# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: NDA 20-262/S-024

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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SEP 25 1997

# CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

sNDA: 20-262/024 Submission Date: June 30, 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® in patients with advanced non-small cell lung cancer who are not candidates for potentially curative surgery or radiotherapy. Taxol® 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 the new indication (i.e. non-small cell lung cancer) will be based on data from two efficacy large, multicenter, and randomized Phase III trials (CA139-165 and CA139-103) with doses of 175 mg/m$^2$ infused over 3 hours, and 135 mg/m$^2$ and 250 mg/m$^2$ infused over 24 hours. The proposed label recommends the dose of 175 mg/m$^2$ over 3 hours; with the option of using an alternate schedule of 135 mg/m$^2$ over 24 hours.

This submission contains no additional information on the pharmacokinetics of paclitaxel. It refers only to some data on gender analysis included in the original NDA for Taxol® (Submission of July 21, 1992). The original NDA was revisited and the data on gender analysis were reviewed.

## Effect of Gender on the Pharmacokinetics of Paclitaxel:

To assess the effect of gender on the pharmacokinetics of paclitaxel, data were obtained from patients with cancer of various histologies (e.g. solid tumors or lymphoma) who received single 170-275 mg/m$^2$ doses of Taxol® over -hour infusions (Studies No. CA139-006, -007, and -009). These data are summarized in the Table below (next page):

## Pharmacokinetic Parameters of Paclitaxel Following 6-Hour Infusions at Dose Levels of 170-275 mg/m$^2$

| Study No. | Dose (mg/m$^2$) | Gender | CLT (L/h/m$^2$) | Vss (L/m$^2$) | T-HALF (h) |
|---|---|---|---|---|---|
| -006 | 170 | M | 9.7 | 73 | 8.2 |
| -006 | 170 | M | 7.5 | 65 | 9.4 |
| -006 | 170 | M | 12 | 113 | 8.5 |
| -007 | 175 | M | 6.1 | 56 | 7.7 |
| -007 | 175 | M | 4.4 | 67 | 16 |
| -009 | 175 | M | 22 | 64 | 2 |
| -009 | 175 | M | 20 | 50 | 4 |
| -007 | 200 | M | 8.6 | 70 | 14 |
| -009 | 200 | M | 11.5 | 86 | 10 |
| -006 | 212 | M | 15.5 | 154 | 10 |
| -009 | 225 | M | 16.5 | 70 | 5.5 |
| -009 | 225 | M | 8.1 | 49 | 6.7 |
| -009 | 225 | M | 8.1 | 50 | 4.1 |
| -007 | 230 | M | 7.8 | 90 | 18 |
| -007 | 230 | M | 10.8 | 132 | 12 |
| -009 | 250 | M | 26 | 135 | 8.7 |
| -006 | 265 | M | 3.9 | 42 | 12 |
| -006 | 250 | M | 14 | 106 | 9 |
| -007 | 275 | M | 5.9 | 27 | 4.6 |
| -009 | 275 | M | 9.4 | 92 | 12 |
| -009 | 275 | M | 6.9 | 40 | 6.8 |
| n | | | 21 | 21 | 21 |
| Mean | | | 11 | 78 | 9 |
| SD | | | 6 | 34 | 4 |
| %CV | | | 54% | 43% | 44% |
| -006 | 170 | F | 5.0 | 72 | 17 |
| -007 | 175 | F | 7.7 | 66 | 8.2 |
| -007 | 200 | F | 8.6 | 70 | 14 |
| -006 | 212 | F | 14.5 | 68 | 3.2 |
| -006 | 212 | F | 19 | 84 | 2.2 |
| -007 | 230 | F | 6.6 | 72 | 13 |
| -009 | 250 | F | 13 | 42 | 3.5 |
| -006 | 265 | F | 4.1 | 46 | 16 |
| -007 | 275 | F | 8.1 | 41 | 6.0 |
| -007 | 275 | F | 3.5 | 57 | 18 |
| n | | | 10 | 10 | 10 |
| Mean | | | 9 | 62 | 10 |
| SD | | | 5 | 14 | 6 |
| %CV | | | 55% | 23% | 60% |

More details are provided in Attachment 1 (Tables 1-10)

Conclusion: These data demonstrates that at doses of 170-275 mg/m$^2$ infused over 6-hours, mean clearance and volume of distribution values for paclitaxel were about 20 % lower in female patients (n=10) than in male patients (n=21); this difference may not be clinically significant. As a result of the decrease in both clearance and in steady-state volume of distribution in female patients, the half-life remained unchanged and was comparable to that in male patients. The lower clearance and volume of distribution may be attributed to slower metabolism and/or higher protein binding capacity in females than in males.

**COMMENTS:**

1. The gender analysis performed using data from studies CA 139-006, -007, and -009 involve cancer patients who received -hour infusions. Since paclitaxel pharmacokinetics are dose and schedule (duration of infusion) dependent, the gender effect observed in these studies using -hour infusions (20% decrease in total body clearance and steady-state volume of distribution) may not be the same as the recommended 3-hour infusions of 175 mg/m2 dose.

2. The statement regarding the gender effect in the Clinical Pharmacology section of the Package Insert as stated by the sponsor,

should be deleted. The information is not appropriate since hour infusion of taxol® is not an approved schedule, and due to nonlinear pharmacokinetics of paclitaxel, results using one infusion rate can not be extrapolated to a different infusion rate.

3. The sponsor should evaluate the gender effect on the pharmacokinetics of paclitaxel at 175 mg/m$^2$ dose given via 3 hour infusion in non small cell lung cancer patients.

**RECOMMENDATION:**

The statement regarding the gender effects on the pharmacokinetics of paclitaxel after hour infusion should be deleted from the package insert.

Please forward the comments to the sponsor.

/S/

Reviewer: Safaa S. Ibrahim, Ph.D.
Division of Pharmaceutical Evaluation I

RD/FT

/S/ 9/25/97

Team Leader: Atiqur Rahman, Ph.D.
Division of Pharmaceutical Evaluation I

cc: sNDA: 20-262/024
HFD-150/Division file
HFD-150/Spillman, Williams, Chico
HFD-850/Lesko
HFD-860/Malinowski, Mehta, Rahman, Ibrahim
CDR (B. Murphy)

# Attachment 1

Table 4. (continued)

PHARMACOKINETICS OF TAXOL FOLLOWING 6-HOUR INFUSIONS
Dose Level = 170 mg/m²

| Study No. | Patient No. | Sex | Dose (mg/m²) | CMAX (ng/mL) | AUC(0-t) (ng · h/mL) | AUC(0-∞) (ng · h/mL) | T-HALF (h) | CLT (L/h/m²) | VSS (L/m²) | UR* (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| CA139-006 | | M | | | | | | | | |
| CA139-006 | | M | | | | | | | | |
| CA139-006 | | M | | | | | | | | |
| CA139-006 | | F | | | | | | | | |
| | | | n | 4 | | 4 | | | | |
| | | | mean | 3346 | | 22711 | | | | |
| | | | SEM | 645 | | 4862 | | | | |
| | | | % cv | 38.6 | | 42.8 | | | | |

* = urine collected for variable durations after start of infusion
** = insufficent data for calculations
ND = no data

039

06 00040

Table 2 (continued)

PHARMACOKINETICS OF TAXOL FOLLOWING 6-HOUR INFUSIONS
Dose Level = 175 mg/m²

| Study No. | Patient No. | Sex | Dose (mg/m²) | CMAX (ng/mL) | AUC(0-t) (ng • h/mL) | AUC(0-∞) (ng • h/mL) | T-HALF (h) | CLT (L/h/m²) | VSS (L/m²) | UR* (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| CA139-007 | | M | | | | | | | | |
| CA139-007 | | F | | | | | | | | |
| CA139-007 | | M | | | | | | | | |
| CA139-007 | | F | | | | | | | | |
| | | | n | 4 | | 3 | | | | |
| | | | mean | 2937 | | 30544 | | | | |
| | | | SEM | 571 | | 5146 | | | | |
| | | | % cv | 38.9 | | 29.2 | | | | |
| CA139-009 | | M | | | | | | | | |
| CA139-009 | | M | | | | | | | | |
| | | | n | 2 | | 2 | | | | |
| | | | mean | 1675 | | 8448 | | | | |
| | | | SEM | 185 | | 402 | | | | |
| | | | % cv | 15.6 | | 6.7 | | | | |
| | | | n | 6 | | 5 | | | | |
| | | | mean | 2517 | | 21706 | | | | |
| | | | SEM | 451 | | 6104 | | | | |
| | | | % cv | 43.9 | | 62.9 | | | | |

* = urine collected for variable durations after start of infusion
** = insufficent data for calculations
ND = no data

040

96 00004

Table 3. ~~(continued)~~

PHARMACOKINETICS OF TAXOL FOLLOWING 6-HOUR INFUSIONS
Dose Level = 200 mg/m²

| Study No. | Patient No. | Sex | Dose (mg/m²) | CMAX (ng/mL) | AUC(0-t) (ng·h/mL) | AUC(0-∞) (ng·h/mL) | T-HALF (h) | CLT (L/h/m²) | VSS (L/m²) | UR* (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| CA139-007 | | F | | | | | | | | |
| CA139-007 | | M | | | | | | | | |
| | | | n | 2 | | 2 | | | | |
| | | | mean | 4500 | | 27695 | | | | |
| | | | SEM | 68 | | 4574 | | | | |
| | | | % cv | 2.1 | | 23.4 | | | | |
| CA139-009 | | M | | | | | | | | |
| | | | n | 1 | | 1 | | | | |
| | | | mean | . | | . | | | | |
| | | | SEM | . | | . | | | | |
| | | | % cv | . | | . | | | | |
| | | | n | 3 | | 3 | | | | |
| | | | mean | 3880 | | 24242 | | | | |
| | | | SEM | 621 | | 4346 | | | | |
| | | | % cv | 27.7 | | 31.1 | | | | |

* = urine collected for variable durations after start of infusion
** = insufficent data for calculations
ND = no data

Table 4
~~(continued)~~

PHARMACOKINETICS OF TAXOL FOLLOWING 6-HOUR INFUSIONS
Dose Level = 212 mg/m²

| Study No. | Patient No. | Sex | Dose (mg/m²) | CMAX (ng/mL) | AUC(0-t) (ng • h/mL) | AUC(0-∞) (ng • h/mL) | T-HALF (h) | CLT (L/h/m²) | VSS (L/m²) | UR* (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| CA139-006 | | M | | | | | | | | |
| CA139-006 | | F | | | | | | | | |
| CA139-006 | | F | | | | | | | | |
| | | | n | 3 | | 3 | | | | |
| | | | mean | 2397 | | 13122 | | | | |
| | | | SEM | 282 | | 945 | | | | |
| | | | % cv | 20.4 | | 12.5 | | | | |

* = urine collected for variable durations after start of infusion
** = insufficent data for calculations
ND = no data

042

06 000043

Table 5.
(continued)

PHARMACOKINETICS OF TAXOL FOLLOWING 6-HOUR INFUSIONS
Dose Level = 225 mg/m²

| Study No. | Patient No. | Sex | Dose (mg/m²) | CMAX (ng/mL) | AUC(0-t) (ng • h/mL) | AUC(0-∞) (ng • h/mL) | T-HALF (h) | CLT (L/h/m²) | VSS (L/m²) | UR* (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| CA139-009 | | M | | | | | | | | |
| CA139-009 | | M | | | | | | | | |
| CA139-009 | | M | | | | | | | | |
| | | | n | 3 | | 3 | | | | |
| | | | mean | 3740 | | 22390 | | | | |
| | | | SEM | 710 | | 4425 | | | | |
| | | | % cv | 32.9 | | 34.2 | | | | |

* = urine collected for variable durations after start of infusion
** = insufficent data for calculations
ND = no data

043

Table 6.
(continued)

PHARMACOKINETICS OF TAXOL FOLLOWING 6-HOUR INFUSIONS
Dose Level = 230 mg/m²

| Study No. | Patient No. | Sex | Dose (mg/m²) | CMAX (ng/mL) | AUC(0-t) (ng • h/mL) | AUC(0-∞) (ng • h/mL) | T-HALF (h) | CLT (L/h/m²) | VSS (L/m²) | UR* (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| CA139-007 | | M | | | | | | | | |
| CA139-007 | | M | | | | | | | | |
| CA139-007 | | F | | | | | | | | |
| | | | n | 3 | | 3 | | | | |
| | | | mean | 3495 | | 28451 | | | | |
| | | | SEM | 777 | | 3890 | | | | |
| | | | % cv | 38.5 | | 23.7 | | | | |

* = urine collected for variable durations after start of infusion
** = insufficent data for calculations
ND = no data

470

540005 06

Table 7.
(continued)

PHARMACOKINETICS OF TAXOL FOLLOWING 6-HOUR INFUSIONS
Dose Level = 250 mg/m²

| Study No. | Patient No. | Sex | Dose (mg/m²) | CMAX (ng/mL) | AUC(0-t) (ng • h/mL) | AUC(0-∞) (ng • h/mL) | T-HALF (h) | CLT (L/h/m²) | VSS (L/m²) | UR* (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| CA139-009 | | F | | | | | | | | |
| CA139-009 | | M | | | | | | | | |
| | | | n | 2 | | 2 | | | | |
| | | | mean | 2470 | | 14244 | | | | |
| | | | SEM | 1060 | | 4695 | | | | |
| | | | % cv | 60.7 | | 46.6 | | | | |

* = urine collected for variable durations after start of infusion
** = insufficent data for calculations
ND = no data

045

8

Table 4.
(continued)

PHARMACOKINETICS OF TAXOL FOLLOWING 6-HOUR INFUSIONS
Dose Level = 265 mg/m²

| Study No. | Patient No. | Sex | Dose (mg/m²) | CMAX (ng/mL) | AUC(0-t) (ng • h/mL) | AUC(0-∞) (ng • h/mL) | T-HALF (h) | CLT (L/h/m²) | VSS (L/m²) | UR* (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| CA139-006 | | M | | | | | | | | |
| CA139-006 | | M | | | | | | | | |
| CA139-006 | | F | | | | | | | | |
| | | | n | 3 | | 3 | | | | |
| | | | mean | 8267 | | 50937 | | | | |
| | | | SEM | 2484 | | 15937 | | | | |
| | | | % cv | 52.0 | | 54.2 | | | | |

* = urine collected for variable durations after start of infusion
** = insufficent data for calculations
ND = no data

Table 9.
(continued)

PHARMACOKINETICS OF TAXOL FOLLOWING 6-HOUR INFUSIONS
Dose Level = 275 mg/m²

| Study No. | Patient No. | Sex | Dose (mg/m²) | CMAX (ng/mL) | AUC(0-t) (ng·h/mL) | AUC(0-∞) (ng·h/mL) | T-HALF (h) | CLT (L/h/m²) | VSS (L/m²) | UR* (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| CA139-007 | | F | | | | | | | | |
| CA139-007 | | M | | | | | | | | |
| CA139-007 | | F | | | | | | | | |
| | | | n | 3 | | 3 | | | | |
| | | | mean | 7093 | | 53299 | | | | |
| | | | SEM | 1191 | | 13582 | | | | |
| | | | % cv | 29.1 | | 44.1 | | | | |
| CA139-009 | | M | | | | | | | | |
| CA139-009 | | M | | | | | | | | |
| | | | n | 2 | | 2 | | | | |
| | | | mean | 5690 | | 34527 | | | | |
| | | | SEM | 1600 | | 5211 | | | | |
| | | | % cv | 39.8 | | 21.3 | | | | |
| | | | n | 5 | | 5 | | | | |
| | | | mean | 6532 | | 45790 | | | | |
| | | | SEM | 894 | | 8899 | | | | |
| | | | % cv | 30.6 | | 43.5 | | | | |

* = urine collected for variable durations after start of infusion
** = insufficent data for calculations
ND = no data

047

06 000048

Table 10.

KEY PHARMACOKINETIC PARAMETERS FOLLOWING 6-HOUR INFUSIONS: MEAN VALUES AND EFFECT OF GENDER (Dose Levels = 170-275 mg/m²)

| Study No. | Patient No. | Sex | Dose (mg/m²) | T-HALF (h) | CLT (L/h/m²) | VSS (L/m²) | UR* (%) |
|---|---|---|---|---|---|---|---|
| CA139-006<br>CA139-007<br>CA139-009 | ALL | M/F | 170-275 | | | | |
| | | | n | 31 | 31 | 31 | 17 |
| | | | mean | 9.5 | 10.41 | 74 | 6.0 |
| | | | SEM | 0.9 | 1.02 | 6 | 1.3 |
| | | | % cv | 53.3 | 54.4 | 41.7 | 90.0 |
| CA139-006<br>CA139-007<br>CA139-009 | ALL | M | 170-275 | | | | |
| | | | n | 21 | 21 | 21 | 13 |
| | | | mean | 9.4 | 11.07 | 79 | 5.8 |
| | | | SEM | 1.0 | 1.30 | 8 | 1.7 |
| | | | % cv | 50.1 | 53.8 | 43.8 | 105.1 |
| CA139-006<br>CA139-007<br>CA139-009 | ALL | F | 170-275 | | | | |
| | | | n | 10 | 10 | 10 | 4 |
| | | | mean | 10.1 | 9.02 | 62* | 6.8 |
| | | | SEM | 2.0 | 1.57 | 5 | 1.4 |
| | | | % cv | 61.5 | 55.2 | 23.6 | 40.4 |

* = urine collected for variable durations after start of infusion
*significantly different (p=0.01) from value for males; see Appendix B

↓ 18% in F/M

↓ 20% in F/M

050

06 000051