

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21-660/S-010

Trade Name: Abraxane

Generic Name: paclitaxel

Sponsor: Abraxis BioScience, Inc.

Approval Date: February 15, 2007

Indications: For the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-660/S-010

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-660/S-010

Abraxis BioScience, Inc.
Attention: Monica Batra
Manager, Regulatory Affairs
4503 Glencoe Ave.
Marina Del Rey, CA 90292

Dear Ms. Batra:

Please refer to your supplemental new drug application dated April 14, 2006, received April 18, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ABRAXANE[®] for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension).

We acknowledge receipt of your submissions dated June 14 and 29; July 21 and December 5, 2006; January 15; February 9 and 14 (electronic), 2007.

This supplemental new drug application provides revised prescribing information with updated safety and efficacy information for ABRAXANE[®] Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) in the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/oc/datacouncil/spl.html>, that is identical in content to the enclosed labeling. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination.

The final printed labeling (FPL) for this supplement S-010 must be identical to the enclosed labeling (text for the package insert, and text for the patient package insert) submitted February 9, 2007. Please note that your final printed labeling submitted January 20, 2005, for this NDA has been superseded but will be retained in the file.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "FPL for approved supplement NDA 21-660/S-010." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitment in your submission dated January 4, 2004, listed below.

2. You should evaluate ABRAXANE[®] safety and pharmacokinetics in subjects with hepatic impairment, to allow the determination of dosing adjustment for this population.

Protocol Submission: April 2005

Study Start: November/December 2005

Final Report Submission: December 2006

Per your submission of December 5, 2006, we understand that the final report submission for this postmarketing study commitment will be delayed until November 2007. This is acceptable.

We have reviewed your submissions dated June 28 and August 12, 2005, and conclude that the following commitment from the January 7, 2005, approval letter was fulfilled.

1. Survival data and analysis results should be submitted from randomized study CA012-0 when 80% of the patients have died. Data should be available for submission approximately June 2005.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **“Postmarketing Study Commitment Protocol”**, **“Postmarketing Study Commitment Final Report”**, or **“Postmarketing Study Commitment Correspondence.”**

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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If you have any questions, please call Frank Cross, Project Manager, at (301) 796-0876.

Sincerely,

{See appended electronic signature page}

Ann Farrell, M.D.
Acting Deputy Division Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ann Farrell
2/15/2007 03:29:58 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-660/S-010

LABELING

Version: January 2007

Rx Only

ABRAXANE[®] for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound)

(Patient Information Enclosed)

WARNING

ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

ABRAXANE therapy should not be administered to patients with metastatic breast cancer who have baseline neutrophil counts of less than 1,500 cells/mm³. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving ABRAXANE.

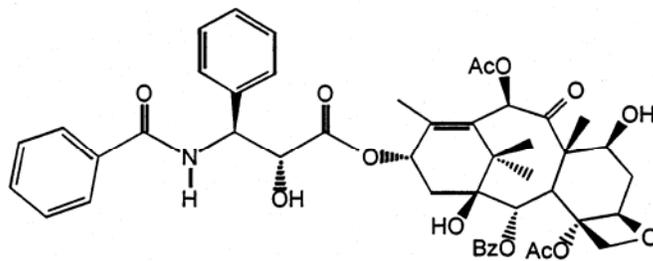
Note: An albumin form of paclitaxel may substantially affect a drug's functional properties relative to those of drug in solution. DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS.

DESCRIPTION

ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. ABRAXANE is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. ABRAXANE is free of solvents.

The active agent in ABRAXANE[®] is paclitaxel, a natural product with antitumor activity. Paclitaxel is obtained from *Taxus media*. The chemical name for paclitaxel is 5 β ,20-Epoxy-1,2 α ,4,7 β ,10 β ,13 α -hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine.

Paclitaxel has the following structural formula:



Paclitaxel is a white to off-white crystalline powder with the empirical formula C₄₇H₅₁NO₁₄ and a molecular weight of 853.91. It is highly lipophilic, insoluble in water, and melts at approximately 216°C to 217°C.

CLINICAL PHARMACOLOGY

Mechanism of Action

ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. Paclitaxel induces abnormal arrays or “bundles” of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Human Pharmacokinetics

The pharmacokinetics of total paclitaxel following 30 and 180-minute infusions of ABRAXANE at dose levels of 80 to 375 mg/m² were determined in clinical studies. Dose levels of mg/m² refer to mg of paclitaxel in ABRAXANE. Following intravenous administration of ABRAXANE, paclitaxel plasma concentrations declined in a biphasic manner, the initial rapid decline

representing distribution to the peripheral compartment and the slower second phase representing drug elimination. The terminal half-life was about 27 hours.

The drug exposure (AUCs) was dose proportional over 80 to 375 mg/m² and the pharmacokinetics of paclitaxel for ABRAXANE[®] were independent of the duration of administration. At the recommended ABRAXANE clinical dose, 260 mg/m², the mean maximum concentration of paclitaxel, which occurred at the end of the infusion, was 18,741 ng/mL. The mean total clearance was 15 L/hr/m². The mean volume of distribution was 632 L/m²; the large volume of distribution indicates extensive extravascular distribution and/or tissue binding of paclitaxel.

The pharmacokinetic data of 260 mg/m² ABRAXANE administered over 30 minutes was compared to the pharmacokinetics of 175 mg/m² paclitaxel injection over 3 hours. The clearance of ABRAXANE was larger (43%) than for the clearance of paclitaxel injection and the volume of distribution of ABRAXANE was also higher (53%). Differences in C_{max} and C_{max} corrected for dose reflected differences in total dose and rate of infusion. There were no differences in terminal half-lives.

In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 µg/mL, indicate that between 89% to 98% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

After a 30-minute infusion of 260 mg/m² doses of ABRAXANE, the mean values for cumulative urinary recovery of unchanged drug (4%) indicated extensive non-renal clearance. Less than 1% of the total administered dose was excreted in urine as the metabolites 6α-hydroxypaclitaxel and 3'-*p*-hydroxypaclitaxel. Fecal excretion was approximately 20% of the total dose administered.

In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6α-hydroxypaclitaxel by CYP2C8; and to two minor metabolites, 3'-*p*-hydroxypaclitaxel and 6α, 3'-*p*-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole,

verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17 α -ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6 α -hydroxypaclitaxel *in vitro*. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4. (see **PRECAUTIONS: Drug Interactions**). The effect of renal or hepatic dysfunction on the disposition of ABRAXANE[®] has not been investigated.

Possible interactions of paclitaxel with concomitantly administered medications have not been formally investigated.

CLINICAL STUDIES

Metastatic Breast Carcinoma:

Data from 106 patients accrued in two single arm open label studies and from 460 patients enrolled in a randomized comparative study were available to support the use of ABRAXANE in metastatic breast cancer.

Single Arm Open Label Studies- In one study, ABRAXANE was administered as a 30-minute infusion at a dose of 175 mg/m² to 43 patients with metastatic breast cancer. The second trial utilized a dose of 300 mg/m² as a 30 minute infusion in 63 patients with metastatic breast cancer. Cycles were administered at 3 week intervals. Objective responses were observed in both studies.

Randomized Comparative Study- This multicenter trial was conducted in 460 patients with metastatic breast cancer. Patients were randomized to receive ABRAXANE at a dose of 260 mg/m² given as a 30-minute infusion, or paclitaxel injection at 175 mg/m² given as a 3-hour infusion. Sixty-four percent of patients had impaired performance status (ECOG 1 or 2) at study entry; 79% had visceral metastases; and 76% had > 3 sites of metastases. Fourteen percent of the patients had not received prior chemotherapy; 27% had received chemotherapy in the adjuvant setting, 40% in the metastatic setting and 19% in both metastatic and adjuvant settings. Fifty-

nine percent received study drug as second or greater than second-line therapy. Seventy-seven percent of the patients had been previously exposed to anthracyclines.

In this trial, patients in the ABRAXANE[®] treatment arm had a statistically significantly higher reconciled target lesion response rate (the trial primary endpoint) of 21.5% (95% CI: 16.2% to 26.7%), compared to 11.1% (95% CI: 6.9% to 15.1%) for patients in the paclitaxel injection treatment arm. See Table 1. There was no statistically significant difference in overall survival between the two study arms.

Table 1: Efficacy Results from Randomized Trial

| | | ABRAXANE 260 mg/m² | Paclitaxel Injection 175 mg/m² |
|--|----------------------|--|--|
| Reconciled Target Lesion Response Rate (primary endpoint)^a | | | |
| All randomized patients | Response Rate | 50/233 (21.5%) | 25/227 (11.1%) |
| | [95% CI] | [16.19% – 26.73%] | [6.94% – 15.09%] |
| | P-value ^b | 0.003 | |
| Patients who had failed combination chemotherapy or relapsed within 6 months of adjuvant chemotherapy ^c | Response Rate | 20/129 (15.5%) | 12/143 (8.4%) |
| | [95% CI] | [9.26% – 21.75%] | [3.85% – 12.94%] |

^a Reconciled Target Lesion Response Rate (TLRR) was the prospectively defined protocol specific endpoint, based on independent radiologic assessment of tumor responses reconciled with investigator responses (which also included clinical information) for the first 6 cycles of therapy. The reconciled TLRR was lower than the investigator Reported Response Rates, which are based on all cycles of therapy.

^b From Cochran-Mantel-Haenszel test stratified by 1st line vs. > 1st line therapy.

^c Prior therapy included an anthracycline unless clinically contraindicated

INDICATION

ABRAXANE[®] for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

CONTRAINDICATIONS

ABRAXANE should not be used in patients who have baseline neutrophil counts of $< 1,500$ cells/mm³.

WARNINGS

Bone marrow suppression (primarily neutropenia) is dose dependent and a dose limiting toxicity. ABRAXANE should not be administered to patients with baseline neutrophil counts of $< 1,500$ cells/mm³. Frequent monitoring of blood counts should be instituted during ABRAXANE treatment. Patients should not be retreated with subsequent cycles of ABRAXANE until neutrophils recover to a level $>1,500$ cells/mm³ and platelets recover to a level $>100,000$ cells/mm³.

The use of ABRAXANE has not been studied in patients with hepatic or renal dysfunction. In the randomized controlled trial, patients were excluded for baseline serum bilirubin >1.5 mg/dL or baseline serum creatinine >2 mg/dL.

Pregnancy – Teratogenic Effects: Pregnancy Category D: ABRAXANE can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel protein-bound particles to rats on gestation days 7 to 17 at doses of 6 mg/m² (approximately 2% of the daily maximum recommended human dose on a mg/m² basis) caused embryo- and fetotoxicity, as indicated by intrauterine mortality, increased resorptions (up to 5-fold), reduced numbers of litters and live fetuses, reduction in fetal body weight and increase in fetal anomalies. Fetal anomalies included soft tissue and skeletal malformations, such as eye bulge, folded retina, microphthalmia, and dilation of brain ventricles. A lower incidence of soft tissue and skeletal

malformations were also exhibited at 3 mg/m² (approximately 1% of the daily maximum recommended human dose on a mg/m² basis).

There are no adequate and well-controlled studies in pregnant women using ABRAXANE[®]. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with ABRAXANE.

Use in Males: Men should be advised to not father a child while receiving treatment with ABRAXANE (see **PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility** for discussion of effects of ABRAXANE exposure on male fertility and embryonic viability).

Albumin (Human): ABRAXANE contains albumin (human), a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob Disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

PRECAUTIONS

Drug Interactions: No drug interaction studies have been conducted with ABRAXANE.

The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering ABRAXANE (paclitaxel protein-bound particles for injectable suspension) concomitantly with known substrates or inhibitors of CYP2C8 and CYP3A4 (see **CLINICAL PHARMACOLOGY**).

Potential interactions between paclitaxel, a substrate of CYP3A4, and protease inhibitors (such as ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials.

Hematology: ABRAXANE[®] therapy should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm³. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving ABRAXANE. Patients should not be retreated with subsequent cycles of ABRAXANE until neutrophils recover to a level >1,500 cells/mm³ and platelets recover to a level >100,000 cells/mm³. In the case of severe neutropenia (<500 cells/mm³ for seven days or more) during a course of ABRAXANE therapy, a dose reduction for subsequent courses of therapy is recommended (see **DOSAGE and ADMINISTRATION**).

Nervous System: Sensory neuropathy occurs frequently with ABRAXANE. The occurrence of grade 1 or 2 sensory neuropathy does not generally require dose modification. If grade 3 sensory neuropathy develops, treatment should be withheld until resolution to grade 1 or 2 followed by a dose reduction for all subsequent courses of ABRAXANE (see **DOSAGE and ADMINISTRATION**).

Injection Site Reaction: Injection site reactions occur infrequently with ABRAXANE and were mild in the randomized clinical trial. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The carcinogenic potential of ABRAXANE has not been studied.

Paclitaxel has been shown to be clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). ABRAXANE was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay.

Administration of paclitaxel protein-bound particles to male rats at 42 mg/m² on a weekly basis (approximately 16% of the daily maximum recommended human exposure on a mg/m² basis) for 11 weeks prior to mating with untreated female rats resulted in significantly reduced fertility accompanied by decreased pregnancy rates and increased loss of embryos in mated females. A low incidence of skeletal and soft tissue fetal anomalies was also observed at doses of 3 and 12

mg/m²/week in this study (approximately 1 to 5% of the daily maximum recommended human exposure on a mg/m² basis). Testicular atrophy/degeneration has also been observed in single-dose toxicology studies in rodents administered paclitaxel protein-bound particles at 54 mg/m² and dogs administered 175 mg/m² (see **WARNINGS**).

Pregnancy: Teratogenic Effects: Pregnancy Category D: (See **WARNINGS** section).

Nursing Mothers: It is not known whether paclitaxel is excreted in human milk. Following intravenous administration of carbon-14 labeled paclitaxel to rats on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving ABRAXANE[®] therapy.

Pediatric Use: The safety and effectiveness of ABRAXANE in pediatric patients have not been evaluated.

Geriatric use: Of the 229 patients in the randomized study who received ABRAXANE, 11% were at least 65 years of age and < 2% were 75 years or older. No toxicities occurred notably more frequently among elderly patients who received ABRAXANE.

Information for Patients: (See **Patient Information Leaflet**).

ADVERSE REACTIONS:

The following table shows the frequency of important adverse events in the randomized comparative trial for the patients who received either single-agent ABRAXANE[®] or paclitaxel injection for the treatment of metastatic breast cancer.

Table 2: Frequency^a of Important Treatment Emergent Adverse Events in the Randomized Study on an Every-3-Weeks Schedule

| | Percent of Patients | |
|--|--|--|
| | ABRAXANE [®] 260/30min ^b (n=229) | Paclitaxel Injection 175/3h ^{c,d} (n=225) |
| Bone Marrow | | |
| Neutropenia < 2.0 x 10 ⁹ /L | 80 | 82 |
| < 0.5 x 10 ⁹ /L | 9 | 22 |
| Thrombocytopenia < 100 x 10 ⁹ /L | 2 | 3 |
| < 50 x 10 ⁹ /L | <1 | <1 |
| Anemia < 11 g/dL | 33 | 25 |
| < 8 g/dL | 1 | <1 |
| Infections | 24 | 20 |
| Febrile Neutropenia | 2 | 1 |
| Bleeding | 2 | 2 |
| Hypersensitivity Reaction^e | | |
| All | 4 | 12 |
| Severe ^f | 0 | 2 |
| Cardiovascular | | |
| Vital Sign Changes ^g | | |
| Bradycardia | <1 | <1 |
| Hypotension | 5 | 5 |
| Severe Cardiovascular Events ^f | 3 | 4 |
| Abnormal ECG | | |
| All patients | 60 | 52 |
| Patients with Normal Baseline | 35 | 30 |
| Respiratory | | |
| Cough | 7 | 6 |
| Dyspnea | 12 | 9 |
| Sensory Neuropathy | | |
| Any Symptoms | 71 | 56 |
| Severe Symptoms ^f | 10 | 2 |
| Myalgia / Arthralgia | | |
| Any Symptoms | 44 | 49 |
| Severe Symptoms ^f | 8 | 4 |

Table 2: Frequency^a of Important Treatment Emergent Adverse Events in the Randomized Study on an Every-3-Weeks Schedule, Continued

| | Percent of Patients | |
|--|--|--|
| | ABRAXANE [®] 260/30min ^b (n=229) | Paclitaxel Injection 175/3h ^{c,d} (n=225) |
| Asthenia | | |
| Any Symptoms | 47 | 39 |
| Severe Symptoms ^f | 8 | 3 |
| Fluid Retention/Edema | | |
| Any Symptoms | 10 | 8 |
| Severe Symptoms ^f | 0 | <1 |
| Gastrointestinal | | |
| Nausea | | |
| Any symptoms | 30 | 22 |
| Severe symptoms ^f | 3 | <1 |
| Vomiting | | |
| Any symptoms | 18 | 10 |
| Severe Symptoms ^f | 4 | 1 |
| Diarrhea | | |
| Any Symptoms | 27 | 15 |
| Severe Symptoms ^f | <1 | 1 |
| Mucositis | | |
| Any Symptoms | 7 | 6 |
| Severe Symptoms ^f | <1 | 0 |
| Alopecia | 90 | 94 |
| Hepatic (Patients with Normal Baseline) | | |
| Bilirubin Elevations | 7 | 7 |
| Alkaline Phosphatase Elevations | 36 | 31 |
| AST (SGOT) Elevations | 39 | 32 |
| Injection Site Reaction | <1 | 1 |

^a Based on worst grade

^b ABRAXANE dose in mg/m²/duration in minutes

^c paclitaxel injection dose in mg/m²/duration in hours

^d paclitaxel injection pts received premedication

^e Includes treatment-related events related to hypersensitivity (e.g., flushing, dyspnea, chest pain, hypotension) that began on a day of dosing.

^f Severe events are defined as at least grade 3 toxicity

^g During study drug dosing.

Myelosuppression and sensory neuropathy were dose related.

Adverse Event Experiences by Body System: Unless otherwise noted, the following discussion refers to the primary safety database of 229 patients with metastatic breast cancer treated with single-agent ABRAXANE[®] in the randomized controlled trial. The frequency and severity of important adverse events for the study are presented above in tabular form. In some instances, rare severe events observed with paclitaxel injection may be expected to occur with ABRAXANE.

Hematologic: Neutropenia, the most important hematologic toxicity, was dose dependent and reversible. Among patients with metastatic breast cancer in the randomized trial, neutrophil counts declined below 500 cells/mm³ (Grade 4) in 9% of the patients treated with a dose of 260 mg/m² compared to 22% in patients receiving paclitaxel injection at a dose of 175 mg/m².

In the randomized metastatic breast cancer study, infectious episodes were reported in 24% of the patients treated with a dose of 260 mg/m² given as a 30-minute infusion. Oral candidiasis, respiratory tract infections and pneumonia were the most frequently reported infectious complications. Febrile neutropenia was reported in 2% of patients in the ABRAXANE arm and 1% of patients in the paclitaxel injection arm.

Thrombocytopenia was uncommon. In the randomized metastatic breast cancer study, bleeding episodes were reported in 2% of the patients in each treatment arm.

Anemia (Hb <11 g/dL) was observed in 33% of patients treated with ABRAXANE in the randomized trial and was severe (Hb <8 g/dL) in 1% of the cases. Among all patients with normal baseline hemoglobin, 31% became anemic on study and 1% had severe anemia.

Hypersensitivity Reactions (HSRs): In the randomized controlled metastatic breast cancer study, Grade 1 or 2 HSRs occurred on the day of ABRAXANE administration and consisted of dyspnea (1%) and flushing, hypotension, chest pain, and arrhythmia (all <1%). The use of

ABRAXANE® in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied.

Cardiovascular: Hypotension, during the 30-minute infusion, occurred in 5% of patients in the randomized metastatic breast cancer trial. Bradycardia, during the 30-minute infusion, occurred in <1% of patients. These vital sign changes most often caused no symptoms and required neither specific therapy nor treatment discontinuation.

Severe cardiovascular events possibly related to single-agent ABRAXANE occurred in approximately 3% of patients in the randomized trial. These events included chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension. Cases of cerebrovascular attacks (strokes) and transient ischemic attacks have been reported rarely.

Electrocardiogram (ECG) abnormalities were common among patients at baseline. ECG abnormalities on study did not usually result in symptoms, were not dose-limiting, and required no intervention. ECG abnormalities were noted in 60% of patients in the metastatic breast cancer randomized trial. Among patients with a normal ECG prior to study entry, 35% of all patients developed an abnormal tracing while on study. The most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, and sinus tachycardia.

Respiratory: Reports of dyspnea (12%) and cough (6%) were reported after treatment with ABRAXANE in the randomized trial. Rare reports (<1%) of pneumothorax were reported after treatment with ABRAXANE. Rare reports of interstitial pneumonia, lung fibrosis, and pulmonary embolism have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment. Rare reports of radiation pneumonitis have been received in paclitaxel injection patients receiving concurrent radiotherapy. There is no experience with the use of ABRAXANE with concurrent radiotherapy.

Neurologic: The frequency and severity of neurologic manifestations were influenced by prior and/or concomitant therapy with neurotoxic agents.

In general, the frequency and severity of neurologic manifestations were dose-dependent in patients receiving single-agent ABRAXANE[®]. In the randomized trial, sensory neuropathy was observed in 71% of patients (10% severe) in the ABRAXANE arm and in 56% of patients (2% severe) in the paclitaxel injection arm. The frequency of sensory neuropathy increased with cumulative dose. Sensory neuropathy was the cause of ABRAXANE discontinuation in 7/229 (3%) patients in the randomized trial. In the randomized comparative study, 24 patients (10%) treated with ABRAXANE developed Grade 3 peripheral neuropathy; of these patients, 14 had documented improvement after a median of 22 days; 10 patients resumed treatment at a reduced dose of ABRAXANE and 2 discontinued due to peripheral neuropathy. Of the 10 patients without documented improvement, 4 discontinued the study due to peripheral neuropathy.

No incidences of grade 4 sensory neuropathies were reported in the clinical trial. Only one incident of motor neuropathy (grade 2) was observed in either arm of the controlled trial.

Cranial nerve palsies have been reported during postmarketing surveillance of ABRAXANE. Because these events have been reported during clinical practice, true estimates of frequency cannot be made and a causal relationship to the events has not been established.

Reports of autonomic neuropathy resulting in paralytic ileus have been received as part of the continuing surveillance of paclitaxel injection safety.

Ocular/visual disturbances occurred in 13% of all patients (n=366) treated with ABRAXANE in single arm and randomized trials and 1% were severe. The severe cases (keratitis and blurred vision) were reported in patients in a single arm study who received higher doses than those recommended (300 or 375 mg/m²). These effects generally have been reversible. However, rare reports in the literature of abnormal visual evoked potentials in patients treated with paclitaxel injection have suggested persistent optic nerve damage.

Arthralgia/Myalgia: Forty-four percent of patients treated in the randomized trial experienced arthralgia/myalgia; 8% experienced severe symptoms. The symptoms were usually transient, occurred two or three days after ABRAXANE[®] administration, and resolved within a few days.

Hepatic: Among patients with normal baseline liver function treated with ABRAXANE in the randomized trial, 7%, 36%, and 39% had elevations in bilirubin, alkaline phosphatase, and AST (SGOT), respectively. Grade 3 or 4 elevations in GGT were reported for 14% of patients treated with ABRAXANE and 10% of patients treated with paclitaxel injection in the randomized trial.

Rare reports of hepatic necrosis and hepatic encephalopathy leading to death have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment.

Renal: Overall 11% of patients experienced creatinine elevation, 1% severe. No discontinuations, dose reductions, or dose delays were caused by renal toxicities.

Gastrointestinal (GI): Nausea/vomiting, diarrhea, and mucositis were reported by 33%, 27%, and 7% of ABRAXANE treated patients in the randomized trial.

Rare reports of intestinal obstruction, intestinal perforation, pancreatitis, and ischemic colitis have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment. Rare reports of neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, were observed in patients treated with paclitaxel injection alone and in combination with other chemotherapeutic agents.

Injection Site Reaction: Injection site reactions have occurred infrequently with ABRAXANE and were mild in the randomized clinical trial. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel injection at a different site, i.e., “recall”, has been reported rarely.

Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been received as part of the continuing surveillance of paclitaxel injection safety. In some cases the onset of the injection site reaction in paclitaxel injection patients either occurred during a prolonged infusion or was delayed by a week to ten days.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Asthenia: Asthenia was reported in 47% of patients (8% severe) treated with ABRAXANE[®] in the randomized trial. Asthenia included reports of asthenia, fatigue, weakness, lethargy and malaise.

Other Clinical Events: Rare cases of cardiac ischemia/infarction and thrombosis/embolism possibly related to ABRAXANE treatment have been reported. Alopecia was observed in almost all of the patients. Nail changes (changes in pigmentation or discoloration of nail bed) were uncommon. Edema (fluid retention) was infrequent (10% of randomized trial patients); no patients had severe edema.

The following rare adverse events have been reported as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment: skin abnormalities related to radiation recall as well as reports of Stevens-Johnson syndrome, toxic epidermal necrolysis, conjunctivitis, and increased lacrimation. As part of the continuing surveillance of ABRAXANE, skin reactions including generalized or maculo-papular rash, erythema, and pruritis have been observed. Additionally, there have been case reports of photosensitivity reactions, radiation recall phenomenon, and in some patients previously exposed to capecitabine, reports of palmar-plantar erythrodysesthesiae. Because these events have been reported during clinical practice, true estimates of frequency cannot be made and a causal relationship to the events has not been established.

Accidental Exposure: No reports of accidental exposure to ABRAXANE[®] have been received. However, upon inhalation of paclitaxel, dyspnea, chest pain, burning eyes, sore throat, and

nausea have been reported. Following topical exposure, events have included tingling, burning, and redness.

OVERDOSAGE

There is no known antidote for ABRAXANE overdose. The primary anticipated complications of overdose would consist of bone marrow suppression, sensory neurotoxicity, and mucositis.

DOSAGE AND ADMINISTRATION

After failure of combination chemotherapy for metastatic breast cancer or relapse within 6 months of adjuvant chemotherapy, the recommended regimen for ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is 260 mg/m² administered intravenously over 30 minutes every 3 weeks.

Hepatic Impairment: The appropriate dose of ABRAXANE for patients with bilirubin greater than 1.5 mg/dL is not known.

Dose Reduction: Patients who experience severe neutropenia (neutrophil <500 cells/mm³ for a week or longer) or severe sensory neuropathy during ABRAXANE therapy should have dosage reduced to 220 mg/m² for subsequent courses of ABRAXANE. For recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m². For grade 3 sensory neuropathy hold treatment until resolution to grade 1 or 2, followed by a dose reduction for all subsequent courses of ABRAXANE.

Preparation and Administration Precautions: ABRAXANE is a cytotoxic anticancer drug and, as with other potentially toxic paclitaxel compounds, caution should be exercised in handling ABRAXANE. The use of gloves is recommended. If ABRAXANE (lyophilized cake or reconstituted suspension) contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure to paclitaxel, events may include tingling, burning and redness. If ABRAXANE[®] contacts mucous membranes, the membranes should be flushed thoroughly with water.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. Limiting the infusion of ABRAXANE to 30 minutes, as directed, reduces the likelihood of infusion-related reactions (see **PRECAUTIONS: Injection Site Reaction**).

No premedication to prevent hypersensitivity reactions is required prior to administration of ABRAXANE.

Preparation for Intravenous Administration: ABRAXANE is supplied as a sterile lyophilized powder for reconstitution before use. **AVOID ERRORS, READ ENTIRE PREPARATION INSTRUCTIONS PRIOR TO RECONSTITUTION.**

1. Aseptically, reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP.
2. Slowly inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of 1 minute, using the sterile syringe to direct the solution flow onto the INSIDE WALL OF THE VIAL.



3. DO NOT INJECT the 0.9% Sodium Chloride Injection, USP, directly onto the lyophilized cake as this will result in foaming.
4. Once the injection is complete, allow the vial to sit for a minimum of 5 minutes to ensure proper wetting of the lyophilized cake/powder.
5. Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs. Avoid generation of foam.
6. If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.

Each mL of the reconstituted formulation will contain 5 mg/mL paclitaxel.

Calculate the exact total dosing volume of 5 mg/mL suspension required for the patient: Dosing volume (mL) = Total dose (mg)/5 (mg/mL)

The reconstituted suspension should be milky and homogenous without visible particulates. If particulates or settling are visible, the vial should be **gently** inverted again to ensure complete resuspension prior to use. Discard the reconstituted suspension if precipitates are observed. Discard any unused portion.

Inject the appropriate amount of reconstituted ABRAXANE[®] into an empty, sterile IV bag (plasticized polyvinyl chloride (PVC) containers, PVC or non-PVC type IV bag). The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer ABRAXANE infusions. The use of an in-line filter is not recommended.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Stability: Unopened vials of ABRAXANE are stable until the date indicated on the package when stored between 20 C to 25 C (68 F to 77 F), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product.

Stability of Reconstituted Suspension in the Vial

Reconstituted ABRAXANE should be used immediately, but may be refrigerated at 2 C to 8 C (36 F to 46 F) for a maximum of 8 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion.

Stability of Reconstituted Suspension in the Infusion Bag

The suspension for infusion prepared as recommended in an infusion bag should be used immediately, but may be stored at ambient temperature (approximately 25 C) and lighting conditions for up to 8 hours.

HOW SUPPLIED

Product No. 103450

NDC No. 68817-134-50 100 mg of paclitaxel in a single use vial, individually packaged in a carton.

Storage: Store the vials in original cartons at 20 C to 25 C (68 F to 77 F). Retain in the original package to protect from bright light.

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.¹⁻⁸ There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

U.S. Patent Numbers: 5,439,686; 5,498,421; 6,096,331; 6,506,405;
6,537,579; 6,749,868; 6,753,006

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Issued: XX/XX/XXXX

ABRAXIS
ONCOLOGY

A Division of Abraxis BioScience, Inc.
Los Angeles, CA 90049

PATIENT INFORMATION

ABRAXANE® for Injectable Suspension

**[generic name = (paclitaxel protein-bound particles for injectable suspension)
(albumin-bound)]**

WHAT IS ABRAXANE?

ABRAXANE is a prescription cancer medicine. It is injected into a vein and it is used to treat advanced breast cancer.

WHAT IS CANCER?

Under normal conditions, the cells in your body divide and grow in an orderly, controlled way. Cell division and growth are necessary for the human body to perform its functions and to repair itself, when necessary. Cancer cells are different from normal cells because they are not able to control their own growth. The reasons for this abnormal growth are not yet fully understood. A tumor is a mass of unhealthy cells that are dividing and growing fast and in an uncontrolled way. When a tumor invades surrounding healthy body tissue it is known as a malignant tumor. A malignant tumor can spread (metastasize) from its original site to other parts of the body if not found and treated early.

HOW DOES ABRAXANE WORK?

ABRAXANE is a type of medical treatment called chemotherapy. The purpose of chemotherapy is to kill cancer cells or prevent their growth.

All cells, whether they are healthy cells or cancer cells, go through several stages of growth. During one of the stages, the cell starts to divide. ABRAXANE may stop the cells from dividing and growing, so they eventually die. In addition, normal cells may also be affected by ABRAXANE causing some of the side effects. (see **WHAT ARE THE POSSIBLE SIDE EFFECTS OF ABRAXANE?** below).

WHO SHOULD NOT TAKE ABRAXANE?

ABRAXANE should not be given to patients with dangerously low white blood cell counts.

HOW IS ABRAXANE® GIVEN?

ABRAXANE is injected into a vein [intravenous (I.V.) infusion] over 30 minutes.

WHAT PREMEDICATION IS REQUIRED WITH ABRAXANE?

While reactions can occur to any medication, severe allergic reactions to ABRAXANE are uncommon and premedication is not required. However, you should make your doctor aware of any allergies you may have so he/she can determine the course of action required.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF ABRAXANE?

Most patients taking ABRAXANE will experience side effects, although it is not always possible to tell whether such effects are caused by ABRAXANE, another medicine they may be taking, or the cancer itself. Important side effects are described below; however, some patients may experience other side effects that are less common. *Report any unusual symptoms to your doctor.*

Important side effects observed in studies of patients taking ABRAXANE were as follows:

Hair Loss: Complete hair loss, or alopecia, almost always occurs with ABRAXANE. This usually involves the loss of eyebrows, eyelashes, and pubic hair, as well as scalp hair. It can occur suddenly after treatment has begun, but usually happens 14 to 21 days after treatment. *Hair generally grows back after you've finished your ABRAXANE treatment.*

Infections Due to Low White Blood Cell Count: Among the body's defenses against bacterial infections are white blood cells. Between your ABRAXANE treatment cycles, you will often have blood tests to check your white blood cell counts. ABRAXANE usually causes a brief drop in white blood cells. *If you have a fever (temperature above 100.4°F) or other sign of infection, tell your doctor right away. Sometimes serious infections develop that require treatment in the hospital with antibiotics. Serious illness or death could result if such infections are not treated when white blood cell counts are low.*

Numbness, Tingling, or Burning in the Hands and/or Feet (Neuropathy): These symptoms occur often with ABRAXANE[®] and usually get better or go away without medication within three weeks of interrupting treatment. Be sure to tell your doctor about any numbness, tingling or burning that you have in your hands or feet so that he/she can decide the best approach for relief of your symptoms. Sometimes it is necessary to interrupt treatment with ABRAXANE until these symptoms improve. After improvement, treatment can be restarted at a lower dose.

Fatigue and Weakness: ABRAXANE may cause asthenia, fatigue, weakness, lethargy and malaise. These side effects are usually self-limited and do not require dose modification or interruption.

Low Red Blood Cell Count: Red blood cells deliver oxygen to tissues throughout all parts of the body and take carbon dioxide from the tissues by using a protein called hemoglobin. A lowering of the volume of red blood cells may occur following ABRAXANE treatment causing anemia. Some patients may need a blood transfusion to treat the anemia. Patients can feel tired, tire easily, appear pale, and become short of breath. Contact your doctor if you experience any of these symptoms following ABRAXANE treatment.

Mouth or Lip Sores (Mucositis): Some patients develop redness and/or sores in the mouth or on the lips. These symptoms might occur a few days after the ABRAXANE treatment and usually decrease or disappear within one week. Talk with your doctor about proper mouth care and other ways to prevent or reduce your chances of developing mucositis.

Joint and Muscle Pain: You may get joint and muscle pain a few days after your ABRAXANE treatment. These symptoms usually disappear in a few days. Although pain medicine may not be necessary, tell your doctor if you are uncomfortable.

Stomach Upset and Diarrhea: Some patients experience nausea, vomiting, and/or diarrhea following ABRAXANE use. If you experience nausea or stomach upset, tell your doctor because medicines can be given that almost always reduce or eliminate these symptoms.

Diarrhea will usually disappear without treatment; however, *if you experience severe abdominal or stomach area pain and/or severe diarrhea, tell your doctor right away.*

Heart and Blood Vessel (Cardiovascular) Effects: ABRAXANE® may cause a drop in heart rate (bradycardia) and low blood pressure (hypotension). The patient usually does not notice these changes. These changes usually do not require treatment. You should notify your doctor if you have a history of heart disease.

Irritation at the Injection Site: ABRAXANE may cause irritation at the site where it enters the vein. Reactions may include discomfort, redness, swelling, inflammation (of the surrounding skin or of the vein itself), and ulceration (open sores). These reactions are usually caused by the I.V. (intravenous) fluid leaking into the surrounding area. *If you notice anything unusual at the site of the injection (needle), either during or after treatment, tell your doctor right away.*

Talk with your doctor or other healthcare professional to discuss ways to prevent or reduce some of these side effects. Because this leaflet does not include all possible side effects that can occur with ABRAXANE, it is important to talk with your doctor about other possible side effects.

CAN I TAKE ABRAXANE IF I AM PREGNANT OR NURSING A BABY?

ABRAXANE could harm the fetus when given to a pregnant woman. Women should avoid becoming pregnant while they are undergoing treatment with ABRAXANE. *Tell your doctor if you become pregnant or plan to become pregnant while taking ABRAXANE.*

Men should be advised not to father a child while receiving treatment with ABRAXANE.

Because studies have shown the active agent (paclitaxel) in ABRAXANE to be present in the breast milk of animals receiving the active agent, it may be present in human breast milk as well. Therefore, nursing a baby while taking ABRAXANE is NOT recommended. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving ABRAXANE therapy.

This medicine was prescribed for your particular condition. This summary does not include everything there is to know about ABRAXANE[®]. Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. If you have questions or concerns, or want more information about ABRAXANE, your doctor and pharmacist have the complete prescribing information upon which this guide is based. You may want to read it and discuss it with your doctor. Remember, no written summary can replace careful discussion with your doctor.

ABRAXIS
ONCOLOGY

A Division of Abraxis BioScience, Inc.
Los Angeles, CA 90049

This Patient Information Leaflet has been approved by the U.S. Food and Drug Administration.

Based on: ABRAXANE Package Insert issued: XX/XX/XXXX

Revised: xx//200

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-660/S-010

SUMMARY REVIEW

Acting Deputy Division Director Summary Review of NDA 21-660
Drug: Abraxane for Injection
Applicant: Abraxis BioScience Inc.
Date: February 5, 2007

On April 14, 2006, Abraxis BioScience submitted an SE8/labeling supplement with clinical data for Abraxane. The supplement was submitted to fulfill a post-marketing request. In addition, the sponsor requested that the labeling be updated with their (b) (4) overall survival analyses.

(b) (4)

the review team felt that the following statement should be incorporated into the labeling, "There was no statistically significant difference in overall survival between the two study arms."

Conclusion:

Based on the Medical Officer's review, I concur with the recommendation of the review team for this supplement.

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this page is the manifestation of the electronic signature.**

/s/

Ann Farrell
2/12/2007 10:34:29 AM
MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-660/S-010

CROSS DISCIPLINE TEAM LEADER REVIEW

**DIVISION OF DRUG ONCOLOGY PRODUCTS
REGULATORY PROJECT MANAGER REVIEW**

NDA NUMBER: NDA 21-660/SE8-010

DRUG: ABRAXANE[®] for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension)

APPLICANT: Abraxis BioScience, Inc.

DATES OF SUBMISSIONS:

| Submission | Receipt Date |
|-----------------------|---------------------|
| NDA 21-660 FA | January 24, 2005 |
| NDA 21-660/SE8-010 | April 18, 2006 |
| NDA 21-660/SE8-010 BL | December 6, 2006 |
| NDA 21-660/SE8-010 BL | January 16, 2007 |

BACKGROUND:

NDA 21-660 FA provide for final printed labeling (FPL) submitted in response to the January 7, 2005, approval letter. This FPL has been superseded by the labeling submitted with the efficacy supplement described below.

NDA 21-660/SE8-010 provides for revisions to the labeling with updated labeling and efficacy data from the following Clinical Study “CA012-0 A Controlled Randomized, Phase III, Multicenter, Open Label Study of ABI-007 (A Cremophor[®]-Free, Protein Stabilized, Nanoparticle Paclitaxel) and Taxol[®] in Patients With Metastatic Breast Cancer”. This data was submitted in fulfillment of Post Marketing Commitment # 1 from the January 7, 2005, Approval Letter:

“1. Survival data and analysis results should be submitted from randomized study CA012-0 when 80% of the patients have died. Data should be available for submission approximately June 2005.”

DISCUSSION:

1. The Tradename: ABRAXANE[™] has been revised to ABRAXANE[®] throughout the label.

PM Comment: This change is acceptable.

I have completed the review of the applicant's submissions referenced above by comparison with the approved labeling for NDA 21-660, approved January 7, 2005.

Other than changes submitted to SE8-010 which were reviewed and found acceptable to the review team as amended, no significant differences were noted.

Conclusions

Recommend issuance of Approval Letter for NDA 21-660/SE8-010. Approval Letter should state that the FPL submitted for NDA 21-660 has been superseded by this labeling for NDA 21-660/SE8-010.

Frank Cross, CPMS, DDOP

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this page is the manifestation of the electronic signature.**

/s/

Frank Cross
2/12/2007 11:16:28 AM
CSO

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-660/S-010

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type NDA
Submission Number 21-660/S010
Submission Code SE 8

Letter Date April 14, 2006
Stamp Date April 18, 2006
PDUFA Goal Date February 18, 2007

Reviewer Name Nancy S. Scher, M.D.
Review Completion Date December 21, 2006

Established Name Paclitaxel protein-bound particles for
injectable suspension (albumin-bound)
Trade Name Abraxane for Injectable Suspension
Therapeutic Class Cytotoxic Antineoplastic (Taxane)
Applicant Abraxis BioScience, Inc.

Priority Designation S

Formulation Lyophilized powder 100 mg vial
Dosing Regimen 260 mg/m² IV 30 minutes every 3 weeks
Indication Metastatic Breast Cancer (No new indication)
Intended Population After the failure of combination
chemotherapy for metastatic disease or relapse within 6 months of adjuvant
chemotherapy. Prior therapy should have included an anthracycline unless
clinically contraindicated

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The Labeling Efficacy Supplement should be approved, with changes. The applicant proposed to add to the label survival (b) (4) results from a randomized controlled, multi-center, phase 3 trial in metastatic breast cancer comparing Abraxane (ABI-007) with Taxol (study CA012-0). (b) (4)

(b) (4) The statement "There was no statistically significant difference in overall survival between the two study arms" should be incorporated into the Clinical Studies section of the label. (b) (4)

1.2 Recommendation on Postmarketing Actions

None

1.2.1 Risk Management Activity

None

1.2.2 Required Phase 4 Commitments

There are no new phase 4 commitments. The applicant is conducting a clinical study to evaluate Abraxane in patients with hepatic impairment. As of November 2006, Abraxis has enrolled 16/30 patients to this study, and anticipates the study report will be available November 2007.

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The original NDA for Abraxane (ABI-007) was filed under Section 505 (b)(2) of the Food, Drug and Cosmetics Act, referencing the label, efficacy and safety of Taxol (paclitaxel) Injection. A single randomized controlled, multi-center, open-label, phase 3 trial in 460 women with metastatic breast cancer demonstrated that ABI-007 260 mg/m² intravenous (IV) infusion over 30 minutes every 3 weeks was superior to Taxol 175 mg/m² IV infusion over 3 hours every 3 weeks for the primary response rate endpoint, with a similar safety profile. Data in two single

arm trials from 103 patients with metastatic breast cancer were supportive of the efficacy and safety of ABI-007. FDA granted marketing approval on January 7, 2005. The applicant was required, as a postmarketing commitment, to provide survival data and analysis for randomized trial CA012-0 after 80% of patients had died. The applicant submitted the data and an addendum to the clinical study report (CSR) June 28, 2005. The data cut-off date was November 16, 2004. The applicant resubmitted the same data as a labeling supplement, on April 14, 2006, with some additional tables, graphs and analyses. In response to FDA request, Abraxis provided an addendum to the CSR July 21, 2006, to clarify the methods and analyses supporting their request to add (b) (4) survival data to the Abraxane label.

1.3.2 Efficacy

The original Abraxane NDA was a 505 (b)(2) application, referencing the label, efficacy and safety of Taxol (paclitaxel) Injection. A single randomized controlled, multi-center, open-label, phase 3 trial in 460 women with metastatic breast cancer demonstrated that ABI-007 260 mg/m² intravenous (IV) infusion over 30 minutes every 3 weeks was superior to Taxol 175 mg/m² IV infusion over 3 hours every 3 weeks for the primary response rate endpoint (trial CA012-0). There were 233 women randomized to the ABI-007 treatment arm, and 227 patients to the Taxol treatment arm. A total of 272 patients (58%) met the Taxol indication, of whom 129 were randomized to receive ABI-007 and 143 patients were randomized to receive Taxol.

The primary efficacy endpoint was the confirmed reconciled Target Lesion Response Rate (*recTLRR*), relying on modified RECIST criteria. The *recTLRR* was based on independent, blinded radiologic assessment of digitized images through cycle 6, reconciled by an algorithm with investigator assessments of response (*invTLRR*). The *invTLRR* also included clinical data and assessments beyond cycle 6. The confirmed *recTLRR* was 21.5% (95% CI: 16.2%-26.7%) for ABI-007 patients and 11.1% (95% CI: 6.94-15.09) for Taxol patients (p=0.003). For the subgroup of 272 patients who met the Taxol indication, the responses were 15.5% and 8.4%, respectively. Although the difference was not statistically significant in this subgroup, the trend was in the same direction as for the overall study population.

Mature survival (b) (4) data are provided in the current sNDA and efficacy labeling supplement. The overall survival for all randomized patients was not superior in the ABI-007 treatment arm compared with the Taxol treatment arm. (b) (4)

(b) (4)

(b) (4)

1.3.3 Safety

In the original NDA the toxicity profile for ABI-007 was generally similar to that of Taxol, in spite of the 59% higher dose of paclitaxel delivered with each ABI-007 treatment. The substitution of albumin in ABI-007 for the Cremophor in Taxol as a solubilizing agent for paclitaxel improved the safety profile and permitted the use of a more intense dosing regimen. Although routine corticosteroid premedication was not given with ABI-007, hypersensitivity reactions were significantly fewer for ABI-007 compared with the Taxol treatment group (4% vs. 12%). Fewer patients experienced neutropenia $<0.5 \times 10^9$ /L with ABI-007 (9%) than for Taxol (22%). The incidence of febrile neutropenia was low for both groups (2% and 1%, respectively). No grade 4 sensory neuropathy occurred, but the percent of patients with any sensory neuropathy or grade 3 was higher for ABI-007 (71% and 10%, respectively) than for Taxol (56 % and 2%, respectively).

Very limited new safety data were provided in this supplemental NDA. At the time of the data cut-off for the CSR (April 7, 2003), only 5 of 454 patients who were randomized and treated in the study were still receiving study drug (3 in the ABI-007 arm and 2 in the Taxol study arm). One non-randomized patient, a participant in the pharmacokinetic (PK) portion of the trial, was under therapy. Two patients in the ABI-007 group experienced serious adverse events (SAEs), grade 4 neutropenia. Minor changes are proposed to the Adverse Reactions sections of the label, based on the 120 Day Safety Update and on postmarketing safety reporting.

1.3.4 Dosing Regimen and Administration

The dosing regimen for Abraxane is 260 mg/m² intravenously over 30 minutes every 3 weeks. No premedication with corticosteroids, antihistamines or H2-blockers is required.

1.3.5 Drug-Drug Interactions

No new information was provided. Paclitaxel is metabolized by CYP2C8 and CYP3A4, so that caution is indicated if therapy is given concomitantly with substrates or inhibitors of these enzymes.

1.3.6 Special Populations

No new information was provided in the sNDA. A hepatic impairment trial is ongoing, with a clinical study report expected in November 2007. ABI-007 has not been studied in patients with renal dysfunction. The randomized controlled trial excluded patients with baseline serum creatinine > 2 mg/dL and baseline serum bilirubin > 1.5 mg/dL.

The ABI-007 breast cancer trials enrolled only females. In the randomized trial CA012-0, there were 97% Caucasians in each arm of the trial; in the entire trial, 6 patients (1%) were black and 5 (1%) were Hispanic. Therefore, no evaluation could be made regarding the effect of gender, race or ethnicity on the safety and efficacy of ABI-007. The number of patients \geq age 65 was too

small to make meaningful conclusions regarding the impact of age (30/229 in the ABI-007 arm and 32/225 in the Taxol arm).

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

- Established Name: Paclitaxel protein-bound particles for injectable suspension (albumin-bound); Company Code Name ABI-007
- Trade Name: Abraxane for injectable suspension
- Applicant: Abraxis BioScience, Inc. (ABI)
4503 Glencoe Avenue
Marina Del Rey, CA 90292
- Drug Class: Cytotoxic antineoplastic (taxane)
- Formulation: Sterile lyophilized powder, 100 mg of paclitaxel and 900 mg of human albumin, in a single use vial, for reconstitution in 20 ml of 0.9% Sodium Chloride Injection. Each ml of the reconstituted formulation contains 5 mg of paclitaxel.

Currently Approved Indication:

Treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

Currently Approved Dosage and Administration:

The proposed (and approved) regimen is 260 mg/m² intravenous infusion over 30 minutes every 3 weeks.

2.2 Currently Available Treatment for Indications

NDA 21660 was submitted in March 2004 as a 505(b)(2) application, referencing the label, efficacy and safety of Taxol (paclitaxel) Injection and, in addition, clinical trial data were provided, which supported the (Taxol) indication: "Treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated." A number of chemotherapy drugs and drug combinations are approved or available in this clinical setting. For patients with metastatic breast cancer that is hormone receptor positive, hormonal therapy may be appropriate. For patients with HER-2 over-expressing breast cancer, trastuzumab is an important part of therapy.

Several treatment choices are available at the present time for patients who have failed chemotherapy for metastatic disease or relapsed early after adjuvant therapy, and have previous exposure to or contraindication for anthracycline therapy. Approaches include combination chemotherapy, and or sequential single agent treatment. Single agents with reasonable response rates in second-line or greater therapy include the taxanes (paclitaxel injection (Taxol) and docetaxel injection concentrate), oral capecitabine, (b) (4)

(b) (4) Many patients will have already been exposed to cyclophosphamide as part of adjuvant or first-line therapy. An older combination regimen, mitomycin and vinblastine, is used less commonly since the development of newer agents and combinations. In 2001, oral capecitabine was approved with docetaxel after failure of anthracyclines. Gemcitabine was approved in 2004 as first-line therapy in combination with paclitaxel after failure/contraindication of anthracyclines in the adjuvant setting (b) (4)

Additional drugs with activity in metastatic breast cancer include carboplatin, irinotecan, etoposide, and thiotepa. For patients who have not received maximal doses of anthracyclines, liposomal doxorubicin and mitoxantrone are additional available therapies.

2.3 Availability of Proposed Active Ingredient in the United States

Abraxane has been marketed in the United States since January 2005. Paclitaxel injection (Taxol), formulated with Cremophor EL, has been marketed in the United States since approval in December 1992 for ovarian cancer and, subsequently, for additional indications, including, in April 1994, for metastatic breast cancer and, in October 1999, for adjuvant therapy of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy. Paclitaxel formulated with Cremophor EL is also available as a generic product (multiple manufacturers).

2.4 Important Issues With Pharmacologically Related Products

The other marketed taxanes, paclitaxel (Taxol) and docetaxel (Taxotere), require premedication with corticosteroids to diminish the risk of hypersensitivity reactions and, for docetaxel, to diminish the risk of severe fluid retention. Both require the use of special intravenous tubing and containers formulated without plasticized polyvinyl chloride (PVC) to minimize leaching of the plasticizer into the intravenous infusion.

To achieve solubility, Taxol is formulated with 527 mg Cremophor-EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol for each ml of solution containing 6 mg of paclitaxel. To reduce the incidence and severity of Cremophor-related acute hypersensitivity reactions, patients must be premedicated with corticosteroids and H1 and H2 blockers (antihistamines). Taxotere is formulated with polysorbate 80 to enhance solubility and requires a diluent consisting of 13% (w/w) ethanol in water. Premedication with corticosteroids is required, with 3 three days of oral dexamethasone in the labeled regimen, to reduce the incidence of acute hypersensitivity reactions and fluid retention with Taxotere.

ABI-007 is formulated without Cremophor (or polysorbate 80) and is solubilized with albumin to create the “protein-bound particles” formulation. The differences in formulation obviate the need to premedicate patients with corticosteroids and antihistamines to reduce the incidence of severe hypersensitivity reactions and the need to use specialized non-PVC drug delivery systems. The formulation of Taxol with Cremophor may limit the dose of paclitaxel that can be administered and require longer infusion times.

2.5 Presubmission Regulatory Activity

See clinical review dated January 2005 for details of regulatory activity prior to NDA submission on March 8, 2004. NDA 21-660 was filed as a standard review on May 7, 2004. FDA granted marketing approval for Abraxane on January 7, 2005. The approval letter listed two postmarketing study commitments. There was a requirement to evaluate Abraxane safety and pharmacokinetics in subjects with hepatic impairment and the applicant was to provide mature survival data for randomized trial CA012-0.

Survival data and analysis results should be submitted from randomized study CA012-0 when 80% of the patients have died. Data should be available for submission approximately June 2005.

On June 28, 2005, the applicant submitted updated survival data and overall survival analysis in fulfillment of the phase 4 commitment. This submission included updated time to tumor progression (TTP) and progression free survival (PFS) analyses. Addendum 1 to the CA012-0 clinical study report (CSR), dated March 23, 2005, was provided in the submission. The data cut-off was November 16, 2004, and was the final study database. The submission did not include any proposed labeling changes.

In a letter dated April 14, 2006, the applicant submitted a labeling supplement to include “updated safety and efficacy data” resubmitting the same data submitted in June 2005, in fulfillment of the phase 4 commitment. Some additional tables, graphs and analyses were provided, but there was no narrative discussion of the methods, and no addendum to the CA012 CSR was provided. FDA requested the applicant provide an addendum to the CSR for study CA012. In response to this request, Abraxis BioScience provided Addendum 3 to CSR CA012-0 on July 21, 2006. No new data was provided with the addendum. (b) (4)

2.6 Other Relevant Background Information

Abraxis filed a new drug submission to Health Canada in June 2005, and Abraxane was approved in June 2006. (b) (4)

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

No new CMC information was submitted with this supplement.

3.2 Animal Pharmacology/Toxicology

No new animal pharmacology/toxicology data were submitted.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 SOURCES OF CLINICAL DATA

This efficacy supplement to NDA 21-660 is an electronic submission. In fulfillment of a phase 4 commitment, in June 2005, the applicant submitted an addendum to the CA012 CSR with updated survival data and overall survival analysis, as well as updated TTP and PFS analyses. Updates of “key safety tables” were also provided, since 6 patients were still receiving treatment at the time of the database lock for the original study report. The applicant resubmitted the same data in April 2006, with some additional analyses, as a Labeling Efficacy Supplement. (b) (4)

No addendum to the CA012-0 clinical study report (CSR) was provided with the April 2006 submission. FDA requested the applicant provide a description of methods used in the new analyses and an addendum to the CSR for study CA012. In response to this request, Abraxis BioScience provided a letter dated June 14, 2006, outlining their methods and an addendum to CSR CA012 on July 21, 2006. No new data was provided with the addendum (or subsequent to June 2005).

4.2 Tables of Clinical Studies

The following table is taken from the clinical review of the original NDA and shows the clinical trials submitted to the original NDA. The current review considers only data from randomized, controlled trial CA012-0.

Table 1: Clinical Trials Submitted to NDA 21-660 (Reviewer Table)

| STUDY NUMBER | POPULATION | TREATMENT | NUMBER of PATIENTS | PRIMARY ENDPOINT |
|--------------------|--------------------------|---|--|--|
| CA012-0 Phase 3 | Metastatic breast cancer | ABI-007 260 mg/m ² IVq3wk Vs. Taxol 175 mg/m ² IVq3wk | ABI = 233 (plus PK sub study = 12) Taxol = 227 | Reconciled Target Lesion Response Rate (recTLRR) |
| CA002-0 Phase 2 | Metastatic breast cancer | ABI-007 300 mg/m ² IVq3wk | 63 | Safety, tolerability, anti-tumor effect (TLRR) |

| | | | | |
|-----------------------|--------------------------------|---|------------|--|
| CA002-0LD Phase 2 | Metastatic breast cancer | ABI-007 175 mg/m ² IVq3wk | 43 | Safety, tolerability, anti-tumor effect (TLRR) |
| DM97-123 Phase 1-2 | Solid tumors/ breast cancer | ABI-007 135, 200, 300 or 375 mg/m ² IVq3wk | 19 (16 PK) | Dose ranging, safety, and PK |

4.3 Review Strategy

The clinical review of this supplemental NDA is based on updated efficacy and safety data from study CA012, a phase 3, open label, multicenter, randomized controlled trial in women with metastatic breast cancer. The following materials were reviewed by the medical officer (also see sections 4.1 and 6.1.1):

- The regulatory history of the application
- The electronic submission of the original NDA submitted March 2004 (CSR data cut-off April 7, 2003) and FDA reviews of the original NDA
- The electronic submission of updated survival and safety data and addendum to CSR submitted June 28, 2005, in fulfillment of a phase 4 commitment (data cut-off November 16, 2004) and FDA reviews of the submission
- The electronic submission of the supplemental NDA, datasets and analyses, without supplemental CSR, submitted as a Labeling Efficacy Supplement on April 18, 2006 (data cut-off date November 16, 2004)
- Applicant letter dated June 14, 2006, responding to FDA questions about methodology employed in new (b) (4) survival analyses for Labeling Supplement
- Applicant slide presentation to FDA on June 23, 2006
- Electronic addendum to CSR CA012, submitted July 21, 2006
- Applicant's proposed changes to the product label
- Taxol package insert
- Relevant published literature

4.4 Data Quality and Integrity

For the initial NDA review, FDA's Division of Scientific Investigation (DSI) inspected five sites in each of two cities in Russia, Moscow and St. Petersburg. These sites enrolled a combined total of 141 patients of the 460 patients accrued to the trial. The FDA also consulted an independent radiologist to audit selected patient radiographs by review of digitized images provided remotely to FDA computers by (b) (4), the applicant's contract, blinded radiology group. The data quality and integrity seemed satisfactory. For this supplement, there was no additional DSI review or radiographic audit performed.

4.5 Compliance with Good Clinical Practices

No new information was submitted with this supplement. See review of original NDA.

4.6 Financial Disclosures

No new information was submitted with this supplement. See original NDA review.

5 CLINICAL PHARMACOLOGY

No new clinical pharmacology data were submitted with this supplement.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Abraxane was approved January 7, 2005, for the Taxol indication for metastatic breast cancer: Treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

6.1.1 Methods

The efficacy review is based on the updated survival and progression data from study CA012, first provided by the applicant in June 2005, in fulfillment of a phase 4 commitment. The applicant resubmitted the same data in April 2006, with some additional analyses as an Efficacy Labeling Supplement. In response to FDA request, the applicant submitted an addendum to the CSR for CA012 in July 2006. The CSR included explanations of the methodology used by the applicant in their analyses. The Efficacy data for this supplement and relevant analyses were verified by reviewers in the FDA Biometrics Division. The updated survival data for all randomized patients was verified by Dr. Meiyu Shen (see review in DFS December 2005), who also performed an analysis for first-line therapy patients and for second or greater line therapy patients. Dr. Xiaoping Jiang, for the current review, has verified the analysis (b) (4)

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint for study CA012 was the Target Lesion Response Rate (TLRR), relying on modified RECIST criteria (see section 6.1.3). Following Amendments to the protocol, the reconciled Target Lesion Response Rate (*rec*TLRR) was defined as the primary efficacy endpoint. The *rec*TLRR incorporates the results of independent assessment of response based on blinded radiologic review performed during the first 6 cycles of therapy, using an algorithm to reconcile disagreements with investigator assessments of response (*inv*TLRR). The

investigator assessments could include clinical data. *RecTLRR* required confirmation of best response by cycle 6, since there were no independent assessments after cycle 6.

Secondary endpoints

- Investigator Overall Response Rate (*invORR*) based on the *investigator's* assessment of best confirmed response through all cycles, including evaluation of TLs and nonTLs, including disease which could be evaluated by physical examination and sonogram.
- Time to Disease Progression (TTP)
- Overall Survival (OS)

Reviewer comment: (b) (4) clarified that the June 2005 analysis of TTP was based on investigator assessments during therapy, with one month follow-up for 3 months (by telephone) after discontinuing therapy and then every 3-month (telephone) follow-up. The database cut-off was November 16, 2004, the final database of the study.

(b) (4)

6.1.3 Study Design

See medical officer clinical review of initial NDA 21-660 (dated January 2005) for additional details of protocol CA012 design and amendments.

Protocol CA012-0 is a multi-center (70 sites), international (22 sites in North America, 20 sites in U.K., 28 sites in Russia/Ukraine), randomized, controlled, open label, phase 3 trial comparing safety/tolerability and anti-tumor effect of ABI-007 to Taxol in women with metastatic breast cancer. Within each country, patients were randomized separately according to whether they had or had not previous anthracycline therapy. The requirement for patients to have had previous chemotherapy in the metastatic setting (or progression within 6 months of adjuvant chemotherapy) and previous anthracycline exposure was waived after accrual of > 100 patients in each arm of the trial.

The randomization ratio was 1:1, for patients to be treated intravenously every 3 weeks with either ABI-007 260 mg/m² IV over 30 minutes or Taxol 175 mg/m² IV over 3 hours. Patients were to be treated for up to 6 cycles and patients without progression could be treated for a longer period, at the discretion of the investigator. Patients were to be assessed with imaging studies for response after cycles 2, 3, and 5, with confirmation of response at weeks 9 and 15.

The protocol defines the primary efficacy endpoint as the target lesion response rate achieved after a minimum of two cycles of treatment, using Response Evaluation Criteria in Solid Tumors

(RECIST). The trial was designed as a non-inferiority trial, with a goal of enrolling 210 evaluable patients per arm, with at least 100 patients per arm who had previously been treated with anthracycline-based chemotherapy. Interim analysis was prespecified in order to re-estimate sample size after 105 patients in each arm were treated and evaluated for 2 cycles.

Reviewer comment: *The specified primary efficacy endpoint is a modification of RECIST. RECIST requires designation of an overall response taking into consideration both target and non-target lesion responses, and development of new disease. Although amendment 1 to the protocol specified only target lesions would be assessed for the primary endpoint, subsequently, the applicant specified that patients would not be considered to have a target lesion response if there were progression of non-target lesions or any new disease. In the study report, the applicant further defined the primary efficacy endpoint as the “reconciled Target Lesion response” (recTLRR).” This endpoint was chosen to decrease bias, since it incorporates the blinded assessment of response performed by the contract (b) (4) radiologist. An algorithm prespecifies how to reconcile disagreements between the independent radiologist and investigator assessments of response (which could include clinical data). Since (b) (4) only reviewed images for the first 6 cycles of therapy, the primary endpoint required confirmation of response by cycle 6*

In the study report, the “investigator Overall Response Rate” (invORR) is described as a secondary endpoint, based on the investigator’s assessment of best confirmed response through all cycles, including evaluation of TLs and nonTLs, including disease which could be evaluated by physical examination and sonogram, not accessible to (b) (4) .

The protocol (section 5.2.5) specifies that patients are “to be evaluated post-study, via telephone, every month for the first three months and every three months thereafter in order to obtain post-study survival data and time to disease progression.”

Reviewer comment: *Although survival data can be obtained by telephone, disease progression data cannot reliably be obtained by telephone evaluation alone.*

Major inclusion criteria include:

- Female, non-pregnant and not lactating, > 18 years old
- Histologically or cytologically confirmed measurable metastatic breast cancer, and a candidate for paclitaxel chemotherapy
- If patient received prior adjuvant taxane therapy, she has not relapsed within one year of completing such therapy
- No other malignancy within 5 years, except non-melanoma skin cancer, cervical intraepithelial neoplasia (CIN) or in-situ cervical cancer (CIS)
- Adequate renal, hepatic and bone marrow function
- Expected survival \geq 12 weeks

Patients were to be excluded for ECOG performance status > 2.

Reviewer comment: *Initial enrollment criteria required that patients meet criteria similar to the Taxol indication, i.e. patients must have failed prior chemotherapy either in the adjuvant or metastatic setting and prior therapy should have included an anthracycline unless contraindicated. After enrolling more than 100 patients in each arm of the trial who had previous anthracycline exposure, the requirement for prior therapy was waived, so that patients could be treated with study drug as first-line therapy in the metastatic setting.*

Patients were stratified at enrollment by:

- Country
- History of anthracycline exposure.

6.1.4 Efficacy Findings

See medical officer clinical review (dated January 2005) of the initial submission of NDA 21-660 for full study details.

Enrollment and Disposition

A total of 472 patients were enrolled in the trial and 460 were randomized to receive treatment with either ABI-004 (n=233) or Taxol (n=227). The randomized patients were recruited from 28 sites in Russia/Ukraine (n=353, 77% of patients), 20 sites in U.K. (n=67, 15%) and 22 sites in U.S./Canada (n=40, 9%). The 12 patients who were the subject of PK studies were not randomized, but were assigned directly to treatment with ABI-007. These patients were recruited from 4 of the Russian sites and were not included in any of the analysis populations. The largest centers for study enrollment were in Russia (n=34, each of 2 sites). Many sites, particularly in North America and U.K., enrolled only 1 (n=15) or 2 (n=17) patients per site.

The following table (taken from my original review), shows the number of patients in each arm of the study who were treated with ≤ 6 cycles or > 6 cycles of study therapy.

Table 2: Number of Cycles by Treatment Arm (Reviewer Table)

| Number of Cycles Delivered Per Patient | ABI-007 N=229 (%) | Taxol N=225 (%) |
|--|----------------------|--------------------|
| ≤ 6 | 168 (73%) | 182 (81%) |
| > 6 | 65 (28%) | 45 (20%) |

Source: Dataset “patient”; all randomized patients

Approximately three quarters of patients from both treatment arms were discontinued after receiving ≤ 6 cycles of therapy. The mean/median number of cycles administered for randomized patients was 5.6/6 for the ABI-007 treatment arm and 5.2/5 for the Taxol treatment arm.

Reviewer comment: *It should be noted that the primary endpoint, recTLRR, which included blinded radiology review, required confirmation of response during the first 6 cycles of*

treatment. The secondary endpoint, invORR could include the best confirmed response observed over all treatment cycles.

The largest category of patients was discontinued from therapy due to progressive disease (ABI-007: 46%; Taxol: 55%). The reported incidence of withdrawal for treatment related toxicity was slightly higher for ABI-007 (5%) compared with Taxol patients (3%).

Baseline Demographics

There were no significant differences in baseline demographic factors between the treatment arms. All patients were female; 97% were Caucasian. The mean age was approximately 53 years for both treatment groups. The menopausal status was similar for both groups, 17% premenopausal and 83% postmenopausal in both treatment groups. For each geographic area, the number of patients treated in each arm of the study was balanced. Approximately 77% of all patients were enrolled from Russia/Ukraine, 15% from the U.K. and 9% from the U.S./Canada.

Baseline Disease Characteristics

There were no significant differences between treatment groups for major disease-related characteristics, including previous exposure to chemotherapy. At baseline, 88% of ABI-007 patients and 85% of Taxol patients had had prior chemotherapy. Seventy-seven percent and 78%, respectively had been exposed to anthracycline in either the adjuvant or metastatic setting. Fifty percent of ABI-007 patients and 58% of Taxol patients had previous exposure to anthracycline in the metastatic setting. Only 1% of patients in either treatment arm had prior exposure to taxane. The next table, from the original study report, displays the number of prior therapies for metastatic breast cancer by treatment arm. The percent of patients that received study drug as first-line therapy for metastatic disease was 42% for the ABI-007 group and 40% for the Taxol group.

Table 3: Prior Treatment for Metastatic Breast Cancer (Applicant Table)

| Number of Prior Metastatic Treatments | Number (%) of Patients | | |
|---|------------------------|--------------------|------------------|
| | ABI-007 (N = 229) | Taxol (N = 225) | All (N = 454) |
| 0 (study drug as 1 st -line therapy) | 97 (42%) | 89 (40%) | 186 (41%) |
| ≥ 1 (study drug as > 1 st -line therapy) | 132 (58%) | 136 (60%) | 268 (59%) |
| 1 | 94 (41%) | 96 (43%) | 190 (42%) |
| 2 | 23 (10%) | 35 (16%) | 58 (13%) |
| ≥ 3 | 15 (7%) | 5 (2%) | 20 (4%) |

Applicant In-Text Table 28; source Summary table 13.0 and listings 8.0, 8.1 and 8.2

Analysis Populations

The applicant defined the following analysis populations:

- All Randomized (AR): Includes all patients randomized, even if not treated (n=460)
- Intention to Treat (ITT): Patients randomized and received ≥ 1 cycle of therapy (n=454)
- Per Protocol (PP): Patients from the ITT population who were evaluated for response after 2 cycles and have no major protocol violations (ABI-007: n=211; Taxol: n=218)

The applicant-defined ITT population excluded 6 patients (4 ABI-007 and 2 Taxol) who were randomized, but not treated. The applicant ITT population was the same as the safety population. The next applicant table, taken from the original NDA study report, displays the number of prior chemotherapy lines of therapy for the analysis populations and by treatment arm.

Table 4: Prior Therapy by Analysis Population and Study Arm (Applicant Table)

| Study Population | Number (%) of Patients | | |
|---|------------------------|------------|------------|
| | ABI-007 | Taxol | All |
| All Randomized (AR) | 233 | 227 | 460 |
| Intent-to-Treat (ITT) | 229 (100%) | 225 (100%) | 454 (100%) |
| Receiving study drug as 1 st -line therapy | 97 (42%) | 89 (40%) | 186 (41%) |
| Receiving study drug as > 1 st -line therapy | 132 (58%) | 136 (60%) | 268 (59%) |
| Anthracycline-exposed (adjuvant or metastatic) | 176 (77%) | 175 (78%) | 351 (77%) |
| Anthracycline-exposed (metastatic only) | 115 (50%) | 130 (58%) | 245 (54%) |
| Per Protocol (PP) ^a | 211 | 218 | 429 |
| Safety | 229 | 225 | 454 |

Source: In-Text Table 20 (from Summary Tables 1 and 13, and Listing 1.1)

Primary Endpoint

The primary efficacy endpoint for study CA012 was the reconciled Target Lesion Response Rate (*recTLRR*), relying on modified RECIST criteria. (See sections 6.1.2 and 6.1.3). The *recTLRR* incorporates the results of independent assessment of response based on blinded radiologic review performed during the first 6 cycles of therapy, using an algorithm to reconcile disagreements with investigator assessments of response (*invTLRR*). The investigator assessments could include clinical data. *RecTLRR* required confirmation of best response by cycle 6, since there were no independent assessments after cycle 6.

The table below summarizes the efficacy results from the randomized trial, based on the true ITT population and as adjudicated by FDA. The table is taken from the Abraxane label approved in January 2005. The data was analyzed for the overall study population and for the patients who conformed to the Taxol indication for metastatic breast cancer.

Table 5: Efficacy Results (Abraxane Label)

| | | ABRAXANE 260 mg/m² | Paclitaxel Injection 175 mg/m² |
|--|----------------------|--|--|
| Reconciled Target Lesion Response Rate (primary endpoint)^a | | | |
| All randomized patients | Response Rate | 50/233 (21.5%) | 25/227 (11.1%) |
| | [95% CI] | [16.19% – 26.73%] | [6.94% – 15.09%] |
| | P-value ^b | 0.003 | |
| Patients who had failed combination chemotherapy or relapsed within 6 months of adjuvant chemotherapy ^c | Response Rate | 20/129 (15.5%) | 12/143 (8.4%) |
| | [95% CI] | [9.26% – 21.75%] | [3.85% – 12.94%] |

^a Reconciled Target Lesion Response Rate (TLRR) was the prospectively defined protocol specific endpoint, based on independent radiologic assessment of tumor responses reconciled with investigator responses (which also included clinical information) for the first 6 cycles of therapy. The reconciled TLRR was lower than the investigator Reported Response Rates, which are based on all cycles of therapy.

^b From Cochran-Mantel-Haenszel test stratified by 1st line vs. > 1st line therapy.

^c Prior therapy should have included an anthracycline unless clinically contraindicated

For the 272 patients who conformed to the Taxol indication, there were 20 and 12 responders in the ABI-007 and Taxol treatment arms, for respective response rates of 15.5% and 8.4%. The P-value from the Chi-Square Test calculated by the FDA statistical reviewer was 0.069. Although the difference was not statistically significant in this subgroup, the trend was in the same direction as for the overall study population.

For the 189 first-line patients, the FDA-adjudicated response rates were 31.3% and 17.8%, respectively, also favoring ABI-007. The ratio of response rates (ABI-007/Taxol) was 1.761, with 95% confidence interval 1.035-2.997. The p-value from the Chi-Square Test was 0.032.

Secondary Endpoints June 2005 Submission

At the time of the data cut-off for the initial NDA review, (b) (4) survival data were not mature. At that time, 49% of the patients in the ABI-007 treatment group and 58% of the patients in the Taxol treatment group had progressed, and 32% and 37% in the respective groups had died.

The data cut-off for Addendum 1 to the CSR, dated March 23, 2005, was November 16, 2004. The additional progression and survival data were submitted to FDA in June of 2005 in fulfillment of a phase 4 commitment, which required submission of survival data when 80% of patients in study CA012 had died. The data showed that the time to death was numerically longer but not statistically significantly longer with ABI-007 than with Taxol for all patients. Time to death was statistically significantly longer with ABI-007 for patients receiving $\geq 2^{\text{nd}}$ line therapy, but shorter for patients receiving first line therapy, although the difference was not statistically significant.

The statistical reviewer, Dr. Meiyu Shen, recalculated survival time as time from randomization (as opposed to the date of first dose as performed by applicant) to date of death and based on data from all randomized patients. The applicant's analysis excluded 4 patients randomized to ABI-007 therapy and 2 patients randomized to Taxol therapy, all of whom received no treatment. The results of Dr. Shen's analysis were consistent with those of the sponsor. The next table is taken from Dr. Shen's review, dated December 2005.

Table 6: Statistical Reviewer's Survival Analysis 2005

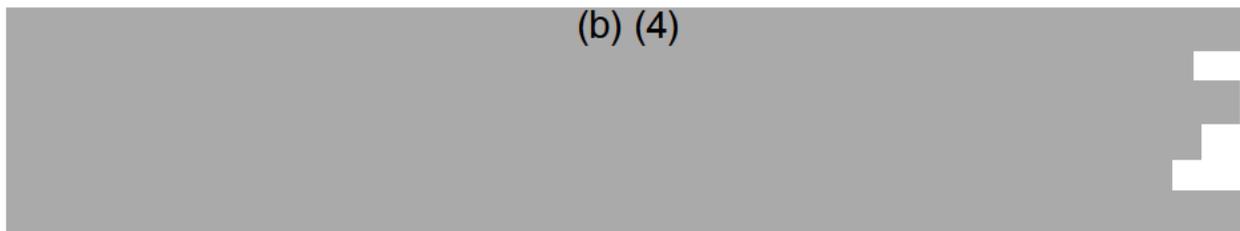
| Category | ABI-007 | Taxol |
|--|----------------------------|----------------------------|
| All randomized patients | | |
| Number of all randomized patients | 233 | 227 |
| Number (%) of patients who died | 172 (73.82%) | 175 (77.09%) |
| Median time to death, weeks, (95% confidence interval) | 65.286 (53.857, 77.000) | 55.429 (48.286, 66.571) |
| P-value from (two-sided) Logrank test | 0.3484 | |
| Hazard ratio ^a (95% confidence interval) | 0.904 (0.732, 1.116) | |
| First line therapy patients only | | |
| Number of randomized patients to 1 st line therapy | 100 | 90 |
| Number (%) of patients who died | 73 (73%) | 60 (66.67%) |
| Median time to death, weeks, (95% confidence interval) | 71.143 (60.000, 88.143) | 78.000 (58.286, 98.143) |
| P-value from (two-sided) Logrank test | 0.2433 | |
| Hazard ratio ^a (95% confidence interval) | 1.225 (0.870, 1.724) | |
| Second or greater line therapy patients | | |
| Number of randomized patients to $\geq 2^{\text{nd}}$ line therapy | 133 | 137 |
| Number (%) of patients who died | 99 (74.44%) | 115 (83.94%) |
| Median death time, weeks, (95% confidence interval) | 56.571 (45.571, 76.571) | 47.000 (39.143, 55.429) |
| P-value from (two-sided) Logrank test | 0.0206 | |
| Hazard ratio ^a (95% confidence interval) | 0.727 (0.554, 0.954) | |

Note: Time to death is defined as the number of weeks from the randomization date to patient death. Patients who have not died are censored at the last known time the patient was alive.

^a Hazard ratio of ABI-007/Taxol, based on the Cox progression model without any covariate.

All p-values are not adjusted by multiplicity.

Source: Dr. Meiyu Shen's Review, December 2005



(b) (4)

(b) (4)

**Secondary Endpoints
April 2006 Submission**

In April 2006, the applicant resubmitted the same data, but with some differences in analyses and request for labeling change. Analyses were performed, using the all randomized (n=460) ^{(b) (4)}

the next table summarizes the applicant's survival analyses from Addendum 3 to the CSR (submitted July 2006). Survival was defined as the duration from randomization date to date of death due to any cause, analyzed by Kaplan-Meier methods.

Table 8: Applicant's Survival Analysis 2006

| | ABI-007 | Taxol | P-value^a | Hazard Ratio |
|--------------------------------|----------------|--------------|----------------------------|---------------------|
| <u>All Randomized Patients</u> | N=233 | N=227 | | |
| Patients Who Died, n (%) | 172 (74%) | 175 (77%) | | |
| Median Time to Death (weeks) | 65.3 | 55.4 | 0.348 | 0.904 |
| 95% Confidence Interval | 53.9, 77.0 | 48.3, 66.6 | | 0.732, 1.116 |

(b) (4)

Note: Analysis included patient survival information during study follow-up. Patients who did not die were censored at the last known time the patient was alive.

^a P-value from log-rank test. * P < 0.050.

(b) (4)

Source Data: [Summary Table 3](#) and [Summary Table 4](#).

Source: Applicant's In-Text Table 2 from Addendum 3 to CSR for Study CA012

(b) (4)

(b) (4)

Efficacy for gender, age and racial subgroups

See original NDA review for more detail. The data did not permit useful comparisons of gender, age and racial subgroups. Study CA012 enrolled only females; 97% of patients in both arms of the trial were Caucasians. The number of patients older than age 65 was too small to make meaningful conclusions regarding the impact of age (30/229 in the ABI-007 arm and 32/225 in the Taxol arm).

6.1.5 Clinical Microbiology

No microbiology information was submitted with this supplement.

Efficacy Conclusions

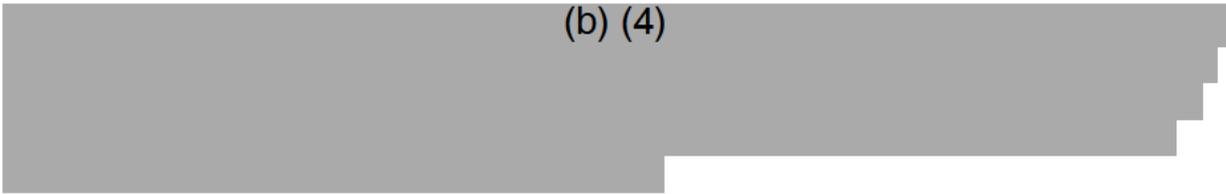
The original NDA for Abraxane was filed under Section 505(b)(2), referencing the label, efficacy and safety of Taxol Injection. The applicant demonstrated superiority of Abraxane in objective response rate to Taxol in a single randomized trial in metastatic breast cancer (CA012). At least 100 patients in each arm were to match the Taxol indication, which is “treatment of metastatic breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.”

The primary endpoint for study CA012 was recTLRR. (See section 6.1.2.) Secondary endpoints included *inv*ORR, TTP and OS. The current sNDA and efficacy labeling supplement provides survival (b) (4) analyses based on the final study data cut-off date, November 16, 2004.

The overall survival for all randomized patients was not superior in the ABI-007 treatment arm compared with Taxol treatment arm. (b) (4)

(b) (4)

(b) (4)



7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Very limited new safety data were provided as part of this supplemental NDA. At the time of the data cut-off for the CSR (April 7, 2003), only 5 of 454 patients who were randomized and treated in the study were still receiving study drug. Three of these patients were treated in the ABI-007 arm and 2 patients were treated in the Taxol study arm. One additional patient, who participated in the non-randomized pharmacokinetic (PK) portion of the trial was under therapy. Two patients in the ABI-007 group experienced serious adverse events (SAEs), grade 4 neutropenia. The data contained in the sNDA are the same data presented with Addendum 1 to the CSR submitted June 2005. The same safety (and efficacy) data were resubmitted as part of the Labeling Efficacy Supplement submitted April 14, 2006. Minor changes are proposed to Table 2 (frequency of AEs) and AE Experience by Body System sections of the label, based on the 120 Day Safety Update submitted July 7, 2004, and based on postmarketing safety reporting.

The limited safety information provided with this supplement is discussed above. There is no new information to discuss in sections 7.1.1 through 7.4.3.

7.1.1 Deaths

7.1.2 Other Serious Adverse Events

7.1.3 Dropouts and Other Significant Adverse Events

7.1.4 Other Search Strategies

7.1.5 Common Adverse Events

7.1.6 Less Common Adverse Events

7.1.7 Laboratory Findings

7.1.8 Vital Signs

7.1.9 Electrocardiograms (ECGs)

7.1.10 Immunogenicity

7.1.11 Human Carcinogenicity

7.1.12 Special Safety Studies

7.1.13 Withdrawal Phenomena and/or Abuse Potential

7.1.14 Human Reproduction and Pregnancy Data

7.1.15 Assessment of Effect on Growth

7.1.16 Overdose Experience

7.1.17 Postmarketing Experience

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.2 Demographics

7.2.1.3 Extent of exposure (dose/duration)

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

7.2.2.2 Postmarketing experience

7.2.2.3 Literature

7.2.3 Adequacy of Overall Clinical Experience

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

7.2.5 Adequacy of Routine Clinical Testing

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

7.2.8 Assessment of Quality and Completeness of Data

7.2.9 Additional Submissions, Including Safety Update

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

7.4.1.2 Combining data`

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

7.4.2.2 Explorations for time dependency for adverse findings

7.4.2.3 Explorations for drug-demographic interactions

7.4.2.4 Explorations for drug-disease interactions

7.4.2.5 Explorations for drug-drug interactions

7.4.3 Causality Determination

8 ADDITIONAL CLINICAL ISSUES

No new additional information was provided with the supplement regarding dosing and administration, drug-drug interactions, or special populations.

8.1 Dosing Regimen and Administration

8.2 Drug-Drug Interactions

8.3 Special Populations

8.4 Pediatrics

8.5 Advisory Committee Meeting

This will not be taken to an advisory committee.

8.6 Literature Review

The applicant did not provide any references from the literature with the current submission. Recent references from the literature are included in the Appendix to this review.

8.7 Postmarketing Risk Management Plan

There is no postmarketing risk management plan.

8.8 Other Relevant Materials

None

9 OVERALL ASSESSMENT

9.1 Conclusions

The applicant submitted updated survival data and overall survival analysis (b) (4) from Study CA012 as a Labeling Efficacy Supplement. The overall

survival for all randomized patients was not superior in the ABI-007 treatment arm compared with the Taxol treatment arm. (b) (4)

(b) (4)

(b) (4)

9.2 Recommendation on Regulatory Action

The Labeling Efficacy Supplement should be approved, with changes. (b) (4)

The statement “There was no statistically significant difference in overall survival between the two study arms” should be incorporated in the label. (b) (4)

9.3 Recommendation on Postmarketing Actions

None

9.3.1 Risk Management Activity

No special risk management activities are recommended.

9.3.2 Required Phase 4 Commitments

At the time of Abraxane approval on January 7, 2005, the applicant committed to do a clinical study to evaluate Abraxane in patients with hepatic impairment. As of November 2006, Abraxis has enrolled 16/30 patients to this study, and anticipates the study report will be available November 2007.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

(b) (4)

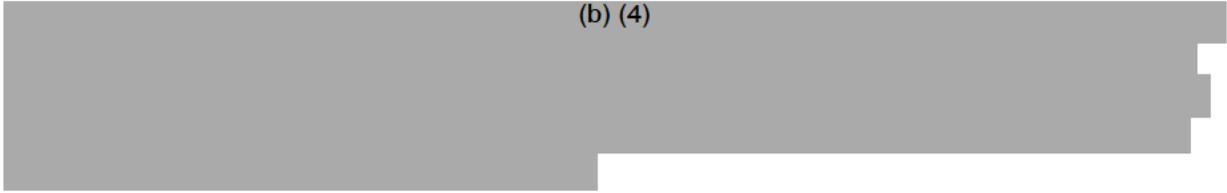


Table 10: Applicant's Proposal for Label

Table 1: Efficacy Results from Randomized Trial

| Reconciled Target Lesion Response Rate (primary endpoint) ^a | | ABRAXANE 260 mg/m ² | Paclitaxel Injection 175 mg/m ² |
|---|---------------------------|-------------------------------------|---|
| All randomized patients | Response Rate [95% CI] | 50/233 (21.5%) [16.19% – 26.73%] | 25/227 (11.1%) [6.94% – 15.09%] |
| | P-value ^b | 0.003 | |
| Patients who had failed combination chemotherapy or relapsed within 6 months of adjuvant chemotherapy ^c | Response Rate [95% CI] | 20/129 (15.5%) [9.26% – 21.75%] | 12/143 (8.4%) [3.85% – 12.94%] |

(b) (4)

9.5 Comments to Applicant

FDA sent an email to the applicant November 9, 2006, proposing that the following sentence be added to the Clinical Trials section of the label:

“There was no statistically significant difference in overall survival between the two study arms.”

(b) (4)

FDA agreed to applicant’s proposed minor changes to Table 2, “Frequency of Important Treatment Emergent Adverse Events in the Randomized Study...”

FDA forwarded to the applicant a revised label reflecting these changes November 9, 2006. We await the applicant’s response to the proposed label.

10 Appendices

10.1 Review of Individual Study Reports

No additional study reports are reviewed.

10.2 Line-by-Line Labeling Review

See label.

REFERENCES

- Desai N, Trieu V, Yao Z, et al. Increased Antitumor Activity, Intratumor Paclitaxel Concentrations, and Endothelial Cell Transport of Cremophor-Free, Albumin-Bound Paclitaxel, ABI-007, Compared with Cremophor-Based Paclitaxel 10.1158/1078-0432.CCR-05-1634. *Clin Cancer Res.* Feb 15, 2006; 12(4):1317-1324.
- Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III Trial of Nanoparticle Albumin-Bound Paclitaxel Compared With Polyethylated Castor Oil-Based Paclitaxel in Women With Breast Cancer. *J Clin Oncol.* Nov 1, 2005; 23(31):7794-7803.
- Harries M, Ellis P, Harper P. Nanoparticle Albumin-Bound Paclitaxel for Metastatic Breast Cancer. *J Clin Oncol.* Nov 1, 2005; 23(31):7768-7771.
- Ibrahim NK, Samuels B, Page R, et al. Multicenter phase II trial of ABI-007, an albumin-bound paclitaxel, in women with metastatic breast cancer. *J Clin Oncol.* Sep 1, 2005; 23(25):6019-6026.
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- Nyman DW, Campbell KJ, Hersh E, et al. Phase I and Pharmacokinetics Trial of ABI-007, a Novel Nanoparticle Formulation of Paclitaxel in Patients With Advanced Nonhematologic Malignancies. *J Clin Oncol.* Nov 1 2005; 23(31):7785-7793.
- Sparreboom A, Scripture CD, Trieu V, et al. Comparative preclinical and clinical pharmacokinetics of a cremophor-free, nanoparticle albumin-bound paclitaxel (ABI-007) and paclitaxel formulated in Cremophor (Taxol). *Clin Cancer Res.* Jun 1 2005; 11(11):4136-4143.
- Sparreboom A, Baker SD, Verweij J. Paclitaxel repackaged in an albumin-stabilized nanoparticle: Handy or just a dandy? *J Clin Oncol.* Nov 1 2005; 23(31):7765-7767.

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/s/

Nancy Scher
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MEDICAL OFFICER

Ramzi Dagher
12/22/2006 02:49:56 PM
MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-660/S-010

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number: 21-660 / S010

Drug Name: Abraxane (ABI-007)

Indications: Metastatic Breast Cancer

Applicant: Abraxis BioScience

Date(s): Submission Date: April 18, 2006
PDUFA Date: February 18, 2007

Review Priority: Standard.

Biometrics Division: Division of Biometrics V (HFD-711)

Statistical Reviewer: Xiaoping (Janet) Jiang, Ph.D.

Concurring Reviewers: Team Leader: Rajeshwari Sridhara, Ph.D.
Division Director: Aloka Chakravarty, Ph.D.

Medical Division: Division of Drug Oncology Product (HFD-150)

Clinical Team: Reviewers: Nancy Scher, M.D.
Team Leader: Ramzi Dagher, M.D.

Project Managers: Amy Baird, Carl Huntley

Keywords: Survival, log-rank test.

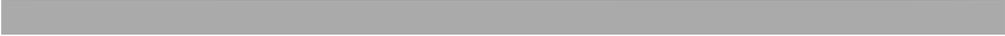
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1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

The sponsor submitted an efficacy supplement to new drug application (sNDA) seeking approval of amending labeling of Abraxane® by revising the current prescribing information with updated safety and efficacy data. When FDA granted approval of Abraxane® for metastatic breast cancer on January 7, 2005, the sponsor was required to submit survival data and analysis results from the pivotal randomized open-label study CA012 when 80 percent of patients had died. On June 28, 2005, the sponsor submitted the survival results in order to fulfill the commitment. This sNDA includes no updated data since last submission for fulfillment of the commitment (b) (4)



1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

On January 7, 2005, Abraxane® was approved for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension). Abraxane® was indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated. The approval was based on response rate resulted from the pivotal study CA012. Study CA012-0 was a randomized, multi-center, open-label, Phase III trial, conducted in 70 sites, located in Russia/Ukraine, Canada, the U.S. and the United Kingdom. A total of 460 patients with metastatic breast cancer were randomized to receive either ABI-007 or Taxol. Of those 460 randomized patients, 233 patients were randomized to the ABI-007 arm and 227 patients to the Taxol arm. Also, there were 272 patients who met the Taxol indication in the study. Please refer Dr. Peiling Yang and Dr. Meiyu Shen's statistical reviews of original NDA and (b) (4) respectively, for more details of this pivotal study.

1.3 STATISTICAL ISSUES AND FINDINGS

The survival data from the pivotal study CA012 were not mature at the time of ABI-007 approval. In this sNDA, the sponsor proposed to include the matured overall survival (OS) (b) (4) results from the study CA012 to the labeling. The (b) (4) OS results were presented in all randomized 460 patients (b) (4)

Statistical Issues:

There are following statistical issues in this sNDA:

- (b) (4)
- (b) (4)
- (b) (4)

Findings

- Following Table A, Table B and Table C show the sponsor's OS (b) (4)

Table A: The Sponsor's Results of Overall Survival

| | ABI-007 | Taxol | P-value (log-rank) | Hazard Ratio |
|--------------------------------|----------------|--------------|-------------------------------|-------------------------|
| All Randomized Patients | N=233 | N=227 | | |
| Patients Who Died, n (%) | 172 (74%) | 175 (77%) | 0.348 | 0.904 (0.732, 1.116) |
| Median Time to Death (weeks) | 65.3 | 55.4 | | |
| | 53.9, 77.0 | 48.3, 66.6 | | |

(b) (4)

(b) (4)

(b) (4)



2 INTRODUCTION

2.1 OVERVIEW

Abraxane for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. On January 7, 2005, Abraxane was approved for treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. The approval was based on the response rates obtained from the pivotal study CA012-0. Study CA012-0 was a randomized, multi-center, open-label, Phase III trial. At the time of ABI-007 approval, the survival data were not mature. In this sNDA submission, the sponsor was seeking approval of inserting (b) (4) survival results presented in all randomized patients (b) (4) into the product label.

Study CA012-0 randomized 460 patients and included 272 patients in the approval indication populations. The indication population is defined as patients who failed combination chemotherapy or relapsed within 6 months of adjuvant chemotherapy where prior chemotherapy included an anthracycline unless clinically contraindicated.

2.2 DATA SOURCES

Per sponsor, the database for the (b) (4) OS results presented in this sNDA (Clinical Study Report Addendum 3) was the same database used for Clinical Study Report Addendum 1 (i.e. the final database – all data collected through 16 November 2004). Data used in this review were from the electronic submission received in April 2006. The network path was “\\Cdsub1\N021660\S_010\2006-04-14” in the EDR.

3 STATISTICAL EVALUATION

This review will be focused on the survival (b) (4). For details of the pivotal study CA012-0 and the survival (b) (4) results in all randomized population, please see Dr. Peiling Yang and Dr. Meiyu Shen’s statistical reviews.

3.1 EVALUATION OF EFFICACY

This section is focused on evaluating efficacy of ABI-007 in terms of the OS (b) (4) results in all randomized population (b) (4) provided from the sponsor’s clinical study reports addendum 3.

3.1.1 SURVIVAL RESULTS

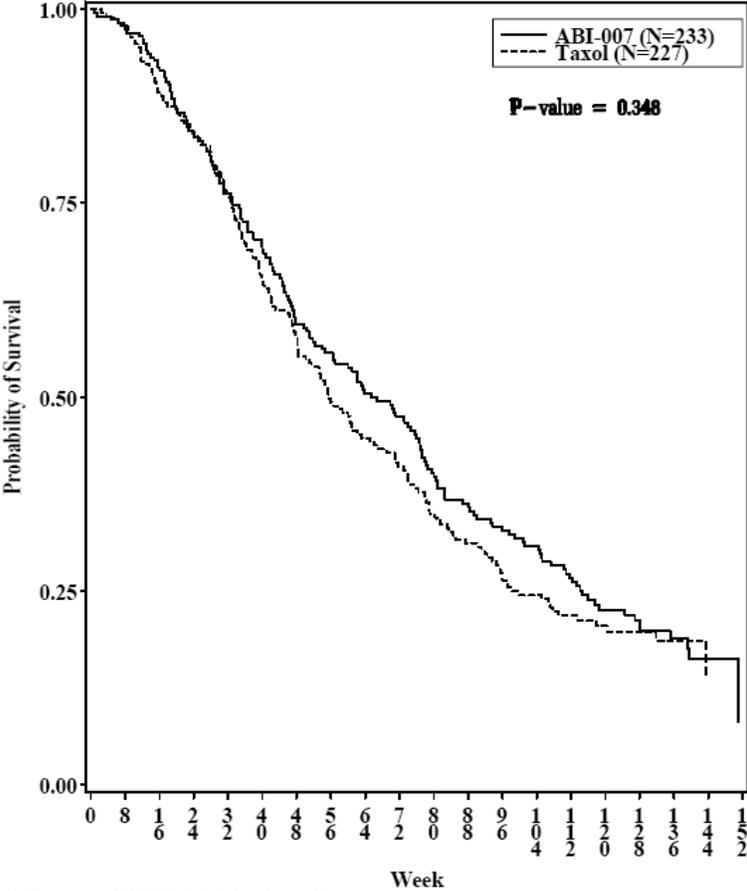
Overall survival was one of the secondary endpoints in the study CA012-0. In June 2005, the sponsor submitted the OS results, including the results in all randomized population, from study CA012 to fulfill the commitment. For more details of the statistical review of this commitment, please see Dr. Meiyu Shen’s statistical review. The following Table 1 shows the sponsor’s OS results in all randomized population and approval indication population. In this sNDA, the sponsor proposed to include these overall survival results in the product label.

Table 1: The Sponsor's Results of Overall Survival

| | ABI-007 | Taxol | P-value (log-rank) | Hazard Ratio |
|---------------------------------|----------------|--------------|-------------------------------|-------------------------|
| All Randomized Patients | N=233 | N=227 | | |
| Patients Who Died, n (%) | 172 (74%) | 175 (77%) | | |
| Median Time to Death (weeks) | 65.3 | 55.4 | 0.348 | 0.904 |
| 95% Confidence Interval | (53.9, 77.0) | (48.3, 66.6) | | (0.732, 1.116) |

(b) (4)

Figure 1: Sponsor’s Kaplan-Meier Overall Survival Curves (ITT Population)



[Source: Clinical Study Report: CA012-0 Addendum 3]
Note: p-value was from log-rank test.

(b) (4)

Reviewer Comments:

- [1] The overall survival results based on all randomized patients (b) (4) were verified by FDA statistical reviewer Dr. Meiyu Shen and this reviewer, respectively.
- [2] There is no statistically significant difference in OS between two treatment arms at the significant level of 0.05. (b) (4)
- [3] The study failed to demonstrate the survival advantage in the overall population (b) (4)

3.2 EVALUATION OF SAFETY

Please refer to FDA clinical reviews provided by Dr. Nancy Scher for safety evaluation of Abraxane.

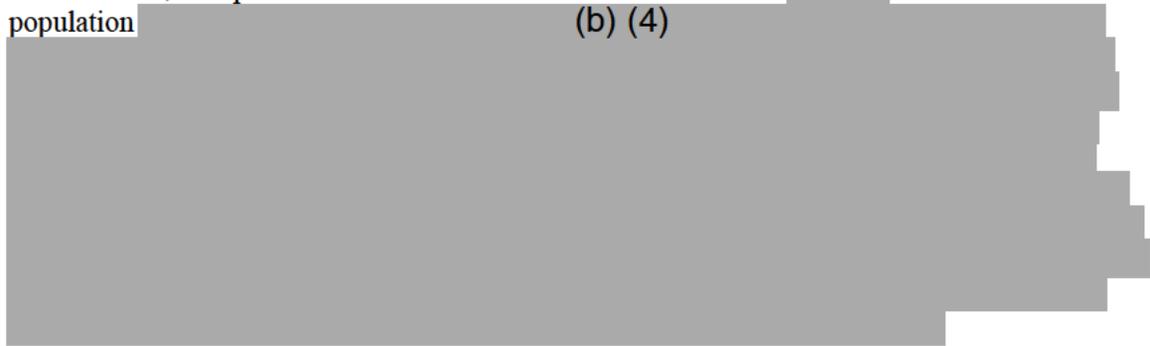
4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Since all the patients in study CA012 were female and about 97 percent of patients were Caucasian, overall survival analyses for subgroups of gender and race were not performed. For survival results in other subgroups, such as age, please see Dr. Meiyu Shen's review.

5 SUMMARY AND CONCLUSIONS

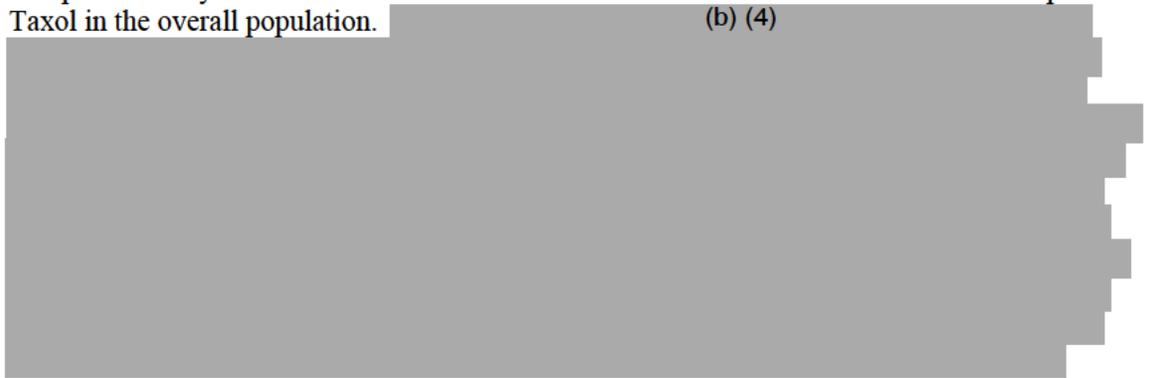
5.1 SPONSOR'S EFFICACY CONCLUSIONS

In this sNDA, the sponsor submitted the results of overall survival (b) (4) on the entire population (b) (4)



5.2 CONCLUSIONS AND RECOMMENDATIONS

The pivotal study CA012 failed to demonstrate overall survival benefit of Abraxane compared to Taxol in the overall population. (b) (4)



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Aloka Chakravarty
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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-660/S-010

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-660

SUPPL # SE8-010

HFD # 150

Trade Name ABRAXANE® for Injectable Suspension

Generic Name paclitaxel protein-bound particles for injectable suspension

Applicant Name Abraxis BioScience, Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE8 supplement provides revised prescribing information with updated safety and efficacy information for ABRAXANE® Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) in the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA

#(s).

NDA# 21-660

ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension)

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

CA012-0 (Continuation of pivotal trial submitted in original NDA. Continuation requested as a Post Marketing Commitment in original NDA.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

21-660 Updated information from CA012-0

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 55,974 YES ! NO
! Explain:

Investigation #2
IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
! YES
! NO
! Explain:

Investigation #2
!
! YES
! NO
! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

Name of person completing form: Frank Cross
Title: Project Manager
Date: February 12, 2007

Name of Office/Division Director signing form: Ann Farrell, M.D.
Title: Acting Deputy Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

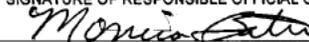
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/s/

Ann Farrell
2/12/2007 11:48:46 AM

| | | |
|---|---------------------------|--|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION | | Form Approved: OMB No. 0910-0338 Expiration Date: September 30, 2008 See OMB Statement on page 2. |
| APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE <i>(Title 21, Code of Federal Regulations, Parts 314 & 601)</i> | | FOR FDA USE ONLY |
| | | APPLICATION NUMBER |
| APPLICANT INFORMATION | | |
| NAME OF APPLICANT American BioScience, Inc. | | DATE OF SUBMISSION 4/14/06 |
| TELEPHONE NO. (Include Area Code) 310 883 1300 | | FACSIMILE (FAX) Number (Include Area Code) 310 998 5830 |
| APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 2730 Wilshire Blvd. Suite 110 Santa Monica, CA 90403 | | AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Not Applicable |
| PRODUCT DESCRIPTION | | |
| NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-660 | | |
| ESTABLISHED NAME (e.g., Proper name, USP/USAN name) paclitaxel protein-bound particles for injectable suspension (albumin-bound) | | PROPRIETARY NAME (trade name) IF ANY Abraxane® for Injectable Suspension |
| CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) 5B,-20-epoxy-1,2a,4,7B,13a,-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-n-benzoyl-3-phenylisoserine | | CODE NAME (If any) ABI-007 |
| DOSAGE FORM: Lyophilized Cake For Injectable Suspension | STRENGTHS: 100 mg/Vial | ROUTE OF ADMINISTRATION: Intravenous Infusion |
| (PROPOSED) INDICATION(S) FOR USE: | | |
| APPLICATION DESCRIPTION | | |
| APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601) | | |
| IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input checked="" type="checkbox"/> 505 (b)(2) | | |
| IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION | | |
| Name of Drug _____ Holder of Approved Application _____ | | |
| TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input checked="" type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER | | |
| IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____ | | |
| IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA) | | |
| REASON FOR SUBMISSION To revise the current prescribing information with updated safety and efficacy data | | |
| PROPOSED MARKET STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC) | | |
| NUMBER OF VOLUMES SUBMITTED <u> 1 </u> THIS APPLICATION IS <input type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input checked="" type="checkbox"/> ELECTRONIC | | |
| ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready. | | |
| Drug Substance Manufacturer _____ (b) (4) | | |
| Sites are ready for inspection. | | |
| Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application) | | |

(b) (4)

| | | |
|--|---|--|
| This application contains the following items: (Check all that apply) | | |
| <input checked="" type="checkbox"/> | 1. Index | |
| <input checked="" type="checkbox"/> | 2. Labeling (check one) | <input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling |
| <input type="checkbox"/> | 3. Summary (21 CFR 314.50 (c)) | |
| <input type="checkbox"/> | 4. Chemistry section | |
| <input type="checkbox"/> | A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2) | |
| <input type="checkbox"/> | B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request) | |
| <input type="checkbox"/> | C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2) | |
| <input type="checkbox"/> | 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2) | |
| <input type="checkbox"/> | 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2) | |
| <input type="checkbox"/> | 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4)) | |
| <input checked="" type="checkbox"/> | 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2) | |
| <input type="checkbox"/> | 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2) | |
| <input type="checkbox"/> | 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2) | |
| <input checked="" type="checkbox"/> | 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2) | |
| <input type="checkbox"/> | 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2) | |
| <input type="checkbox"/> | 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c)) | |
| <input type="checkbox"/> | 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A)) | |
| <input type="checkbox"/> | 15. Establishment description (21 CFR Part 600, if applicable) | |
| <input type="checkbox"/> | 16. Debarment certification (FD&C Act 306 (k)(1)) | |
| <input type="checkbox"/> | 17. Field copy certification (21 CFR 314.50 (l)(3)) | |
| <input type="checkbox"/> | 18. User Fee Cover Sheet (Form FDA 3397) | |
| <input type="checkbox"/> | 19. Financial Information (21 CFR Part 54) | |
| <input type="checkbox"/> | 20. OTHER (Specify) | |
| CERTIFICATION | | |
| I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following: | | |
| 1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820. | | |
| 2. Biological establishment standards in 21 CFR Part 600. | | |
| 3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809. | | |
| 4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202. | | |
| 5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12. | | |
| 6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81. | | |
| 7. Local, state and Federal environmental impact laws. | | |
| If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision. | | |
| The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate. | | |
| Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001. | | |
| SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT  | TYPED NAME AND TITLE Monica R. Batra, Senior Regulatory Scientist | DATE: 4/14/06 |
| ADDRESS (Street, City, State, and ZIP Code) 2730 Wilshire Boulevard, Suite 500, Santa Monica, CA 90403 | Telephone Number (310) 883 3144 | |
| Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: | | |

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Central Document Room
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DIVISION OF DRUG ONCOLOGY PRODUCTS

Center for Drug Evaluation and Research

White Oak, Bldg. 22, Room 2173

10903 New Hampshire Ave., Silver Spring, MD 20903

To: Monica Batra

From: Amy Baird, CSO

Fax: 310-437-7788

Fax: 301-796-9845

Phone: 310-437-7741

Phone: 301-796-1325

Pages (including cover): 1

Date: November 2, 2006

Re: NDA 21-660/SE8-010. Specifically, your submission dated April 14, 2006.

Urgent **For Review** **Please Comment** **Please Reply** **Please Recycle**

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● **Comments:**

Per the request of the FDA clinical review team, please provide the following:

1. A version of the proposed labeling submitted with S-010 in Word format.
2. (b) (4)
3. Also, has AB Science filed for marketing authorization in another jurisdiction (non-US) as yet, and when are you likely to?
4. What is the status of your phase 4 commitment to do a clinical study to evaluate Abraxane in patients with hepatic impairment?

Please call should you have any questions.

Thank you,

Amy Baird

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/s/

Amy Baird
11/2/2006 11:06:53 AM
CSO

Fax



DIVISION OF DRUG ONCOLOGY PRODUCTS

Center for Drug Evaluation and Research

White Oak, Bldg. 22, Room 2173

10903 New Hampshire Ave., Silver Spring, MD 20903

To: Monica Batra

From: Amy Baird, CSO

Fax: 310-437-7788

Fax: 301-796-9845

Phone: 310-437-7741

Phone: 301-796-1325

Pages (including cover): 1

Date: July 11, 2006

Re: NDA 21-660/SE8-010. Specifically, your submission dated April 14, 2006.

Urgent **For Review** **Please Comment** **Please Reply** **Please Recycle**

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● **Comments:**

Per the request of the Abraxane review team, please provide the following information:

We request that you submit an updated Addendum to the Study Report for clinical trial CA012-0. This should include a description of study results and all analyses, tables, and graphs generated since the June 2005 addendum. Include source dataset names for tables and graphs. Please provide justification of how the findings support the proposed labeling changes.

Please call should you have any questions.

Thank you,

Amy Baird

Amy Baird

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this page is the manifestation of the electronic signature.**

/s/

Frank Cross
12/21/2006 10:39:43 AM
CSO
Faxed to sponsor on 7/11/06.

TELECON MINUTES

MEETING/TELECON DATE: June 8, 2006 **TIME:** 10:00 a.m.

IND/NDA: 21-660/S-010 **Meeting Request Submission Date:** N/A
Briefing Document Submission Date: N/A

DRUG: ABRAXANE™ for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension)

SPONSOR/APPLICANT: Abraxis Bioscience, Inc., (formerly American Bioscience Inc.)

FDA PARTICIPANTS:

Nancy Scher, M.D., Medical Reviewer
Frank Cross, Project Manager (for Amy Baird, Project Manager)

INDUSTRY PARTICIPANTS:

Mitchall G. Clark, Vice President, Regulatory Affairs

Agency:

Since there is no study report with the sNDA submission, we request that the sponsor provide us with a current study update.

Sponsor:

The sponsor stated that there was no new data in this April 2006 submission compared with the June 2005 submission, which included efficacy (death) and safety data updated through Nov 2004, provided as their Post Marketing Commitment. They reiterated their request for a label change based on the previously submitted data.

(b) (4)

We requested that the sponsor submit written documentation of the information provided during today's teleconference. The sponsor was also requested to submit the censoring rules.

Frank Cross
Project Manager

Concurrence Chair: _____
Nancy Scher, M.D.
Medical Reviewer

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/s/

Frank Cross
7/21/2006 03:42:29 PM
CSO

Nancy Scher
7/24/2006 05:21:38 PM
MEDICAL OFFICER