FDA Analysis of Dose Reductions

Dose Reductions for study 165 was analyzed two ways. First, courses which were identified by the sponsor in the electronic database as "dose reduced" were counted and the reasons for dose reduction were tabulated for each drug.

Table No. 47
Dose Reduction, Study 165

	Taxol/Cisplatin		HD-Taxol/ Cisplatin		Cisplatin/ Etoposide	
Courses Reduced/ Total Courses (%)						
Taxol	117/967 (12%)		90/881 (10%)			
Cisplatin	77/971 (8%)		71/890 (8%)		34/800 (4%)	
Etoposide					98/787 (12%)	
Reason for Dose Reduction						
	Taxol	**Cisplatin**	**Taxol**	**Cisplatin**	**Etoposide**	**Cisplatin**
Hematologic	**83**(71%)	**6** (8%)	**32** (36%)	**2**(3%)	**83** (85%)	**5** (15%)
Renal	--	**30** (39%)	--	**16**(22%)	--	**10**(30%)
Non-hematologic	**29**(25%)	**35** (45%)	**46** (60%)	**43** (60%)	**10** (10%)	**13**(38%)
GI toxicity	17	23	25	22	9	10
Neurotoxicity	10	10	18	21	--	2
Others	**5**(4%)	**6** (8%)	**12** (13%)	**10**(14%)	**5** (5%)	**6** (18%)
TOTAL	**117**	**77**	**90**	**71**	**98**	**34**

Taxol was reduced at a similar rate in the two taxol arms; however, a larger proportion of reductions in the taxol/cisplatin arm were due to hematologic toxicity. Dose reduction in the HD-taxol/cisplatin arm were more due to non-hematologic toxicity. This may be evidence that G-CSF offers protection from severe myelosuppression; however, since the rate of taxol dose reductions were very similar in the two arms, this means that the non-hematologic toxicites became more manifest with increasing the dose of taxol.

In the second analysis, the FDA reviewer examined the actual doses received by the patients in each course. In this analysis, a "dose reduction" occurred if the dose was lower than midvalue between the first and next lower dose level for each drug.

In looking at the two analyses, there is a difference between the number of courses that were identified by the sponsor in the database as "reduced" compared to the actual number of reduced doses given to patients. This difference was attributed to courses of treatment that were not identified by the sponsor as "reduced" if they were the same as a previous course already identified as such.

Table No. 48
Dose Reduction, Study 165

	Taxol/Cisplatin	HD-Taxol/ Cisplatin	Cisplatin/ Etoposide
No. of Courses Reduced			
Taxol	281/971 (29%)	208/890 (23%)	
Cisplatin	123/947 (13%)	99/878 (11%)	53/800 (7%)
Etoposide			160/796 (20%)
	No. of Courses Reduced (%)		
Dose Reduction			
Taxol (Arm A)	n=971		
111-124 mg/m^2	9 (1)		
91-110 mg/m^2	93 (10)		
≤ 90 mg/m^2	179 (18)		
(Arm B)		n=890	
201-225 mg/m^2		6 (<1)	
176-200 mg/m^2		92 (10)	
<175 mg/m^2		110 (12)	
Cisplatin	n=947	n=878	n=800
37.6-56.25 mg/m^2	32 (3)	30 (3)	26 (3)
≤ 37.5 mg/m^2	91 (10)	69 (8)	27 (3)
Etoposide			n=796
85-92.5 mg/m^2			50 (6)
71-84 mg/m^2			23 (3)
≤ 70 mg/m^2			90 (11)

There were more dose reductions observed compared to the prior analysis. Taxol was reduced in 29% of courses in the taxol/cisplatin arm and 23% of courses in the HD-taxol/cisplatin arm. Taxol was reduced more often compared to cisplatin in both arms. The

dose of taxol was reduced to less than half the starting dose in 110/890 (12%) of the courses in the HD-taxol/cisplatin arm and 179/971 (18%) of the courses in the taxol/cisplatin arm. There were also more cisplatin dose reductions in the taxol containing arms.

Note that more courses of taxol was given compared to cisplatin in both the taxol arms. This was due to a number of patients who received taxol alone especially in the latter courses of treatment. The protocol allowed patients to receive taxol alone only for clinical hearing loss or if the serum creatinine exceeded 2.0 during the previous cycle; which was not true in most cases.

***Reviewer's comment**: These data on actual doses in study 165 were requested by the agency specifically since they were not included in the original NDA submission of June 1997. The sponsor submitted the data on drug dosing in January 1998; but cautioned the FDA reviewers they were "not clean".*

In Study 103, the overall proportion of patients with dose reductions was 33% in the teniposide/cisplatin arm and 20% in the taxol/cisplatin arm (p=0.008). Hematologic toxicity was the main reason for dose reduction in the teniposide/cisplatin arm while it was nonhematologic toxicity for the taxol/cisplatin arm. Hematologic toxicity was the most frequent reason for dose reduction in the teniposide/cisplatin arm.

In Study 208, first dose reductions were more frequent in the taxol/cisplatin combination arm than in the cisplatin arm. An analysis of the first six courses did not show a difference in dose reductions for each of the drugs. A dose reduction is defined if the actual dose of drug given is less than midvalue between the first and second dose levels. In a majority of cases for each of the drugs, the reason for dose reduction was not recorded in the electronic data.

Table No. 49
Dose Reduction: First Six Courses, Study 208

	Cisplatin	Taxol/ Cisplatin	
		Taxol	Cisplatin
Total No. of Courses	746	900	849
Courses Reduced (%)	25 (3)	27 (3)	24 (3)
Reason for Reduction			
Hematologic	3	4	7
Non-hematologic	6	6	6
Others	1	1	1
Not entered	15	16	10

Dose Delays

There were more treatment delays reported in the cisplatin/etoposide arm compared to either taxol arms in study 165. Reasons for treatment delay were due to hematologic toxicity in a majority of cases in the cisplatin/etoposide arm, while it was due to "other" reasons for the taxol containing arms. "Other" reasons could be by patient's request, personal or other medical reasons.

Table No. 50
Dose Delays-Study 165

	Taxol/Cisplatin		HD-Taxol/ Cisplatin		Cisplatin/ Etoposide	
	Taxol	**Cisplatin**	**Taxol**	**Cisplatin**	**Cisplatin**	**Etoposide**
Total No. of Courses	967	947	880	878	799	785
Delayed Courses (%)	125 (13)	122 (13)	121 (14)	125 (14)	241 (30)	230 (29)
Reasons for Delay						
Hematologic	21 (17)	22 (35)	10 (8)	10 (8)	126 (52)	123 (53)
Non-Hematologic	14	12	14	15	14	11
Others	90	88	97	100	96	91

An analysis of proportions showed that there were significantly more courses of treatment that were delayed in the cisplatin/etoposide arm versus the taxol/cisplatin arm ($p<0.0001$) and HD-taxol arm ($p<0.0001$). Treatment delays due to hematologic toxicity were significantly higher in the cisplatin/etoposide arm. Since the taxol combination was more myelosuppressive, it was surprising that the taxol-containing treatment arms had less treatment delays due to hematologic toxicity.

Treatment delays were more frequent in the teniposide/cisplatin arm with only 40% of all courses given on time as compared to over 80% in the taxol/cisplatin arm. Hematologic toxicity was the most common reason for treatment delay in the teniposide/cisplatin arm. In study 208, there were more treatment delays in the cisplatin arm and proportionately more delays due to hematologic toxicity.(45% vs 16%)

Hospitalizations

Patients in study 165 were hospitalized in 22% (580/2661) of all treatment courses. The treatment arm distribution and reasons for hospitalization were analyzed from the electronic data listings. The majority of hospitalizations were due to "other" reasons which were for management of emesis, procedures, pain control, etc.

Table No. 51
Hospitalizations-Study 165

All Courses (n=2661)	Taxol/Cisplatin	HD-Taxol/ Cisplatin	Cisplatin/ Etoposide
Courses w/ Hospitalization (%) (n=580)	213 (37%)	185 (32%)	182 (31%)
Reason for Hospitalization			
Fever/Neutropenia	35 (16%)	29 (16%)	18 (10%)
Documented Infection	26	25	29
Tumor Progression	9	5	11
Drug Treatment Side Effects	52 (24%)	45 (24%)	37 (20%)
Dehydration	10	10	5
Hypersensitivity	1	3	--
r/o Infection	7	8	2
Fever (w/o neutropenia)	5	1	--
Neutropenia	--	1	1
Renal failure	1	--	--
Other Reasons	67 (31%)	58 (31%)	79 (43%)

For study 103, there were a total of 136 courses in which hospitalizations were reported, 80 (59%) on the teniposide/cisplatin arm and 56 (41%) on the taxol/cisplatin arm. Unfortunately, the reasons for hospitalization on this study was not found in the database.

FDA Review of Hematologic and Non-Hematologic Toxicities

According to the sponsor, the higher incidence of hematologic toxicity in the taxol/cisplatin arm was possibly due to the higher median number of courses received. An analysis of the first course hematologic toxicities using the electronic database for study 208 showed the following:

Table No. 52
First Course Hematologic Toxicities- Study 208

	Cisplatin (%) (n=206)	Cisplatin/Taxol (%) (n=202)
Neutropenia		
All Grade	40 (19)	72 (36)
Grade III + IV	2 (1)	27 (13)
Anemia		
All Grade	96 (47)	139 (69)
Grade III + IV	3 (1)	7 (3)
Thrombocytopenia		
All Grade	59 (29)	35 (17)
Grade III + IV	6 (3)	3 (1)

Using fishers exact test, the incidence of severe neutropenia (grade III and IV) was significantly higher in the cisplatin/taxol arm after the first course of chemotherapy ($p<0.0001$). The difference in severe anemia and thrombocytopenia were not significant ($p=0.217$ and 0.503, respectively).

The following two tables review the incidence of several toxicities in the three studies. The shaded areas represent those where there was a significant difference by Fisher's exact test compared to the control arm in each study.

Table No. 53
Summary of Severe (Gr III and IV) Hematologic Toxicities - Study 165, 103, 208

	Number of Patients (%)						
	Study 165[a]			**Study 103**		**Study 208**	
	T/C (n=195)	C/E (n=196)	HD-T/C (n=197)	Ten/C (n=163)	T/C (n=159	C (n=204	T/C (n=200)
Neutropenia (Grade 4 only)	144(74) p=.001	108(55)	128(65) p=.063	108(69) p<.0001	44(28)	34 (17)	90 (46) p<.0001
Fever/Neutropenia	Na[b]	NA	NA	60(36) p<.0001	8(5)	1 (<1)	8 (4) p=0.019
Thrombocytopenia (Grade 4 only)	1 (1)	9 (5)	9 (5)	30 (18) p<.0001	2 (1)	1 (<1)	1 (<1)
Anemia	42 (22)	54 (28)	38 (20)	37 (22) p=.0014	15 (10)	140 (68)	135 (67)
Bleeding	17 (9)	23 (13)	18 (10)	35 (21)	35 (22)	33 (16)	34 (17)

Legend: T= taxol, C= cisplatin, Ten= teniposide
[a] p-values listed under taxol arm was compared against cisplatin/etoposide
[b] fever/neutropenia was not analyzed in this study

Table No. 54
Summary of Severe (Gr III and IV) Non-Hematologic Toxicities - Study 165, 103, 208

	Number of Patients (%)						
	Study 165[a]			Study 103		Study 208	
	T/C (n=195)	C/E (n=196	HD-T/C (n=197)	Ten/C (n=163)	T/C (n=159)	C (n=204	T/C (n=200)
Hypersensitivity	1(1)	1(1)	8(4) p=.009	1(1)	2(1)	5 (2)	15 (7) p=.022
Cardiovascular	26(14)	15(8)	23(12)	10(6)	12(8)	6 (3)	10 (5)
Neurosensory	25(13)	15(8)	55(28) p=.04	1(1)	14(9) p=.0003	2 (1)	8 (4)
Alopecia	128(66)	130(67)	151(77)	144(88)	143(90)	39 (19)	174 (87) p<.0001
Arthralgia/Myalgia	5(3)	1(1)	21(11) p<.001	1(1)	6(4)	4 (2)	10 (5)
All grades (I-IV)	40(21) p=.001	17(9)	83(43) p<.001	28(17)	79(49) <.001	41 (20)	92 (46) p<.0001
Diarrhea	12(6)	9(5)	17(9)	6(3)	2(2)		
All grades (I-IV)	67(34) p=.035	48(24)	94(48) p<.001	50(29)	49(30)	22 (11)	40 (20) p=.014
Mucositis	2(1)	3(2)	7(4)	1(1)	2(1)	1 (<1)	2 (1)
All grades (I-IV)	36(19)	31(17)	55(29) p=.005	42(26)	30(19)	21 (10)	24 (12)
Nausea/Vomiting	53(27)	44(22)	58(30)	32(20)	22(14)	32 (16)	24 (12)

Ototoxicity	--	--	--	7 (11)	7 (5)	33 (16) p=.0001	9 (4)
Tx Discontinued due to Toxicity	75(38%) p=.003	48(24%)	92(46%) p<.001	26 (16)	30 (19)	51 (25%)	38 (18)

Legend: T= taxol, C= cisplatin, Ten= teniposide
[a]p-values listed under taxol arm was compared against cisplatin/etoposide

Shaded areas on the table show comparisons with statistically significant differences in toxicity compared to the corresponding control arm . In study 165, the HD-taxol/cisplatin/G-CSF arm is significantly less tolerated than the cisplatin/etoposide arms shows significant difference in the occurrence of severe hypersensitivity and neurologic events. All grades considered, patients in this arm also experienced more arthralgia/ myalgia, mucositis and diarrhea. More patients enrolled in this arm discontinued treatment compared to the other treatment arms. Patients in the taxol/cisplatin arm experienced significantly more diarrhea, arthralgia/ myalgia and mucositis compared to cisplatin/etoposide.

The teniposide/cisplatin combination in study 103 resulted in significantly worse hematologic toxicities and fever/neutropenia; but significantly less arthralgia, myalgia and neurosensory toxicity compared to the taxol/cisplatin combination. For study 208, treatment with cisplatin/taxol resulted in significantly more first and worst degree neutropenia and more fever/neutropenia compared to cisplatin.

APPEARS THIS WAY
ON ORIGINAL

OVERALL CONCLUSION

There are approved treatments and several investigational drugs available for advanced non-operable non-small cell lung cancer. It is important that a favorable ratio of benefit to risk be established before approving a drug for this indication. In the controlled studies submitted to the NDA, the addition of taxol to cisplatin would need to have clearly demonstrated an advantage in efficacy and tolerable toxicity. Efficacy could have been demonstrated by a significant increment in survival, or by convincing superiority in response rates, time to tumor progression, plus a believable increment in measured quality of life. However, it is this reviewer's opinion that the sponsor has not demonstrated a favorable ratio of benefit to risk with taxol in combination with cisplatin as a three-hour or 24-hour infusion in patients with non-small cell lung cancer.

ADVISORY COMMITTEE RECOMMENDATION

A majority of the advisory committee members voted that Study 165 was adequate and well-controlled and recommended approval of taxol as a 24-hour infusion in combination with cisplatin for the treatment of patients with non-small cell lung cancer who are not candidates for potentially curative surgery or radiotherapy. The 3-hour infusion schedule of taxol in combination with cisplatin was not supported by the committee. (See voting results and discussion notes in the following section)

/S/ 4/6/98

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HFD-150/Division File
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APPENDIX I. FOUR MONTH SAFETY UPDATE

NDA # 20-262/SE1-024 **Submission Date: October 27, 1997**
Review Date: February 20, 1998

Applicant: Bristol-Myers Squibb

During the interval of the report from June to October 1997, there were no new reports of patients who died or whose treatment were terminated due to adverse events. No new serious, unexpected events that would require revision of the proposed package insert were reported. There were six 15-day reports of serious/unexpected events inpatients with lung cancer obtained from post-marketing surveillance who died of the following:

1. Patient : died with pulmonary fibrosis and progression of disease after the second cycle of taxol/ carboplatin
2. Patient : died after experiencing paralysis, convulsions and coma after two weeks of taxol/cisplatin
3. Patient : unexpected development of a "lump" on the arm and a large area of induration on the calf
4. Patient : death from pulmonary fibrosis after receiving taxol + RT
5. Patient : unexpected sever hiccups on the first day taxol/carboplatin therapy was given
6. Patient seizures with aphasia without evidence of CNS pathology by MRI or EEG

APPENDIX II. ODAC Questions and Answers

NDA #20-262/SE1-024
Paclitaxel Injection for Non-Small Cell Lung Cancer
March 20, 1998

Three randomized, prospective, multicenter clinical trials in more than 1300 patients compared taxol in combination with cisplatin to cisplatin/etoposide in study 165, cisplatin/teniposide in study 103, and a higher dose of cisplatin alone in study 208 with the following efficacy results:

Efficacy Results/FDA Analysis- Taxol Pivotal Studies[a]

	Number of Patients (%)						
	Study 165 (24-hr taxol infusion)			Study 103 (3-hr taxol infusion)		Study 208 (3-hr taxol infusion)	
	T/C (n=198)	HD-T/C (n=201)	C/E (n=200)	T/ C (n=166)	Ten/C (n=166)	T/C (n=190)	C (n=197)
Response rate (p-value)	21% **p=.01**[b]	24% **p=.001**[b]	12%	33% **p=.02**	21%	26% **p=.04**	17%
Time to Progression Median (months) (p-value)	4.3 p=.05[b]	4.9 **p=.004**[b]	2.7	5.1 p=.72	5.0	4.3 p=.08	3.2
Survival Median (months) (p-value)	9.3 p=.13[b]	10.0 p=.08[b]	7.4	9.5	9.9 p=.80	8.1	8.6 p=.86

T= taxol, C= cisplatin, E= etoposide, Ten= teniposide
[a] areas shaded show statistical significance
[b] versus cisplatin/etoposide, α= .0125

The taxol combination arms in the three trials showed superior response rates compared to the control arms. A significant increase in time to tumor progression was shown only in the HD-taxol/cisplatin arm in study 165. There was no statistically significant difference in overall survival between treatment arms in any of the studies.

The taxol combination arms were more toxic than the cisplatin/etoposide arm in study 165; and compared to a higher dose of cisplatin in study 208. In study 103, the teniposide/cisplatin arm had significantly more hematologic toxicities while the taxol/cisplatin arm had more arthralgia, myalgia and neurosensory events. Adverse events with statistically significant differences are shaded in the following table:

Safety Results- Taxol Pivotal Studies

Toxicity	Number of Patients (%)						
	Study 165 (24-hr taxol infusion)			Study 103 (3-hr taxol infusion)		Study 208 (3-hr taxol infusion)	
	T/C (n=195)	HD-T/C (n=197)	C/E (n=196)	T/ C (n=159)	Ten/C (n=163)	T/C (n=200)	C (n=204)
Neutropenia [a]	144 (74) p=.001	128 (65) p=.06	108 (55)	44 (28)	108 (69) p<.001	90 (46) p<.0001	34 (17)
Fever/Neutropenia	NS	NS	NS	8 (5)	60 (36) p<.0001	8 (4) p=.02	1 (<1)
Thrombocytopenia[a]	1 (1)	9 (5)	9 (5) p=.02	2 (1)	30 (18) p<.0001	1 (<1)	1 (<1)
Hypersensitivity[b]	1 (1)	8 (4) p=.01	1 (1)	2 (1)	1 (1)	15 (7) p=.02	5 (2)
Neurosensory[b]	25 (13)	55 (28) p=.04	15 (8)	14 (9) p=.0003	1 (1)	8 (4)	2 (1)
Arthralgia/Myalgia[c]	40 (21) p=.001	83 (43) p<.001	17 (9)	79 (49) p<.001	28 (17)	92 (46) p<.0001	41 (20)
Diarrhea[c]	67 (34) p=.04	94 (48) p=.005	48 (24)	49 (30)	50 (29)	40 (20) p=.01	22 (11)
Alopecia[b]	128 (66)	151 (77)	130 (67)	143 (90)	144 (88)	174 (87) p<.0001	39 (19)
Ototoxicity[b]	--	--	--	7 (5)	7 (11)	9 (4)	33 (16) p=.0001

T= taxol, C= Cisplatin, E= etoposide, Ten= teniposide, NS= data not submitted
[a] grade IV only
[b] grades III-IV
[c] grades I-IV

The indication sought by the Applicant is for the treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy. The Applicant's recommendation is that taxol be administered over three hours at a dose of 175 mg/m^2 followed by a platinum compound given every three weeks, and that should a 24-hour infusion of taxol be selected for combination with a platinum compound, the recommended dose of taxol should be 135 mg/m^2 every three weeks.

QUESTIONS:

1. Do Studies 103 and 208 serve as adequate and well controlled trials demonstrating the efficacy and safety of 175 mg/m^2 of taxol as a 3-hour infusion in combination with cisplatin for the treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and /or radiation therapy?

1 YES **5** NO **2** Abstain

Discussion Notes:

According to Dr. Albain, she voted "no" since she believed that the studies lacked scientific rigor, and there was no survival advantage shown.

Dr. Schilsky voted "yes" since he thought that the studies were adequate and well-controlled; but no efficacy advantage was shown.

2. Does Study 165 serve as an adequate and well controlled trial demonstrating the efficacy and safety of 135 mg/m^2 of taxol as a 24-hour taxol infusion in combination with cisplatin for the treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and /or radiation therapy?

7 YES **1** NO

Discussion Notes:

The following were the reasons given by the members of the committee who voted "yes"

Dr. Schilsky: modest survival advantage, QOL life advantage

Dr. Albain: impressed by one-year survival differences, lack of other treatments

Dr. Swain: time to tumor progression and response rate advantage; but thought hat the QOL data was weak

Dr. Dutcher: one year survival difference and time to tumor progression

Dr. Simon: small survival advantage, QOL

3. Should taxol as a 3-hour infusion at 175 mg/m^2 in combination with cisplatin be approved for the treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and /or radiation therapy?

2 YES **5** NO **1** Abstain

Discussion Notes:

Dr. Schilsky: no, since clinical trials did not demonstrate overall benefit

4. Should taxol as a 24-hour infusion at 135 mg/m^2 in combination with cisplatin be approved for the treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and /or radiation therapy?

5 YES **2** NO **1** Abstain

Discussion Notes:

Dr. Schilsky: yes, clinical trial demonstrated overall benefit

Dr. Simon: no, wants to see the results of other clinical trials

APPENDIX III. Review of Labeling for sNDA 20-262 (version 1)

NDA # 20-262/SE1-026
Taxol for NSCLC
Applicant: Bristol-Myers Squibb

Submission Date: June 30, 1997
Review Date: March 30, 1998

RECOMMENDATIONS:

The following comments should be sent to the applicant by FAX transmission. Revisions proposed by the medical reviewer are annotated in the attached copy of the proposed label and italicized in the review. A revised draft labeling should be prepared by the applicant in response to the following comments:

Redacted 2

pages of trade secret and/or confidential commercial information