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**21-660**

*APPLICATION NUMBER:*

**PHARMACOLOGY REVIEW(S)**



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION**

NDA NUMBER: 21, 660  
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DATE RECEIVED BY CENTER: 03/07/04  
PRODUCT: ABI-007  
INTENDED CLINICAL POPULATION: —  
SPONSOR: American Bioscience, Inc.  
DOCUMENTS REVIEWED: Electronic submission  
REVIEW DIVISION: Division of Oncology Drug Products (HFD-150)  
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### Executive Summary

#### I. Recommendations

- A. Recommendation on Approvability: Approve
- B. Recommendation for Nonclinical Studies: Approve
- C. Recommendations on Labeling: See separate labeling review

#### II. Summary of Nonclinical Findings

##### A. Brief Overview of Nonclinical Findings

Abraxane is composed of a Cremophor-free formulation of paclitaxel formulated in human serum albumin. The name Abraxane refers to the clinical formulation of the drug product used in Phase 3 studies, which is to be used commercially. This name refers to the natural biosource material, *T. media*, and a ratio of 1:9:: paclitaxel: human serum albumin. Other biosource materials (manufactured by differing suppliers) of the drug used for pre-clinical and earlier clinical trials include: \_\_\_\_\_ paclitaxel. Suppliers of human serum albumin and ratios of paclitaxel to human serum albumin have also varied during the development of this Taxol analog. Names for the drug used for pre-clinical studies with these varying biosource and human serum albumin concentrations are known as Capxol and ABI-007. Pre-clinical pharmacokinetic studies comparing the differing biosource formulations and differing paclitaxel to HSA ratios have indicated only minor changes which would not significantly impact the comparative toxicity of the drug. However, since the natural biosource was utilized for Phase 3 studies and will be used commercially, it should be noted that this ABI-007 biosource exhibited a slightly higher systemic exposure, with an extended half-life compared to the \_\_\_\_\_ biosources.

In general, acute toxicity and lethality of ABI-007 were significantly reduced as compared to Taxol, based on comparative lethal doses and MTDs. However, renal toxicity was observed in multiple toxicology studies with ABI-007-dosed rodents. Single-dose studies with ABI-007 in rats indicated renal toxicity at doses >540mg/m<sup>2</sup>. In these studies, lethality was observed at doses >720mg/m<sup>2</sup> and myelosuppression was reduced compared to Taxol. Rats administered ABI-007 exhibited swollen nerve root axons of the spinal cord at 540mg/m<sup>2</sup>, and urinary bladder hyperplasia, kidney fibrosis, adrenal hyperplasia, and testicular atrophy at doses ≥54mg/m<sup>2</sup>; these findings were not observed with concurrently administered Taxol animals. In rodent pharmacokinetics studies, ABI-007 appears to be rapidly distributed to tissues with a greater volume of distribution and longer serum half-life compared to Taxol.

Toxicology studies in dogs, and possibly swine were complicated by the immunological reaction of the human albumin to these animal models. Even so, neurotoxicity of ABI-007 in dogs appeared to be enhanced compared to that of Taxol.

Abraxane is embryotoxic and fetotoxic when administered to rats at doses ≥6mg/m<sup>2</sup>, (approximately 0.02 of the daily maximum recommended human dose on a mg/m<sup>2</sup> basis) on gestation days 7-17. Significant changes in reproductive parameters included increase of early and late resorptions (4.5 fold), reduction in litter size and live fetuses (up to 3-fold), significant reduction in fetal BW and significant increase in numbers of fetuses with abnormalities. All fetuses were born dead or resorbed at 24mg/m<sup>2</sup> in this study. Biologically significant fetal anomalies included fused digits, bulging eyes, folded retinas, microphthalmia, dilation of brain ventricles, septal defects in heart vasculature, fused lungs, small eye sockets, presence of extra cervical ribs, and incomplete or absent ossification of ribs and sternum. Eye anomalies and extra cervical ribs were also observed at the lowest dose tested, 3mg/m<sup>2</sup>. In another study, significant changes in reproductive parameters included significantly reduced sperm count and sperm motility, absence of implantations and viable embryos, absence of fertility index, significant reduction of dams with viable fetuses, and maternal lethality. Testicular atrophy/degeneration has also been observed in single-dose toxicology studies in rodents administered Abraxane at ≥54mg/m<sup>2</sup> and dogs administered 175mg/m<sup>2</sup>.

##### B. Pharmacologic Activity

The effects of Taxol and ABI-007 on tumor free survival and tumor growth rate were compared for HT29 colon tumor, PC-3 prostate tumor, NCI-H522 lung tumor, SK-OV-3 ovarian tumor and MX-1 mammary tumor. Abraxane

was less toxic in tumor-bearing mice as measured by MTDs and LD<sub>50</sub>. The LD<sub>50</sub> was calculated to be 47 and 30mg/kg/d for ABI-007 and Taxol, respectively. Antitumor activity of ABI-007 was similar to that of Taxol in some of these studies at these dose levels; in other studies, antitumor of ABI-007 was superior to that of Taxol. In a different study, the binding of ABI-007 to albumin, microtubules, and endothelial cells appeared to be superior to that of Taxol.

C. Nonclinical Safety Issues Relevant to Clinical Use

The incidence of Grade 3 sensory neuropathy was greater in Abraxane-treated patients in the Phase 3 comparative study of Abraxane vs. Taxol with lower frequency of neutropenia with Abraxane. Neurotoxicity appears to follow a similar pattern preclinically, although dog studies were complicated by the immunological reaction of the human serum albumin component of ABI-007. Differences in neurotoxicity between Abraxane and Taxol therapy have been addressed clinically. Testicular atrophy/degeneration was observed in multiple studies with Abraxane. Abraxane is embryotoxic and fetotoxic to rats at doses of 0.05 the maximum daily recommended human dose on a mg/m<sup>2</sup> basis. These findings have been addressed in the label. A study was submitted which justified the increase in shelf-life specification of \_\_\_\_\_ impurity \_\_\_\_\_ from \_\_\_\_\_

III. Administrative

A. Reviewer signature: \_\_\_\_\_

B. Supervisor signature: Concurrence - \_\_\_\_\_

Non-Concurrence - \_\_\_\_\_  
(see memo attached)

C. cc: list:

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