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APPLICATION NUMBER:

21-660

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21,660
Brand Name:	Abraxane
Generic Name:	Paclitaxel protein-bound particles for injectable suspension (albumin bound)
Indication:	[redacted]
Dosage Form:	100 mg of paclitaxel and 900 mg of human albumin
Strength:	Each milliliter (ml) of reconstituted suspension contains 5 mg paclitaxel
Route of Administration:	IV Infusion
Dosage and administration:	260 mg/m^2 over 30 minutes every 3 weeks
Applicant:	American Bioscience, Inc. Santa Monica, CA 90403
OCPB Division:	Division of Pharmaceutical Evaluation I (HFD-860)
OND Division:	Division of Oncology Drug Products (HFD-150)
Submission Date:	19-MAR-2004; 21-JUN-2004; 7-JUL-2004; 22-JUL-2004; 11-OCT-2004
Primary Reviewer:	Angela Yuxin Men, M.D., Ph.D.
Acting Team Leader:	Brian Booth, Ph.D.
Pharmacometrics Team Leader:	Jogarao Gobburu, Ph.D.

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I Executive Summary

The applicant submitted the original NDA 21-660, Abraxane, seeking marketing approval for the use of Abraxane in patients with metastatic breast cancer through the 505(b)(2) approach using Taxol® as a reference drug.

Abraxane is a Cremophor–free formulation of paclitaxel. It is developed with the objective of eliminating Cremophor-EL and alcohol from Taxol to overcome some problems associated with these solvents, such as hypersensitivity. The clinical pharmacology section contains 4 study reports (CA005-0, DM97-123, CA012-0, and CA008-0) in patients with non-hematologic malignancies/solid tumor/metastatic breast cancer. In summary, pharmacokinetic (PK) studies were conducted in 65 cancer patients aged 33 to 83 years old. Patients were dosed from 80 to 375 mg/m^2. Exposure increased linearly with doses between 80 to 375 mg/m^2. Compared to Taxol, Abraxane showed higher total clearance (43%) and larger volume of distribution (53%). The terminal half-life, about 21 hours, was identical for Abraxane and Taxol. The applicant did not study the safety and pharmacokinetics of Abraxane in hepatic impaired patients. In the Phase 3 comparison study, 260 mg/m^2 Abraxane was more efficacious than 175 mg/m^2 Taxol. Abraxane demonstrated significantly higher reconciled target lesion response rate compared to Taxol. Abraxane did not require any pre-medication for hypersensitivity and there were no severe hypersensitivity reactions observed for Abraxane. This review evaluates the submitted data and provides recommendations on the labeling.

A. Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) finds the submitted data in NDA 21-660 for Abraxane acceptable, with some revisions to the applicant's proposed label (please refer to Section III on page 24).

B. Phase IV Commitment

The applicant should evaluate Abraxane safety and pharmacokinetics in subjects with hepatic impairment, to allow the determination of dosing adjustment for this population.

C. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Abraxane (paclitaxel protein-bound particles for injectable suspension) is an albumin bound paclitaxel, which is free of Cremophor-EL solvents. The active ingredient, paclitaxel, is the same as Taxol. Pharmacokinetic parameters of total paclitaxel were determined in Phase 1, 2 and 3 studies after intravenous infusion of Abraxane over 30- and 180- minutes in cancer patients at doses of 80-375 mg/m^2. The maximal tolerated dose (MTD) of Abraxane was determined to be 300 mg/m^2, which was about 50% higher than the MTD for Taxol. Linear pharmacokinetics (PK) of Abraxane were observed

between 80 to 375 mg/m^2. The total clearance of Abraxane was 15 L/hr/m^2 and the volume of distribution was 632 L/m^2. The total clearance and volume of distribution of paclitaxel were higher when administered as Abraxane compared to Taxol. The terminal half-life of 21-hour was the same as Taxol. Urinary excretion of Abraxane accounted for <6% of paclitaxel and the renal clearance was 0.16 to 1.08 L/hr/m^2 which indicates that extra-renal elimination was extensive. Fecal excretion accounted for 22% of total dose. Paclitaxel accounted for 3% and its metabolite, 6α-hydroxypaclitaxel, 18%.

In the Phase 3 study, Abraxane 260 mg/m^2 was more efficacious than Taxol 175 mg/m^2 in the treatment of patients with breast cancer. Patients with metastatic breast cancer who received Abraxane demonstrated significantly higher Reconciled Target Lesion Response Rate (22% vs 11%, P = 0.003). Unlike Taxol, without any pre-medication, there were no severe hypersensitivity reactions observed for Abraxane. In the Phase 3 comparison of Abraxane versus Taxol, patients treated with Abraxane experienced less neutropenia despite a 49% higher dose of paclitaxel. However, compared to Taxol, sensory neuropathy was more common in patients treated with Abraxane.

_____ Date: _____

Angela Yuxin Men, Ph.D.
Reviewer
Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

_____ Date: _____

Brian Booth, Ph.D.
Acting Team Leader
Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

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