) on PC did not complete the treatment program because of disease progression or death. Fifteen women (8%) on PT and 21 on PC (10%) did not complete study therapy because of toxicity or refusal.

The authors reported that there was no difference in the delivered dose of cisplatin.

Reviewer Comment:

1. These values are comparable to those reported by the sponsor.

2. The sponsor also demonstrated that both arms received comparable amounts of cisplatin. However, the sponsor demonstrated a difference in dose-intensity in favor of the PT arm, due primarily to the ability to treat on time.

Toxicity:

Toxicity assessments were collapsed into a smaller number of categories. More toxicity was observed with PT.

Reviewer Comment:

The sponsor provides greater detail about the toxicity profiles in each arm. However, neither the GOG report nor the sponsor's study report noted any new toxicities not previously described for paclitaxel.

Results:

Clinical Response:

Two hundred sixteen women had measurable disease and were evaluable for response. The published response rates were 60% for the PC arm and 73% for the PT arm; the complete response rates were 31% and 51% respectively (p=0.01).

Pathologic response:

Of the 386 women, 24 in each treatment group or a total of 48 refused a second-look laparotomy or had medical contraindications to the procedure. The incidence of negative second-look surgery (pathologic CR) was 20% for PC and 26% for PT, a non-significant difference.

Progression-free survival:

At a median duration of follow up of 37 months, the median progression-free survival for PC was 13 months (95% CI: 11, 15) and for PT was 18 months (95% CI: 16, 21). This difference was significant with a relative risk of 0.7 (95% CI: 0.5-0.8; $p<0.001$).

Overall survival:

The median survival with PC was 24 months (95% CI: 21-30) compared with 38 months for PT (95% CI: 32-44). These figures corresponded to a relative risk of 0.6 in favor of the paclitaxel arm (95% CI, 0.5-0.8; $p<0.001$). McGuire and colleagues stated that additional analyses of survival including the 24 ineligible patients did not significantly alter the results. Analyses of survival in women with and without measurable disease in each group and by stage consistently showed an advantage for the paclitaxel arm (data not shown).

Reviewer Comment:

1. The differences in the efficacy parameters reported by the GOG and the sponsor are listed in the following table:

Table 27. Comparison of study report and published results of GOG 111

Efficacy Parameter	BMS results of GOG 111			Published results of GOG 111		
	Cisplatin-paclitaxel	Cisplatin-CTX	p-value	Cisplatin-paclitaxel	Cisplatin-CTX	p-value
Clinical complete response	40/113 (35%)	32/127 (25%)	0.092	51/100 (51%)	36/116 (31%)	0.01
Clinical partial response	28/113 (25%)	32/127 (25%)		22/100 (22%)	34/116 (29%)	
Overall clinical response	68/113 (60%)	64/127 (50%)	0.153	73/100 (73%)	70/116 (60%)	0.01
Complete pathologic response	42/196 (21%)	35/214 (16%)	0.196	42/ 184 (26%)	35/202 (20%)	NS
Microscopic residual disease	25/196 (13%)	8/214 (4%)		23/184 (14%)	7/202 (4%)	
Overall pathologic response rate	67/196 (34%)	43/214 (20%)	0.001	65/184 (35%)	42/202 (21%)	
Median progression free survival	16.6 months	13.0 months	0.0008	18 months	13 months	<0.001
Median survival	35.5 months	24.2 months	0.0002	38 months	24 months	<0.001

The primary difference between the two sets of data calculations lies in the response assessment. The GOG authors found a statistically significant improvement in clinical complete response and clinical overall response, while the sponsor did not. The sponsor states that the difference in significance level is due to two factors: BMS included all randomized patients, while the GOG included only eligible patients; and BMS required confirmation of response, as mandated by WHO response criteria. The GOG in contrast did not always require confirmation

of response. Overall, the sponsor has applied more stringent criteria in evaluating response.

The results for PFS and OS are comparable between the two groups. The sponsor has reported somewhat shorter durations for these parameters, attributable to the intent-to-treat analysis.

11.0 Literature Review

Paclitaxel was initially approved for use after failure of first-line or subsequent chemotherapy for the treatment of metastatic carcinoma of the ovary. It is also indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy; patients should have received an anthracycline unless clinically contraindicated. Recently, a supplemental NDA was approvable for the use of paclitaxel in the treatment of AIDS-related Kaposi's sarcoma. In addition to these FDA-approved indications, paclitaxel has been used and extensively reported in the literature in other malignant diseases and as part of multidrug regimens. This background section will be limited to a discussion of published literature of paclitaxel as first-line therapy for advanced (stage IIB-IV) ovarian cancer. The primary source for this review was a MedLine search performed by the reviewer; additional documentation from the randomized trials was provided by the sponsor as noted below. The published results of GOG 111 (McGuire WP, Hoskins WJ, Brady MF, et al. NEJM 334: 1-6, 1996; McGuire WP, Hoskins WJ, Brady MF, et al. Semin.Oncol. 24 [1] Suppl 2: S2-13--S2-16, 1997) were discussed in Section 10.0. Two papers based on the results of GOG 111 calculated the cost-effectiveness of therapy with cyclophosphamide-cisplatin in comparison to paclitaxel-cisplatin (Elit LM, Gafni A, and Levine MN. J. Clin. Oncol. 15: 632-9, 1997; McGuire W, Neugut AI, Arikian S, et al. J. Clin. Oncol. 15: 640-45, 1997). Because the FDA does not consider cost in the approval process, these papers will not be reviewed. Finally, only two drug combinations (paclitaxel plus a platinum compound) with standard dosing are reviewed; the literature on paclitaxel as a single agent, as part of a 3- or more drug combination, or as part of a high-dose transplant regimen is not considered. This review includes some but not all trials cited by the sponsor in Tables 1 and 2; it includes several trials not referenced by the sponsor. The response rates cited in this section do not always agree exactly with those listed in Table 2.

11.1 Phase I trials of paclitaxel in combination with cisplatin

Several Phase I trials of paclitaxel in combination with cisplatin have been performed. The **National Cancer Institute of Canada (NCI-C)** conducted a Phase I study of biweekly paclitaxel and cisplatin as first-line therapy for high-risk ovarian cancer patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1 and residual macroscopic disease after laparotomy (Gelmon K, Semin.Oncol. 21[5] suppl 8: 29-33, 1994; Swenerton K, Hoskins P, Stuart G, et al. Ann.Oncol. 7[10]: 1077-9, 1996). The starting dose of paclitaxel was 90 mg/m^2 given over 3 hours, followed by cisplatin at a fixed dose of 60 mg/m^2; paclitaxel was escalated by 10 mg/m^2 in each subsequent dose level. Treatment was repeated every 2 weeks for

a total of 8 cycles. A standard modified Fibonacci Phase I design was used. Twenty-eight eligible patients were entered on study; 16 had measurable disease. The maximum tolerated dose of paclitaxel was 120 mg/m^2, and the observed DLT consisted of granulocytopenia. Of the patients with measurable disease, 7/16 achieved a CR and 3/16 a PR for a total response rate of 63%. The median progression-free survival for the entire group was 12 months. The recommended phase II dose of paclitaxel was 110 mg/m^2 over 3 hours in combination with cisplatin 60 mg/m^2 every 2 weeks.

Investigators at the **Cleveland Clinic** treated 35 women with paclitaxel at 175 mg/m^2 infused over 3 hours followed by cisplatin at 75 mg/m^2 (Connelly E, Markman M, Webster K, et al. Proc. ASCO 14: abstract 777, page 277, 1995). Thirty-one percent of the administered cycles required a dose-reduction in paclitaxel to 135 mg/m^2. Colony stimulating factors were not used routinely. Fourteen of 35 women (40%) developed neuropathy, predominantly grade 1. Sixty-six percent experienced neutropenia. The other observed toxicities included elevated creatinine (2/35 or 6%), allergic reaction (1/35 or 3%), emesis (12/35 or 35%) and total alopecia in all patients. No episodes of febrile neutropenia were observed. No formal response assessments were made. However, 32 of the 35 patients had elevated CA-125 values at baseline. All 32 demonstrated a greater than 50% reduction in the CA-125 level with therapy; 21 patients had a greater than 90% decrease in CA-125. The investigators concluded that this regimen was tolerable, but that the 3 hour paclitaxel infusion produced more neuropathy than the 24 hour infusion.

Mendiola and colleagues presented the results of a Phase I trial of paclitaxel given over 1 hour in combination with cisplatin 80 mg/m^2 given every 21 days in women with untreated stage IIB-IV ovarian cancer (Mendiola C, del Campo JM, Massuti B, et al. Proc. ASCO 16: 359a, abstract 1276, 1997; Cervantes A, Mendiola C, del Campo JM, et al. Semin. Oncol. 24 [5] Suppl 15: S15-40--S15-43, 1997). The starting dose of paclitaxel was 175 mg/m^2; subsequent dose levels for intrapatient dose escalation were 200 and 225 mg/m^2. Sixty-eight women were enrolled in the study. Six patients could not have the dose escalated, 6 women had the dose escalated to 200 mg/m^2, and 45 patients reached the maximum dose of 225 mg/m^2. Of these 45 patients, 11 women received 225 mg/m^2 but subsequently required a dose reduction. Thirty-eight percent of the patients had grade 3-4 neutropenia, but only 1 patient had febrile neutropenia. No grade 3 or 4 thrombocytopenia was observed. Peripheral neuropathy occurred as grade 1 toxicity in 40% of patients, as grade 2 in 43%, and as grade 3 in 9%; this toxicity was dose-limiting. Sixty-seven patients were evaluable for response: 35 had a clinical CR [cCR] (51.4%) and 20 had a PR (29.4%) for a total response rate of 80.8%. Thirty-two of the 35 patients with a cCR underwent a second-look laparotomy, and 20 were confirmed to have a pathologic complete response [pPR] (29.4% of the total population). No time to progression or survival data are available.

These Phase I studies used paclitaxel as a 1-hour or 3-hour infusion rather than a 24 hour infusion, as in the pivotal trial. Cisplatin doses ranged from 60 to 80 mg/m^2, and paclitaxel doses ranged from 110 to 225 mg/m^2. While neutropenia was observed, peripheral neuropathy was the DLT in 2 of these 3 studies. These trials demonstrate the feasibility of administering paclitaxel and cisplatin in these schedules, but do not provide any information about its efficacy relative to the cisplatin-cyclophosphamide combination.

11.2 Phase II/III studies of paclitaxel in combination with cisplatin

The GOG, on the basis of the Phase I data, performed trial GOG 111, the pivotal trial in this application. Following the completion of the GOG 111 study and its presentation at ASCO and subsequent publication, several confirmatory studies have opened; none are complete. Preliminary information from these trials is important, however, in verifying the benefit observed in GOG 111.

The **European-Canadian Study group** performed a "confirmatory" trial of cisplatin and paclitaxel (CP) as first-line therapy of Stage IIB-IV ovarian cancer compared with a control arm of cisplatin-cyclophosphamide (CC). This trial was published in abstract form only (Piccart MJ, Bertelsen K, Stuart G, et al. Proc. Amer. Soc. Clin. Onc. 16: page 352a, abstract 1258, 1997) and included toxicity data alone. The authors updated their data in their oral presentation (Oncology News International 6 [7] Suppl 2: 22, 1997) and copies of the slides, a transcript of the presentation, the statistical report, and the original protocol document were supplied by BMS in this NDA. No primary data have been submitted to or reviewed by FDA. The treatment regimens were cyclophosphamide 750 mg/m^2 IV followed by cisplatin 75 mg/m^2 (PC) or paclitaxel 175 mg/m^2 IV over 3 hours followed by the same dose of cisplatin (PT). The primary objective of the trial was to detect a difference in progression-free survival. Six hundred eighty patients were randomized on study, of which 668 were considered eligible. Reasons for ineligibility included incorrect histology (6), second non-ovarian malignancy (4), incorrect stage of disease (1), and poor medical condition (1). The PT arm contained 338 eligible patients, and the PC arm contained 330 eligible patients. The treatment arms were well-balanced for age, PS, cell type, tumor grade, FIGO stage, residual disease after staging laparotomy, and measurability. Less than 10% of patients were Stage II, a stage of disease excluded from the GOG trial. Two hundred thirty-nine patients, balanced between the two arms, had optimally debulked Stage III disease, a second group excluded from GOG 111. Patients could undergo interval debulking after 3 cycles of chemotherapy; this surgery was performed in 8% (28 patients) of PC patients and 9% (31) of PT patients. Although up to 9 cycles of chemotherapy were allowed, the median number was 6 in each arm. The protocol permitted substitution of carboplatin for cisplatin for toxicity; this option was exercised in 12% (43) of patients on PT and in 9% (30) of patients on PC. Paclitaxel doses were escalated in 233 (70%) of patients on PT. In terms of delivered dose, 17% (58) of PT patients required cisplatin dose reductions and 23% (77) experienced dosing delays. In the PC arm, these figures were 15% (49) and 42% (137) respectively. The delivered dose-intensity (DI; dose per unit time) of cisplatin was 24.4 mg/m^2/week in the PT arm and 22.3 mg/m^2/week in the PC arm ($p<0.001$).

Three hundred patients had measurable disease at baseline and were evaluated for response. The response rate was 57% in the PT arm and 43% in the PC arm ($p=0.02$) for patients who had the required confirmatory evaluation one month later. If the investigators included all patients with a response, with or without confirmation, these figures were 77% and 66% ($p=0.03$). One hundred twenty-five patients underwent a second-look laparotomy (70 PT; 55 PC). The pathologic CR rate was 33/70 or 47% for PT and was 13/55 or 24% for PC. Pathologic response rates for pCR plus microscopic residual disease were 46/70 (66%) and 23/55 (42%) respectively.

At a follow-up time of 20 months for the 675 patients with available data (intent-to-treat, regardless of eligibility), the progression-free survival was 16.6 months for CP patients compared to 12 months for the CC patients (p=0.0001). The risk ratio was 0.66 (95% CI: 0.65-0.80). An analysis adjusted for prognostic factors for ovarian cancer was performed. The factors included age, PS, FIGO stage, histologic subtype, cytology, measurability, and amount of residual disease. The difference in PFS remained significant after adjustment. In order to assess PFS in a group comparable to that included in GOG 111, this endpoint was evaluated in the subset of patients with suboptimally debulked Stage III disease (428 patients). In this subset, PFS was approximately 14 months for PT and 10 months for PC. The values for the optimally debulked patients were 24 months and 18 months respectively.

Paclitaxel-based therapy was associated with a higher incidence of neurotoxicity (14% grade 3-4 neurosensory toxicity on PT; 1% on PC), arthralgia/myalgia (9% grade 3 toxicity on PT; 1% on PC), alopecia (48% grade 3-4 toxicity on PT; 20% PC), and hypersensitivity (5% grade 3-4 toxicity on PT; 2% PC), but less emesis (23% PT; 35% PC). Hematologic toxicity was similar in both arms.

BMS sent a copy of the abstract of this study submitted to the 1998 Proceedings of the ASCO. An updated analysis with a median follow-up of 28 months confirmed the difference in progression-free survival: 131 of 342 patients (38.3%) treated with cisplatin and paclitaxel had progressed, compared to 168 of 337 (49.9%) on the cisplatin/cyclophosphamide arm. At this time point, a significant difference in overall survival was observed. The median survival on PT was 35 months, compared to 25 months on PC (p<0.001).

There are several differences between this study and GOG 111, the pivotal study in this application (Ozols RF, Semin. Oncol. 24[1]Suppl 2: S2-1--S2-9, 1997) that may limit their comparability.

- *First*, patients with Stages IIB through IV disease were entered in the Intergroup trial; only patients with suboptimal stage III-IV were entered on the GOG study.

  - The first issue should not significantly influence the results of the studies. Although the Intergroup trial included patients with a better prognosis (IIB and optimally debulked III), they were randomly distributed between the study arms. Thus, a survival difference between the 2 arms should still be apparent if present.

- *Second*, paclitaxel was given at a dose of 175-200 mg/m^2 as a 3-hour infusion in the Intergroup study; the GOG study gave paclitaxel at a dose of 135 mg/m^2 over 24 hours.

  The second issue raises an unresolved question about the relative importance of the dose and/or the infusion duration for paclitaxel. Paclitaxel exhibits non-linear pharmacokinetics with increasing dose, and studies of 135 mg/m^2 in breast cancer patients have reported results that are inferior to those obtained with doses of 175 mg/m^2 or greater. Trials in several different malignancies have shown a trend toward higher response rates with increasing doses, but whether the increased response rate translates into a meaningful clinical benefit for the patient,

particularly with the increased toxicity seen with higher doses, is unknown. The infusion length may affect efficacy, also. Preclinical data suggest that prolonged exposure to paclitaxel results in greater tumor cell death. A comparison of 3- and 24-hour infusions in previously treated ovarian cancer patients showed no difference in response rates, but less toxicity with the 3 hour infusion. However, in untreated patients, the duration of exposure may be important, and current studies are exploring the utility of 96-hour paclitaxel infusions. It is unclear in the untreated ovarian cancer population whether the optimal administration of paclitaxel is achieved by increasing the dose, prolonging its infusion, or using a combination of these factors.

- *Third,* the EORTC study permitted 9 cycles of chemotherapy, compared to 6 in the GOG study.

  Six cycles of chemotherapy has been the standard of care for first-line therapy of ovarian cancer; additional cycles add toxicity, but do not clearly add benefit. The median number of cycles administered was 6, suggesting that few patients received additional treatment.

- *Fourth*, patients treated with CC in the Intergroup trial could receive paclitaxel as salvage therapy; patients treated with CC in the GOG study did not have this option available to them, as paclitaxel was not approved for use as second-line therapy in ovarian cancer.

  With regard to the third point, Ozols noted that patients who failed CC and received paclitaxel may live longer than patients who failed CC and received other salvage drugs. Therefore, a survival difference might not be observed in the European-Canadian study because of improved salvage therapy on the CC arm. Patients in the PC arm were prohibited from receiving paclitaxel until there was objective evidence of progressive disease. Therefore, the large sample size (680 patients) and its well-defined time to progression endpoint (rather than survival) should allow a statistically meaningful comparison of the two arms. However, although paclitaxel was approved as second-line therapy for ovarian cancer, the data do not clearly indicate a survival benefit in this situation. It is unlikely that crossover therapy will change a survival endpoint. This hypothesis is supported by the latest results from the Intergroup study, which demonstrate a survival benefit with initial paclitaxel therapy.

- *Fifth*, second-look laparotomy was not required in the EORTC study, which also permitted interim debulking.

  The 5th difference (requirement for second-look laparotomy) is important in confirming response, but will not affect time to progression or survival endpoints.

The authors concluded that the results of this trial confirmed the results obtained in GOG 111. The higher incidence of neurotoxicity in this trial compared to GOG 111 was ascribed to the 3 hour infusion schedule of paclitaxel, the higher dose of paclitaxel, and an increased number of cycles.

Several ancillary studies were performed in conjunction with the EORTC study. A prospective study of quality of life was conducted in 2 of the 4 cooperative groups involved in this trial (the Gynecological Cancer Cooperative Group [GCCG] of the EORTC and the NCI-C). The GCCG also performed a cost-effectiveness study. All groups evaluated CA-125 as a marker of clinical outcome. Results of these ancillary studies are not available at present.

Other published material from this trial includes a toxicity report from Cavaletti and colleagues (Cavaletti G, Bogliun G, Crespi V, et al. J. Clin. Oncol. 15[1]: 199-206, 1997). This report comprises results of extended neurologic and otologic testing on a subset of patients enrolled in the larger European-Canadian study, the 51 patients entered at the authors' affiliated institution. Forty-six patients consented to additional testing. Baseline neurologic status was similar in both treatment groups. Comparisons between the baseline examination (exam 1) and examination 2 as well as between examinations 1 and 3 and examinations 1 and 4 were performed. Both groups showed statistically significant differences in sensory-neurologic status between the first and third examinations; however, both treatments produced the same degree of sensory impairment. No evidence of motor dysfunction was found in either group. Similarly, both groups showed progressive impairment by audiometry, but there was no significant difference in the degree of impairment induced by the two treatments. Ten of 22 patients (45%) on the PC arm had an objective response to therapy compared to 16/24 (67%) on the PT arm. Because this patient group represents a subset analysis, the efficacy data cannot be considered definitive. However, the detailed safety testing provides important information about the relative toxicity and tolerability of the two regimens.

This large multicenter prospective randomized trial, despite differences in trial design, supports the conclusions of GOG 111. A significant difference in TTP and OS was observed with first-line paclitaxel therapy; these data are comparable to those obtained in GOG 111. Exploratory subset analysis indicates that the benefit is observed in both suboptimally and optimally debulked disease, suggesting clinical utility in patients with Stage IIB through Stage IV disease.

The **GOG 132** study randomized suboptimal Stage III and Stage IV ovarian cancer patients to receive cisplatin 100 mg/m^2 IV every 21 days x 6 versus paclitaxel 200 mg/m^2 over 24 hours every 21 days x 6 versus cisplatin 75 mg/m^2 and paclitaxel 135 mg/m^2 over 24 hours every 21 days x 6 (Ozols RF, Semin.Oncol. 22[5] Suppl 12: 61-6, 1995; Ozols RF, Semin.Oncol. 22[6] Suppl 15: 1-6, 1995). Patients were stratified by measurable versus non-measurable disease. Filgrastim was not used prophylactically, but could be added for patients with febrile neutropenia or delayed recovery of neutrophil counts. A second-look laparotomy was required for patients with a clinical complete response after 6 cycles of treatment. The GOG 132 trial was presented in abstract form at the 1997 ASCO meeting. Copies of the slides, transcript, statistical report, and original protocol document were included in the sponsor's application. No primary data have been submitted to or reviewed by FDA. Six hundred forty-eight patients were randomized; 615 were eligible. For cisplatin alone, 209 were randomized, and 200 were evaluable. For

paclitaxel alone, 224 were randomized and 213 were evaluable. For the combination, 215 were randomized and 201 were evaluable. Reasons for ineligibility included wrong primary (17), incorrect disease stage (5), wrong cytology (4), second non-ovarian malignancy (4), improper prior therapy (2), and poor PS (2). Data was analyzed for the eligible patients:

The patient groups were well-balanced for baseline prognostic factors. The median number of cycles given in each arm was 6. However, a greater percentage of patients completed PT therapy (83%) compared to P (69%) or T (71%). Eighteen percent of patients on P discontinued therapy because of toxicity or refusal, compared to 5% on PT and 4% on T. Discontinuation because of progressive disease occurred in 19% of patients treated with taxol alone, compared to 8% on cisplatin and 6% on PT. Discontinuations for other reasons or due to death on study were comparable between the 3 arms.

Clinical response was evaluated in patients with measurable disease (PT). The response rates were 75% for cisplatin alone, 46% for paclitaxel alone, and 72% for the PT combination; the paclitaxel alone arm was statistically significantly inferior to the other two ($p<0.05$), which did not differ significantly from each other.

Pathologic response was evaluated in the 614 eligible patients with available data. The incidence of pathologic CR was 15% (29/200) P, 6% (12/213) T, and 22% (44/201) PT. Response in the P and PT arms was statistically significantly better than in the T arm. The difference between P and PT was not significantly different ($p=0.07$). If residual microscopic disease was included, the rates were 25%, 12%, and 33% respectively. The same statistical relationships exist as for pathologic CR.

The median progression-free survivals were 16.4 months for P, 11.4 months for T, and 14.1 months for PT. At the time of analysis, 524 or 85% of patients had progressed. Treatment with paclitaxel as a single agent was a negative prognostic sign, with a relative risk of 1.39 (95% CI 1.12, 1.71). The times to progression observed with P compared to PT were not significantly different. Cox multivariate analysis demonstrated that the presence of measurable disease, clear cell/mucinous histology, and treatment with paclitaxel alone were significant poor prognostic factors.

Median survivals were 30.2, 26.0, and 26.6 months respectively. At the time of analysis, 408 or 66% of the patients had died. A Cox multivariate analysis for survival identified clear cell/mucinous histology as the only significant negative prognostic factor. There were no significant differences in survival between the 3 arms.

In the analysis of this trial, the sponsor notes that salvage therapy was used frequently and affected TTP and OS. Patients who discontinued therapy due to toxicity or refusal began salvage therapy prior to documentation of progression. Of the 209 patients randomized to P, 54% crossed over to paclitaxel; of the 224 patients randomized to T, 71% crossed over to cisplatin or carboplatin regimens; and of the 215 patients randomized to PT, 24% received subsequent paclitaxel and 39% received additional cisplatin or carboplatin. The authors hypothesize that because patients assigned to paclitaxel generally received cisplatin for salvage and patients assigned to cisplatin generally received paclitaxel for survival, the survival advantage conveyed by the cisplatin/paclitaxel combination was masked.

In terms of toxicity, paclitaxel alone or in combination with cisplatin induced grade 3-4 neutropenia/leukopenia in 97% and 95% of patients respectively, compared with 49% with

cisplatin alone. Anemia (grade 3-4) was more common with cisplatin alone (12%) compared to T (6%) and PT (9%). Thrombocytopenia (grade 3-4) was comparable between the 3 arms, as was grade 3-4 fever. Grade 3-4 gastrointestinal toxicity was more common in the cisplatin arm (33%) than in T (10%) or PT (18%), as was renal toxicity (5%, 1%, 0 respectively). Any grade of neurologic toxicity was observed in 41% of patients treated with P, 32% of those treated with T, and 40% treated with PT. Grade 3-4 neurotoxicity was observed in 12%, 2%, and 5% respectively.

The investigators concluded that cisplatin and cisplatin-paclitaxel had comparable efficacy, but the combination therapy required fewer dose reductions and treatment delays. Both gave results superior to paclitaxel alone. However, they noted that sequential therapies should be further evaluated.

This trial, in contrast to GOG 111 and the Intergroup trial, showed no survival advantage for the combination of paclitaxel and cisplatin over cisplatin alone and demonstrated comparable results between single agent cisplatin and the PT combination. The PFS and OS values for cisplatin alone and for PT in this study are comparable to those observed for the PT arm in GOG 111. This study raises the question of whether paclitaxel adds any efficacy to dose-intense delivery of cisplatin, particularly since single agent paclitaxel produced inferior results for clinical response, pathologic response, and progression-free survival. It should be noted, however, that there was a higher discontinuation rate on the cisplatin alone arm, primarily because of patient refusal or toxicity. Paclitaxel may add efficacy when a lower dose of cisplatin is used and may change the pattern of toxicity, allowing greater compliance with the regimen.

The **ICON3** trial is the largest trial of paclitaxel or cyclophosphamide given as first-line therapy in ovarian cancer; this trial continues to accrue patients. Information about this study was obtained from a Lancet editorial, which described ICON 3 as a large trial comparing paclitaxel plus carboplatin versus "an appropriate platinum control" (Editorial, Lancet 349: 1635, 1997). This trial had accrued 1254 patients at the time of publication, with a target accrual of 2000 patients. The editorial noted that a representative of BMS and the managing director of the UK office of Bristol-Myers Squibb had claimed superiority for the paclitaxel arm and recommended early closure of the study. An independent data monitoring committee stated in an open meeting on June 2 that the outcome and toxicity data did not mandate early closure, and that the size of this trial made its completion critical to fully evaluating the efficacy of the paclitaxel-cisplatin combination. The committee made a strong recommendation for continuing the trial. A recent publication by Harper (Semin.Oncol. 24[5] Suppl 15: S15-23--S15-25, 1997) and the submission of the protocol document by BMS at the request of the FDA reviewers in the NDA provided additional information on the study design. Previously untreated ovarian cancer patients are randomized to receive paclitaxel 175 mg/m^2 IV over 3 hours in combination with carboplatin given at a dose calculated to provide an AUC of 5 or 6 (depending on the method used to derive creatinine clearance: measured or calculated), or to receive either carboplatin alone or CAP, at the discretion of the investigator. Carboplatin alone is given at a dose calculated to produce an AUC of 5 or 6. The doses in the CAP regimen are cyclophosphamide 500 mg/m^2, doxorubicin 50 mg/m^2, and cisplatin 50 mg/m^2. All regimens are repeated every 3 weeks for a total of 6 cycles. Patients are randomized 2:1 in favor of the control arm. The primary endpoint of this trial is mortality; secondary endpoints include response, progression-free interval, quality

of life, and health economics. An interim analysis is planned for "mid-1997." This trial to date has accrued almost twice as many patients as the EORTC-Canada study and 3 times as many women entered on GOG 111; when accrual is complete, it will contain 3 times as many patients as the EORTC-Canada study and 5 times as many patients as the GOG study. Review of these results will be important in determining the value of paclitaxel as first-line therapy. Although the trial has not been analyzed, the FDA has requested results of interim analyses if available during the course of the NDA review.

The other GOG trial relevant to this NDA is **GOG 114** (SWOG 9227/ECOG G0114), in which optimally debulked Stage III ovarian cancer patients were randomized to receive cisplatin 75 mg/m^2 and paclitaxel 135 mg/m^2 over 24 hours every 21 days for 6 cycles versus carboplatin dosed to produce an AUC of 9 for 2 cycles followed by intraperitoneal cisplatin at a dose of 100 mg/m^2 plus paclitaxel 135 mg/m^2 IV over 24 hours every 21 days for 6 cycles (Ozols RF, Semin.Oncol. 22[3] suppl 6: 78-83, 1995; Alberts DS, Semin.Oncol. 22[5]Suppl 12: 88-90, 1995). This trial originally had a third arm of intravenous cisplatin/cyclophosphamide, but this arm was closed when the pivotal study of this application was reported to show superior survival for the cisplatin/paclitaxel arm. No results are available to date. Because of the early closure of arm 3, no confirmatory data of the results of GOG 111 will be forthcoming.

Waltzman and colleagues conducted a retrospective analysis of ovarian cancer patients treated at **Memorial Sloan-Kettering Cancer Center** with platinum and paclitaxel as first-line therapy (Waltzman R, Phatak N, Venkatraman E, et al. Proc. ASCO 16: 381a, abstract 1358, 1997). One hundred twenty-two patients were identified; 78 received paclitaxel at a dose of 135 mg/m^2 over 24 hours followed by cisplatin 75 mg/m^2, and 44 received paclitaxel 175 mg/m^2 over 3 hours with carboplatin 300-650 mg/m^2. In the advanced stage group (48 patients), the pathologic CR rate was 33%. Advanced stage suboptimal ovarian cancer patients in this series had a median survival of approximately 2 years. These results are similar to those reported in the pivotal trial. This group also separately reported the toxicity for these patients (Waltzman R, Phatak N, Shapiro F, et al. Proc. ASCO 16: 382a, abstract 1359, 1997). The patients who received carboplatin were older (median age of 66 compared to 55 in the cisplatin group) and had a higher chronic disease score. The hospitalization rate was similar in both groups (9% and 8%); one patient treated with carboplatin died during treatment. Because older patients with comorbid conditions were preferentially treated with carboplatin, this retrospective study does not provide an unbiased account of relative toxicity and gives uncontrolled response data.

11.3 Phase I trials of paclitaxel in combination with carboplatin

Because the results of the GOG 111 study have been widely disseminated, paclitaxel and cisplatin are now considered as "standard" therapy for untreated advanced-stage ovarian cancer in the United States and by some groups in Europe. All current GOG studies use paclitaxel-platinum control arms and explore the relative contributions of cisplatin and carboplatin, the optimal infusion duration of paclitaxel (24 compared with 96 hours), and the role of interim debulking surgery during primary chemotherapy. The following publications discuss the paclitaxel-carboplatin combinations; carboplatin was substituted for cisplatin in the CP combination in order to reduce toxicity.

Investigators from the **European Cancer Center** conducted a Phase I trial of paclitaxel and carboplatin in women with stage III (>3 cm) or stage IV ovarian cancer who had not received prior chemotherapy or radiotherapy (Semin.Oncol. 21[5], suppl 8: 34-38, 1994; follow-up reports by ten Bokkel Huinick et al, Semin.Oncol. 22[3] Suppl 6: 97-100, 1995; Semin. Oncol. 24[1] Suppl 2: S2-31--S2-33, 1997). The starting doses were 125 mg/m^2 of paclitaxel as a 3-hour infusion followed by 300 mg/m^2 carboplatin, repeated every 4 weeks. Paclitaxel doses were escalated by 25 mg/m^2 increments alternating with carboplatin dose increments of 50 mg/m^2 (an increase of 100 mg/m^2 was permitted for the first escalation). The study was performed without the use of colony stimulating factors; these factors could be added when dose-limiting toxicity (DLT) for neutropenia was reached. Once the MTD for the 4-week cycle was established, the MTD for a 21-day cycle was determined, starting 2 dose levels below the MTD for the 28 day cycle. Forty-six patients were entered on study with a PS of 0-2. The MTD for the 28 day cycle was 600 mg/m^2 of carboplatin with 225 mg/m^2 of paclitaxel; the corresponding doses for the 21 day cycle were 550 mg/m^2 and 200 mg/m^2 respectively. The primary toxicity was neutropenia which did not exceed 7 days (the threshold for adding G-CSF); thus, the above doses can be administered without the use of growth factors. Non-hematologic toxicity included grade 3 bone pain and myalgia, grade 2 peripheral neuropathy and hypersensitivity, and grade 2 nausea and vomiting. Twenty of 46 patients achieved a clinical complete response (CR) (43.5%), 9 documented pathologically by second-look laparotomy, and 13 of 46 achieved a partial response (PR) (28.3%) for a response rate of 71.8%. Pharmacokinetic studies were performed on these patients (van Warmerdam LJC, Huizing MT, Giaccone G, et al. Semin. Oncol. 24 [1] Suppl 2: S2-97--S2-104, 1997). The carboplatin AUC was not altered by increasing doses of paclitaxel. Although there was no apparent pharmacokinetic interaction between the two drugs, paclitaxel diminished the thrombocytopenia usually seen with carboplatin by an unknown mechanism.

The **GOG 9202** study was a phase I dose-escalation trial of paclitaxel followed by carboplatin, designed to determine the MTD of this combination with and without G-CSF (Ozols RF, Ann.Oncol. 5[suppl 6]: S39-S43, 1994; Ozols RF, Semin.Oncol. 22[3] suppl 6: 78-83, 1995; Ozols RF, Semin.Oncol. 22[5] Suppl 12: 61-6, 1995; Bookman MA et al, Proc.Am.Soc.Clin.Onc 14: 271, 1995 abstract; Bookman MA et al, J. Clin. Oncol. 14: 1895-1902, 1996). Thirty-five previously untreated patients with suboptimal Stage III-IV ovarian cancer were entered. In part 1 of the trial, patients received a fixed dose of paclitaxel at 135 mg/m^2 over 24 hours with escalating doses of carboplatin. Once the MTD was reached, the same combination was given with G-CSF. In part 2 of the trial, the MTD of carboplatin was used with subsequent dose-escalation of paclitaxel to 175 mg/m^2 over 24 hours with G-CSF; if tolerated, paclitaxel was further escalated to 225 mg/m^2. In part 3, the MTD of carboplatin was administered with paclitaxel at 175 mg/m^2 now given over 3 hours without G-CSF; if tolerated, paclitaxel was escalated to 225 mg/m^2 over 3 hours without G-CSF. In this study, carboplatin was dosed by the Calvert formula; the target AUC for dose level one was 5, with subsequent escalations to 7.5 and 10. Cycles were repeated every 21 days.

The results of part 1 indicated that an AUC of 10 for carboplatin produced dose-limiting hematologic toxicity. Carboplatin dosed to a target AUC of 7.5 with a fixed-dose of paclitaxel at 135 mg/m^2 was tolerated with G-CSF; carboplatin dosed to a target AUC of 5 was tolerated without G-CSF. In part 2, both paclitaxel doses (175 and 225 mg/m^2) could be given with

carboplatin at an AUC of 7.5 with G-CSF support. However, even with growth factor support, dose delays and reductions due to neutropenia were common at a paclitaxel dose of 225 mg/m^2 and occurred during the first cycle. At a dose of 175 mg/m^2, no treatment delays or dose reductions were needed during cycles 1-3, but occurred during cycles 4-6. Thus, G-CSF did not allow escalation of paclitaxel when given as a 24 hour infusion. In part 3, the ability of G-CSF to permit dose-escalation of paclitaxel as a 3 hour infusion was examined. At 225 mg/m^2 of paclitaxel, the use of G-CSF allowed full doses only for cycle 1. All subsequent cycles required dose reductions or delays. The MTD of paclitaxel over 3 hours without G-CSF was defined as 175 mg/m^2 , but G-CSF was needed in cycles 4-6 to avoid dose reductions. The predominant toxicity observed in all parts of the trial was hematologic toxicity. Non-hematologic toxicity was uncommon; neuropathy did not exceed grade 2. In terms of efficacy, 24 patients had measurable disease. There were 16 CR and 2 PR (clinical assessments) for a response rate of 75%. Second-look laparotomy was not required in this trial; 9 patients underwent the procedure, two of whom had no pathologic evidence of disease. This trial examined various schedules of paclitaxel administration, with and without G-CSF, and defined the MTDs for paclitaxel and carboplatin.

Bookman and colleagues reported the results of **GOG 9406**, in which patients with suboptimal stage III-IV disease were treated with a 96 hour infusion of paclitaxel at a dose of 120 mg/m^2 followed by carboplatin given at a dose calculated to produce an AUC of 7.5 (Bookman MA et al, J. Clin. Oncol. 14: 1895-1902, 1996). The use of colony stimulating factors was prohibited on the first cycle, but could be used subsequently if needed. Four patients were treated on this protocol. Two of the 4 patients were admitted for febrile neutropenia on the first cycle. During the second cycle, which was given on day 21, the patients met the hematologic criteria for re-treatment, but subsequently experienced rapid hematologic nadirs. The cycle length was changed to 28 days with improvement in the white blood cell counts. Non-hematologic toxicity did not occur in these patients. No efficacy data is available.

Calvert and colleagues at **Newcastle Hospital** performed a Phase I trial of paclitaxel and carboplatin (Semin.Oncol 22[5] Suppl 12: 91-98, 1995). Carboplatin was administered at a dose calculated to produce an AUC of 7; the dose levels of paclitaxel were 150, 175, 200, and 225 mg/m^2 given as a 3 hour infusion prior to carboplatin. Cycles were repeated every 4 weeks. A classic modified Fibonacci scheme was used. At the time of publication, 11 patients had completed 3 dose levels without reaching dose-limiting toxicity. Short-term neutropenia without fever was the predominant toxicity. Non-hematologic toxicities included myalgia and paresthesia. No efficacy data was reported.

Investigators at the **Institute Gustave Roussy** performed a Phase I trial of escalating doses of paclitaxel as a 3 hour infusion in combination with a fixed dose of carboplatin 400 mg/m^2 IV (Lhomme C, Kerbrat P, Lejeune C, et al. Symposium: Emerging Concepts in Clinical Oncology. Paris, October 1995, pps. 25-6 [abstract]). Two parallel groups were assessed: the first group was treated every 21 days and the second group, every 28 days. The starting dose of paclitaxel was 110 mg/m^2, with subsequent elevations to 135, 150, 175, 200, 225, 250, and 275 mg/m^2 in Group 2; the doses were 175, 200, and 225 mg/m^2 in Group 1. Twenty-seven patients had been entered into group 2 and 23 in group 1. Febrile neutropenia was uncommon (2 episodes in group 2 and 1 in group 1). Neutropenia was common but of short duration. Few dose reductions or delays were necessary. Colony stimulating factors were not administered.

Neuropathy, constipation (grade 3, paclitaxel 110 mg/m^2 q 4 wk), and diarrhea (grade 3, paclitaxel 250 mg/m^2 q 4 wk) were the observed non-hematologic toxicities. The neuropathy occurred as grade 2 in 4 patients (paclitaxel 200 mg/m^2 q 4 weeks, 1 patient; paclitaxel 225 mg/m^2 q 3 weeks, 3 patients) and as grade 3 in 1 patient (paclitaxel 225 mg/m^2 q 3 weeks). The MTD had not been reached at 275 mg/m^2 in group 2 nor at 225 mg/m^2 in group 1.

Zamagni and colleagues at **S. Orsola-Malpighi** Hospital began a Phase I trial of 3 hour paclitaxel with carboplatin in chemotherapy-naive women with Stage III-IV ovarian cancer (Zamagni C, Martoni A, Cacciari N, and Pannuti F. Eur. J. Cancer 31A [Suppl 5]: S109, 1995, abstract 510). The starting doses were paclitaxel 125 mg/m^2 and carboplatin 250 mg/m^2, with escalation of paclitaxel by 25 mg/m^2 alternating with escalation of carboplatin by 50 mg/m^2. At the time of publication, 9 patients had been entered and the third dose level reached without identifying the MTD. Toxicities included alopecia, nausea, vomiting, and neutropenia with no grade 4 episodes.

Bolis **(University of Milan)** published the results of a pilot study in 27 patients with Stage III or IV ovarian cancer who were treated with paclitaxel as a 3 hour infusion followed by carboplatin at 300 mg/m^2(Bolis G, Semin.Oncol. 22[6] Suppl 14: 32-4, 1995; Semin. Oncol. 24[1] Suppl 2: S2-23--S2-25, 1997). The starting dose of paclitaxel was 150 mg/m^2 with subsequent escalations in 25 mg/m^2 increments. Therapy was repeated every 28 days for a total of 6 cycles. Second-look laparotomy was used to verify response. The MTD as prospectively defined in the protocol had not been reached at a dose-level of 250 mg/m^2 of paclitaxel. However, at this dose level, 65% of patients required a dose reduction of paclitaxel because of grade 2 neurotoxicity. Other adverse events included hematologic toxicity that did not require hospitalization or the use of colony-stimulating factors, myalgias, mild cardiac toxicity, and hypersensitivity reactions. Twenty-one patients were evaluable for response. Fourteen complete responses (67%) and 3 partial responses (14%) were confirmed pathologically for an overall response rate of 81%.

Meerpohl and colleagues treated ovarian cancer patients with Stages II through IV with paclitaxel given as a 3 hour infusion at a starting dose of 135 mg/m^2 followed by carboplatin dosed to produce an AUC of 5 (Semin.Oncol. 22[6] Suppl 15: 7-12, 1995; Semin. Oncol. 24[1] Suppl 2: S2-17--S2-22, 1997). Cycles were repeated every 21 days for a maximum of 6 cycles. Paclitaxel was escalated first in 25 mg/m^2 increments to a dose of 210 mg/m^2; at dose levels 5 and 6, paclitaxel was reduced to 185 mg/m^2 and carboplatin was given at an AUC of 6, then 7.5. Thirty patients were entered on the trial. The maximum tolerated doses were paclitaxel 185 mg/m^2 and carboplatin dosed to produce an AUC 6. Dose-limiting toxicity was neutropenia. Peripheral neuropathy was found in 17 of 23 patients evaluable for this toxicity; it was grade 1 or 2 with the exception of one case of grade 4 neurotoxicity at dose level 5. Fourteen patients were evaluable for response, with a 57% response rate.

Siddiqui and colleagues performed a Phase I dose-escalation study of paclitaxel and carboplatin in 12 patients with untreated Stage IIb to IV ovarian cancer (Br.J.Cancer 75[2]: 287-94, 1997). Paclitaxel was administered at a starting dose of 150 mg/m^2 over 3 hours followed by carboplatin at a fixed dose of an AUC of 7. Paclitaxel was escalated by 25 mg/m^2. Pharmacokinetics were performed on 9 of these patients. Hematologic toxicity was common, but did not require hospitalization or the administration of colony stimulating factors. The most

common non-hematologic toxicity was peripheral neuropathy. Responses were reported in 8 of 9 patients who had elevated pre-treatment CA-125 levels (normalization of tumor marker). Six patients had pre-treatment CT scans with measurable disease; 5 of these 6 patients had a radiographic CR and the 6th had a laparoscopically documented CR. No MTD was reported.

The **Hellenic Cooperative Oncology Group** randomized 90 women with previously untreated Stage IIC-IV ovarian cancer to receive paclitaxel 175 mg/m^2 as a 3 hour infusion in combination with either carboplatin administered to produce an AUC of 7 or carboplatin administered to produce an AUC of 7 alternating with cisplatin 75 mg/m^2 (Skarlos DV, Aravantinos G, Kosmidis P, et al. Semin. Oncol. 24 [5] Suppl 15: S15-57--S15-61, 1997). In the alternating platinum regimen, carboplatin was given on cycles 1, 3, and 5; cisplatin was given on cycles 2, 4, and 6. Therapy was repeated every 3 weeks for a total of 6 cycles. Sixty-one patients had measurable or evaluable disease; among these women, a 52% CR rate was observed for carboplatin alone compared to a 39% CR rate for the alternating schedule. The partial response rates were 30% and 18% respectively, for overall responses of 82% and 57%. However, to date there is no significant difference in time to progression or survival between the two groups. No significant differences in toxicity have been observed between the two groups.

Markman and colleagues published a retrospective review of the Cleveland Clinic experience with this two-drug combination (Markman M, Kennedy A, Webster K, et al. Semin. Oncol. 24 [5] Suppl 15: S15-26--S-15-29, 1997). Ninety-two patients (80 ovarian cancer patients and 12 patients with other gynecologic malignancies) received carboplatin designed to produce AUCs of 4 (25 patients), 5 (46 patients), 6 (13 patients), or 7.5 (8 patients); they also received paclitaxel at either 135 mg/m^2 (26 patients) or 175 mg/m^2 (66 patients) as a 3 hour intravenous infusion. The regimen was generally well-tolerated. The common adverse events included alopecia (nearly all patients), hypersensitivity reactions (13% of patients with paclitaxel, 3% of patients with carboplatin), peripheral neuropathy (14%), and bone marrow suppression (21% with grade 3-4 neutropenia; 9% with grades 2-4 thrombocytopenia). Sixty-two of the 80 ovarian cancer patients had elevated CA-125 levels; 54 patients had at least a 50% drop in the CA-125 from baseline, and 46 patients had a greater than 90% decrease.

These Phase I trials have defined the MTD of carboplatin in combination with paclitaxel in a variety of schedules, with and without the use of colony stimulating factors. These trials have provided information on the spectrum of toxicities observed with these schedules, but do not provide efficacy data.

11.4 Phase II/III trials of paclitaxel in combination with carboplatin

Adams and colleagues at **Velindre** Hospital enrolled 22 women with untreated advanced ovarian cancer with paclitaxel 175 mg/m^2 over 3 hours on day 1 followed by carboplatin given at a dose calculated to produce an AUC of 7 mg/ml/min on day 21 (Adams M, Mort D, Coleman R, et al. Eur. J. Cancer 31A [Suppl. 5]: S106, 1995, abstract 496). A total of 5 cycles (cycle=49 days) was given. Toxicities associated with paclitaxel were myalgia in 60% of patients, arthralgia 40%, paresthesias 25%, nausea and vomiting 21%, neutropenia 81% (32% grade 3 and 15% grade 4), and alopecia. Toxicities associated with carboplatin included nausea and vomiting in 66% of patients, neutropenia in 81% (28% grade 3 and 15% grade 4), and thrombocytopenia in

72% (grade 3 23%, grade 4 8%). The complete response rate was 36% and the partial response rate was 36% for an overall response rate of 72%. At 18 months, the observed survival is 74%. Although this regimen was well-tolerated, the sequential nature of the therapy does not permit comparison to other trial results.

Two studies have compared the relative efficacies of carboplatin and cisplatin in combination with paclitaxel. A randomized Phase III study of paclitaxel-cisplatin versus paclitaxel-carboplatin in untreated Stage IIB-IV ovarian cancer patients was conducted by **Neijt** and colleagues (Neijt JP and Lund B, Semin.Oncol. 23 [6] Suppl 15: 2-4, 1996; Neijt JP, Hansen M, Hansen SW, et al. Proc. ASCO 16: 352a, abstract 1259, 1997; Neijt JP, Engelholm SA, Witteveen PO, et al. Semin. Oncol. 24 [5] Suppl 15: S15-36--S15-39, 1997). This study was conducted as a cooperative trial by Dutch, Danish, and Swiss academic centers. Copies of the original protocol, the ASCO abstract, transcript, and slides were provided by the sponsor in the NDA. Two hundred eleven patients were randomized to receive paclitaxel 175 mg/m^2 over 3 hours followed by either cisplatin 75 mg/m^2 or carboplatin calculated to produce an AUC of 5, given every 21 days for 6 cycles. Patients with stable disease received 2 additional cycles of chemotherapy; patients with a partial response were to continue therapy until progression or toxicity, and patients with a complete response were to receive 3 additional cycles of therapy. Interval cytoreduction and second-look laparotomy were permitted but not required. An interim analysis was performed in 182 patients (97 PT, 85 T-CBDCA). The patients were well-balanced by pretreatment characteristics. Eleven percent of the patients on each arm had Stage II disease, and 33% of the PT and 35% of the T-CBDCA patients had residual disease less than 1 cm. In both arms, the median number of cycles administered was 6. However, 26% of the patients in the carboplatin arm were able to continue chemotherapy beyond 6 cycles, compared to 13% in the cisplatin-treated patients. Ninety-six patients were evaluable for clinical response. The response rates were 54% for PT and 51% for T-CBDCA. Pathologic response (complete plus residual microscopic) rates were 16% and 19% respectively. These differences were not statistically significantly different. The primary endpoint of this study is time to progression. At the time of analysis, the median follow-up was less than 1 year, with no significant difference between the two arms. Similarly, there were no observed differences in survival or in CA-125 levels as a surrogate for progression between the two arms.

In terms of toxicity, grade 3-4 granulocytopenia occurred in 76% of the T-CBDCA patients and in 52% of the PT patients (p=0.007). The incidence of fever and infection was low and was comparable in both arms. Emesis (grade 2-3) was more common with PT (64%) than with T-CBDCA (46%) [p=0.03]. The sponsor reports that alopecia was more common with PT as well (100% compared to 94%; p=0.037); however, the reviewer feels this difference is not clinically significant. Peripheral neuropathy of any grade was common (34% compared with 20%; difference not significant); the incidence of grade 3 toxicity was 6% for PT compared with 2% for T-CBDCA. Patients on PT developed grade 2-3 neuropathy in a median of 7 months, compared to 10 months for the carboplatin arm (P=0.001).

The authors concluded that with the available preliminary efficacy data, paclitaxel-carboplatin was comparable to paclitaxel-cisplatin but was associated with less severe neurotoxicity. They also cautioned that this study was not designed as an equivalence trial. Thus, efficacy results will be meaningful only if one regimen is superior to the other. From the

available material for review, it is not clear that there is a difference in the degree of neuropathy associated with the two regimens. The authors reported a difference in the time to development of grade 2-3 neuropathy; a careful review of the primary toxicity data and of the clinical evaluation methods and schedule will be necessary to confirm this statement. This trial will not be sufficient to establish comparability of cisplatin and carboplatin in combination with paclitaxel as first-line therapy of ovarian cancer.

du Bois and colleagues conducted a trial of paclitaxel-cisplatin versus paclitaxel-carboplatin in untreated Stage IIb-IV ovarian cancer patients in the AGO, a cooperative group of German institutions (du Bois A, Nitz U, Schroder W, et al. Proc. ASCO 16: 357a, abstract 1272, 1997; du Bois A, Luck HJ, Meier W, et al. Semin. Oncol. 24 [5] Suppl 15: S15-44--S15-52, 1997). Randomization was stratified by optimal versus suboptimal debulking. The sponsor submitted the original protocol, the ASCO abstract, and a copy of the poster in the NDA. An interim analysis was presented at ASCO. Paclitaxel was given at a dose of 185 mg/m^2 over 3 hours; the cisplatin dose was 185 mg/m^2 and carboplatin was given at a dose calculated to produce an AUC of 6. Cycles were repeated every 3 weeks for 6 cycles. Supportive therapy with G-CSF was permitted after an episode of febrile neutropenia, infection, or prolonged neutropenia as defined in the protocol. Patients were not required to undergo second-look laparotomy. The primary objective of the study is to compare PFS between the two arms. A sample size of 660 patients is planned, and accrual was anticipated to be complete in 10/97. An interim analysis of 550 evaluable patients was performed. Patients with optimal debulking had a higher incidence of PS 0, were more likely to have Stage II disease, and were more likely to have non-measurable disease (50% had no residual disease) than patients with suboptimal debulking. Information on dosing was available for 345 patients (170 PT, 175 T-CBDCA). The dose level of cisplatin was maintained over 6 cycles, while the mean dose of carboplatin decreased from 400 mg/m^2 to 370 mg/m^2. Treatment delays were more common with carboplatin than cisplatin (13% v. 9%).

Efficacy data remains blinded. Overall, there are 54 patients with measurable disease at baseline. Among the patients with measurable disease, 22 patients have had a cCR (41%) and 20 (37%) a PR. Review by the data safety monitoring committee did not identify a reason to stop the study early.

Quality of life data was obtained during this study, and a preliminary report in 192 patients was presented for cycle 3 relative to cycle 1 (92 PT, 100 T-CBDCA). The sponsor reports that the data indicate a slightly better outcome for patients on T-CBDCA. However, the curves differ from each other by less than 4%, a clinically insignificant difference. Data from all patients with extended follow up will be needed to evaluate any differences in quality of life.

Myelosuppression was more common with carboplatin (21% grade 3-4 compared to 7% with PT). However, there was no difference in the incidence of fever or infection. Emesis was more common with PT than with the carboplatin-containing arm (18% versus 5%); constipation was more common with T-CBDCA than with PT (16% and 10% respectively). Other toxicities were comparable. Neurologic toxicity overall was similar in the two arms, but grade 2-3 neurotoxicity had a more rapid onset with PT than with T-CBDCA (cycle 2 versus cycle 3; $p < 0.05$).

The authors concluded that administration of either regimen was feasible and safe; efficacy comparisons will require longer follow up.

This trial was designed to evaluate the relative efficacy of cisplatin and carboplatin in combination with paclitaxel. Its sample size will permit a comparison of the two regimens, unlike the Neijt study. To date, there is no information to support the assertion that carboplatin plus paclitaxel is as effective as cisplatin plus paclitaxel.

12.0 Reviewer Summary of NDA 20-262/S-026

The basis for approval of this supplemental NDA is GOG 111, a prospective randomized trial of cisplatin and paclitaxel versus cisplatin and cyclophosphamide as first-line therapy in patients with suboptimally debulked Stage III and Stage IV ovarian cancer. The PT combination resulted in a significant improvement in TTP and OS that was of both statistical and clinical significance. This difference was observed in the FDA analysis of the data as well. The two analyses are summarized below:

Table 28. FDA and sponsor's efficacy analyses

Efficacy Parameter	BMS Analysis			FDA Analysis		
	Cisplatin-paclitaxel	Cisplatin-CTX	p-value	Cisplatin-paclitaxel	Cisplatin-CTX	p-value
Median survival	35.5 mo	24.2 mo	0.0002	35.5 mo	24.2 mo	0.0002
Median progression-free survival	16.6 mo	13.0 mo	0.0008	16.8 mo	13.4 mo	0.006
Overall clinical response rate	68/113 (60%)	64/127 (50%)	0.153	70/113 (62%)	61/127 (48%)	0.04

The toxicity profile was consistent with previously documented adverse events of paclitaxel. Despite the observed toxicity, patients on PT were more likely to complete the planned therapy (86% versus 78%) and received more dose-intense therapy, indicating the tolerability of the regimen relative to PC.

It is difficult to understand how PT can produce significant improvements in TTP and OS without significantly affecting response rate. It is likely that the lack of significance is due to the difficulty in assessing response in ovarian cancer patients. A recent publication by Thiesse and colleagues outlined reasons for interobserver variability in response assessment (Thiesse P. Ollivier L. Di Stefano-Louineau D, et al. J. Clin. Oncol. 15: 3507-3514, 1997); many of these points apply to the current trial. The authors listed the following difficulties:

- Measurement of nonmaximal or nonperpendicular diameters
- Intraobserver and interobserver variability
- Technical considerations

- ♦ Timing of IV contrast injection on CT scan
- ♦ Incorrect selection of a CT slice for measurement based on anatomic landmarks, which move with respiration, rather than on the slice with the maximal axial tumor diameters
- ♦ Difficulty of measuring tubular-like lesions
- ♦ Need for precise measuring implements when working with film images

• Errors in target selection

- ♦ Inappropriate use of cystic or calcified masses as tumor markers
- ♦ Difficulty of assessing lesions in the presence of malignant effusions
- ♦ Permanently modified organ morphology due to tumor involvement, regardless of tumor regression
- ♦ Absence of significant contrast between the tumor and adjacent structures
- ♦ Enlargement of tiny tumor masses not designated as the followable lesion
- ♦ New lesions that appeared outside the targeted imaging areas

• Intercurrent illness mistaken for tumor

Ovarian cancer is difficult to assess because of its sheet-like growth pattern and associated effusions; its growth pattern contributes to the diagnosis of ovarian cancer at a late stage in the majority of patients. Its natural history, the need for precise imaging and measurement, and the recent surgery in ovarian cancer patients at the time of baseline assessment confound the evaluation process. Despite these limitations, there are suggestions that PT probably does affect response rate. First, the response rates for PT were consistently although not significantly higher than with PC. Second, a different measuring system by different observers (McGuire and colleagues) yielded clinical response rates of 73% and 60% respectively, a significant difference. Third, the response rates of 57% PT and 43% PC in the EORTC study were comparable to the 60% and 50% results reported for GOG 111 by the sponsor; the GOG 132 study reported a 72% clinical response rate for the PT arm. All of these results are concordant.

Because of the difficulties in reliably and reproducibly measuring response, time to progression and survival have been more commonly used as endpoints in oncology trials. The progression free survival in GOG 111 was 16.6 months for PT and 13.0 months for PC. In the EORTC study, the values were 16.6 months and 12 months respectively. Both the absolute values and the relative difference in PFS are comparable between the two studies. Survival measurements were 35.5 months for PT and 24.2 months for PC in GOG 111, comparable to the 35 months and 25 months observed in the EORTC study. These results are summarized in the following table:

Table 29. Results of GOG 111 and the EORTC Intergroup trial

Efficacy Parameter	GOG 111			EORTC#		
	Cisplatin-paclitaxel	Cisplatin-CTX	p-value	Cisplatin-paclitaxel	Cisplatin-CTX	p-value
Clinical complete response	40/113 (35%)	32/127 (25%)	0.092	58/149 (39%)	40/151 (26%)	
Clinical partial response	28/113 (25%)	32/127 (25%)		27/149 (18%)	25/151 (17%)	
Overall clinical response	68/113 (60%)	64/127 (50%)	0.153	85/149 57%	65/151 43%	0.01
Complete pathologic response	42/196 (21%)	35/214 (16%)	0.196	33/70 (47%)	13/55 (24%)	
Microscopic residual disease	25/196 (13%)	8/214 (4%)				
Overall pathologic response rate	67/196 (34%)	43/214 (20%)	0.001	46/70 (66%)*	23/55 (42%)*	
Median progression free survival	16.6 months	13.0 months	0.0008	16.6 months	12 months	0.0001
Median survival	35.5 months	24.2 months	0.0002	35 months	25 months	0.001

* Included complete response plus "macroscopic CR"

Trial results from the literature only; primary data not submitted for review

These two trials provide independent confirmation of the efficacy of paclitaxel and cisplatin as first-line therapy of advanced stage ovarian cancer. In the reviewer's opinion, paclitaxel should be approved for this indication.

Signatures:

/S/

Susan Flamm Honig, M.D.
Medical Reviewer

/S/

3/25/04

Grant Williams, M.D.
Team Leader

cc: HFD-150/
Division files
sNDA 20-262/S-026
HFD-150/DIV FILES
/S. Honig
/G. Williams
/D. Spillman

Appendix A. Patient Evaluation Flow Sheet (TAXOL protocol CA129-022; Page 10, GOG protocol 111; Page 218, volume 3 of NDA 20-262)

7.0 STUDY PARAMETERS AND SERIAL OBSERVATIONS

7.1 Tests and Observations

Tests and Observations	Prior to Study	Weekly	During Treatment		Post-treatment	
			Prior to each course	Every 2 cycles	6 wks after completion of therapy	Q 3 mo after completion of therapy
History	X		X			X
Physical Exam	X		X			X
Tumor measurements	X		X			
Performance status	X		X			
Hgb/Hct	X	X	X			
WBC	X	X	X			
Differential	X	X	X			
Platelet count	X	X	X			
Creatinine	X		X			X
Bilirubin	X		X			X
SGOT	X		X			X
Alkaline phosphatase	X		X			X
Ca/PO4/Mg	X		X			X
CA-125	1					X
CXR	X		2			
ECG	X		2			
Urinalysis	X		2			
CT abdomen/pelvis	6			4	5	
Audiogram	2		2			
Reassessment laparotomy					3	
Neuro assess	X				7	

1- Optional but if patient registered for extra points with level drawn it must be repeated prior to each course.
2- As clinically indicated.
3- Mandatory in patient entered as non-measurable if CA-125 < 100. Mandatory in all patients who are in clinical complete remission (except Stage IV patients).
4- If CT is used to follow lesion, repeat scans must be done every 2 courses
5- Mandatory if no 2nd look done
6- Postoperative CT scan is mandatory. Follow-up study is indicated if postoperative scan shows measurable disease if no 2nd look.
7- 4-6 weeks after last treatment

NOTE: THE ABOVE GUIDELINES FOR FOLLOW-UP STUDIES, WHILE REQUIRED FOR PROPER MEDICAL CARE OF THE PATIENT, RECOGNIZE THAT CIRCUMSTANCES MAY NECESSITATE MINOR DEVIATIONS FROM TIME TO TIME, WHICH ARE PERMISSIBLE WITHIN THE JUDGEMENT OF THE RESPONSIBLE INVESTIGATOR OR HIS DESIGNATED REPRESENTATIVE.

Appendix B. Oncologic Drugs Advisory Committee questions and vote

sNDA 20-262/SE1-026: Taxol™ (paclitaxel), Bristol-Myers Squibb Pharmaceutical Research Institute

Proposed Indication: First-line or second-line therapy for the treatment of advanced carcinoma of the ovary

Study Design:

One multicenter trial, GOG 111 (CA139-022), was submitted for review. This study was a prospective 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 endpoint was progression-free survival; survival was the secondary endpoint; response was a tertiary endpoint. The efficacy findings from the study report and from the FDA analysis are presented below:

Table 1. GOG 111 Efficacy

Efficacy Parameter	BMS Analysis			FDA Analysis		
	Cisplatin-paclitaxel	Cisplatin-CTX	p-value	Cisplatin-paclitaxel	Cisplatin-CTX	p-value
Median survival	35.5 mo	24.2 mo	0.0002	35.5 mo	24.2 mo	0.0002
Median progression-free survival	16.6 mo	13.0 mo	0.0008	15.7 mo	12.6 mo	0.002
Overall clinical response rate	68/113 (60%)	64/127 (50%)	0.153	70/113 (62%)	61/127 (48%)	0.04

Note: The FDA TTP analysis was updated after ODAC; the review reflects the correct figures for TTP: 16.8 months for PT and 13.4 months for PC

Question 1. Is trial GOG 111 an adequate and well-controlled trial demonstrating the efficacy and safety of paclitaxel in combination with cisplatin in patients with advanced stage ovarian cancer?

Yes - 9 No - 0

Question 2. Should paclitaxel in combination with cisplatin be approved for the first-line treatment of patients with advanced ovarian cancer?

Yes - 9 No - 0

Discussion: The studies and their analyses were all considered to be of very high quality and the clinical response of paclitaxel and cisplatin showed a significantly improved clinical response over the cyclophosphamide and cisplatin control arm.

Appendix C. Labeling Review

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:	10/7/98
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 chcek 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 dated 3/10/98, the sponsor agreed to retain the original statement.

Page 4:

The sponsor's efficacy table is as follows:

Efficacy in the Phase 3 First-line Ovarian Carcinoma Study

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

Efficacy in the Phase 3 First-line Ovarian Carcinoma Study

These revisions are based on the reviewer's analysis of clinical response. The sponsor was informed of these differences in a facsimile dated 2/6/99. The sponsor replied on 2/25/98; review of these responses is incorporated into the above revisions.

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

cyclophosphamide/cisplatin, rather than respectively.

The rate of all hypersensitivity reactions on taxol/cisplatin should be

The rate of any symptoms from peripheral neuropathy for taxol/cisplatin should read

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

B. Additions

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 hour infusion. The Division has not reviewed data utilizing a hour infusion.

For the 120-day Safety Update Review, see 3-25-98 Medical Officer Review .

CENTER FOR DRUG EVALUATION AND RESEARCH

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

CHEMISTRY REVIEW(S)

APR - 2 1998

CHEMISTRY REVIEW

Division of Oncology Drug Products

Labeling Review

TYPE AND NUMBER OF APPLICATION : NDA 20-262/S-026 & S-028
LABELING SUB. : 2/19/98 (S-026) & 11/18/97 & 1/9/98 (S-028) ASSIGNED DATE: 3/27/98

STATUS OF APPLICATION: Active
NAME OF SPONSOR: **Bristol-Myers Squibb**
PRODUCT NAME: Taxol (paclitaxel) Injection
Proprietary: TAXOL®
Nonproprietary: paclitaxel
CHEMICAL STRUCTURE:

DOSAGE FORM, STRENGTH, AND ROUTE OF ADMINISTRATION:
Intravenous Injection, 6 mg/mL, 30 mg (5 mL) , 100 mg (16.7 mL),

PROPOSED MARKETING STATUS: Rx

PHARMACOL. CATEGORY/ INDICATION:
antimicrotubule agent, antitumor.

Package Insert:

Comments: NDA 20-262/S-013 requested the change in storage temperature to controlled temperature This change was supported by stability data. The range °C is within the temperature range provided in Supplement No. 13. From a CMC view point, this new range is acceptable.

The statement in the original package insert is replaced by

Comments: The following statement

remain unchanged. This statement is of importance, since it further explains the state of the components in the vial as it relates to stability. From a CMC point of view, this change is acceptable.

Storage:
The temperature range is changed compared to the approved package insert, from to

Comments: Please see comments in the **Stability** section.

HOW SUPPLIED

/S/ 4/2/98
Review Chemist, DNDC I, (HFD-150)

cc:
ORIG. NDA 20-262/S-026 & S-028
HFD-150/Div. File
HFD-150/JJee/ 4-02-98
HFD-150/RWood
HFD-150/DSpillman
R/D Init. by: 4-2-98
Doc. #: 20262s28.lab

SPILLMAN

FEB - 3 1998

Chemistry Manufacturing Controls Review

Labeling Review

NDA:	20-262 / SE1-024 & 20-262/SE1-026
Product:	Taxol (paclitaxel)
Applicant:	Bristol-Myers Squibb
Date of Submission:	June 30, 1997 & October 7, 1997
Stamp Data:	August 19, 1997
Date of Review:	February 2, 1998
Material Reviewed:	TAXOL® (paclitaxel) for the Treatment of Advanced Non-Small Cell Lung Cancer (S-024, Vol. 1.2 and 2.2) & Ovarian Cancer (S-026, Vol. 1.2 and 2.2))
Other Documents:	NDA 20-262 and its supplements

Drug Substance

Drug substance by the same manufacturer was approved more recently on March 5,1997.

Manufacturer and Site

BMS-Swords and BMS Syracuse.

Method of Synthesis

More recently submitted in DMF

Specifications and Methods

More recently submitted in Supplement 17.

Stability Data.

Submitted in Supplement 17.

Drug Product

Refer to NDA 20-262 and its supplements.

Environmental Assessment (EA)

Found satisfactory by N. Sager on 11/6/97.

Labeling:

Submitted on Vol. 1 under section of Labeling. Description, Dosage and Administration, Preparation and Administration, Preparation for Intravenous Administration, Stability, How Supplied, and Storage sections were not revised.

Conclusions and Recommendations.

No new CMC information is submitted in these supplements. Reference for CMC would have to be from previous approved application/ supplements. These reviews mainly concentrate in the EA and Labeling revisions.

/S/

2/2/98

Josephine M. Jee, Review Chemist, HFD-150, DNDC I

/S/ 2-3-98

Rebecca H. Wood, Ph.D., Chemistry Team Leader, HFD-150, DNDC I

cc:
NDA 20-262/SE1-024 & SE1-26
HFD-150/Division File
HFD-150/JJee/ 2-2-98
HFD-150/RWood
HFD-150/DSpillman
F/T by JJee/ 2-2-98
R/D by:
File: 20262s24.lab

CENTER FOR DRUG EVALUATION AND RESEARCH

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

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

Spillman

NOV - 6 1997

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

TAXOL®

(paclitaxel)

INJECTION

NDA 20-262/S-026

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ONCOLOGY DRUG PRODUCTS
(HFD-150)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-262/S-026

TAXOL® (paclitaxel) INJECTION

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not, individually or cumulatively, have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their supplemental new drug application for **TAXOL® (paclitaxel) INJECTION, Bristol-Myers Squibb Company** has prepared an environmental assessment in accordance with 21 CFR Part 25 (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

The supplemental application provides for a new use of TAXOL® as a first line treatment of ovarian cancer. The product is currently approved for use in the treatment of metastatic ovarian cancer after failure of first-line or subsequent chemotherapy and in the treatment of several other forms of cancer. The drug substance will be manufactured by the applicant in Swords, Ireland and Syracuse, New York. Extraction of the starting material from the biomass is performed in Italy. The drug product will be manufactured by the applicant in Mayaguez, Puerto Rico or Latina, Italy. The finished drug product will be used in hospitals and clinics.

The drug substance, paclitaxel, is produced by a semi-synthetic process. The starting material, 10-deacetyl baccatin III, is obtained from either *Taxus baccata* (European yews) or *Taxus wallichiana* (Himalayan yews). Biomass from *Taxus baccata* is collected from plants cultivated in public and private parks and gardens as well as from plantations in Europe. Biomass from *Taxus wallichiana* has been collected in India from wild plants or those cultivated on plantations. Future collection of biomass from *Taxus wallichiana* is not planned unless there is a supply problem with *Taxus baccata* and if performed, collection will only occur from plantation sources. In either case (*Taxus baccata* or *Taxus wallichiana*), renewable resources are used in that only twigs and needles are harvested by supervised, controlled pruning of the plants.

Taxus wallichiana is listed in Appendix II of the Convention on International Trade in Endangered Species of Wild Flora and Fauna (CITES). Collection of *Taxus wallichiana* biomass used by the applicant occurred prior to the species being listed in CITES. The applicant has stated that the appropriate CITES documentation is obtained from the regional authorities in order to export the material collected from *Taxus wallichiana*. Example CITES documentation was provided to support this statement.

Paclitaxel and/or its metabolites may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites. Ecotoxicity data previously submitted by the applicant indicates that, at the expected environmental concentration from use based on all treatement indications, no adverse effects on environmental organisms should be observed.

Disposal in the United States may result from returned, recalled or expired goods and user disposal of empty or partly used product and packaging. Disposal of pharmaceutical waste in the U.S. by the manufacturer will be handled consistent with EPA regulations and permitted disposal facilities will be used. Returned, recalled or expired goods will be sent by the manufacturer to a licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic procedures.

Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

11/1/97
DATE

/S/

PREPARED BY
Nancy B. Sager
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

11-6-97
DATE

/S/

CONCURRED
Eric B. Sheinin, Ph.D.
Director, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Attachments: Environmental Assessment

c.c. original to NDA 20-262/S-026 through DSpillman/HFD-150 /DNFiles
HFD-357/EA File NDA #20-262/S-026 /DSpillman
HFD-357/Docket File /J.Lee
HFD-205/FOI COPY
OCC (to N. Sager for distribution)

SPILMAN

REVIEW

NOV - 6 1997

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-262/S-024/~~S-026~~

TAXOL®

(paclitaxel)

INJECTION

DIVISION OF ONCOLOGY DRUG PRODUCTS (HFD-150)

CENTER FOR DRUG EVALUATION AND RESEARCH

DATE COMPLETED: November 1, 1997

SUMMARY:

A FONSI is recommended.

EAs have been submitted for efficacy supplements S-024 (non-small cell lung cancer) and S-026 (first line ovarian cancer). A Federal Register notice, Paclitaxel Drug Products; Environmental Information Needed in New Drug Applications, Abbreviated New Drug Applications, and Investigational New Drug Applications, was published in the November 18, 1996 Federal Register [61 FR 58694]. This notice was issued to clarify the environmental information that must be submitted to CDER for drug products containing paclitaxel derived from Pacific Yew trees. The supplemental applications to approved NDA 20-262 cannot be categorically excluded under 21 CFR § 25.31(b) because paclitaxel derived from the bark of Pacific Yew trees (*Taxus brevifolia*) was used in a clinical trial that provides underlying data to support the application.

The EAs submitted are essentially identical to the environmental assessment information submitted in support of NDA 20-262/S-022 for which a FONSI was issued on August 4, 1997. Neither the total use estimate (120 kg) nor biomass source information has changed.

Toxicity of this compound to environmental organisms is not a concern. The expected introduction concentration into the environment for all approved and proposed uses (no consideration of metabolism or depletion mechanisms) is more than 4 orders of magnitude lower than the concentration of paclitaxel observed to cause effects in environmental organisms (acute toxicity testing/ laboratory studies).

The relevant environmental issue relating to this application is whether any increase in harvesting that may occur as a result of the approval for this new indication will have a significant environmental impact. The starting material, 10-deacetyl baccatin III, is obtained from either *Taxus baccata* (European yews) or *Taxus wallichiana* (Himalayan yews). Biomass from *Taxus baccata* is collected from plants cultivated in public and private parks and gardens as well as from plantations in Europe. Biomass from *Taxus wallichiana* has been collected in India from both wild plants or those cultivated on plantations. Future collection of biomass from *Taxus wallichiana* is not planned unless there is a supply problem with *Taxus baccata* and if performed, collection will only occur from plantation sources. In either case (*Taxus baccata* or *Taxus wallichiana*), renewable resources are used in that only twigs and needles are harvested by supervised, controlled pruning of the plants.

Taxus wallichiana is listed in Appendix II of the Convention on International Trade in Endangered Species of Wild Flora and Fauna (CITES). Listing in CITES does not prohibit harvesting but provides for heightened oversight of harvesting and export/import of material. Local officials, the Ministry of Forests and the Department of Forests, oversee the harvesting of the needles and twigs by issuance of a "Harvesting" permit. It is stated that IDENA obtains relevant documentation, as required by CITES, to export the biomass to Italy for further processing. CITES documentation was provided to support this statement. Collection of *Taxus wallichiana* biomass occurred prior to the species being listed in CITES and if any more biomass is collected it will be from plantations.

No significant environmental impact is anticipated based on (1) the supervised, controlled harvesting of the biomass, (2) the use of a renewable source of biomass (pruned twigs and leaves), (3) future biomass collection is planned only from cultivated sources, and (4) the information indicating that there is/has been appropriate government oversight, when necessary, of the harvesting.

ENVIRONMENTAL ASSESSMENT

1. Date:

EA dated: 9/4/97 (S-024)
EA dated: 9/5/97 (S-026)

CSO: Diane Spillman

2. Name of applicant/petitioner:

Bristol Myers Squibb Company

3. Address:

P.O. Box 4000
Princeton, NJ 08543-4000

Note:
The environmental information provided in support of NDA 20-262/S-024 (non-small cell lung cancer) and S-026 (first line ovarian cancer) is essentially identical to the information provided and reviewed for NDA 20-262/S-022. A FONSI was issued for NDA 20-262/S-022 on August 4, 1997. BMS, on October 27, 1997, provided an outline of the differences among the EA information provided in the supplements. The changes are mostly administrative. Neither the total use estimate (120 kg) nor biomass source information has changed. Only the differences between the new supplements and S-022 are documented in this review. Refer to the reviews for S-022 for the detailed environmental review.

1. The EAs have been revised to indicate the new indications that are proposed.

Adequate.

2. Information has been added for an alternate manufacturing site for the drug product (Latina, Italy). A certification of environmental compliance has been provided in a confidential appendix. In the past the applicant would have been asked to move this type of information to a non-confidential appendix. However, since under the new EA regulations manufacturing site information is not needed unless there is an extraordinary circumstance (and there is no evidence of an extraordinary circumstance), inclusion of

this information in a confidential appendix will not be cited as a deficiency.

Adequate.

3. Information that BMS submitted as an addendum to the EA for S-022 has been incorporated into the text.

Adequate.

Endorsements:

HFD-357/NBSager 11/1/97

HFD-800/EBSheinin 11-6-97

CC: Original to NDA 20-262/through PM: D. Spillman/HFD-150
HFD-150 / Div File / D. Spillman / J. Lee
EA File 20262

Y:\WPFILE\MICHELLE\SAGER\EA\REVIEWS\20262S24.26

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

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

PHARMACOLOGY REVIEW(S)

See the 2-3-98 Pharm/Tox & the 2-3-98 & 4-2-98 Chemistry Labeling Reviews under the Pharmacology and Chemistry Review tabs.

Spillman

FEB - 3 1998

DIVISION OF ONCOLOGY DRUG PRODUCTS, HFD-150
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
NDA Supplemental Indication

SNDA Nos. 20,262/SE1-024
20,262/SE1-026

Date(s) of Submission: June 30, 1997
October 7, 1997

Information to be Conveyed to Sponsor: YES

Reviewer: Margaret E. Brower, Ph.D.

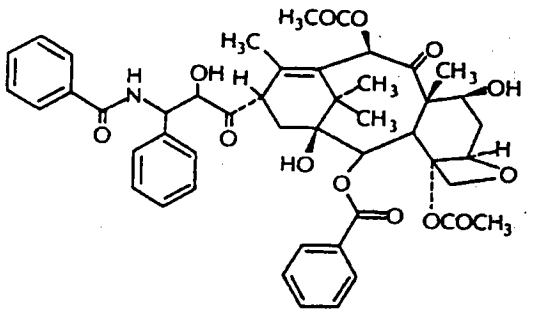
Date Review Completed: February 3, 1998

Sponsor: Bristol-Meyers Squibb
Wallingford, CT

Drug Name: Primary: Paclitaxel
Other names: Taxol

Chemical Name: 5β, 20-Epoxy-1, 2α, 4, 7β, 10β, 13α-hexahydroxytax-11-en-9-one 4, 10-diacetate 2-benzoate 13 ester with (2R,3S)-N-benzoyl-3-phenylisoserine

Structure:



CAS Number: 33069-62-4

Molecular Weight and formula: 853.9, $C_{47}H_{51}NO_{14}$

Related INDs/NDAs:NDA 20-261

Pharmacologic Class: cytotoxic antineoplastic agent

Indication: Non-small cell lung cancer, 1st line treatment of ovarian cancer

Comments:
1. The proposed label for the NSCLC indication for Taxol

These changes should be incorporated.

2. Since specific clinical data on paclitaxel overdosing are available, these data should be incorporated into the overdosage section of the label. If these data are not available, preclinical data should be added.

3. The drug label has been reviewed. All other pharmacology/toxicology data have been previously reviewed.

/S/

Margaret F. Brower, Ph.D.

2/3/98
Date

cc:
NDAORIG. and Div.File
HFD-150
/PAndrews
/MBrower
/DSpillman

2/3/98

CENTER FOR DRUG EVALUATION AND RESEARCH

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

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA#: 20-262/SE1-026

Applicant: Bristol-Myers Squibb

Name of Drug: Taxol(paclitaxel)

Indication: Primary treatment of ovarian cancer

Documents Reviewed: Vols. 3 - 12 of submission dated October 7, 1998

Medical Officer: Susan Honig, M.D.

Statistical Issue:

(I) Covariate adjustment in logistic and Cox regression

The selection of potential prognostic factors among efficacy variables was inconsistent. Residual diameter was selected as a potential prognostic factor using TTP and survival. Residual diameter was not selected as a prognostic factor using the objective response endpoint. Liver function was selected as a potential prognostic factor using objective response. It was not selected using either TTP or survival. The treatment effect was statistically significant between the two treatment groups in favor of Taxol for the TTP and survival endpoints. The treatment effect was statistically significant in patients with small residual diameter favoring the Taxol arm and not statistically significant in patients with large residual diameter for the TTP endpoint. The treatment effect was statistically significant in patients with small residual diameter favoring the Taxol arm and marginally statistically significant in patients with large residual diameter for the survival endpoint.

In Section 1 we give a brief background on Taxol. Section 2 contains a description of the pivotal study CA139-022. Section 3 contains the efficacy results and this reviewer's comments. Section 4 contains the conclusions regarding this application. An Appendix is included at the end of this review with tables and graphs regarding some of the efficacy endpoints.

I. Background

In this NDA the sponsor seeks approval of Taxol in combination with Cisplatin for the treatment of patients with advanced ovarian cancer. Taxol will be administered at a dose of 135 mg/m2 as a 24 hour infusion followed by Cisplatin on day 2 at a dose of 75 mg/m2.

II. Description of Study

Protocol CA139-022:

Study Design:
Study CA139-022 "was a prospective multicenter, open label, randomized phase III trial comparing TAXOL/Cisplatin versus Cyclophosphamide/Cisplatin in patients with previously untreated, advanced ovarian cancer [in patients with suboptimal Stage III and Stage IV ovarian cancer]." The study was stratified by institution and clinical measurability of disease.

Number of Patients:
Four hundred and ten patients were randomized into the trial (196 in the treatment arm, 213 in the control arm). One patient in the cyclophosphamide died before receiving a study medication.

Diagnosis and Eligibility:
Women with pathologically verified FIGO Stage III epithelial ovarian cancer after suboptimal surgery (>1 cm residual mass) or FIGO stage IV disease are eligible. They could have clinically measurable or nonmeasurable disease with no previous chemotherapy or radiation for ovarian cancer.

Dose, Route, and Schedule:
Both the standard and experimental therapies were repeated every 21 days or when hematologic and non-hematologic recovery was documented. Dose reductions based on Grade IV hematologic toxicity were required for both treatment arms.

Treatment of duration:
Patients received a total of six cycles of therapy unless there was progression of disease or toxicity.

Efficacy Variables:
The primary endpoint of this study was time to progression, and the secondary endpoints were response rates, duration of clinical

and pathological response, and survival. This study was powered (n=360) "to detect an increase of 40% in the median time to progression based on a median of 10.3 months and 14.4 months for patients with measurable and non-measurable disease respectively" with 84.6% of power at one-sided 0.05 type I error.

III. Efficacy Results and Comments:

Tumor Response:

Reviewer's Table 3.1 shows the number of patients in each treatment group with respect to measurable disease. In the Taxol/Cisplatin group, 113 (57.7%) patients had measurable disease and 83 (42.3%) patients had non-measurable disease. In the Cyclophosphamide/Cisplatin group, 127 (59.3%)patients had measurable disease and 87 (40.7%) patients had non-measurable disease.

Reviewer's Table 3.1: Sample Size with respect to Measurability

	Taxol/ Cisplatin	Cyclophosphamide/ Cisplatin
Measurable	113 (102, 11)*	127 (117, 10)**
Non-Measurable	83	87
Total	196	214

*102 and 117 are the number of evaluable patients in Taxol/Cisplatin and Cyclophosphamide/Cisplatin groups, respectively.
**11 and 10 are the number of unevaluable patients in Taxol/Cisplatin and Cyclophosphamide/Cisplatin groups, respectively.

Reviewer's Table 3.2 shows the number of responders (both complete and partial responders) among patients with measurable disease in each treatment group.

Reviewer's Table 3.2: Number of Responders in Each Treatment Group (Measurable Patients)

	Taxol/ Cisplatin	Cyclophosphamide/ Cisplatin
# of Responders	68	64
Complete	40	32
Partial	28	32

Reviewer's Table 3.3 shows the overall and complete response rates in each treatment group among measurable patients. The difference in the overall response or complete response rates between the two treatment groups was not statistically significant at the 0.05 level.

Reviewer's Table 3.3: Response Rate in Each Treatment Group (All Measurable Patients)

	Taxol/ Cisplatin (N=113)	Cyclophosphamide/ Cisplatin (N=127)
Overall Response Rate	60.2% (95% CI: 50.5% - 69.3%)	50.4% (95% CI: 41.4% - 59.4%)
	P-value*:0.153	
Complete Response Rate	35.4% (95% CI: 26.6% - 45.0%)	25.2% (95% CI: 17.9% - 33.7%)
	P-value*:0.092	

*P-values were derived by Fisher's two tailed exact test.

Reviewer's Table 3.4 shows the overall and complete response rates in each treatment group among both measurable and evaluable patients. Neither difference was statistically significant at the 0.05 level.

Reviewer's Table 3.4: Response Rate in Each Treatment Group (All Measurable and Evaluable Patients)

	Taxol/ Cisplatin (N=102)	Cyclophosphamide/ Cisplatin (N=117)
Overall Response Rate	66.7% (95% CI: 56.6% - 75.7%)	54.7% (95% CI: 45.2% - 63.9%)
	P-value*:0.074	
Complete Response Rate	39.2% (95% CI: 29.7% - 49.4%)	27.4% (95% CI: 19.5% - 36.4%)
	P-value*:0.083	

*P-values were derived by Fisher's two tailed exact test.

The sponsor investigated the effect of potential prognostic factors on the response rate such as age, performance status, stage, residual tumor diameter, histological grade, cell type, and baseline liver function. This reviewer confirmed the results

presented on sponsor's Table 25. The sponsor performed univariate analysis for each factor (sponsor's Table 26). Among these factors, liver function was found to be a potential prognostic factor. This reviewer confirmed this result. The sponsor also applied a stepwise procedure without including treatment in the model to identify potential prognostic factors. Only liver function was found to be statistically significant.

Reviewer's Table 3.5 shows the results from logistic regression analysis adjusting for liver function, which confirms the sponsor's results. The treatment effect of Taxol/Cisplatin over Cyclophosphamide/Cisplatin was not statistically significant at the 0.05 level.

Reviewer's Table 3.5: Results from logistic regression analysis of objective response adjusting for liver function (All Measurable Patients)

	Odds Ratio	95%CI	p-value
Trt effect*	1.486	0.887 - 2.490	0.133

Trt effect* is the treatment effect of Taxol/Cisplatin over Cyclophosphamide/Cisplatin.

This reviewer applied stepwise logistic regression to select possible prognostic factors without including treatment in the model **for the complete responders** among all measurable patients. Two potential prognostic factors, liver function and residual tumor diameter, were selected. Reviewer's Table 3.6 shows this result.

Reviewer's Table 3.6: Results from logistic regression analysis of complete responders adjusting for liver function and residual tumor diameter (All Measurable Patients)

	Odds Ratio	95%CI	p-value
Trt effect*	1.779	1.000 - 3.164	0.050

Trt effect* is the treatment effect of Taxol/Cisplatin over Cyclophosphamide/Cisplatin.

The treatment effect of Taxol/Cisplatin over Cyclophosphamide/Cisplatin with respect to complete response rate among measurable disease patients was found to be marginally statistically significant (P-value = 0.05).

Reviewer's Table 3.7 summarizes the results from logistic regression of objective response adjusting for liver function and

of complete response adjusting for residual diameter. The treatment effect is statistically significant in complete responders after adjusting for residual diameter in both cases (measurable and, measurable and evaluable disease).

Reviewer's Table 3.7: Results from Logistic Regression Adjusting for Potential Prognostic Factor(s) in Measurable, and Measurable/Evaluable Disease Patients

MEASURABLE DISEASE (N=240)				
Overall Response Rate				
	Odds Ratio	**95%CI**	**p-value**	**Prognostic Factor(s)**
Trt Effect	1.486	0.887 - 2.490	0.133	liver function
Complete Response Rate				
	Odds Ratio	**95%CI**	**p-value**	**Prognostic Factor(s)***
Trt Effect	1.807	1.019 - 3.206	0.043	Dia1**
MEASURABLE and EVALUABLE (n=219)				
Overall Response Rate				
	Odds Ratio	**95%CI**	**p-value**	**Prognostic Factor(s)**
Trt Effect	1.656	0.956 - 2.869	0.072	none
Complete Response Rate				
	Odds Ratio	**95%CI**	**p-value**	**Prognostic Factor(s)**
Trt Effect	1.923	1.069 - 3.461	0.0292	Dia1

*Liver function and residual diameter were found to be possible prognostic factors. This reviewer selected only residual diameter after putting treatment as factor in the model.
**Dia1 stands for a residual diameter (<=5 cm vs. > 5 cm).

This reviewer investigated the effect of the residual diameter variable on the complete response rate. Reviewer's APPENDICES 1,2 and 3 summarize the results. The sponsor applied a 5 cm cut-off criteria to dichotomize the continuous variable of residual diameter. Notice from reviewer's Appendix 1, the sample size was not well balanced between the two categories within each treatment group for the 5 cm cut-off. Hence, this reviewer applied also a 4 cm and a 3 cm cut-off criteria.

The complete response rate was statistically significantly different between the two treatment groups in the lower residual diameter category for measurable and measurable/evaluable patients across the three cut-off criteria. The complete response rate was not statistically significantly different between the two treatment groups in the upper residual diameter category for measurable and evaluable/measurable patients across the three cut-off criteria. Therefore, this reviewer consider the residual diameter variable as an effect modifier, indicating that the magnitude of the treatment effect depended on the size of the residual diameter (the treatment effect was not consistent across the residual diameter categories but it was higher in the Taxol arm than the control).

The same analyses were applied to the overall response rate using the same three cut-off criteria. The residual diameter variable was not found to be an effect modifier.

Time to Progression:

Time to progression (TTP) was calculated in two ways: in Method 1, the duration was calculated "from the day of randomization until the date that clinical evidence of recurrence or progressive disease was first reported. Patients who did not progress were censored at their last date of follow-up. Patients who died of disease and for whom a date of progression was not available were considered to have progressed on the day of their death." In Method 2, patients were considered to be censored "at the time of any therapy following removal from the study, but prior to clinical evidence of recurrence or progression."

Reviewer's Table 3.8 summarizes the results derived by Method 1. This reviewer confirmed the sponsor's results. The relative risk favoring the Taxol treatment was statistically significant.

Reviewer's Table 3.8:Summary of Time to Progression Data (Method 1)

	Taxol/ Cisplatin	Cyclophosphamide/ Cisplatin
Total Patients	196	214
# of Events	163 (83%)	191 (89%)
# of Censored	33 (17%)	23 (11%)
Median Time (months) 95% CI	16.7 14.7 - 19.7	13.0 11.5 - 14.7
Logrank Test: p=0.0006 Relative Risk with 95%CI: 0.695 (0.563 - 0.858)		

Reviewer's Table 3.9 summarizes the results of Method 2. This reviewer confirmed the sponsor's results. The relative risk was statistically significant favoring the Taxol treatment.

Reviewer's Table 3.9:Summary of Time to Progression Data (Method 2)

	Taxol/ Cisplatin	Cyclophosphamide/ Cisplatin
Total Patients	196	214
# of Events	70 (36%)	98 (46%)
# of Censored	126 (64%)	116 (54%)
Median Time (months) 95% CI	16.6 13.9 - 21.0	13.4 10.3 - 16.6
Logrank Test: p=0.0163 Relative Risk with 95%CI: 0.687 (0.505 - 0.935)		

The sponsor investigated the effect of possible prognostic factors on time to progression using Method 1. This reviewer confirmed the results shown in sponsor's Table 32 except for the p-value comparing TTP for non-measurable to measurable patients. This reviewer obtained p=0.0267 for the non-measurable vs measurable variable in a univariate analysis, instead of p=0.009 reported in Sponsor's Table 32.

Reviewer's Table 3.10 shows the result from Cox regression adjusting for the non-measurable vs measurable variable. This

result was slightly different from the one reported by the sponsor (Sponsor's Table 33).

Reviewer's Table 3.10: Final Cox Regression Model for Time to Progression

Factor	Relative Risk	95% CI	P-Value
Treatment	0.697	0.565 - 0.861	0.0008

This reviewer investigated the effect of the residual diameter factor on time to progression. Reviewer's APPENDICES 4,5, and 6 summarize the results. In reviewer's APPENDIX 4, the effect of this variable was investigated in measurable patients across three cut-off criteria. In two criteria (<= 4cm vs. > 4cm and <= 3 cm vs. > 3cm), the relative risk favoring the Taxol treatment was found to be statistically significant in the lower categories, and not to be statistically significant in the upper categories. The magnitude of the relative risk in the lower categories (<= 4 cm or <= 3cm) and the higher categories (> 4 cm or > 3 cm) was about the same and less than 1. This indicated that the residual diameter variable was an effect modifier. In the 5 cm cut off criterion the residual diameter variable found to be an effect modifier, but the direction of the magnitude of the relative risk was opposite, i.e., in the higher category the effect of the Taxol treatment was more favorable than that in the lower category (> 5 cm vs. <= 5cm).

Reviewer's APPENDIX 5 shows the results of the non-measurable patients across the three cut-off criteria. This reviewer observed the same phenomenon in these patients as before. That is, the relative risk favoring the Taxol treatment was statistically significant in the lower category across the three cut-off points and was not statistically significant in the higher category across the three cut-off points. The direction of the magnitude of the relative risk in both categories (lower vs higher) was the same, i.e., <1. Therefore, this reviewer consider the residual diameter variable as an effect modifier in non-measurable disease patients.

Reviewer's APPENDIX 6 shows the results in all patients across the three cut-off criteria. The results were similar as in measurable and non-measurable disease patients. Again, this reviewer determined the residual diameter variable to be an effect modifier. We observe that the treatment effect was statistically significant in the lower stratum favoring the Taxol

arm and that the treatment effect in the upper stratum was not statistically significant.

Survival:

Survival time was calculated "from the day of randomization to death. Otherwise, survival was censored at the last day the patient was known to be alive".

Reviewer's Table 3.11 summarizes the survival analysis results. This reviewer confirmed the sponsor's results. The relative risk favoring the Taxol treatment was statistically significant using the logrank test.

Reviewer's Table 3.11: Summary of Survival Data

	Taxol/ Cisplatin	Cyclophosphamide/ Cisplatin
Total Patients	196	214
# of Deaths	114 (58%)	152 (71%)
# of Censored	82 (42%)	62 (29%)
Median Time (months) 95% CI	35.2 29.6 - 39.6	24.2 20.6 - 29.0
Logrank Test: p=0.0002 Relative Risk with 95%CI: 0.630 (0.494 - 0.805)		

The sponsor investigated the effect of possible baseline prognostic factors on survival time. Three approaches were examined: a univariate, forward selection, and stepwise selection. This reviewer confirmed the sponsor's results reported in Tables 36 and 37. The residual diameter variable was selected as a potential prognostic factor from these approaches.

This reviewer investigated the effect of the residual diameter variable on patients' survival. Reviewer's Appendices 7, 8, and 9 summarize results within each strata. A stratified logrank test across the three different cut-off criteria (<= 5 cm vs. > 5 cm, <= 4 cm vs. > 4 cm, and <= 3 cm vs. > 3 cm) is also included.

Reviewer's APPENDIX 7 shows the results using the 5 cm cut-off criterion. The treatment effect (relative risk) favoring the Taxol treatment was statistically significant and marginally

significant in the lower and upper strata, respectively. Reviewer's Figures 1 and 2 show the Kaplan-Meier curves for survival in the lower stratum (<= 5 cm) and in the upper stratum (> 5 cm). Notice that the sample size in each stratum was not balanced equally.

Reviewer's APPENDIX 8 shows the results using the 4 cm cut-off criterion. The treatment effect (relative risk) was statistically significant in the lower stratum favoring the Taxol treatment and not statistically significant in the upper stratum. The relative risk was less than 1 in both strata. Reviewer's Figures 3 and 4 show the treatment effect in each stratum.

Reviewer's APPENDIX 9 shows the results using the 3 cm cut-off criterion. We observed a similar treatment effect as in the 4 cm cut-off criterion. Reviewer's Figures 5 and 6 show the treatment effect in each stratum.

Considering these results from the three different cut-off criteria, we see that the treatment effect was statistically significant in the lower stratum favoring the Taxol arm and that the treatment effect in the upper stratum was marginally statistically significant or not statistically significant across the three criteria. The estimated relative risk in both strata was less than 1 across all three categories. Therefore, this reviewer considered the residual diameter to be an effect modifier.

IV. Conclusion:

Three endpoints, tumor response rate, time to progression, and survival time, were investigated in this review. This reviewer found that the treatment difference between the two arms favored the Taxol treatment with respect to complete response, time to progression, and survival (Reviewer's Tables 3.7, 3.8, 3.9, and 3.11)

This reviewer investigated the effect of potential prognostic factors on the three endpoints by a univariate analysis, forward and stepwise logistic and Cox regression analyses. This reviewer confirmed the results reported by the sponsor.

This reviewer investigated the effect of the selected prognostic factor of residual diameter in all three endpoints and applied different cut-off criteria for sensitivity analyses (<= 3 cm vs. > 3 cm, <= 4 cm vs. > 4 cm, and <= 5cm vs. > 5 cm). In all three

endpoints, this reviewer observed that there existed a larger treatment effect in the lower stratum of the Taxol treatment group and a small treatment effect in the upper stratum using the three different cut-off criteria. Therefore, this reviewer concluded that the residual diameter was an effect modifier. This indicates that we could expect a stronger treatment effect in the Taxol treatment arm if most of the tumor is removed at operation.

This reviewer believes that treatment with Taxol is effective in this population.

/S/

Masahiro Takeuchi Sc.D
Mathematical Statistician

Concur: Dr. Koutsoukos /S/ 4/3/98
Dr. Chi

04/03/98

cc:
NDA#20-262/SE1-026
HFD-150 / Division File
HFD-150 / Dr. Williams
HFD-344 / Dr. Barton
HFD-150 / Dr. Honig
HFD-150 / Ms. Spillman,CSO
HFD-710 / Dr. Chi
HFD-710 / Dr. Koutsoukos
HFD-710 / Dr. Takeuchi
HFD-710 / Chron

Takeuchi / 02-26-98/ WP6.1 - Taxol_Review
This review consists of 13 pages of text, 9 Appendices (Appendix 1-9) and 6 Figures (Figures 1-6).

Reviewer's APPENDIX 1: Complete Response Rate in Measurable and Measurable/Evaluable Patients for Each Residual Diameter Category (<= 5 cm vs > 5cm)

Measurable Patients (N=240)				
Residual Diameter				
	<= 5 cm		> 5 cm	
	Taxol	Cys*	Taxol	Cys*
Responders (30.0%)	32 (45.7%)	26 (29.2%)	8 (18.6%)	6 (15.8%)
Nonresponders (70.0%)	38 (52.3%)	63 (70.3%)	35 (81.4%)	32 (84.2%)
	Odds Ratio: 2.04 95% CI:(1.06 - 3.94) p = 0.033		Odds Ratio: 1.22 95% CI: (0.38 - 3.89) p = 0.738	
Measurable and Evaluable Patients (N=219)				
Residual Diameter				
	<= 5 cm		> 5 cm	
	Taxol	Cys*	Taxol	Cys*
Responders (32.9%)	32 (50.0%)	26 (31.0%)	8 (21.1%)	6 (18.2%)
Nonresponders (67.1%)	32 (50.0%)	58 (69.0%)	30 (78.9%)	27 (81.8%)
	Odds Ratio: 2.231 95% CI: (1.14 - 4.37) p = 0.020		Odds Ratio: 1.200 95% CI: (0.37 - 3.91) p = 0.76	

*: Cys stands for Cyclophosphamide/Cisplatin

Reviewer's APPENDIX 2: Complete Response Rate in Measurable and Measurable/Evaluable Patients for Each Residual Diameter Category (<= 4 cm vs > 4cm)

Measurable Patients (N=240)				
Residual Diameter				
	<= 4 cm		> 4 cm	
	Taxol	Cys*	Taxol	Cys*
Responders (30.0%)	25 (43.1%)	18 (26.9%)	15 (30.0%)	14 (23.3%)
Nonresponders (70.0%)	33 (56.9%)	49 (73.1%)	40 (70.0%)	46 (76.7%)
	Odds Ratio: 2.06 95% CI:(0.91 - 4.37) p = 0.0584		Odds Ratio: 1.23 95% CI: (0.53 - 2.87) p = 0.627	
Measurable and Evaluable Patients (N=219)				
Residual Diameter				
	<= 4 cm		> 4 cm	
	Taxol	Cys*	Taxol	Cys*
Responders (32.9%)	25 (46.3%)	18 (28.6%)	15 (31.3%)	14 (25.9%)
Nonresponders (67.1%)	29 (53.7%)	45 (71.4%)	33 (68.7%)	40 (74.1%)
	Odds Ratio: 2.155 95% CI: (1.00 - 4.63) p = 0.049		Odds Ratio: 1.299 95% CI: (0.55 - 3.08) p = 0.55	

*: Cys stands for Cyclophosphamide/cisplatin

Reviewer's APPENDIX 3: Complete Response Rate in Measurable and Measurable/Evaluable Patients for Each Residual Diameter Category (<= 3 cm vs > 3cm)

Measurable Patients (N=240)				
Residual Diameter				
	<= 3 cm		> 3 cm	
	Taxol	Cys*	Taxol	Cys*
Responders (30.0%)	21 (44.7%)	10 (22.2%)	19 (28.8%)	22 (26.8%)
Nonresponders (70.0%)	26 (55.3%)	35 (77.8%)	47 (71.2%)	60 (73.2%)
	Odds Ratio: 3.06 95% CI:(1.21 - 7.73) p = 0.0185		Odds Ratio: 1.14 95% CI: (0.55 - 2.40) p = 0.720	
Measurable and Evaluable Patients (N=219)				
Residual Diameter				
	<= 3 cm		> 3 cm	
	Taxol	Cys*	Taxol	Cys*
Responder (32.9%)	21 (48.8%)	10 (23.8%)	19 (32.2%)	22 (29.3%)
Nonresponder (67.1%)	22 (51.2%)	32 (76.2%)	40 (67.8%)	53 (70.7%)
	Odds Ratio: 2.83 95% CI: (1.14 - 7.01) p = 0.025		Odds Ratio: 1.10 95% CI: (0.54 - 2.27) p = 0.79	

*: Cys stands for Cyclophosphamide/cisplatin

Reviewer's APPENDIX 4: Relative Risk Rate in Time to Progression for Measurable Disease Patients for Each Residual Diameter Category

Measurable Disease Patients (N=240)					
Dia1=0					
Total	**Event**	**Censored**	**RR**	**95%CI**	**P-value**
159	141	18	0.784	0.561 - 1.097	0.156
Dia1=1					
81	72	9	0.571	0.354 - 0.920	0.0214
Dia2=0					
Total	**Event**	**Censored**	**RR**	**95%CI**	**P-value**
125	113	12	0.670	0.459 - 0.978	0.0380
Dia2=1					
115	100	15	0.755	0.509 - 1.120	0.163
Dia3=0					
Total	**Event**	**Censored**	**RR**	**95%CI**	**P-value**
92	82	10	0.631	0.404 - 0.983	0.042
Dia3=1					
148	131	17	0.771	0.546 - 1.090	0.141

RR: Relative risk (Taxol vs the control)
Dia1: <= 5 cm vs > 5 cm
Dia2: <= 4 cm vs > 4 cm
Dia3: <= 3 cm vs > 3 cm

Reviewer's APPENDIX 5: Relative Risk Rate in Time to Progression in Non-measurable Disease Patients for Each Residual Diameter Category

Non-measurable Disease Patients (N=170)					
Dia1=0					
Total	**Event**	**Censored**	**RR**	**95%CI**	**P-value**
140	113	27	0.672	0.463 - 0.975	0.0364
Dia1=1					
30	28	2	0.824	0.371 - 1.832	0.635
Dia2=0					
Total	**Event**	**Censored**	**RR**	**95%CI**	**P-value**
129	104	25	0.639	0.433 - 0.941	0.0233
Dia2=1					
41	37	4	0.814	0.418 - 1.607	0.562
Dia3=0					
Total	**Event**	**Censored**	**RR**	**95%CI**	**P-value**
118	95	23	0.611	0.407 - 0.918	0.0177
Dia3=1					
52	46	6	0.808	0.448 - 1.460	0.481

RR: Relative risk (Taxol vs the control)
Dia1: <= 5 cm vs > 5 cm
Dia2: <= 4 cm vs > 4 cm
Dia3: <= 3 cm vs > 3 cm

Reviewer's APPENDIX 6: Relative Risk Rate in Time to Progression for Each Residual Diameter Category Including All Patients

Dia1=0					
Total	**Event**	**Censored**	**RR**	**95%CI**	**P-value**
299	254	45	0.714	0.557 - 0.915	0.0078
Dia1=1					
111	100	11	0.625	0.417 - 0.935	0.021
Dia2=0					
Total	**Event**	**Censored**	**RR**	**95%CI**	**P-value**
254	217	37	0.643	0.491 - 0.842	0.0013
Dia2=1					
156	137	19	0.792	0.565 - 1.110	0.176
Dia3=0					
Total	**Event**	**Censored**	**RR**	**95%CI**	**P-value**
210	177	33	0.618	0.458 - 0.834	0.0016
Dia3=1					
200	177	23	0.795	0.591 - 1.071	0.131

RR: Relative risk (Taxol vs the control)
Dia1: <= 5 cm vs > 5 cm
Dia2: <= 4 cm vs > 4 cm
Dia3: <= 3 cm vs > 3 cm

Reviewer's Appendix 7 : Summary of Survival Analysis with Respect to the Residual Diameter Variable (<= 5 cm vs > 5 cm)

	<=5 cm			> 5 cm		
	Total SS	Failure	Censored	Total SS	Failure	Censored
Cyclo*	156	108	48	58	44	14
Taxol	143	78	65	53	36	17
Total	299	186	113	111	80	31
	Median (Month)	95% CI		Median	95%CI	
Cyclo*	24.80	22.28 - 31.15		17.80	13.83 - 28.98	
Taxol	37.91	34.33 - 47.74		24.61	19.09 - 37.52	
Relative Risk	0.610			0.665		
95% CI	0.455 - 0.817			0.424 - 1.043		
p-value	0.0009			0.0758		
p-value (logrank)	0.0008			0.0738		
	Stratified Logrank: Test of Homogeneity: p=0.0035 combined p-value**:0.0002					

*Cyclo stands for cyclophosphamide/cisplatin treatment.
**Combined p-value was obtained using the stratified logrank test. A homegeneity test indicates heterogeneity of the treatment effect between strata, which implies that we should not combine the two categories.

Reviewer's Appendix 8 : Summary of Survival Analysis with Respect to the Residual Diameter variable (<= 4 cm vs > 4 cm)

	<=4 cm			> 4 cm		
	Total SS	Failure	Censored	Total SS	Failure	Censored
Cyclo*	129	91	38	85	61	24
Taxol	125	66	59	71	48	23
Total	254	157	97	156	109	47
	Median (Month)	95%CI		Median (Month)	95%CI	
Cyclo*	24.80	21.19 - 31.15		23.06	16.00 - 29.60	
Taxol	38.80	35.08 - 48.00		26.81	21.68 - 37.26	
Relative Risk	0.552			0.781		
95% CI	0.401 - 0.760			0.534 - 1.142		
p-value	0.0003			0.201		
p-value (logrank)	0.0002			0.200		
	Stratified Logrank: Test of Homogeneity: p=0.0162 combined p-value**:0.0003					

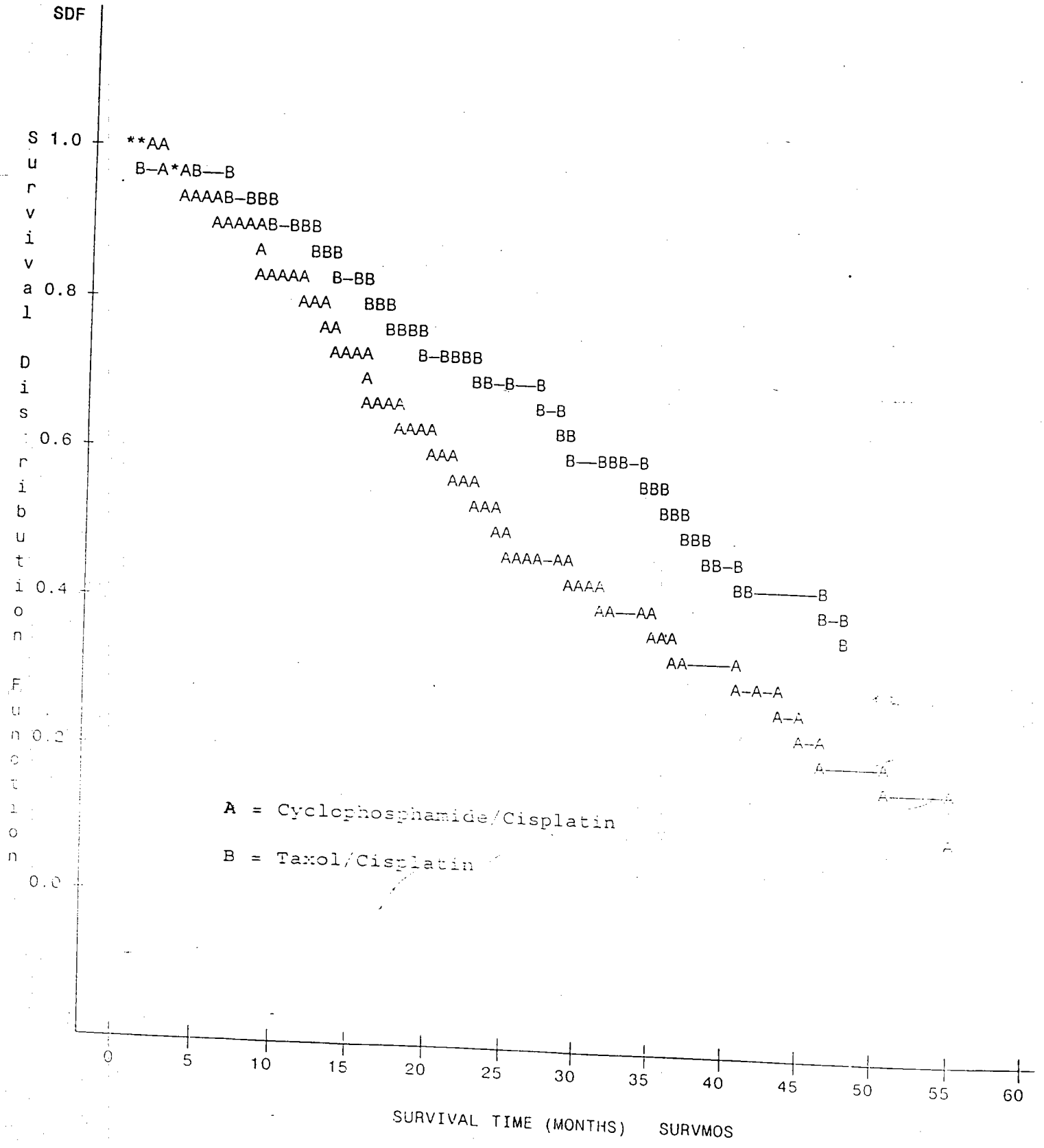
*Cyclo stands for cyclophosphamide/cisplatin treatment.
**Combined p-value was obtained using the stratified logrank test. A homegeneity test indicates heterogeneity of the treatment effect between strata, which implies that we should not combine the two categories.

Reviewer's Appendix 9 : Summary of Survival Analysis with Respect to the Residual Diameter variable (<= 3 cm vs > 3 cm)

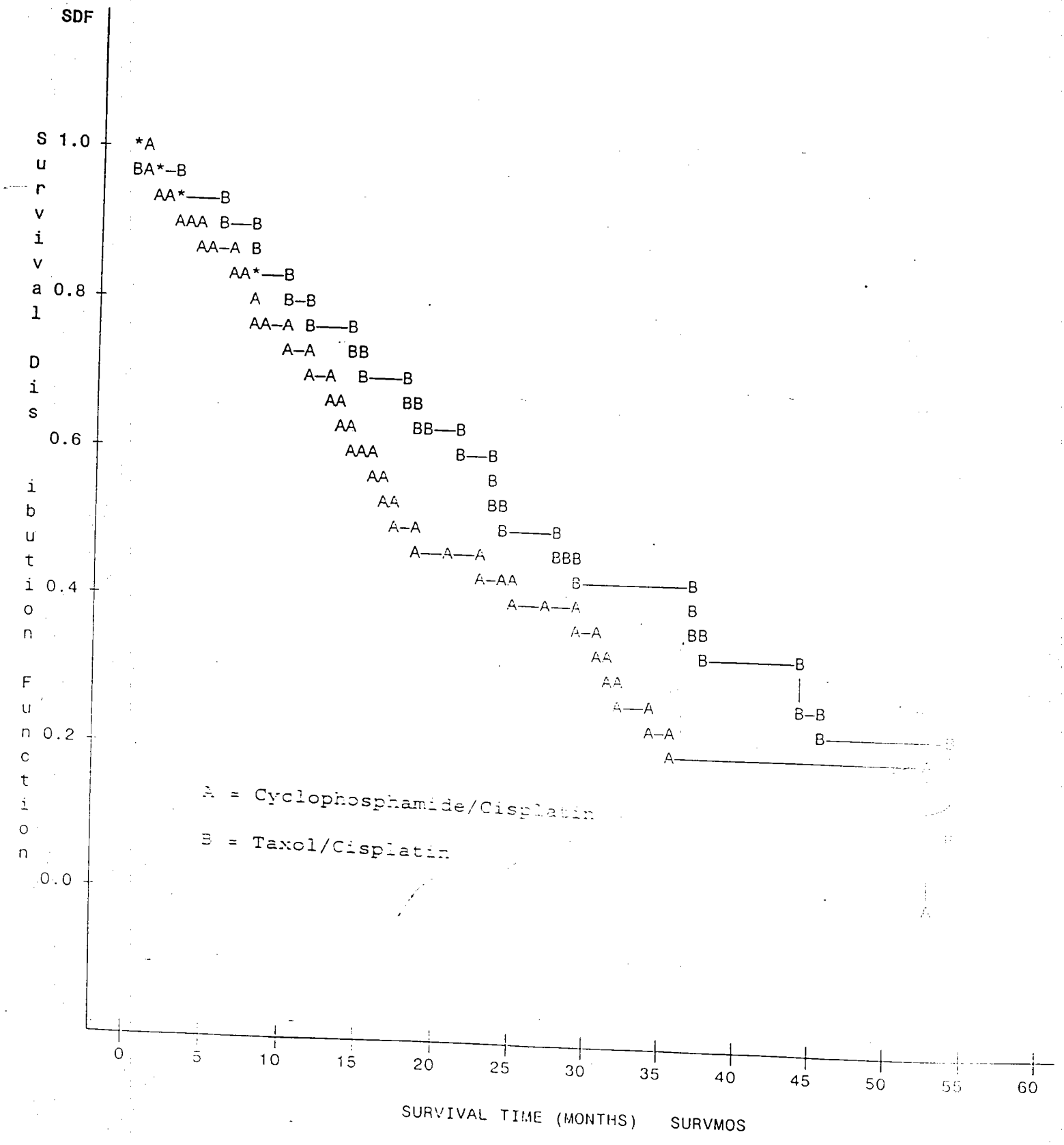
	<=3 cm			> 3 cm		
	Total SS	Failure	Censored	Total SS	Failure	Censored
Cyclo*	103	72	31	111	80	31
Taxol	107	56	51	89	58	31
Total	210	128	82	200	138	62
	Median (Month)	95%CI		Median (Month)	95%CI	
Cyclo*	25.30	21.19 - 31.15		23.06	16.99 - 29.60	
Taxol	38.60	35.02 - .		28.94	23.89 - 37.52	
Trt.Effect	0.551			0.741		
95% CI	0.388 - 0.784			0.528 - 1.041		
p-value	0.0009			0.0837		
p-value (logrank)	0.0008			0.0825		
	Stratified Logrank: Homogeneity: p=0.0147 combined p-value**: 0.0004					

*Cyclo stands for cyclophosphamide/cisplatin treatment.
**Combined p-value was obtained using the stratified logrank test. A homegeneity test indicates heterogeneity of the treatment effect between strata, which implies that we should not combine the two categories.

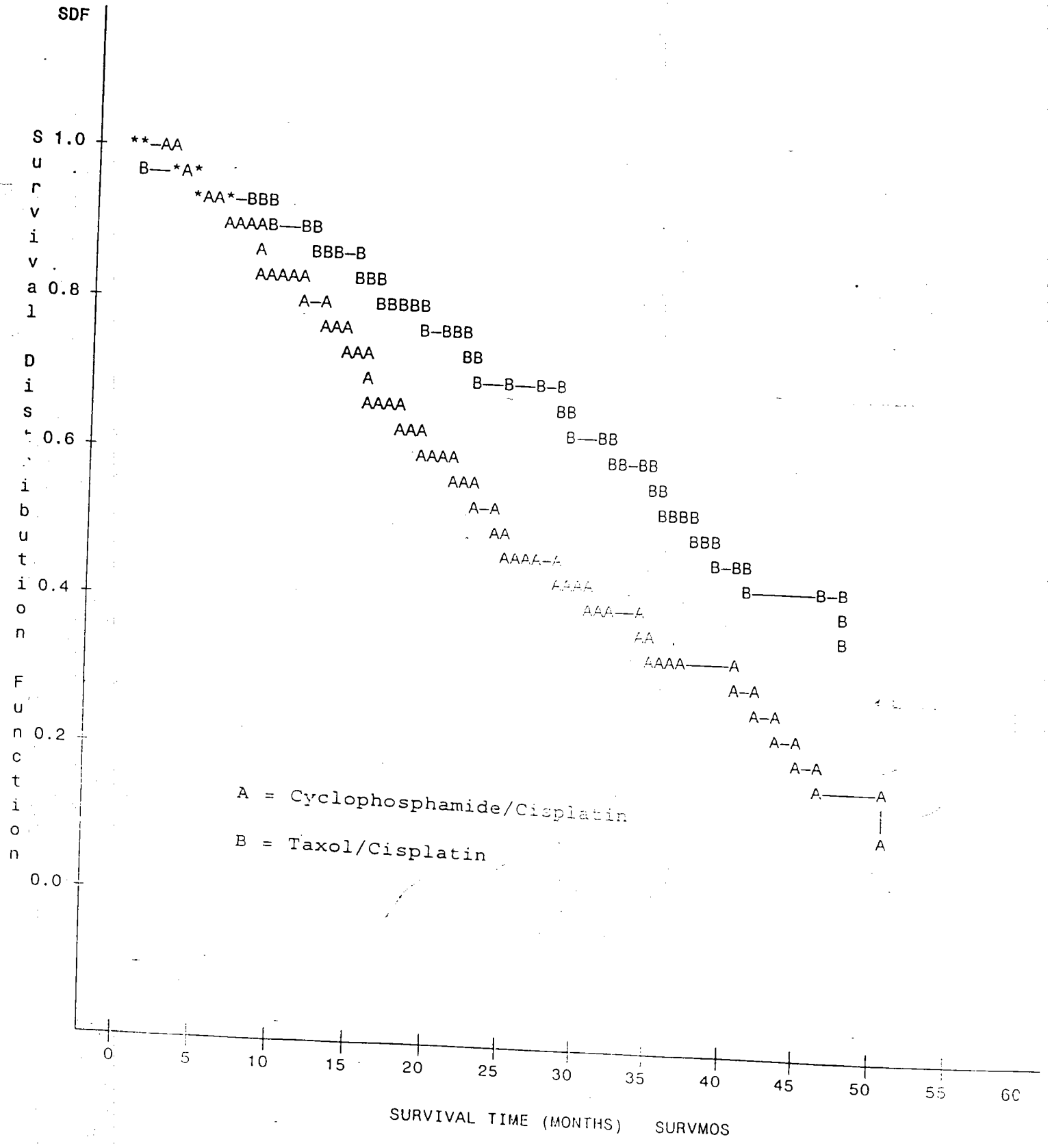
Reviewer's Figure 1: Kaplan-Meier Curves for <= 5 cm Residual Diameter



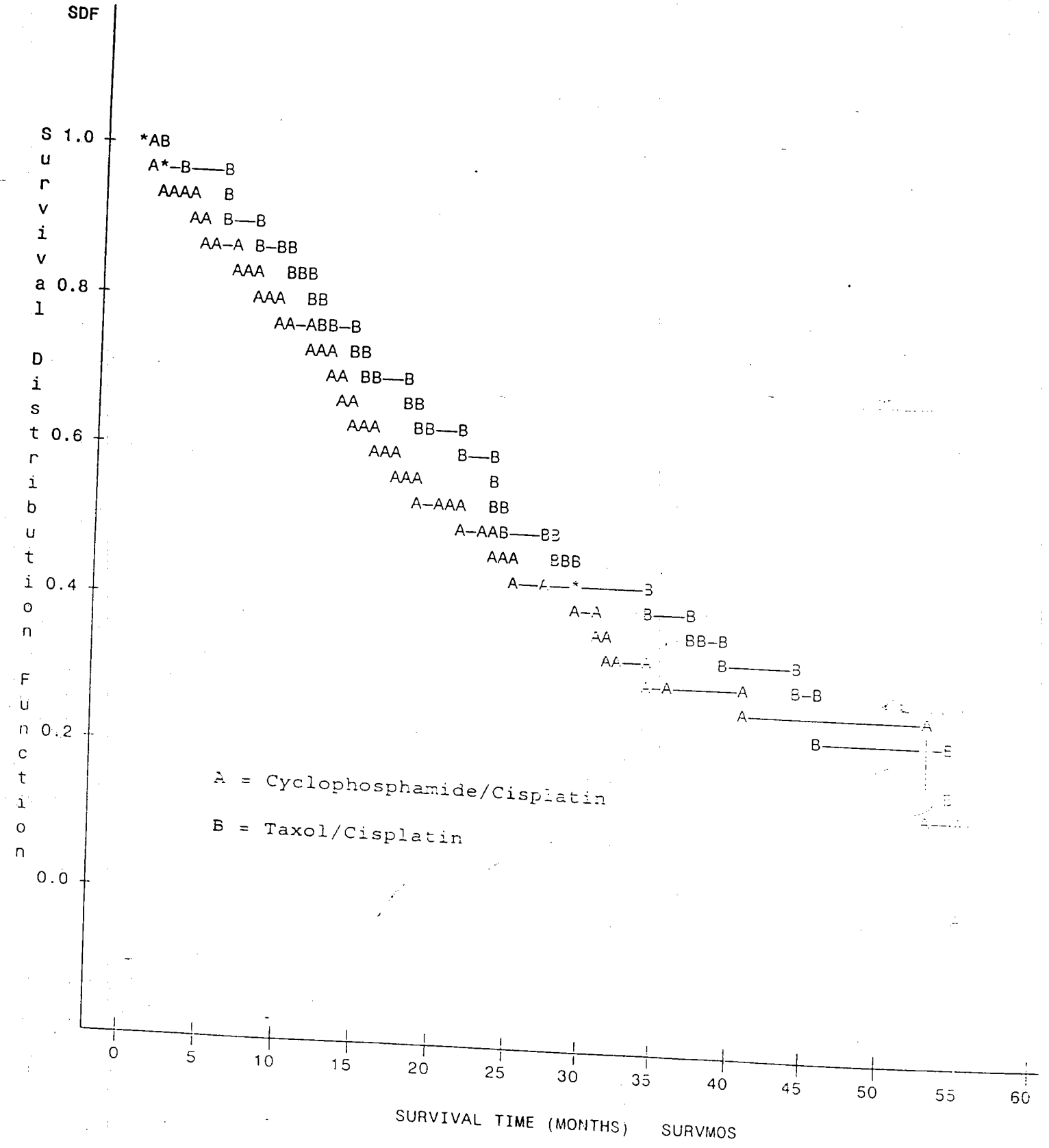
Reviewer's Figure 2: Kaplan-Meier Curves for > 5 cm Residual Diameter



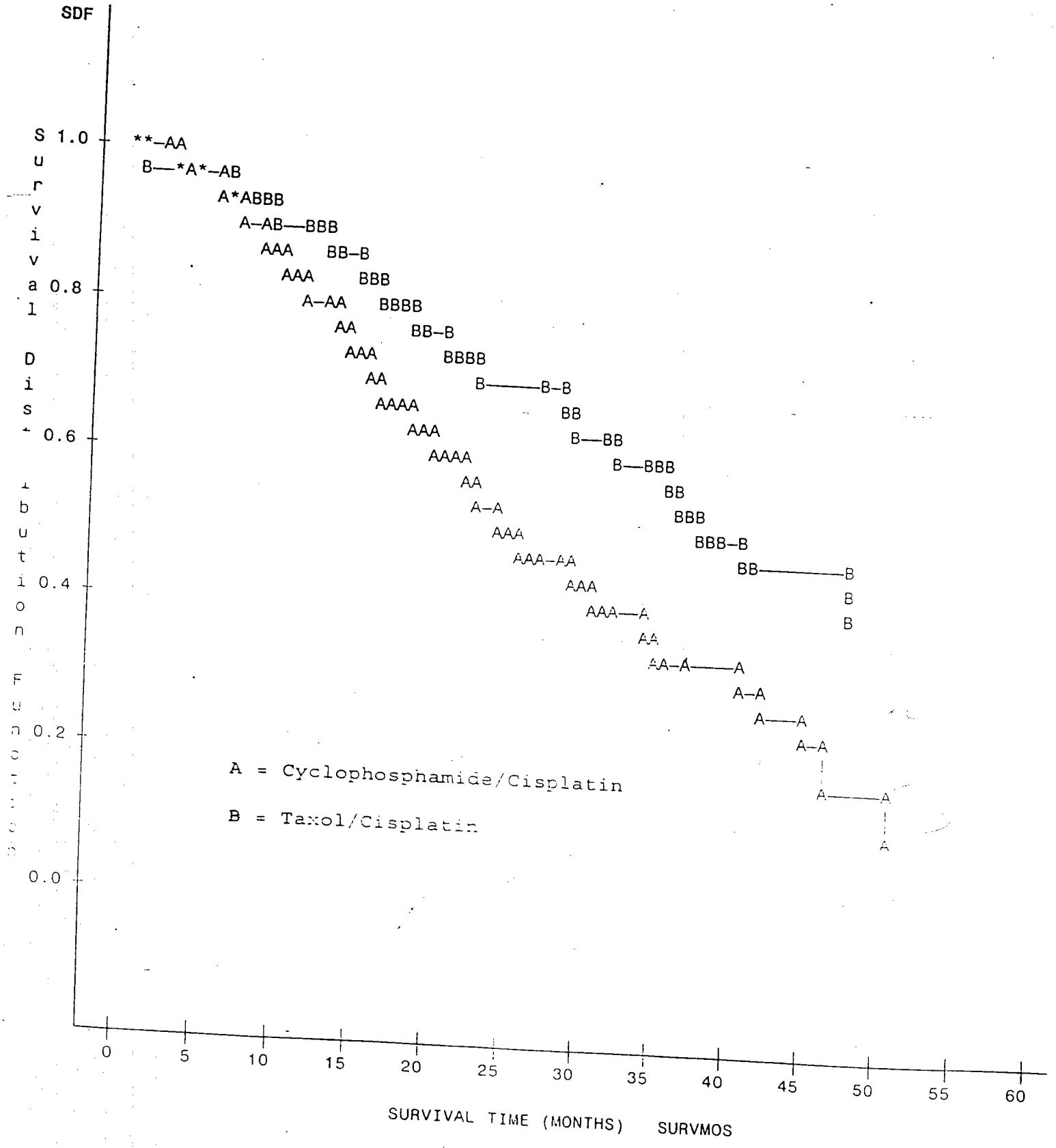
Reviewer's Figure 3: Kaplan-Meier Curves for <= 4 cm Residual Diameter



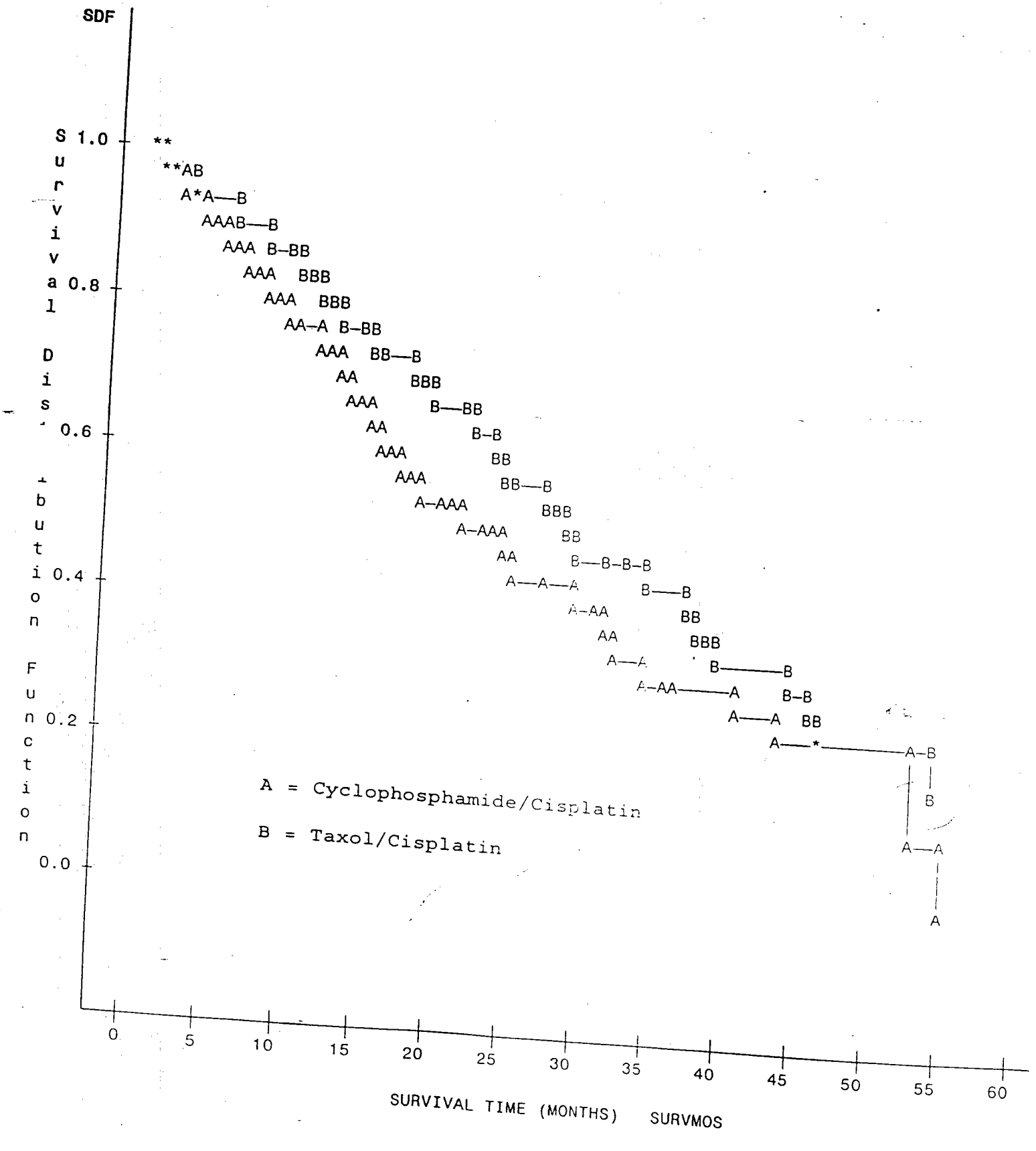
Reviewer's Figure 4: Kaplan-Meier Curves for > 4 cm Residual Diameter



Reviewer's Figure 5: Kaplan-Meier Curves for <= 3 cm Residual Diameter



Reviewer's Figure 6: Kaplan-Meier Curves for > 3 cm Residual Diameter



CENTER FOR DRUG EVALUATION AND RESEARCH

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

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

SPILLMAN

FEB - 3 1998

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

sNDA: 20-262/026 Submission Date: October 7, 1997

Paclitaxel (Taxol®) Injection: 30 mg/5 mL and 100 mg/16.7 mL Multidose Vials.

Sponsor: Bristol-Myers Squibb
Wallingford, CT

Reviewer: Safaa Ibrahim, Ph.D.

Type of Submission: Efficacy Supplement

BACKGROUND

This efficacy supplement to NDA 20-262 is for the use of Taxol® /cisplatin combination in patients with advanced ovarian cancer. Taxol® as monotherapy is currently approved for the treatment of metastatic carcinoma of the ovary after failure of the first-line or subsequent chemotherapy and for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Approval for this supplemental NDA is based on data from one randomized, multicenter, Phase III trial (CA139-022) comparing the efficacy/safey of Taxol® /cisplatin combination with a standard combination of cyclophosphamide/cisplatin in patients with advanced ovarian cancer (n=410). The experimental therapy (i.e.,Taxol® /cisplatin) consists of 135 mg/m^2 paclitaxel infused over 24 hours followed by 75 mg/m^2 cisplatin infused at a rate of 1 mg/minute. The standard therapy (i.e., cyclophosphamide/ cisplatin) consists of 75 mg/m^2 cisplatin infused at a rate of 1 mg /minute and concomitant intravenous administration of 750 mg/m^2 cyclophosphamide (See Attachment 1).

This submission contains no additional information on the pharmacokinetics of paclitaxel. The potential for drug interaction between paclitaxel and cisplatin has been studied before and the result of 33 % decrease in paclitaxel clearance when it was administered following cisplatin is incorporated in the current package insert for Taxol® (See Attachment 2).

COMMENTS:

1. The sponsor is requested to submit the study report/results of the effect of hepatic dysfunction on paclitaxel disposition to the Agency for review.

sponsor response sent 3.10.98

2. The revised labeling statement on page 3:

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

RECOMMENDATION:

Please forward Comments 1 and 2 to the sponsor.

/S/

Reviewer: Safaa S. Ibrahim, Ph.D.
Division of Pharmaceutical Evaluation I

RD/FT

/S/ 2/3/98

Team Leader: Atiqur Rahman, Ph.D.
Division of Pharmaceutical Evaluation I

cc: sNDA: 20-262/024
HFD-150/Division file
HFD-150/Spillman, Williams, Honig
HFD-850/Lesko
HFD-860/Malinowski, Mehta, Rahman, Ibrahim
CDR (B. Murphy)

Attachment 1

TAXOL Protocol CA139-022

BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE

SUMMARY

Title of Study: Phase III Randomized Study of Cyclophosphamide (NSC 26271) and Cisplatin (NSC 119875) versus TAXOL (NSC 125973) and Cisplatin (NSC 119875) in Patients with Suboptimal Stage III and Stage IV Epithelial Ovarian Carcinoma. Gynecologic Oncology Group Protocol No. 111. Bristol-Myers Squibb Protocol No. CA139-022.

Investigator, Location of Trial: Multicentric trial conducted by the Gynecologic Oncology Group involving 86 institutions in the United States of America. Principal Investigator, William P. McGuire, M.D.

Publication: McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY, Clarke-Pearson DL, Davidson M. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with Stage III and Stage IV ovarian cancer. New England Journal of Medicine, 1996; 334 (1), 1-6.

McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Look KY, and Davidson M. TAXOL and cisplatin (TP) improves outcome in advanced ovarian cancer (AOC) as compared to cytoxan and cisplatin (CP). Proceedings of ASCO 1995; 14 (Abstract #771).

McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY, Partridge EE, et al. A phase III trial comparing cisplatin/cytoxan (PC) and cisplatin/TAXOL (PT) in advanced ovarian cancer (AOC) Proceedings of ASCO 1993; 12 (Abstract #808).

Study Period: Patients were accrued from April 13, 1990 to March 2, 1992.

Clinical Phase: Phase III

Objectives: The present study was undertaken to compare, in a randomized setting, the objective response rate, time to progression, survival, and the incidence and severity of adverse events of TAXOL/cisplatin with a standard regimen in patients with suboptimal Stage III and Stage IV ovarian cancer.

Study Design: This was a prospective multicentric study of two platinum-based chemotherapy regimens, a standard regimen with cyclophosphamide and an experimental regimen with TAXOL. Treatments were randomly assigned with equal probability after stratification according to institution and the clinical measurability of disease. The study

was conducted by the Gynecologic Oncology Group under the IND of the National Cancer Institute, USA.

Number of Patients: Four hundred ten patients were randomized into the trial. One patient in the cyclophosphamide died before receiving study medication.

Diagnosis and Eligibility: Women with pathologically verified FIGO Stage III epithelial ovarian cancer after suboptimal surgery (> 1 cm residual mass) or FIGO Stage IV disease were eligible. They could have clinically measurable or nonmeasurable disease. Eligibility also required no previous chemotherapy or radiation for ovarian cancer.

Test Product Formulation: TAXOL was supplied by the National Cancer Institute as a concentrated sterile solution, 6 mg/ml in a 5 ml ampule (30 mg/ampule) in polyoxyethylated castor oil (Cremophor® EL) 50% and dehydrated alcohol USP 50%.

Dose, Route, Schedule and Sequence of Administration: The standard therapy consisted of an intravenous infusion of cisplatin, 75 mg/m², given at a rate of approximately 1 mg/minute and the concomitant administration of cyclophosphamide, 750 mg/m² intravenously. The experimental therapy consisted of TAXOL, 135 mg/m², administered as a continuous intravenous infusion over 24 hours followed by an intravenous infusion of cisplatin, 75 mg/m² at a rate of 1 mg/minute. Prior to each TAXOL administration patients were premedicated with a 3-drug regimen consisting of an orally administered steroid followed by intravenous injections of H_1 and H_2 antihistamines. Both the standard and experimental therapies were repeated every 21 days or when hematologic and non-hematologic recovery was documented. Dose reductions based on Grade IV hematologic toxicity were required for cyclophosphamide and TAXOL. No reduction in the cisplatin dose was planned. Lot numbers of TAXOL used for this study were: LIF 19, 89-219, 89-220R, 90-214R, 90-232, 90-236, 90-241, 90-241A, 91-216, S91G044M, S91J048M (Mayaguez lot H1F29), S91J048M-C.

Treatment Duration: Patients were to receive a total of six cycles of therapy unless there was progression of disease or toxicity. Patients who were clinically free of disease were then scheduled for a second look surgery.

Statistical Considerations: The study was powered (n=360) to detect an increase of 40% in the median time to progression based on a median of 10.3 months and 14.4 months for patients with measurable and non-measurable disease respectively. This sample size was also sufficient to detect a 19% increase in clinical complete response rate in the experimental arm, based on a 30% complete response rate among patients with measurable disease treated with cyclophosphamide and cisplatin.

Criteria for Evaluation: The critical endpoints consisted of: tumor response, based on shrinkage of measurable or evaluable lesions, pathological response, duration of clinical and pathological response, time to progression, and survival. Patients were also monitored for adverse reactions. Performance status and ancillary neurologic assessment were used as indicators of quality of life.

Patient Characteristics: The diagnosis of invasive ovarian carcinoma was confirmed in 392 patients (96%), with serous adenocarcinoma in 74% of patients in the TAXOL arm and 64% in the cyclophosphamide arm ($p = 0.025$). All other pretreatment characteristics were well balanced between the two arms. The median age across both arms was 59 years. Performance status was ≤ 1 at entry in 84% of the patients. At the time of initial surgery, Stage III and Stage IV disease was noted in 271 patients (66%) and 138 patients (34%), respectively. For the 240 patients with measurable disease, the most common sites of disease were pelvis (43%) and abdomen (34%). CT scans were used in 70% of the patients to evaluate tumor responses. Pleural effusions (51%) and ascites (38%) were the most common disease sites in the 170 patients with nonmeasurable disease.

Number of Courses Administered, Dose Reductions, Dose Delays and Dose Intensity: There were 1074 courses of TAXOL/cisplatin administered to 196 patients; and 1145 courses of cyclophosphamide/cisplatin were given to 213 patients. The median number of courses administered in both arms was six (range, 1-6 courses). The overall frequency of dose reductions was 28% and 22% for the TAXOL and cyclophosphamide arms, respectively ($p = 0.003$). However, treatment delays were less frequent in the TAXOL arm, 21% of courses, compared to 55% of courses in the cyclophosphamide arm ($p < 0.001$). In the TAXOL arm the median number of days to the next course was 21 days and in the cyclophosphamide arm 28 days. Hematologic toxicity (neutropenia) was the principal reason for dose reductions and delays. Overall, dose reductions and delays resulted in a significantly reduced treatment intensity for the cyclophosphamide arm as compared to the TAXOL arm ($p < 0.001$).

Efficacy: Two hundred and forty patients had measurable disease and were included in the analysis of clinical response. All 410 randomized patients were included in the analysis of pathological response, time to progression and survival.

Clinical response: In the TAXOL arm there were 40 complete responses (35%) and 28 partial responses (25%) for an overall clinical response rate of 60% (68/113). In the cyclophosphamide arm, 32 patients achieved a complete response (25%) and 32 patients had a partial response (25%) for an overall clinical response rate of 50% (64/127). There was no statistically significant difference between the treatment arms in overall clinical response ($p = 0.153$) or complete clinical response ($p = 0.092$). After adjustment for a number of potential prognostic factors using logistic regression, no factor had a

statistically significant effect on the likelihood of achieving a clinical response.

Time-to response: The median time to clinical response for patients receiving the combination of TAXOL/cisplatin was 7.9 weeks versus 8.6 weeks for patients receiving cyclophosphamide/cisplatin.

Duration of response: The median duration of response for clinical responders was 15.8 months for patients on the TAXOL arm and 16.4 for patients on the cyclophosphamide arm. For complete responders, the median duration was 14.9 months on the TAXOL arm and 15.7 on the cyclophosphamide arm.

Pathological response: In the TAXOL arm there were 42 pathological complete responses (21%) and 25 patients with microscopic residual disease (13%) for a pathological response rate of 34% (67/196). In the cyclophosphamide arm, 35 patients achieved a pathological complete response (16%) and eight patients had microscopic residual disease (4%) for a pathological response rate of 20% (43/214). The difference between the two arms was statistically significant for pathological response including microscopic residual disease ($p = 0.001$), but not for complete pathological response ($p = 0.196$). An analysis of prognostic factors revealed that only disease stage seemed to have an impact on pathological response. After adjustment for this selected factor and stratum using logistic regression, the treatment effect was unchanged.

Duration of pathological response: The median duration of pathological response for patients who had achieved a pathological complete response or had residual microscopic disease was 28.5 months in the TAXOL arm and 17.5 months in the cyclophosphamide arm. For pathological complete responders, the median duration was 32.2 months on the TAXOL arm and 16.5 on the cyclophosphamide arm.

Time to progression: Disease had progressed in 354 patients, 163/196 (83%) on the TAXOL arm and 191/214 (89%) on the cyclophosphamide arm. Time to progression or median duration of disease control was 16.6 months for patients in the TAXOL arm as compared to the median duration of 13.0 months in the cyclophosphamide arm. This difference was statistically significant ($p = 0.0008$). The difference observed in time to progression in the TAXOL arm corresponds to a reduction in the risk of tumor progression by 30%. After adjusting for selected prognostic factors and for stratum using Cox regression, the treatment differences remained significant ($p = 0.001$).

Survival: A total of 266 patients, 114/196 (58%) on the TAXOL arm and 152/214 (71%) on the cyclophosphamide arm, had died at the time of analysis. The median survival for those on the TAXOL arm was 35.5 months and for those on the cyclophosphamide arm 24.2 months. This difference was statistically significant ($p = 0.0002$). The analysis of

prognostic factors revealed that only the residual tumor diameter had an impact on survival. After adjustment for this selected factor and stratum using Cox regression, the treatment effect remained significant ($p = 0.0002$).

Safety Results: Clinical signs and symptoms on study as well as hemograms and serum chemistries were used to determine safety. A total of 409 patients were evaluable for safety: 196 patients on the TAXOL arm and 213 patients on the cyclophosphamide/ cisplatin arm. Adverse events resulted in the discontinuation of 27 patients from the study, 12 patients in the TAXOL arm and 15 on the cyclophosphamide arm. Ten patients died within 30 days of the last study dose, six on the TAXOL and four on the cyclophosphamide arm. Three patients died as a result of treatment complications, one patient on the TAXOL arm and two on the cyclophosphamide arm.

Neutropenia (worst course) was almost universally observed in the TAXOL/cisplatin arm (96% of the patients) but was usually of short duration (< 7 days) and without clinical consequences in most cases. In the cyclophosphamide arm neutropenia was seen in 92% of the patients. CTC Grade III/IV neutropenia was seen in 92% of the patients in the TAXOL arm and 80% of the patients who received cyclophosphamide ($p = 0.001$). In the TAXOL arm, there were 54 episodes of infections reported in 41 patients (5% of the courses); there were 46 infectious episodes reported in 32 patients (4% of the courses) in the cyclophosphamide arm. Febrile neutropenia occurred in 35 courses in the TAXOL arm compared to nine courses in the cyclophosphamide arm ($p < 0.001$).

Anemia was observed in 87% of the patients at a similar frequency in both arms and was mostly Grade I or II.

Thrombocytopenia was less frequently observed than neutropenia and occurred at a similar frequency in both the TAXOL and cyclophosphamide arms ($p = 0.434$) for the worst course. For the worst course of therapy, 26% of TAXOL treated patients experienced thrombocytopenia (10% Grade III/IV) and 30% of patients who had received cyclophosphamide had thrombocytopenia (9% Grade III/IV).

Peripheral neuropathy, mostly Grade I or II, was observed in 25% of patients treated with TAXOL/cisplatin and 20% of patients treated with cyclophosphamide/cisplatin ($p = 0.282$). Grade III peripheral neuropathy developed in five TAXOL treated patients.

Arthralgia/myalgia was reported in 9% of patients treated in the TAXOL arm and 2% of the patients in the cyclophosphamide arm ($p = 0.002$). One TAXOL treated patient had Grade III symptoms.

Hypersensitivity/allergic reactions were observed in 15 patients (8%) on the TAXOL arm and three patients (1%) on the cyclophosphamide ($p = 0.003$). Six patients (3%) on the TAXOL arm had study drug infusions discontinued for hypersensitivity reactions.

Nausea and vomiting occurred frequently in both arms and was generally mild to moderate in severity. Grade III/IV nausea and vomiting was reported in 10% of the patients in the TAXOL arm and 11% in the cyclophosphamide arm.

Liver function tests were frequently abnormal but there was no difference between the two treatment arms.

Cardiovascular events occurred in 27 % of patients in the TAXOL arm and 7% in the cyclophosphamide arm ($p = 0.001$). Most were Grade I and II events detected during continuous cardiac monitoring required for patients receiving TAXOL. There was no difference between the two arms in the incidence of Grade III/IV events.

Renal function was evaluated using serum creatinine results. Grade I and II elevations were common on this study with no significant differences between the two treatment arms.

Other signs and symptoms were uncommon and were generally mild to moderate. Two symptoms occurred in more than 10% of patients on either arm. *Alopecia* was reported in 107 patients in the TAXOL arm (55%) and 79 patients in the cyclophosphamide arm (37%; $p < 0.001$). *Asthenia* was noted in 33 patients in the TAXOL arm (17%) and in 21 patients in the cyclophosphamide arm (10%; $p = 0.041$).

Quality of Life: Among patients who had both a baseline performance status and at least one performance status reported on treatment, there was no significant difference between the two arms in time or number of courses to deterioration of performance status. A neurologic assessment was performed on a subset of patients and only at selected sites by the Gynecologic Oncology Group. This consisted of a patient self-report questionnaire and a nurse administered neurologic assessment. There was a trend for a worse total score in the patients treated in the TAXOL arm as compared to baseline and as compared to the cyclophosphamide arm. As the data originated from a subset of patients using a non-validated instrument no formal comparison was made.

Conclusion: In this randomized Phase III trial in patients with untreated advanced ovarian cancer, TAXOL was shown to achieve superior clinical and pathological response rates, improved time to progression and prolonged survival time when compared to standard therapy. The 11.3 months increase in median survival is a significant improvement in treatment for this patient population.

This trial revealed that combining TAXOL and cisplatin does not reduce the ability to deliver full doses of cisplatin. Overlapping toxicities did not necessitate dose reductions or delays of cisplatin. The dose intensity of the TAXOL/cisplatin arm was significantly higher than that of the cyclophosphamide/cisplatin arm.

The safety profile of TAXOL single-agent is well documented from both clinical trials and marketed use of the drug. In this trial, the TAXOL combination was associated with an increased frequency of severe neutropenia compared to the standard arm which was easily managed and had no impact on the timing of dose administration. There was no difference between the two arms in the overall incidence of peripheral neurotoxicity, although there was a higher incidence of severe peripheral neurotoxicity on the TAXOL/cisplatin arm. Severe cardiac events were not different between the two arms. Fever, alopecia, asthenia, arthralgia/myalgia and allergic reactions were also more frequent in the TAXOL arm. Severe events were rare and occurred on both arms at the same frequency.

This randomized phase III trial provides unquestionable evidence of superiority for a TAXOL-based regimen over standard therapy. Therefore, the administration of TAXOL, given a dose of 135 mg/m^2 over 24 hours in combination with cisplatin 75 mg/m^2, should be recommended for the primary treatment of patients with advanced carcinoma of the ovary.

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pages of trade

secret and/or

confidential

commercial

information

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)

/S/ Project Manager April 2, 1998

Signature of Preparer and Title Date

cc: Orig NDA/BLA # 20-262/S-026
HFD-150 /Div File / D. Sprimont
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.

Cheryl L. Anderson

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. **First-line Ovarian ODAC presentation.**

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
a:\20262tax.bms\se1-026\mtgs\minutes\980211m-tcm

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 3000 Wallingford, CT 06492-7660

April 7, 1998

NDA SUPPL AMEND
SE1-026
(RL)

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

5 [illegible] P.O. Box 5100 Wallingford, CT 06492-7660

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 HO (SHL)
D/C to BP4 (SI)
3/17/98

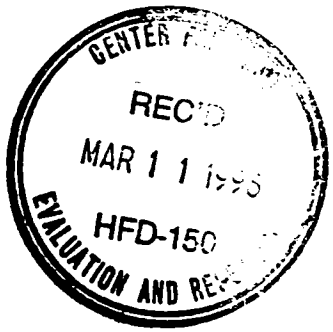
Bristol-Myers Squibb
Pharmaceutical Research Institute

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

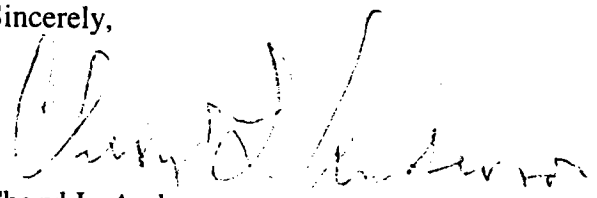
Further comments yesterday from your Division relating to this matter have reinforced this FDA view. Although it is agreed that no further second-line ovary data has been submitted since the Agency originally mandated the inclusion of this statement (in conjunction with the approval of the three-hour 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
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