CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021660Orig1s026

Trade Name:	ABRAXANE for Injectable Suspension
Generic or Proper Name:	paclitaxel protein-bound particles for injectable suspension (albumin-bound)
Sponsor:	Celgene Corporation
Approval Date:	December 23, 2011
Indication:	For the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or replase within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

CENTER FOR DRUG EVALUATION AND RESEARCH

021660Orig1s026

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021660Orig1s026

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021660/S-025
NDA 021660/S-026
NDA 021660/S-029

SUPPLEMENT APPROVAL

Celgene Corporation
Attention: Renu Vaish, M.S.
Executive Director, Global Regulatory Affairs
Therapeutic Franchise Leader - Oncology Solid Tumors
400 Connell Drive, Suite 7000
Berkeley Heights, NJ 07922

Dear Ms. Vaish:

Please refer to your Supplemental New Drug Applications (sNDA) dated March 30, 2010, received March 30, 2010, June 1, 2010, received June 2, 2010, and July 25, 2011, received July 25, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Abraxane for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound), 100 milligram vial.

We acknowledge receipt of your amendments dated December 8, 2010; February 25, 2011; July 8, 2011; August 26, 2011; August 30, 2011; September 1, 2011; September 6, 2011; September 8 (2), 2011; September 13, 2011; September 14, 2011; September 21, 2011, December 5, 2011; December 20, 2011, and December 22 (2), 2011.

“Prior Approval” supplemental new drug application (S-025) provides for inclusion of pyrexia, dehydration, pancytopenia, congestive heart failure, and left ventricular dysfunction in Section 6, ADVERSE REACTIONS of the Package Insert.

“Prior Approval” supplemental new drug application (S-026) provides for revised labeling in the Physican Labeling Rule format.

“Prior Approval” supplemental new drug application (S-029) provides for inclusion of three adverse events: Stevens-Johnson syndrome, toxic epidermal necrolysis and extravasation in Section 6, ADVERSE REACTIONS of the Package Insert and minor administrative, editorial and grammatical revisions throughout the Package Insert.

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)

5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

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

If you have any questions, call Yolanda Adkins, Regulatory Project Manager, at (301) 796-2850.

Sincerely,

{See appended electronic signature page}

Amna Ibrahim, M.D.
Deputy Director
Division of Oncology Products 1
Ofice of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

AMNA IBRAHIM
12/23/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021660Orig1s026

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ABRAXANE safely and effectively. See full prescribing information for ABRAXANE

ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound)
Initial U.S. Approval: 2005

WARNING: NEUTROPENIA
See full prescribing information for complete boxed warning.

- **ABRAXANE therapy should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm^3 (4).**
- **It is recommended that frequent peripheral blood cell counts be performed to monitor the occurrence of bone marrow suppression. (4, 5.1, 6.1)**

DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS

---------- RECENT MAJOR CHANGES ----------

---------- INDICATIONS AND USAGE ----------
ABRAXANE is a microtubule inhibitor 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.

---------- DOSAGE AND ADMINISTRATION ----------
- Recommended dosage: 260 mg/m^2 IV over 30 min every 3 weeks (2.1)
- No adjustment is necessary for patients with mild hepatic impairment. Patients should not receive ABRAXANE if AST > 10 x ULN or bilirubin > 5.0 x ULN. Reduce starting dose in patients with moderate to severe hepatic impairment. (2.2)
- In case of severe neutropenia or severe sensory neuropathy reduce dose to 220 mg/m^2 for subsequent courses. In case of recurrence, further reduce dose to 180 mg/m^2. For grade 3 sensory neuropathy hold treatment until resolution to grade 1 or 2, followed by a dose reduction for all subsequent courses. (2.3)
- Use caution when handling cytotoxic drugs. Closely monitor the infusion site for extravasation and infiltration. No premedication is required prior to administration. (2.4)

---------- DOSAGE FORMS AND STRENGTHS ----------
- Single use vial containing 100 mg of paclitaxel (3)

---------- CONTRAINDICATIONS ----------
- Neutrophil counts of < 1,500 cells/mm^3. (4)
- Severe hypersensitivity reaction to ABRAXANE (4)

---------- WARNINGS AND PRECAUTIONS ----------
- ABRAXANE causes myelosuppression. Monitor CBC and withhold and/or reduce the dose as needed. (5.1)
- Sensory neuropathy occurs frequently and may require dose reduction or treatment interruption. (5.2)
- Exposure and toxicity of paclitaxel can be increased in patients with hepatic impairment; therefore administer with caution. (5.3)
- ABRAXANE contains albumin derived from human blood which has a theoretical risk of viral transmission. (5.4)
- Fetal harm may occur when administered to a pregnant woman. Women of childbearing potential should avoid becoming pregnant while receiving ABRAXANE. (5.5)
- Men should not father a child while on ABRAXANE. (5.6)

---------- ADVERSE REACTIONS ----------
The most common adverse reactions (≥ 20%) are alopecia, neutropenia, sensory neuropathy, abnormal ECG, fatigue/asthenia, myalgia/arthralgia, AST elevation, alkaline phosphatase elevation, anemia, nausea, infections, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Celgene Corporation at 1-888-423-5436 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------
- Use caution when concomitantly administering ABRAXANE with inhibitors or inducers of either CYP2C8 or CYP3A4. (7)

See 17 for PATIENT COUNSELING INFORMATION and see FDA-approved patient labeling.

Revised: 12/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION
ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound)

WARNING: NEUTROPENIA

- **ABRAXANE therapy should not be administered to patients with metastatic breast cancer who have baseline neutrophil counts of less than 1,500 cells/mm^3. 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** *[see Contraindications (4), Warnings and Precautions (5.1) and Adverse Reactions (6.1)].*
- **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.**

1 INDICATIONS AND USAGE

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.

2 DOSAGE AND ADMINISTRATION

2.1 General

After failure of combination chemotherapy for metastatic breast cancer or relapse within 6 months of adjuvant chemotherapy, the recommended regimen for ABRAXANE is 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks.

2.2 Dosage in Patients with Hepatic Impairment

No dose adjustment is necessary for patients with mild hepatic impairment. Patients with moderate and severe hepatic impairment treated with ABRAXANE may be at increased risk of toxicities known to paclitaxel. Patients should not receive ABRAXANE if AST > 10 x ULN or bilirubin > 5.0 x ULN. Recommendations for dosage adjustment for the first course of therapy are shown in Table 1. The dose of ABRAXANE can be increased up to 200 mg/m^2 in patients with severe hepatic impairment in subsequent cycles based on individual tolerance. Patients should be monitored closely *[see Clinical Pharmacology (12.3) and Warnings and Precautions (5.3) and Use in Specific Populations (8.6)].*

Table 1: Recommendations for Starting Dose in Patients with Hepatic Impairment

	SGOT (AST) Levels		Bilirubin Levels	ABRAXANE [a]
Mild	< 10 x ULN		> ULN to ≤ 1.25 x ULN	260 mg/m^2
Moderate	< 10 x ULN	AND	1.26 to 2.0 x ULN	200 mg/m^2
Severe	< 10 x ULN		2.01 to 5.0 x ULN	130 mg/m^2 [b]
	> 10 x ULN	OR	> 5.0 x ULN	not eligible

[a] Dosage recommendations are for the first course of therapy. The need for further dose adjustments in subsequent courses should be based on individual tolerance.
[b] A dose increase to 200 mg/m^2 in subsequent courses should be considered based on individual tolerance.

2.3 Dose Reduction: in Case of Severe Neutropenia or Severe Sensory Neuropathy

Patients who experience severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer) or severe sensory neuropathy during ABRAXANE therapy should have dosage reduced to 220 mg/m^2 for subsequent courses of ABRAXANE. For recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m^2. 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 *[see Contraindications (4), Warnings and Precautions (5.1 and 5.2) and Adverse Reactions (6.1)].*

2.4 Preparation and Administration Precautions

ABRAXANE is a cytotoxic 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 Adverse Reactions (6.2)].*

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

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2.5 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 vis ble, 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.

2.6 Stability

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

Stability of Reconstituted Suspension in the Vial

Reconstituted ABRAXANE in the vial should be used immediately, but may be refrigerated at 2ºC to 8ºC (36ºF to 46ºF) 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 when prepared as recommended in an infusion bag should be used immediately but may be stored at ambient temperature (approximately 25ºC) and lighting conditions for up to 4 hours. Discard any unused portion.

3 DOSAGE FORMS AND STRENGTHS

Single use vials containing 100 mg of paclitaxel.

4 CONTRAINDICATIONS

ABRAXANE should not be used in patients who have baseline neutrophil counts of < 1,500 cells/mm^3. Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be rechallenged with the drug.

5 WARNINGS AND PRECAUTIONS

5.1 Hematologic Effects

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 less than 1,500 cells/mm^3. In order to monitor the occurrence of myelotoxicity, perform frequent peripheral blood cell counts. Retreat with subsequent cycles of ABRAXANE after neutrophils recover to a level >1,500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3. In the case of severe neutropenia (<500 cells/mm^3

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for seven days or more) during a course of ABRAXANE therapy, dose reduce for subsequent courses of therapy. *[see Dosage and Administration (2.3)]*.

5.2 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 (2.3)]*.

5.3 Hepatic Impairment
Because the exposure and toxicity of paclitaxel can be increased with hepatic impairment, administration of ABRAXANE in patients with hepatic impairment should be performed with caution. The starting dose should be reduced for patients with moderate and severe hepatic impairment *[see Dosage and Administration (2.2), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

5.4 Albumin (Human)
ABRAXANE contains albumin (human), a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries a 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.

5.5 Use in Pregnancy
ABRAXANE can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel protein-bound particles to rats during pregnancy at doses lower than the maximum recommended human dose, based on body surface area, caused embryo-fetal toxicities, including intrauterine mortality, increased resorptions, reduced numbers of live fetuses, and malformations.

There are no adequate and well-controlled studies in pregnant women receiving 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 ABRAXANE *[see Use in Specific Populations (8.1)]*.

5.6 Use in Men
Men should be advised not to father a child while receiving ABRAXANE. *[see Nonclinical Toxicology (13.1)]*.

6 ADVERSE REACTIONS
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse reactions (≥ 20%) are alopecia, neutropenia, sensory neuropathy, abnormal ECG, fatigue/asthenia, myalgia/arthralgia, AST elevation, alkaline phosphatase elevation, anemia, nausea, infections, diarrhea.

6.1 Clinical Trials Experience
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 mg/m^2 over 30 min (n=229)	**Paclitaxel Injection 175 mg/m^2 over 3 h[b] (n=225)**
Bone Marrow		
Neutropenia < 2.0 x 10^9/L < 0.5 x 10^9/L	 80 9	 82 22
Thrombocytopenia < 100 x 10^9/L < 50 x 10^9/L	 2 <1	 3 <1
Anemia < 11 g/dL < 8 g/dL	 33 1	 25 <1
Infections	24	20
Febrile Neutropenia	2	1
Bleeding	2	2
Hypersensitivity Reaction[c]		
All	4	12
Severe[d]	0	2

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	Percent of Patients	
	ABRAXANE® **260 mg/m^2 over 30 min** **(n=229)**	**Paclitaxel Injection** **175 mg/m^2 over 3 h[b]** **(n=225)**
Cardiovascular		
Vital Sign Changes During Administration		
Bradycardia	<1	<1
Hypotension	5	5
Severe Cardiovascular Events[d]	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[d]	10	2
Myalgia / Arthralgia		
Any Symptoms	44	49
Severe Symptoms[d]	8	4
Asthenia		
Any Symptoms	47	39
Severe Symptoms[d]	8	3
Fluid Retention/Edema		
Any Symptoms	10	8
Severe Symptoms[d]	0	<1
Gastrointestinal		
Nausea		
Any symptoms	30	22
Severe symptoms[d]	3	<1
Vomiting		
Any symptoms	18	10
Severe Symptoms[d]	4	1
Diarrhea		
Any Symptoms	27	15
Severe Symptoms[d]	<1	1
Mucositis		
Any Symptoms	7	6
Severe Symptoms[d]	<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 by NCI Common Terminology Criteria for Adverse Events (CTCAE) version 2.
[b] Paclitaxel injection pts received premedication.
[c] Includes treatment-related events related to hypersensitivity (e.g., flushing, dyspnea, chest pain, hypotension) that began on a day of dosing.
[d] Severe events are defined as at least grade 3 toxicity.

Adverse Event Experiences by Body System

Hematologic Disorders
Neutropenia was dose dependent and reversible. Among patients with metastatic breast cancer in the randomized trial, neutrophil counts declined below 500 cells/mm^3 (Grade 4) in 9% of the patients treated with a dose of 260 mg/m^2 compared to 22% in patients receiving paclitaxel injection at a dose of 175 mg/m^2. Pancytopenia has been observed in clinical trials.

Infections
Infectious episodes were reported in 24% of the patients treated with ABRAXANE. Oral candidiasis, respiratory tract infections and pneumonia were the most frequently reported infectious complications.

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Hypersensitivity Reactions (HSRs)
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. 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.. These events included cardiac ischemia/infarction, 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.

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. 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
Dyspnea (12%), cough (7%), and pneumothorax (<1%) were reported after treatment with ABRAXANE.

Neurologic
The frequency and severity of sensory neuropathy increased with cumulative dose. Sensory neuropathy was the cause of ABRAXANE discontinuation in 7/229 (3%) patients. Twenty-four 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 grade 4 sensory neuropathies were reported. Only one incident of motor neuropathy (grade 2) was observed in either arm of the controlled trial.

Vision Disorders
Ocular/visual disturbances occurred in 13% of all patients (n=366) treated with ABRAXANE and 1% were severe. The severe cases (keratitis and blurred vision) were reported in patients who received higher doses than those recommended (300 or 375 mg/m^2). These effects generally have been revers ble.

Arthralgia/Myalgia
The symptoms were usually transient, occurred two or three days after ABRAXANE administration, and resolved within a few days.

Hepatic
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.

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

Other Clinical Events
Nail changes (changes in pigmentation or discoloration of nail bed) have been reported. Edema occurred in 10% of patients; no patients had severe edema. Dehydration and pyrexia were also reported.

6.2 Post-Marketing Experience with ABRAXANE and other Paclitaxel Formulations
Unless otherwise noted, the following discussion refers to the adverse reactions that have been identified during post-approval use of ABRAXANE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. In some instances, severe events observed with paclitaxel injection may be expected to occur with ABRAXANE.

Hypersensitivity Reactions
Severe hypersensitivity reactions have been reported with ABRAXANE. The use of ABRAXANE in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied.

Cardiovascular
There have been reports of congestive heart failure and left ventricular dysfunction with ABRAXANE. Most of the individuals were previously exposed to cardiotoxic drugs, such as anthracyclines, or had underlying cardiac history.

Respiratory
There have been reports of interstitial pneumonia and pulmonary embolism in patients receiving ABRAXANE and reports of radiation pneumonitis in patients receiving concurrent radiotherapy. Reports of lung fibrosis have been received as part of the

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continuing surveillance of paclitaxel injection safety and may also be observed with ABRAXANE.

Neurologic
Cranial nerve palsies and vocal cord paresis have been reported as has autonomic neuropathy resulting in paralytic ileus.

Vision Disorders
Reports in the literature of abnormal visual evoked potentials in patients treated with paclitaxel injection suggest persistent optic nerve damage. These may also be observed with ABRAXANE.

Hepatic
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.

Gastrointestinal (GI)
There have been reports of intestinal obstruction, intestinal perforation, pancreatitis, and ischemic colitis following ABRAXANE treatment. There have been reports of neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, occurring in patients treated with paclitaxel injection alone and in combination with other chemotherapeutic agents.

Injection Site Reaction
There have been reports of extravasation of ABRAXANE. Given the possibility of extravasation, it is advisable to monitor closely the ABRAXANE infusion site for poss ble infiltration during drug administration.

Severe events such as phlebitis, cellulitis, induration, necrosis, and fibrosis have been reported 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. 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.

Other Clinical Events
Skin reactions including generalized or maculo-papular rash, erythema, and pruritus have been observed with ABRAXANE. There have been case reports of photosensitivity reactions, radiation recall phenomenon, and in some patients previously exposed to capecitabine, reports of palmar-plantar erythrodysesthesia. Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

There have been reports of conjunctivitis, cellulitis, and increased lacrimation with paclitaxel injection.

6.3 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.

7 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 concomitantly with medicines known to inhibit (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or induce (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine) either CYP2C8 or CYP3A4.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category D *[see Warnings and Precautions (5.5)].*

There are no adequate and well-controlled studies in pregnant women using ABRAXANE. Based on its mechanism of action and findings in animals, ABRAXANE can cause fetal harm when administered to a pregnant woman. 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 ABRAXANE.

Administration of paclitaxel protein-bound particles to rats during pregnancy, on gestation days 7 to 17 at doses of 6 mg/m^2 (approximately 2% of the daily maximum recommended human dose on a mg/m^2 basis) caused embryofetal toxicities, 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/m^2 (approximately 1% of the daily maximum recommended human dose on a mg/m^2 basis).

Reference ID: 3063210

8.3 Nursing Mothers
It is not known whether paclitaxel is excreted in human milk. Paclitaxel and/or its metabolites were excreted into the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

8.5 Geriatric Use
Of the 229 patients in the randomized study who received ABRAXANE, 13% were at least 65 years of age and < 2% were 75 years or older. No toxicities occurred notably more frequently among patients who received ABRAXANE.

8.6 Patients with Hepatic Impairment
Because the exposure and toxicity of paclitaxel can be increased in patients with hepatic impairment, the administration of ABRAXANE should be performed with caution in patients with hepatic impairment *[see Dosage and Administration (2.2), Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

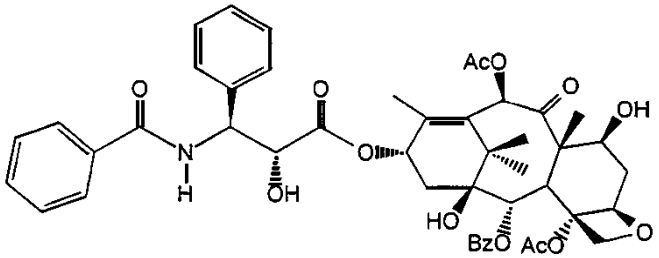
8.7 Patients with Renal Impairment
The use of ABRAXANE has not been studied in patients with renal impairment. Patients were excluded for baseline serum bilirubin >1.5 mg/dL or baseline serum creatinine >2 mg/dL.

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

11 DESCRIPTION
ABRAXANE, a microtubule inhibitor, is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. Paclitaxel exists in the particles in a non-crystalline, amorphous state. 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 (bound to human albumin) and approximately 900 mg of human albumin (containing sodium caprylate and sodium acetyltryptophanate). Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. ABRAXANE is free of solvents.

The active agent in ABRAXANE is paclitaxel. The chemical name for paclitaxel is 5β,20-Epoxy-1,2α,4,7β,10β,13α-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 $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.91. It is highly lipophilic, insoluble in water, and melts at approximately 216°C to 217°C.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
ABRAXANE is a microtubule inh bitor 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.

12.3 Pharmacokinetics

Absorption

The pharmacokinetics of total paclitaxel following 30 and 180-minute infusions of ABRAXANE at dose levels of 80 to 375 mg/m^2 were determined in clinical studies. Dose levels of mg/m^2 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.

Reference ID: 3063210

The drug exposure (AUCs) was dose proportional over 80 to 375 mg/m^2 and the pharmacokinetics of paclitaxel for ABRAXANE were independent of the duration of administration. At the recommended ABRAXANE clinical dose, 260 mg/m^2, 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/m^2. The mean volume of distribution was 632 L/m^2; the large volume of distribution indicates extensive extravascular distribution and/or tissue binding of paclitaxel.

The pharmacokinetic data of 260 mg/m^2 ABRAXANE administered over 30 minutes was compared to the pharmacokinetics of 175 mg/m^2 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.

Distribution

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.

Metabolism

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 inh bited 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, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-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 inh bitors of CYP2C8 and/or CYP3A4 *[see Drug Interactions (7)]*.

Excretion

After a 30-minute infusion of 260 mg/m^2 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.

Effect of Hepatic Impairment

The pharmacokinetic profile of ABRAXANE administered as a 30-minute infusion was evaluated in 15 out of 30 solid tumor patients with mild to severe hepatic impairment defined by serum bilirubin levels and AST levels. Patients with AST > 10 x ULN and bilirubin > 5.0 x ULN were not enrolled. ABRAXANE doses were assigned based on the degree of hepatic impairment as described:

- Mild (bilirubin > ULN to ≤ 1.25 x ULN and AST > ULN and < 10 x ULN): 260 mg/m^2
- Moderate (bilirubin 1.26 to 2.0 x ULN and AST > ULN and < 10 x ULN): 200 mg/m^2
- Severe (bilirubin 2.01 to 5.0 x ULN and AST > ULN and < 10 x ULN): 130 mg/m^2

The 260 mg/m^2 dose for mild impairment and the 200 mg/m^2 dose for moderate hepatic impairment adjusted the paclitaxel exposure to the range seen in patients with normal hepatic function (mean AUC0-∞ = 14789 ± 6703). The 130 mg/m^2 dose in patients with severe hepatic impairment resulted in lower paclitaxel exposures than those seen in normal subjects. In addition, patients with severe hepatic impairment had higher mean cycle 1 absolute neutrophil count (ANC) nadir values than those with mild and moderate hepatic impairment.

Table 3: Exposure ($AUC_{0-\infty}$) of ABRAXANE Administered IV over 30 Minutes in Patients with Hepatic Impairment

	Mild (n=5)	**Moderate (n=5)**	**Severe[a] (n=5)**
Dose	**260 mg/m^2**	**200 mg/m^2**	**130 mg/m^2**
AUC_{inf} (hr*ng/mL)			
Mean ± SD	17434 ± 11454	14159 ± 13346	9187 ± 6475
Median (range)	13755 (7618, 35262)	7866 (5919, 37613)	6134 (5627, 20684)

[a] bilirubin 2.01 to 5.0 x ULN and AST > ULN and < 10 x ULN

A starting dose of 130 mg/m^2 is recommended in patients with severe hepatic impairment. Escalation of the dose up to 200 mg/m^2 should be considered for subsequent cycles in patients with severe hepatic impairment based on individual tolerance. The 200 mg/m^2 dose has not been evaluated in patients with severe hepatic impairment, but it is predicted to adjust the paclitaxel AUC to the range observed in patients with normal hepatic function. There are no data for patients with AST > 10 x ULN and bilirubin > 5.0 x ULN *[see Dosage and Administration (2.2), and Use in Specific Populations (8.6)]*.

Effect of Renal Impairment

The effect of renal impairment on the disposition of ABRAXANE has not been investigated *[see Use in Specific Populations (8.7)]*.

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Drug Interactions
Poss ble interactions of paclitaxel with concomitantly administered medications have not been formally investigated.

13 NONCLINICAL TOXICOLOGY

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

Paclitaxel was 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/m^2 on a weekly basis (approximately 16% of the daily maximum recommended human exposure on a body surface area 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/m^2/week in this study (approximately 1 to 5% of the daily maximum recommended human exposure on a mg/m^2 basis). Testicular atrophy/degeneration was observed in single-dose toxicology studies in rodents administered paclitaxel protein-bound particles at doses lower than the recommended human dose; doses were 54 mg/m^2 in rodents and 175 mg/m^2 in dogs.

14 CLINICAL STUDIES

14.1 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/m^2 to 43 patients with metastatic breast cancer. The second trial utilized a dose of 300 mg/m^2 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/m^2 given as a 30-minute infusion, or paclitaxel injection at 175 mg/m^2 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 4. There was no statistically significant difference in overall survival between the two study arms.

Table 4: Efficacy Results from Randomized Trial

		ABRAXANE 260 mg/m^2	**Paclitaxel Injection 175 mg/m^2**
Reconciled Target Lesion Response Rate (primary endpoint) [a]			
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%]

[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.

Reference ID: 3063210

15 REFERENCES

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.

2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html

3. American Society of Health-System Pharmacists. (2006) ASHP Guidelines on Handling Hazardous Drugs. *Am J Health-Syst Pharm.* 2006;63:1172-1193.

4. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Product No.: 103450
NDC No.: 68817-134-50 100 mg of paclitaxel in a single use vial, individually packaged in a carton.

16.2 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.

16.3 Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published *[see References (15)]*. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling.

- Abraxane injection may cause fetal harm. Advise patients to avoid becoming pregnant while receiving this drug. Women of childbearing potential should use effective contraceptives *[see Warnings and Precautions (5.5) and Use in Specific Populations (8.1)].*
- Men should be advised not to father a child while receiving Abraxane *[see Warnings and Precautions (5.6)].*
- Patients must be informed of the risk of low blood cell counts and instructed to contact their physician immediately for fever or evidence of infection.
- Patients should be instructed to contact their physician for persistent vomiting, diarrhea, signs of dehydration, cough or breathing difficulties, or signs of an allergic reaction.
- Patients must be informed that sensory neuropathy occurs frequently with Abraxane and patients should advise their physicians of numbness, tingling, pain or weakness involving the extremities *[see Warnings and Precautions (5.2)].*
- Explain to patients that alopecia,fatigue/asthenia, and myalgia/arthralgia occur frequently with ABRAXANE.

Manufactured for: Celgene Corporation
Summit, NJ 07901

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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; 7,820,788; 7,923,536; and RE41,884

Reference ID: 3063210

Patient Information

ABRAXANE® for Injectable Suspension (ah-BRAKS-ane)
(paclitaxel protein-bound particles for injectable suspension) (albumin-bound)

Read this Patient Information before you start receiving ABRAXANE and before each infusion. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is ABRAXANE?

ABRAXANE is a prescription cancer medicine used to treat advanced breast cancer.

It is not known if ABRAXANE is safe or effective in children.

Who should not receive ABRAXANE?

Do not receive ABRAXANE if:

- your white blood cell count is below 1,500 cells/ mm^3.
- you have had a severe hypersensitivity reaction to ABRAXANE

What should I tell my doctor before receiving ABRAXANE?
Before you receive ABRAXANE, tell your doctor if you:

- have liver or kidney problems
- are a man planning to father a child. You should not father a child during your treatment with ABRAXANE. ABRAXANE can harm the unborn baby of your partner. Talk to your doctor if this is a concern to you.
- are pregnant or plan to become pregnant. ABRAXANE can harm your unborn baby. Women who may become pregnant should use effective birth control (contraception). Talk to your doctor about the best way to prevent pregnancy while receiving ABRAXANE.
- are breastfeeding or plan to breastfeed. It is not known if ABRAXANE passes into your breast milk. You and your doctor should decide if you will receive ABRAXANE or breastfeed.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list to show your doctor and pharmacist each time you get a new medicine.

How will I receive ABRAXANE?

- Your doctor will prescribe ABRAXANE in an amount that is right for you.
- Premedication to prevent allergic reactions is not needed to receive ABRAXANE.
- ABRAXANE will be given to you by intravenous (IV) infusion into your vein.
- Your doctor should do regular blood tests while you receive ABRAXANE.

What are the possible side effects of ABRAXANE?

ABRAXANE may cause serious side effects, including:

decreased blood cell counts. ABRAXANE can cause a severe decrease in neutrophils (a type of white blood cells important in fighting in bacterial infections) and platelets (important for clotting and to control bleeding). Your doctor will check your blood cell count during your treatment with ABRAXANE and after you have stopped your treatment.

- numbness, tingling, or burning in your hands or feet (neuropathy).

The most common side effects of ABRAXANE include:

- hair loss
- numbness or tingling in the hands or feet
- abnormal heart beat
- tiredness
- joint and muscle pain
- changes in your liver function tests
- low red blood cell count (anemia). Tell your doctor if you feel weak, tired or short of breath.
- nausea
- infections. If you have a fever (temperature of greater than 100.4º F) or other signs of infection, tell your doctor right away.
- diarrhea

Reference ID: 3063210

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of ABRAXANE.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet.

This Patient Information leaflet summarizes the important information about ABRAXANE. If you would like more information, ta k to your doctor. You can ask your doctor or pharmacist for information about ABRAXANE that is written for healthcare professionals.

For more information, call 1-800-423-5436.

What are the ingredients in ABRAXANE?

Active ingredient: paclitaxel (bound to human albumin).

Other ingredient: human albumin (containing sodium caprylate and sodium acetyltryptophanate)

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

Revised: December 2011

Manufactured for: Celgene Corporation
Summit, NJ 07901

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7,820,788; 7,923,536; and RE41,884

Reference ID: 3063210

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021660Orig1s026

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA:	21-660/SLR-156 and -163
BRAND NAME:	ABRAXANE
GENERIC NAME:	Paclitaxel Protein-Bound Particles for Injectable Suspension
DOSAGE FORM	Single-Use Vial Containing 100 mg of Paclitaxel
INDICATION:	Metastatic Breast Cancer
SUBMISSION DATES:	30-Mar-2010 and 01-Jun-2010
SUBMISSION TYPE:	NDA-Labeling Supplements
APPLICANT:	Abraxis BioScience, LLC
DDOP:	Division of Drug Oncology Products
OCP DIVISION:	Division of Clinical Pharmacology 5
OCP REVIEWER:	Safaa Burns, Ph.D.
OCP TEAM LEADER:	Qi Liu, Ph.D.

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1. EXECUTIVE SUMMARY

The current supplements to 21-660 (SLR-156 and 163) for ABRAXANE (paclitaxel protein-bound particles for injectable suspension) is to revise the currently approved package insert to meet the new **PLR format** requirements per 21 CFR 201.56 and 21 CFR 201.57.

1.1 RECOMMENDATION

We recommend that the package insert be modified as indicated in the ***Detailed Clinical Pharmacology Labeling Recommendations*** section of this review.

1.2 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

The overall clinical pharmacology information on ABRAXANE (paclitaxel protein-bound particles for injectable suspension) was addressed in the original NDA 21-660 submission dated **19-Mar-2004** (see clinical pharmacology review by Dr. Angela Men).

The originally approved labeling was updated on **26-Jun-2009** to incorporate the results from the post-marketing hepatic impairment **Study CA037** (see clinical pharmacology review by Dr. Jian Wang dated 01-Aug-2008). Study CA037 was submitted to address a post-marketing commitment that was agreed upon in the approval letter dated **07-Jul-2004** for the original NDA submission.

The currently proposed PLR labeling was compared with contents and format to the approved conventional labeling version of **26-Jun-2009** (see Section 3 below of this review)**.**

33 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 2926540

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

/s/

SAFAA BURNS
03/31/2011

QI LIU
04/01/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021660Orig1s026

OTHER REVIEW(S)

Medical Officer Labeling Review
Division of Drug Oncology Products

NDA #: 21,660
Drug: Abraxane for Injectable Suspension [Paclitaxel protein-bound particles for injectable suspension (albumin-bound)]
Sponsor: Abraxis Bioscience (Celgene)
Submission Dates: March 3, 2010, March 30, 2010, June 1, 2010, Dec. 9, 2010, and Feb. 25, 2011
eCTD #: 151, 156, 163, 179, and 183
Submission Type: Labeling supplements 025-026
Formulation: Lyophilized powder 100 mg in a single use vial
Primary Reviewer: Nancy S. Scher, M.D.
Secondary Reviewer/Team Leader: V. Ellen Maher, M.D.
Regulatory Project Manager: Yolanda Adkins
Date Review Completed: July 27, 2011

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.

Background: The Periodic Adverse Drug Experience Report submitted March 3, 2010, (sequence 151, covering the period Jan. 2009-2010) reported 5 adverse events (AE) as safety signals for Abraxane. The sponsor submitted sequence 0156 on March 30, 2010, as a Changes Being Effected Labeling Supplement (CBE) adding these 5 AEs to the labeling. On June 1, 2010, Abraxis submitted sequence 163, a Prior Approval Supplement (PAS) for labeling in PLR format. In response to FDA request, Abraxis submitted sequence 179 on Dec. 9, 2010, containing MedWatch reports related to the Periodic Report. On Feb. 25, 2011, the sponsor submitted a labeling amendment (eCTD 0183) combining supplements 025 and 026. The purpose of this review is to document the available safety data relevant to the proposal to add 5 AEs to the Abraxane label.

The following summary of the number of reports for the 5 AEs is taken from the sponsor's cover letter, which accompanied the Dec. 9, 2010 submission (#179):

- Pyrexia (fever) – 22 reports of serious fever have been reported from a combination of clinical trials serious adverse events (SAE) and spontaneous reports
- Dehydration – 35 reports of serious dehydration have been reported from a combination of clinical trials SAEs and spontaneous reports

- Pancytopenia – 7 reports of pancytopenia have been reported from a combination of clinical trials SAEs and spontaneous reports. Please note that at the time of the last Safety Update Report submission (March 3, 2010), a total of 8 cases reported pancytopenia, however since then, one of those cases has been changed and no longer appears as pancytopenia
- Congestive Heart Failure (CHF) or Left Ventricular Dysfunction (LVD) – 20 serious cases of CHF or LVD have been reported. 3 cases were received from post marketing sources and the remaining 17 involved subjects enrolled in investigator sponsored or Abraxis-sponsored clinical trials

Discussion:

The sponsor wishes to add these 5 adverse events (AEs) to the Company Core Safety Information (CCSI) and product label. The sponsor indicates that there has been no increase in the frequency or severity of events of pyrexia, dehydration or pancytopenia, which have been reported throughout the clinical trial and marketing experience.

The sponsor has conducted an analysis of the case series of 20 subjects with AEs of CHF or LVD. The sponsor has determined that these AEs were usually observed in subjects treated with prior anthracyclines or treated concurrently with other cardiotoxic drugs. They wish to add to section 6.2 of the label (Post-Marketing) the following statement:

> "(b) (4) reports of congestive heart failure and left ventricular dysfunction (b) (4) Abraxane. Most of the individuals were previously exposed to cardiotoxic drugs, such as anthracyclines, or had underlying cardiac history."

The 3 cases identified from post-marketing sources had all been exposed previously to cardiotoxic drugs. Seventeen cases were subjects enrolled in investigator- or Abraxis-sponsored *clinical trials*. The following is a summary of the information for the 20 patients:

- 13/20 (65%) of subjects had no prior exposure to cardiotoxic drugs; 8 of the 13 (61%) had no cardiac history (conversely 5/13 did have cardiac history).
- 10/20 (50%) of cases were believed related to ABI-007 (Abraxane) therapy. 5/10 of these subjects had received an anthracycline or had concurrent administration of known cardiotoxic drugs. Two of the 10 were participants in a trial which utilized bevacizumab.

Conclusion:

- Concur with adding to section 6.1 of the label (Clinical Trials Experience) that there have been reports of pyrexia, dehydration and pancytopenia.

- Based on review of the relevant MedWatch Forms, concur with sponsor's analysis of the 20 serious AEs of CHF or LVD and the addition of the following to section 6.2 of the label (Post-Marketing Experience):

  Cardiovascular
  There have been reports of congestive heart failure and left ventricular dysfunction with ABRAXANE. Most of the individuals were previously exposed to cardiotoxic drugs, such as anthracyclines, or had underlying cardiac history.

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/s/

NANCY S SCHER
09/01/2011

VIRGINIA E MAHER
09/09/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

PATIENT LABELING REVIEW

Date:	August 22, 2011
To:	Robert Justice, MD, Director **Division of Drug Oncology Products (DDOP)**
Through:	LaShawn Griffiths, RN, MSHS-PH, BSN Acting Team Leader, Patient Labeling Reviewer **Division of Risk Management (DRISK)** Barbara Fuller, RN, MSN, CWOCN Acting Team Leader, Patient Labeling Reviewer **Division of Risk Management (DRISK)**
From:	Steve L. Morin, RN, BSN, OCN Patient Labeling Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling (Patient Package Insert)
Drug Name (established name):	ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin bound)
Application Type/Number:	NDA 21-660
Supplement number:	S-025 S-026
Applicant:	**Abraxis Bioscience LLC**
OSE RCM #:	2011-2612

1 INTRODUCTION

On March 30, 2010 Abraxis BioScience, LLC submitted Changes Being Effected (CBE) supplement (S-025) to add five adverse events that were determined to be a safety signal in Periodic Adverse Drug Experience Report submitted to the Agency on March 3, 2010. On June 1, 2010 the Applicant submitted Prior Approval Supplement (PAS) 026 to comply with the Physician Labeling Rule. The Agency plans to take concurrent action on S-025 and S-026.

This review is written in response to a request by the Division of Drug Oncology Products (DDOP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI), for ABRAXANE for Injectable Suspension (paclitaxel protein bound particles for injectable suspension) (albumin-bound).

2 MATERIAL REVIEWED

- Draft ABRAXANE for Injectable Suspension (paclitaxel protein bound particles for injectable suspension) (albumin-bound) Patient Package Insert (PPI) received on June 1, 2010 and revised by the review division throughout the review cycle, and received by DRISK on August 4, 2011.
- Draft prescribing information (PI) ABRAXANE for Injectable Suspension (paclitaxel protein bound particles for injectable suspension) (albumin-bound) received on June 1, 2010 and revised by the review division throughout the review cycle, and received by DRISK on August 4, 2011.
- Approved DOCEFREZ (docetaxel) for injection comparator labeling dated May 3, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the prescribing information (PI)
- rearranged information due to conversion of the PI to PLR format
- removed unnecessary or redundant information

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the PPI are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

11 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

STEVE L MORIN
08/22/2011

LASHAWN M GRIFFITHS
08/22/2011

Chemist Review: # 1	**1. Division:** HFD-150	**NDA Number**: 21-660

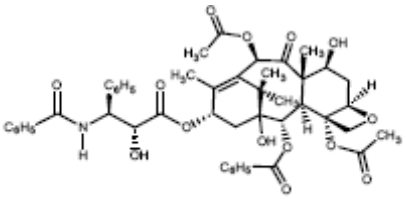
Name and Address of Applicant: Abraxis BioScience 11755 Wilshire Blvd., Suite 2000 Los Angeles, California 90025	**4. Supplement(s):** **Number:** S-026 **Date(s):** June 1, 2010 **Received on 11/30/2010**
5. Name of Drug: Abraxane®	**6. Nonproprietary name:** Paclitaxel, USP

7. Supplement (PA) provides for a labeling change to comply with labeling content and format requirements pursuant to 21CFR 201.56(d) and 201.56(c). Note: This is an OND-managed supplement.	**8. Amendment(s):** None

9. Pharmacological Category: Anti-cancer	**10. How Dispensed:** Rx	**11. Related Documents:** N/A
12. Dosage Form: Lyophilized Powder for Injection	**13. Potency:** 100 mg/vial	

14. Chemical Name and Structure: Chemically, paclitaxel is 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 ;
Molecular Formula: $C_{47}H_{51}NO_{14;}$ Molecular Weight: 853.92 g/mol

CAS #: 33069-62-4



Paclitaxel

15. Comments: This prior approval (PA) labeling supplement provides for a labeling change to comply with labeling content and format requirements pursuant to 21CFR 201.56(d) and 201.56(c).

This review is only applicable to any CMC changes proposed.

The proposed draft labeling is acceptable from the standpoint of CMC.

16. Conclusions and Recommendations: Recommend approval from the CMC standpoint.

17. Name: **Mamta Gautam-Basak, Ph.D., Chemist**	**Signature:**	**Date:** January 13, 2011
18. Concurrence: **Hasmukh Patel, Ph.D., Branch Chief** **ONDQA/DPME/Branch VIII**	**Signature:**	**Date:**

APPEARS THIS WAY ON ORIGINAL

Chemistry Reviewer Notes:
This prior approval (PA) labeling supplement provides for a labeling change to comply with labeling content and format requirements pursuant to 21CFR 201.56(d) and 201.56(c).

NDA 21-660 was approved on January 7, 2005. As per the CFR 201.56(c)(3) the applicant was required to file the proposed conforming label by June 30, 2010. ABRAXANE labeling has been revised to meet the new format requirements per 21 CFR 201.56 and 201.57.

The applicant has provided Annotated Draft Labeling, and draft proposed labeling.

Note: This review only includes evaluation of the CMC related changes (changes are in red). Specifically, changes under Description and How Supplied are reviewed.

APPEARS THIS WAY ON ORIGINAL

11 DESCRIPTION

ABRAXANE is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanom the particles in a non-crystalline, amorphous state. ABRAXANE is supplied as a white to yellow; sterile, lyo reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Each sing mg of paclitaxel and approximately 900 mg of human albumin. Each milliliter (mL) of reconstituted suspens paclitaxel. ABRAXANE is free of solvents.

(b) (4

The chemical name for paclitaxel is 5β,20 1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Product No.: 103450
NDC No.: 68817-134-50 100 mg of paclitaxel in a single use vial, individually packaged in a carton.

16.1 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 fr

16.1 Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on published *[see References (15)]*.[~~1~~ ~~8~~] There is no general agreement that all of the procedures recommended in necessary or appropriate.

Evaluation: Minor changes proposed (shown in red) under Description are acceptable.
Draft labeling provided is acceptable from the standpoint of CMC.

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/s/

MAMTA GAUTAM-BASAK
01/25/2011
Acceptable from the CMC standpoint.

HASMUKH B PATEL
01/25/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021660Orig1s026

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Cross Jr, Frank H

From: Cross Jr, Frank H [Frank.Crossjr@fda.hhs.gov]
Sent: Tuesday, December 20, 2011 1:12 PM
To: Renu Vaish
Cc: Adkins, Yolanda
Subject: RE: FDA Proposed labeling for NDA 021660/S-025, S-026, S-029, Abraxane

Please also make this change

In section 8.5, it says " No toxicities occurred notably more frequently **among who** received Abraxane. Please change to say **among patients who..**

Thanks,

Frank

Frank H. Cross, Jr., MA, MT (ASCP)
Captain, USPHS Commissioned Corps
Chief, Project Management Staff
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
US Food and Drug Administration
White Oak Bldg 22, Room 2110
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-0876 (office)
(301) 796-9845 (fax)
frank.crossjr@fda.hhs.gov

From: Cross Jr, Frank H
Sent: Tuesday, December 20, 2011 12:55 PM
To: 'Renu Vaish'
Cc: Adkins, Yolanda
Subject: FDA Proposed labeling for NDA 021660/S-025, S-026, S-029, Abraxane

****
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/s/

FRANK H CROSS
12/22/2011

Cross Jr, Frank H

From: Cross Jr, Frank H
Sent: Tuesday, December 20, 2011 12:55 PM
To: 'Renu Vaish'
Cc: Adkins, Yolanda
Subject: FDA Proposed labeling for NDA 021660/S-025, S-026, S-029, Abraxane
Attachments: Abraxane.PI.12-18-11.doc.docx

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/s/

FRANK H CROSS
12/20/2011

Cross Jr, Frank H

From: Cross Jr, Frank H
Sent: Thursday, December 08, 2011 1:21 PM
To: 'Renu Vaish'
Cc: Adkins, Yolanda
Subject: FDA Revised labeling - NDA 021660/S-025, S-029 and S-029

Attachments: FDA Revised lbl NDA 021660 s025 so26 s029 dated 12 8 11.doc

Renu,

We have reviewed the labeling-found a couple of typos and also revised to include changes for S-029.

Please review and let me know as soon as possible.

We will be issuing one letter for S-025, S-026 and S-029

Thank you,

Frank Cross

Frank H. Cross, Jr., MA, MT (ASCP)
Captain, USPHS Commissioned Corps
Chief, Project Management Staff
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
US Food and Drug Administration
White Oak Bldg 22, Room 2110
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(301) 796-0876 (office)
(301) 796-9845 (fax)
frank.crossjr@fda.hhs.gov

FDA Revised lbl
NDA 021660 s02...

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/s/

FRANK H CROSS
12/08/2011

Cross Jr, Frank H

From: Adkins, Yolanda
Sent: Wednesday, November 09, 2011 1:14 PM
To: 'Renu Vaish'
Subject: Abraxane NDA 21660 S-025 and S-026

Attachments: ABRAXANE PPI Changes 28Oct11 (Track Changes).docx; ABRAXANE PLR Labeling (celgene track changes 28Oct11).docx

Dear Renu,

The attached copy of the PPI and PI contain language agreed upon during t-con today. Please review and confirm acceptance by the end of this week.

ABRAXANE PPI Changes 28Oct11 (.. ABRAXANE PLR Labeling (celgene...

Thanks,

Yolanda
Yolanda G. Adkins, R.N., MSHA
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
10903 New Hampshire Avenue
Silver Springs, Maryland 20993
White Oak Bldg 22, Room 2101
301 796-2850
yolanda.adkins@fda.hhs.gov

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/s/

FRANK H CROSS
12/06/2011
Sent by RPM to Applicant on 11 9 11

Adkins, Yolanda

Subject: FW: IR for NDA21660

From: Adkins, Yolanda
Sent: Wednesday, August 31, 2011 1:12 PM
To: 'Renu Vaish'
Subject: IR for NDA21660

Dear Renu,
This is information request that is needed asap as well preferably before 2:30 pm edt if possible.

The company indicates that [redacted] (b) (4)

The label currently states [redacted] (b) (4) [redacted] (b) (4) **They can delete** [redacted] (b) (4)**, however, the deletion should be replaced by the correct description of the product,** [redacted] (b) (4)

Thanks,
Yolanda

Yolanda G. Adkins, R.N., MSHA
Regulatory Project Manager
CDER/OND/OODP/DDOP
10903 New Hampshire Avenue
Silver Springs, Maryland 20993
White Oak Bldg 22, Room 6349
301 796-2850

Reference ID: 3009493

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/s/

YOLANDA G ADKINS
09/01/2011

Adkins, Yolanda

From: Adkins, Yolanda
Sent: Thursday, September 01, 2011 12:28 PM
To: 'Renu Vaish'
Subject: RE: NDA 021660 S-025 and S-026

Hello Renu,

I need to request provide feedback on the label to include the PPI by 12 noon on 9/7/11.

Thank you,

Yolanda

Yolanda G. Adkins, R.N., MSHA
Regulatory Project Manager
CDER/OND/OODP/DDOP
10903 New Hampshire Avenue
Silver Springs, Maryland 20993
White Oak Bldg 22, Room 6349
301 796-2850

From: Adkins, Yolanda
Sent: Thursday, September 01, 2011 12:10 PM
To: 'Renu Vaish'
Subject: NDA 021660 S-025 and S-026

Hi Renu,

Please review the proposed labeling changes and return with a strike through copy and clean copy by 9/9/11.
Thank you,
Yolanda << File: ABRAXANE PLR Labeling after 8.31.11 mtg.docx >>

Yolanda G. Adkins, R.N., MSHA
Regulatory Project Manager
CDER/OND/OODP/DDOP
10903 New Hampshire Avenue
Silver Springs, Maryland 20993
White Oak Bldg 22, Room 6349
301 796-2850

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/s/

YOLANDA G ADKINS
09/01/2011

Adkins, Yolanda

From: Adkins, Yolanda
Sent: Thursday, September 01, 2011 12:10 PM
To: 'Renu Vaish'
Subject: NDA 021660 S-025 and S-026

Attachments: ABRAXANE PLR Labeling after 8.31.11 mtg.docx

Hi Renu,

Please review the proposed labeling changes and return with a strike through copy and clean copy by 9/9/11.
Thank you,

ABRAXANE
Labeling after

Yolanda

Yolanda G. Adkins, R.N., MSHA
Regulatory Project Manager
CDER/OND/OODP/DDOP
10903 New Hampshire Avenue
Silver Springs, Maryland 20993
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301 796-2850

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/s/

YOLANDA G ADKINS
09/01/2011

Adkins, Yolanda

From: Adkins, Yolanda
Sent: Wednesday, August 31, 2011 11:46 AM
To: 'Renu Vaish'
Subject: RE: IR to Abraxane

Renu,
I received it and appreciate the prompt response. I have another information request and I need a response preferably before 2:30, today.

Prescribing Information – package insert.

The draft labels provided indicate in section 2.6 that the reconstituted and diluted product is stable for (b)(4) hours at room

temperature. Our current policy is that we do not accept room temperature storage for more than 4 hours without supporting

positive challenge data demonstrating that no growth occurs for at least 2 or 3 times the recommended hold times. This seems

very familiar but I cannot find any place in our records where we have addressed this problem for this particular product.

Please provide the following comment to the sponsor (Abraxis Bioscience). "The recommended holding time in Section 2.6 of

the prescribing information label for the reconstituted and diluted Abraxane is (b)(4) hours at room temperature. We currently do

not accept hold times beyond 4 hours at room temperature or 24 hour refrigerated without data summaries demonstrating that

the drug product will not support microbiological growth for the proposed period of time with a safety margin of 2 or 3 times

the proposed holding time. You can either reduce the hold time in the label to 4 hours at room temperature or provide the

supporting data summaries.

Thanks,

Yolanda

Yolanda G. Adkins, R.N., MSHA

Regulatory Project Manager
CDER/OND/OODP/DDOP
10903 New Hampshire Avenue
Silver Springs, Maryland 20993
White Oak Bldg 22, Room 6349
301 796-2850

From: Renu Vaish [mailto:rvaish@celgene.com]
Sent: Wednesday, August 31, 2011 11:33 AM
To: Adkins, Yolanda
Subject: RE: IR to Abraxane

Hi Yolanda –
I just sent the email response to you a short while ago - you should have received it. Please let me know if it did not come through.
We will also submit this response formally to the NDA.
Kind regards, Renu

_____
Renu Vaish, MS
Executive Director, Global Regulatory Affairs
Therapeutic Area Lead for Oncology - Solid Tumors
Celgene Corporation
(O) 908-673-2035
(M) 908-377-5081
rvaish@celgene.com

From: Adkins, Yolanda [mailto:Yolanda.Adkins@fda.hhs.gov]
Sent: Wednesday, August 31, 2011 11:29 AM
To: Renu Vaish
Subject: RE: IR to Abraxane

Hello Renu,

Is it possible to send the response to me by 2:30 pm edt, today? Also, please submit the response officially as well.
Thank you,
Yolanda

Yolanda G. Adkins, R.N., MSHA
Regulatory Project Manager
CDER/OND/OODP/DDOP
10903 New Hampshire Avenue
Silver Springs, Maryland 20993
White Oak Bldg 22, Room 6349
301 796-2850

nda
ugust 31, 2011 9:57 AM

to Abraxane

Good Morning Renu,

Please response to Information Request regarding the Abraxane by COB, today.

Regarding your Aug. 30 version of the Abraxane label, please clarify if the post-market AEs attributed to paclitaxel injection under "Vision Disorders" and "Respiratory" have actually been observed with Abraxane and if it is accurate to say, as you proposed, "these *may* also be observed with ABRAXANE."

Thanks

Yolanda

Yolanda G. Adkins, R.N., MSHA
Regulatory Project Manager
CDER/OND/OODP/DDOP
10903 New Hampshire Avenue
Silver Springs, Maryland 20993
White Oak Bldg 22, Room 6349
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YOLANDA G ADKINS
08/31/2011

Adkins, Yolanda

From: Adkins, Yolanda
Sent: Wednesday, August 31, 2011 9:57 AM
To: 'Renu Vaish'
Subject: FW: IR to Abraxane

Good Morning Renu,

Please response to Information Request regarding the Abraxane by COB, today.

Regarding your Aug. 30 version of the Abraxane label, please clarify if the post-market AEs attributed to paclitaxel injection under "Vision Disorders" and "Respiratory" have actually been observed with Abraxane and if it is accurate to say, as you proposed, "these *may* also be observed with ABRAXANE."

Thanks

Yolanda

Yolanda G. Adkins, R.N., MSHA
Regulatory Project Manager
CDER/OND/OODP/DDOP
10903 New Hampshire Avenue
Silver Springs, Maryland 20993
White Oak Bldg 22, Room 6349
301 796-2850

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/s/

YOLANDA G ADKINS
08/31/2011

Cross Jr, Frank H

From: Cross Jr, Frank H
Sent: Monday, August 29, 2011 2:49 PM
To: 'Renu Vaish'
Subject: FDA Revised PPI for NDA 021660/S-025 and S-026, Abraxane
Attachments: ABRAXANE PPI 8-29-11.doc

Ms. Vaish,

Attached is our revised PPI.

Please respond by COB, Friday, 9/2/11.

Frank (for Yolanda)

Frank H. Cross, Jr., MA, MT (ASCP)
Captain, USPHS Commissioned Corps
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
US Food and Drug Administration
White Oak Bldg 22, Room 2110
10903 New Hampshire Avenue
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(301) 796-0876 (office)
(301) 796-9845 (fax)
frank.crossjr@fda.hhs.gov

[DRISK Comment: We have re-organized the PPI overall to be consistent with current patient labeling standards, reduced redundancy, and made the information consistent with the PI. Where possible we have retained language that was found in the proposed Patient Information.]

Patient Information
ABRAXANE® for Injectable Suspension ***[DRISK Comment: Applicant should insert phonetic spelling.]***
(paclitaxel protein-bound particles for injectable suspension)
(albumin-bound)

Read this Patient information before you start receiving ABRAXANE and before each infusion. This information does not take the place of talking with your doctor about your medical condition or your treatment. ***[DRISK Comment: We have inserted standard headings and sections that are found in all patient labeling.]***

What is ABRAXANE? ***[DRISK Comment: We have changed the case of the headings as capital only words are more difficult to read than mixed upper and lower case words. Words using only capital letters may be used to spell the drug name throughout the Patient Information and for the title of the Patient Information.]***

ABRAXANE is a prescription (b) (4) cancer medicine used to treat advanced breast cancer.

It is not known if ABRAXANE is safe or effective in children.

Who should not receive ABRAXANE?

Do not receive ABRAXANE if:

- your white blood cell count is below 1,500 cells/ mm^3.
- you have had a severe hypersensitivity reaction to ABRAXANE.

[DRISK Comment: The highlights section for contraindications and Section 4, Contraindications are not consistent. Section 4 states "Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be rechallenged with the drug."
[DRISK comment: We have deleted section entitled (b) (4) ***and relocated the information under the heading "How will I receive ABRAXANE?"]***

What should I tell my doctor before receiving ABRAXANE?
Before you receive ABRAXANE, tell your doctor if you:

- have liver or kidney problems

- are a man planning to father a child. ABRAXANE can harm the unborn baby of your partner.
- are pregnant or plan to become pregnant. ABRAXANE can harm your unborn baby. Women who may become pregnant should use effective birth control (contraception). Talk to your doctor about the best way to prevent pregnancy while receiving ABRAXANE.
- are breastfeeding or plan to breastfeed. It is not known if ABRAXANE passes into your breast milk. You and your doctor should decide if you will receive ABRAXANE or breastfeed.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list to show your doctor and pharmacist each time you get a new medicine.

How will I receive ABRAXANE?

- Your doctor will prescribe ABRAXANE in an amount that is right for you.
- ABRAXANE will be given to you by intravenous (IV) infusion into your vein.
- Your doctor should do regular blood test while you receive ABRAXANE.

What are the possible side effects of ABRAXANE?

ABRAXANE may cause serious side effects, including:

- **Decreased blood cell counts.** ABRAXANE can cause a severe decrease in neutrophils (a type of white blood cells important in fighting in bacterial infections) and platelets (important for clotting and to control bleeding).Your doctor will check your blood cell count during your treatment with ABRAXANE and after you have stopped your treatment.
- numbness, tingling, or burning in your hands or feet (neuropathy).

The most common side effects of ABRAXANE include: ***[DRISK Comment: We have include the most common adverse reactions ≥20% as listed in the highlights and section 6.1 of the PI. We defer to the RD as to the appropriateness of this list. We have listed the common AE's in the order of the most frequent occurrence.]***

- hair loss
- (b) (4)
- numbness or tingling in the hands or feet
- abnormal heart beat
- joint and muscle pain
- tiredness
- changes in your liver function test

- low red blood cell count (anemia). Tell your doctor if you feel weak, tired, or short of breath.
- nausea
- infections. If you have a fever (temperature of greater than 100.4˚F) or other signs of infection tell your doctor right away.
- diarrhea

[DRISK Comment: We have deleted the information below and placed it throughout the PPI as appropriate. Detailed information describing the common side effects should be discussed with their healthcare professional.]

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ABRAXANE. For more information ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. ***[DRISK Comment: This verbatim statement is required for all Medication Guides. Although not required for voluntary PPI's like ABRAXANE, we recommend adding it to all patient labeling for consistency.]***

General information about the safe and effective use of ABRAXANE.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet.

This patient information leaflet summarizes the most important information about ABRAXANE. If you would like more information, talk to your doctor. You can ask your doctor or pharmacist for information about ABRAXANE that is written for healthcare professionals.

For more information, call: 1-800-XXX-XXXX ***[DRISK Comment: The Applicant should add a contact phone number if available.]***

What are the ingredients in ABRAXANE?

Active ingredient: paclitaxel
Inactive ingredient: human albumin

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

Abraxis BioScience

Distributed by Abraxis BioScience, LLC

Bridgewater, NJ 08807

Revised: xx/xxxx ***[DRISK Comment: Please insert date PPI was revised.]***

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/s/

FRANK H CROSS
08/29/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADM NISTRATION	REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: OSE/DRISK**	FROM: Yolanda Adkins DDOP BLDG 22/ Rm 6349/ 301 796-2850

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
7/28/11		021660		

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Abraxane			ASAP no later than 8/29/11

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*: Labeling supplement – PLR conversion

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

DRISK:

Please review the PPI at the attached link for both the PI and PPI:

<\\Cdsnas\transfer\DDOP RPM\Yolanda Adkins\NDA 021660 Abraxane\S025 and S026 combined labeling during labeling mtg 7 27 11.doc>

The PI is substantially complete from DDOP.

SIGNATURE OF REQUESTER Yolanda Adkins	METHOD OF DELIVERY (Check one) x☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

YOLANDA G ADKINS
07/28/2011

Cross Jr, Frank H

From: Cross Jr, Frank H
Sent: Thursday, May 26, 2011 12:14 PM
To: 'Aleece Nolasco'
Cc: Adkins, Yolanda
Subject: NDA 021660/S-025 and S-026, Abraxane
Attachments: Patient Counseling Information revised to applicant.doc

Dear Ms. Nolasco

In accordance with 21 CFR 201.57, lease revise the attached portion of the PI and resubmit as a labeling amendment to S-025 and S-026 in clean and tracked changes.

Thank you
Frank Cross (for Yolanda Adkins, RPM)

Frank H. Cross, Jr., MA, MT (ASCP)
Captain, USPHS Commissioned Corps
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
US Food and Drug Administration
White Oak Bldg 22, Room 2110
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-0876 (office)
(301) 796-9845 (fax)
frank.crossjr@fda.hhs.gov

3 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

FRANK H CROSS
07/14/2011
Sent to Applicant on 5/26/11

Adkins, Yolanda

From: Adkins, Yolanda
Sent: Wednesday, July 13, 2011 3:08 PM
To: 'wcorbett@celgene.com'
Subject: Information Request Abraxane NDA 021660/S-025 and S-026

Dear Wendy,

Please state the CTC version used in grading Table 2. Please provide a response by COB 7/14/11.

Thanks,

Yolanda

Yolanda G. Adkins, R.N., MSHA
Regulatory Project Manager
CDER/OND/OODP/DDOP
10903 New Hampshire Avenue
Silver Springs, Maryland 20993
White Oak Bldg 22, Room 6349
301 796-2850

Reference ID: 2973366

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/s/

YOLANDA G ADKINS
07/13/2011