

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21-660/S-031

Trade Name: Abraxane

Generic Name: paclitaxel protein-bound particles for injectable suspension

Sponsor: Abraxis BioSciences

Approval Date: October 11, 2012

Indication: first-line treatment of locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 21-660/S-031

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 21-660/S-031

APPROVAL LETTER



NDA 21660/S-031

SUPPLEMENT APPROVAL

Abraxis BioScience, LLC, a wholly-owned subsidiary of Celgene Corporation
Attention: Deborah Tady, PharmD, RPh, MBA, RAC
Director, Global Regulatory Affairs
9225 Indian Creek Parkway, Suite 900
Overland Park, KS 66210

Dear Dr. Tady:

Please refer to your Supplemental New Drug Application (sNDA) dated December 9, 2011, and received on December 12, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound), 100 mg vial.

We acknowledge receipt of your amendments dated January 13, 2012; February 17, 2012; March 2, 2012; March 9, 2012; March 30, 2012; May 9, 2012; July 12, 2012; August 2, 2012; August 13, 2012; August 15, 2012; August 23, 2012; September 28, 2012; October 5, 2012; and October 11, 2012.

This Prior Approval supplemental new drug application proposes to include a new indication for first-line treatment of locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.

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

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 and 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).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on October 11, 2012, as soon as they are available, but no more than 30 days after they are printed.

Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 21660/S-031.**” Approval of this submission by FDA is not required before the labeling is used.

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.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable because the disease/condition does not exist in children.

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, contact Monica Hughes, M.S., Lead Regulatory Project Manager, at (301) 796-9225.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling
Carton and Container Labeling

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

/s/

PATRICIA KEEGAN
10/11/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-660/S-031

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.

- Do not administer ABRAXANE therapy to patients with baseline neutrophil counts of less than 1,500 cells/mm³. (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, 6.2)

DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS.

RECENT MAJOR CHANGES

- | | |
|---|---------|
| • Indications and Usage. (1.2) | 10/2012 |
| • Dosage and Administration. (2.2) | 10/2012 |
| • Warnings and Precautions, Hypersensitivity. (5.3) | 09/2012 |

INDICATIONS AND USAGE

ABRAXANE is a microtubule inhibitor indicated for the 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. (1.1)
- Locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC), as first-line treatment in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy. (1.2)

DOSAGE AND ADMINISTRATION

- Metastatic Breast Cancer: Recommended dosage of ABRAXANE is 260 mg/m² intravenously over 30 minutes every 3 weeks. (2.1)
- Non-Small Cell Lung Cancer: Recommended dosage of ABRAXANE is 100 mg/m² intravenously over 30 minutes on Days 1, 8, and 15 of each 21-day cycle; carboplatin AUC 6 mg•min/mL is given intravenously on Day 1 of each 21 day cycle immediately after ABRAXANE administration. (2.2)
- No adjustment is necessary for patients with mild hepatic impairment. Withhold ABRAXANE if AST > 10 x ULN or bilirubin > 5 x ULN. Reduce starting dose in patients with moderate to severe hepatic impairment. (2.3)
- Dose Reductions: Dose reductions or discontinuation may be needed based on severe hematologic or neurologic toxicities. (2.4)

- Use caution when handling cytotoxic drugs. Closely monitor the infusion site for extravasation and infiltration. No premedication is required prior to administration. (2.5)

DOSAGE FORMS AND STRENGTHS

- Single use vial containing 100 mg of paclitaxel. (3)

CONTRAINDICATIONS

- Neutrophil counts of < 1,500 cells/mm³. (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)
- Severe hypersensitivity reactions with fatal outcome have been reported. Do not re-challenge with this drug. (5.3)
- Exposure and toxicity of paclitaxel can be increased in patients with hepatic impairment; therefore administer with caution. (5.4)
- ABRAXANE contains a bumin derived from human blood, which has a theoretical risk of viral transmission. (5.5)
- Fetal harm may occur when administered to a pregnant woman. Advise women of childbearing potential to avoid becoming pregnant while receiving ABRAXANE. (5.6)
- Advise men not to father a child while on ABRAXANE. (5.7)

ADVERSE REACTIONS

- The most common adverse reactions (≥ 20%) in metastatic breast cancer are alopecia, neutropenia, sensory neuropathy, abnormal ECG, fatigue/asthenia, myalgia/arthralgia, AST elevation, alkaline phosphatase elevation, anemia, nausea, infections, and diarrhea. (6.1)
- The most common adverse reactions (≥ 20%) in NSCLC when used in combination with carboplatin are anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue. (6.2)

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 FDA-approved patient labeling (Patient Information).

Revised: October 2012

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FULL PRESCRIBING INFORMATION

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

WARNING: NEUTROPENIA

- Do not administer ABRAXANE therapy to patients 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 [see *Contraindications (4)*, *Warnings and Precautions (5.1)* and *Adverse Reactions (6.1, 6.2)*].
- 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

1.1 Metastatic Breast Cancer

ABRAXANE 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.

1.2 Non-Small Cell Lung Cancer

ABRAXANE is indicated for the first-line treatment of locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Metastatic Breast Cancer

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/m² administered intravenously over 30 minutes every 3 weeks.

2.2 Non-Small Cell Lung Cancer

The recommended dose of ABRAXANE is 100 mg/m² administered as an intravenous infusion over 30 minutes on Days 1, 8, and 15 of each 21-day cycle. The recommended dose of carboplatin is AUC = 6 mg•min/mL on Day 1 only of each 21-day cycle, beginning immediately after the completion of ABRAXANE administration.

2.3 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. Withhold ABRAXANE if AST >10 x ULN or bilirubin > 5 x ULN. Recommendations for dosage adjustment for the first course of therapy are shown in Table 1.

For metastatic breast cancer, the dose of ABRAXANE can be increased from 130 mg/m² up to 200 mg/m² in patients with severe hepatic impairment in subsequent cycles based on individual tolerance.

For non-small cell lung cancer, reduce the dose of ABRAXANE to 50 mg/m² in patients with severe hepatic impairment. In subsequent cycles, the dose of ABRAXANE may be increased to 75 mg/m² as tolerated.

Monitor patients closely [see *Warnings and Precautions (5.4)*, *Use in Specific Populations (8.6)*, and *Clinical Pharmacology (12.3)*].

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

	SGOT (AST) Levels		Bilirubin Levels	ABRAXANE Dose ^a	
				MBC	NSCLC
Mild	< 10 x ULN		> ULN to ≤ 1.25 x ULN	260 mg/m ²	100 mg/m ²
Moderate	< 10 x ULN	AND	1.26 to 2 x ULN	200 mg/m ²	75 mg/m ²
Severe	< 10 x ULN		2.01 to 5 x ULN	130 mg/m ^{2b}	50 mg/m ^{2c}
	> 10 x ULN	OR	> 5 x ULN	not eligible	not eligible

MBC = Metastatic Breast Cancer; NSCLC = Non-Small Cell Lung Cancer.

^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/m² in subsequent courses should be considered based on individual tolerance.

^c Increase dose to 75 mg/m² in subsequent courses, as tolerated.

2.4 Dose Reduction/Discontinuation Recommendations

Metastatic Breast Cancer

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 [see *Contraindications* (4), *Warnings and Precautions* (5.1, 5.2) and *Adverse Reactions* (6.1)].

Non-Small Cell Lung Cancer

- Do not administer ABRAXANE on Day 1 of a cycle until absolute neutrophil count (ANC) is at least 1500 cells/mm³ and platelet count is at least 100,000 cells/mm³ [see *Contraindications* (4), *Warnings and Precautions* (5.1) and *Adverse Reactions* (6.2)].
- In patients who develop severe neutropenia or thrombocytopenia withhold treatment until counts recover to an absolute neutrophil count of at least 1500 cells/mm³ and platelet count of at least 100,000 cells/mm³ on Day 1 or to an absolute neutrophil count of at least 500 cells/mm³ and platelet count of at least 50,000 cells/mm³ on Days 8 or 15 of the cycle. Upon resumption of dosing, permanently reduce ABRAXANE and carboplatin doses as outlined in Table 2.
- Withhold ABRAXANE for Grade 3-4 peripheral neuropathy. Resume ABRAXANE and carboplatin at reduced doses (see Table 2) when peripheral neuropathy improves to Grade 1 or completely resolves [see *Warnings and Precautions* (5.2) and *Adverse Reactions* (6.2)].

Table 2: Permanent Dose Reductions for Hematologic and Neurologic Adverse Drug Reactions in NSCLC

Adverse Drug Reaction	Occurrence	Weekly ABRAXANE Dose (mg/m ²)	Every 3-Week Carboplatin Dose (AUC mg•min/mL)
Neutropenic Fever (ANC less than 500/mm ³ with fever $>38^{\circ}\text{C}$) OR Delay of next cycle by more than 7 days for ANC less than 1500/mm ³ OR ANC less than 500/mm ³ for more than 7 days	First	75	4.5
	Second	50	3
	Third	Discontinue Treatment	
Platelet count less than 50,000/mm ³	First	75	4.5
	Second	Discontinue Treatment	
Severe sensory Neuropathy – Grade 3 or 4	First	75	4.5
	Second	50	3
	Third	Discontinue Treatment	

2.5 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* (6.3)].

Premedication to prevent hypersensitivity reactions is generally not needed prior to the administration of ABRAXANE. Premedication may be needed in patients who have had prior hypersensitivity reactions to ABRAXANE. Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be re-challenged with this drug [see *Warnings and Precautions* (5.3)].

2.6 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: $\text{Dosing volume (mL)} = \text{Total dose (mg)} / 5 \text{ (mg/mL)}$.

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 intravenous bag [plasticized polyvinyl chloride (PVC) containers, PVC or non-PVC type intravenous 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.

2.7 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 in the vial 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 when 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 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 $< 1,500 \text{ cells/mm}^3$.
- 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 of ABRAXANE. In clinical studies, Grade 3-4 neutropenia occurred in 34% of patients with metastatic breast cancer (MBC) and 47% of patients with non-small cell lung cancer (NSCLC).

Monitor for myelotoxicity by performing complete blood cell counts frequently, including prior to dosing on Day 1 (for MBC) and Days 1, 8, and 15 (for NSCLC). Do not administer ABRAXANE to patients with baseline absolute neutrophil counts (ANC) of less than 1,500 cells/mm³. In the case of severe neutropenia (<500 cells/mm³ for seven days or more) during a course of ABRAXANE therapy, reduce the dose of ABRAXANE in subsequent courses in patients with either MBC or NSCLC.

In patients with MBC, resume treatment with every-3-week cycles of ABRAXANE after ANC recovers to a level >1,500 cells/mm³ and platelets recover to a level >100,000 cells/mm³.

In patients with NSCLC, resume treatment if recommended (see Dosage and Administration, Table 2) at permanently reduced doses for both weekly ABRAXANE and every-3-week carboplatin after ANC recovers to at least 1500 cells/mm³ and platelet count of at least 100,000 cells/mm³ on Day 1 or to an ANC of at least 500 cells/mm³ and platelet count of at least 50,000 cells/mm³ on Days 8 or 15 of the cycle [see *Dosage and Administration* (2.4)].

5.2 Nervous System

Sensory neuropathy is dose- and schedule-dependent [see *Adverse Reactions* (6.1, 6.2)]. 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 for metastatic breast cancer or until resolution to ≤ Grade 1 for NSCLC followed by a dose reduction for all subsequent courses of ABRAXANE [see *Dosage and Administration* (2.4)].

5.3 Hypersensitivity

Severe and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, have been reported. Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be re-challenged with this drug.

5.4 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 or severe hepatic impairment [see *Dosage and Administration* (2.3), *Use in Specific Populations* (8.6) and *Clinical Pharmacology* (12.3)].

5.5 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.

5.6 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)].

5.7 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%) with single-agent use of ABRAXANE in metastatic breast cancer are alopecia, neutropenia, sensory neuropathy, abnormal ECG, fatigue/asthenia, myalgia/arthralgia, AST elevation, alkaline phosphatase elevation, anemia, nausea, infections, and diarrhea [see *Adverse Reactions* (6.1)].

The most common adverse reactions (≥ 20%) of ABRAXANE in combination with carboplatin for non-small cell lung cancer are anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue [see *Adverse Reactions* (6.2)]. The most common serious adverse reactions of ABRAXANE in combination with carboplatin for non-small cell lung cancer are anemia (4%) and pneumonia (3%). The most common adverse reactions resulting in permanent discontinuation of ABRAXANE were neutropenia (3%), thrombocytopenia (3%), and peripheral neuropathy (1%). The most common adverse reactions resulting in dose reduction of ABRAXANE were neutropenia (24%), thrombocytopenia (13%), and anemia (6%). The most common adverse reactions leading to withholding or delay in ABRAXANE dosing were neutropenia (41%), thrombocytopenia (30%), and anemia (16%).

6.1 Clinical Trials Experience in Metastatic Breast Cancer

Table 3 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 3: Frequency^a of Important Treatment Emergent Adverse Events in the Randomized Metastatic Breast Cancer 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
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

	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)
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 patients 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/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. 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.

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/m²). These effects generally have been reversible.

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 Clinical Trials Experience in Non-Small Cell Lung Cancer

Adverse reactions were assessed in 514 ABRAXANE/carboplatin-treated patients and 524 paclitaxel injection/carboplatin-treated patients receiving first-line systemic treatment for locally advanced (stage IIIB) or metastatic (IV) non-small cell lung cancer (NSCLC) in a multicenter, randomized, open-label trial. ABRAXANE was administered as an intravenous infusion over 30 minutes at a dose of 100 mg/m² on Days 1, 8, and 15 of each 21-day cycle. Paclitaxel injection was administered as an intravenous infusion over 3 hours at a dose of 200 mg/m², following premedication. In both treatment arms carboplatin at a dose of AUC = 6 mg•min/mL was administered intravenously on Day 1 of each 21-day cycle after completion of ABRAXANE/paclitaxel infusion. The differences in paclitaxel dose and schedule between the two arms limit direct comparison of dose- and schedule-dependent adverse reactions. Among patients evaluable for adverse reactions, the median age was 60 years, 75% were men, 81% were White, 49% had adenocarcinoma, 43% had squamous cell lung cancer, 76% were ECOG PS 1. Patients in both treatment arms received a median of 6 cycles of treatment.

The following common (≥ 10% incidence) adverse reactions were observed at a similar incidence in ABRAXANE plus carboplatin-treated and paclitaxel injection plus carboplatin-treated patients: alopecia 56%, nausea 27%, fatigue 25%, decreased appetite 17%, asthenia 16%, constipation 16%, diarrhea 15%, vomiting 12%, dyspnea 12%, and rash 10% (incidence rates are for the ABRAXANE plus carboplatin treatment group).

Table 4 provides the frequency and severity laboratory-detected abnormalities which occurred with a difference of ≥ 5% for all grades (1-4) or ≥ 2% for Grade 3-4 toxicity between ABRAXANE plus carboplatin-treated patients or paclitaxel injection plus carboplatin-treated patients.

Table 4: Selected Hematologic Laboratory-Detected Abnormalities With a Difference of ≥ 5% for grades (1-4) or ≥ 2% for Grade 3-4 Toxicity Between Treatment Groups

	ABRAXANE (100 mg/m ² weekly) plus carboplatin		Paclitaxel Injection (200 mg/m ² every 3 weeks) plus carboplatin	
	Grades 1-4 (%)	Grade 3-4 (%)	Grades 1-4 (%)	Grade 3-4 (%)
Anemia ^{1,2}	98	28	91	7
Neutropenia ^{1,3}	85	47	83	58
Thrombocytopenia ^{1,3}	68	18	55	9

¹ 508 patients assessed in ABRAXANE/carboplatin-treated group

² 514 patients assessed in paclitaxel injection/carboplatin-treated group

³ 513 patients assessed in paclitaxel injection/carboplatin-treated group

Table 5 provides the frequency and severity of adverse reactions, which occurred with a difference of ≥ 5% for all grades (1-4) or ≥ 2% for Grade 3-4 between either treatment group for the 514 ABRAXANE plus carboplatin-treated patients compared with the 524 patients who received paclitaxel injection plus carboplatin.

Table 5: Selected Adverse Reactions with a Difference of ≥5% for All Grade Toxicity or ≥2% for Grade 3-4 Toxicity Between Treatment Groups

System Organ Class	MedDRA v 12.1 Preferred Term	ABRAXANE (100 mg/m ² weekly) + carboplatin (N=514)		Paclitaxel Injection (200 mg/m ² every 3 weeks) + carboplatin (N=524)	
		Grade 1-4 Toxicity (%)	Grade 3-4 Toxicity (%)	Grades 1-4 Toxicity (%)	Grade 3-4 Toxicity (%)
Nervous system disorders	Peripheral neuropathy ^a	48	3	64	12
General disorders and administration site conditions	Edema peripheral	10	0	4	<1
Respiratory thoracic and	Epistaxis	7	0	2	0

mediastinal disorders					
Musculoskeletal and connective tissue disorders	Arthralgia	13	<1	25	2
	Myalgia	10	<1	19	2

^a Peripheral neuropathy is defined by the MedDRA Version 14.0 SMQ neuropathy (broad scope).

For the ABRAXANE plus carboplatin treated group, 17/514 (3%) patients developed Grade 3 peripheral neuropathy and no patients developed Grade 4 peripheral neuropathy. Grade 3 neuropathy improved to Grade 1 or resolved in 10/17 patients (59%) following interruption or discontinuation of ABRAXANE.

6.3 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 and sometimes fatal 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 pneumonitis, 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 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 well as 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.

Reduced visual acuity due to cystoid macular edema (CME) has been reported during treatment with ABRAXANE as well as with other taxanes. After cessation of treatment, CME improves and visual acuity may return to baseline.

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 possible 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 maculopapular 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.

6.4 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

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.

There are no clinically important pharmacokinetic drug-drug interactions between carboplatin and ABRAXANE [see *Clinical Pharmacology* (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [see *Warnings and Precautions* (5.6)].

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/m² (approximately 2% of the daily maximum recommended human dose on a mg/m² 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/m² (approximately 1% of the daily maximum recommended human dose on a mg/m² basis).

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 for the treatment of metastatic breast cancer, 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.

Of the 514 patients in the randomized study who received ABRAXANE and carboplatin for the first-line treatment of non-small cell lung cancer, 31% were 65 years or older and 3.5% were 75 years or older. Myelosuppression, peripheral neuropathy, and arthralgia were more frequent in patients 65 years or older compared to patients younger than 65 years old. No overall difference in effectiveness, as measured by response rates, was observed between patients 65 years or older compared to patients younger than 65 years old.

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* (2.3), *Warnings and Precautions* (5.4), and *Clinical Pharmacology* (12.3)].

8.7 Patients with Renal Impairment

The use of ABRAXANE has not been studied in patients with renal impairment.

10 OVERDOSAGE

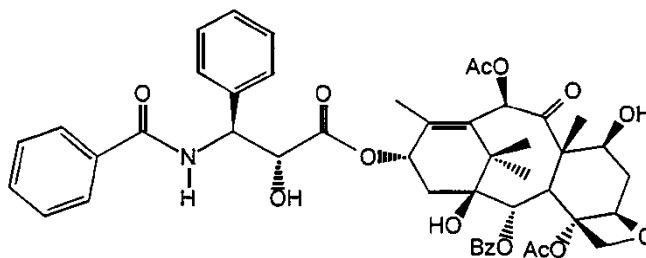
There is no known antidote for ABRAXANE overdose. The primary anticipated complications of overdose would consist of bone marrow suppression, sensory neurotoxicity, and mucositis.

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 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 (2R,3S)-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 inhibitor 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/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 approximately 27 hours.

The drug exposure (AUCs) was dose proportional over 80 to 375 mg/m² and the pharmacokinetics of paclitaxel were independent of the duration of ABRAXANE administration. At the dose of 260 mg/m² for metastatic breast cancer, 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 indicating extensive extravascular distribution and/or tissue binding of paclitaxel.

The pharmacokinetic data of 260 mg/m² ABRAXANE administered over a 30-minute infusion was compared to the pharmacokinetics of 175 mg/m² paclitaxel injection over a 3-hour infusion. The clearance was larger (43%) and the volume of distribution was also higher (53%) for ABRAXANE than for paclitaxel injection. Differences in the maximum concentration (C_{max}) and dose-corrected C_{max} 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 μ g/mL, indicated 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 6 α -hydroxypaclitaxel by CYP2C8; and to two minor metabolites, 3'-*p*-hydroxypaclitaxel and 6 α , 3'-*p*-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6 α -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 Drug Interactions (7)].

Excretion

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 6 α -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 or bilirubin > 5 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/m²
- Moderate (bilirubin 1.26 to 2 x ULN and AST > ULN and < 10 x ULN): 200 mg/m²
- Severe (bilirubin 2.01 to 5 x ULN and AST > ULN and < 10 x ULN): 130 mg/m²

The 260 mg/m² dose for mild hepatic impairment and the 200 mg/m² dose for moderate hepatic impairment resulted in paclitaxel exposures within the range seen in patients with normal hepatic function (mean AUC_{0-∞} = 14,789 $\pm$ 6,703 hr*ng/mL). The 130 mg/m² 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 6 summarizes the AUC values observed in the study. The 200 mg/m² 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 or bilirubin >5 x ULN [see Dosage and Administration (2.3) and Use in Specific Populations (8.6)].

Table 6: Exposure (AUC_{0-∞}) of ABRAXANE Administered Intravenously 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 $\pm$ SD	17434 $\pm$ 11454	14159 $\pm$ 13346	9187 $\pm$ 6475
Median (range)	13755 (7618, 35262)	7866 (5919, 37613)	6134 (5627, 20684)

^abilirubin 2.01 to 5 x ULN and AST > ULN and < 10 x ULN

Effect of Renal Impairment

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

Pharmacokinetic Interactions between Carboplatin and ABRAXANE

Administration of carboplatin immediately after the completion of ABRAXANE infusion to patients with non-small cell lung cancer did not cause clinically important changes in paclitaxel exposure. The observed mean AUC_{inf} of free carboplatin was approximately 23% higher than the targeted value (6 min*mg/mL) but its mean half life and clearance were consistent with those reported in the absence of paclitaxel.

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/m² 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/m²/week in this study (approximately 1 to 5% of the daily maximum recommended human exposure on a mg/m² 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/m² in rodents and 175 mg/m² in dogs.

14 CLINICAL STUDIES

14.1 Metastatic Breast Cancer

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

Table 7: Efficacy Results from Randomized Metastatic Breast Cancer Trial

		ABRAXANE 260 mg/m²	Paclitaxel Injection 175 mg/m²
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.

14.2 Non-Small Cell Lung Cancer

A multicenter, randomized, open-label study was conducted in 1052 chemo-naïve patients with Stage IIIB/IV non-small cell lung cancer to compare ABRAXANE in combination with carboplatin to paclitaxel injection in combination with carboplatin as first-line treatment in patients with advanced non-small cell lung cancer. ABRAXANE was administered as an intravenous infusion over 30 minutes at a dose of 100 mg/m² on Days 1, 8, and 15 of each 21-day cycle. Paclitaxel injection was administered as an intravenous infusion over 3 hours at a dose of 200 mg/m², following premedication. In both treatment arms carboplatin at a dose of AUC = 6 mg•min/mL was administered intravenously on Day 1 of each 21-day cycle after completion of ABRAXANE/paclitaxel infusion. Treatment was administered until disease progression or development of an unacceptable toxicity. The primary efficacy outcome measure was overall response rate as determined by a central independent review committee using RECIST guidelines (Version 1.0).

In the intent-to-treat (all-randomized) population, the median age was 60 years, 75% were men, 81% were White, 49% had adenocarcinoma, 43% had squamous cell lung cancer, 76% were ECOG PS 1, and 73% were current or former smokers. Patients received a median of 6 cycles of treatment in both study arms.

Patients in the ABRAXANE/carboplatin arm had a statistically significantly higher overall response rate compared to patients in the paclitaxel injection/carboplatin arm [(33% versus 25%) see Table 8]. There was no statistically significant difference in overall survival between the two study arms.

Table 8: Efficacy Results from Randomized Non-Small Cell Lung Cancer Trial (Intent-to-Treat Population)

	ABRAXANE (100 mg/m² weekly) + carboplatin (N=521)	Paclitaxel Injection (200 mg/m² every 3 weeks) + carboplatin (N=531)
Overall Response Rate (ORR)		
Confirmed complete or partial overall response, n (%)	170 (33%)	132 (25%)
95% CI	28.6, 36.7	21.2, 28.5
P-value (Chi-Square test)	0.005	
Median DoR in months (95% CI)	6.9 (5.6, 8.0)	6.0 (5.6, 7.1)
Overall Response Rate by Histology		
Carcinoma/Adenocarcinoma	66/254 (26%)	71/264 (27%)
Squamous Cell Carcinoma	94/229 (41%)	54/221 (24%)
Large Cell Carcinoma	3/9 (33%)	2/13 (15%)
Other	7/29 (24%)	5/33 (15%)

CI = confidence interval; DoR= Duration of response

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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 (Patient Information).

- 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 (5.6) and Use in Specific Populations (8.1)*].
- Advise men not to father a child while receiving ABRAXANE [see *Warnings and Precautions (5.7)*].
- 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.
- Patients must be informed that hypersensitivity reactions may occur, which could be severe and sometimes fatal.

Manufactured for: Celgene Corporation
Summit, NJ 07901

ABRAXANE® is a registered trademark of Abraxis BioScience, LLC.

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Abraxis BioScience, LLC is a wholly owned subsidiary of Celgene Corporation.

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; 8,034,375; 8,268,348; and RE41,884.

ABRPI.004/PPI.004 10/12

Patient Information
ABRAXANE® (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 and advanced lung 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/ mm³
- 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 generally not needed to receive ABRAXANE. Premedication may be needed if you have had a prior allergic reactions to ABRAXANE. In case of severe allergic reaction, ABRAXANE should not be used again.
- ABRAXANE will be given to you by intravenous 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 against 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).
- hypersensitivity reactions, which could be severe, and sometimes fatal.

The most common side effects of ABRAXANE include:

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

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.

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, 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 1-888-423-5436.

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: October 2012

Manufactured for: Celgene Corporation
Summit, NJ 07901

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ABRPPI.004 10/12

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 21-660/S-031

SUMMARY REVIEW

Division Director Summary Review

Date	October 11, 2012
From	Patricia Keegan
Subject	Division Director Summary Review
NDA Supplement#	21660/S-031
Applicant Name	Abraxis Bioscience LLC, a wholly owned subsidiary of Celgene Corporation
Date of Submission	December 12, 2011
PDUFA Goal Date	October 12, 2012
Proprietary Name / Established (USAN) Name	Abraxane for Injectable Suspension/ paclitaxel protein-bound particles for injectable suspension) (albumin-bound)
Dosage Forms / Strength	Lyophilized Powder, for Injection
Proposed Indication(s)	(b) (4)
Action:	<i>Approval</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Regulatory Project Manager Review	Monica Hughes
Medical Officer Review	Shakun Malik
Statistical Review	Huanyu (Jade) Chen
ONDQA Review	Huai T. (Ted) Chang
Clinical Pharmacology Review	Lillian Zhang
OPDP/DPDP & DCDP	Carole Broadnax & Karen Munoz-Nero
OSE/DMEPA	Jibril Abdus-Samad
OMPI/DMPP	Nathan Caulk

OND=Office of New Drugs
 ONDQA = Office of New Drug Quality Assurance
 OPDO=Office of Prescription Drug Promotion
 DPDP=Division of Professional Drug Promotion
 DCDP=Division of Consumer Drug Promotion
 DMEPA=Division of Medication Error Prevention and Analysis
 DRISK=Division of Risk Management
 OMPI=Office of Medical Policy Initiatives
 DMPP=Division of Medical Policy Programs

Division Director Summary Review

1. Introduction

This efficacy supplement for Abraxane (paclitaxel protein-bound particles, Abraxis Biosciences, Inc.) is submitted under the provisions of section 505(b)(2) of the Food, Drug, and Cosmetic Act, relying on FDA's prior finding of safety and effectiveness for the listed drug, Taxol[®] (paclitaxel; Bristol Myers Squibb) for the same indication. Although both drugs contain the same active pharmaceutical ingredient, paclitaxel, based on differences in chemical structure of the final drug products, Abraxane and Taxol have clinically important differences in pharmacokinetic profiles with resultant differences in the recommended dose and schedules. Therefore, FDA required that clinical trials be performed to establish that clinical activity of paclitaxel, when administered as Abraxane at a different dose and schedule from Taxol, was preserved. Because the treatment effect of paclitaxel could not be isolated from that of the concurrently administered carboplatin in the current trial (CA031) and because the treatment effect supporting approval of paclitaxel was based on a different dose/schedule and different platinum backbone (cisplatin rather than carboplatin), FDA stated that in order to rely on the prior findings of efficacy for Taxol, the comparative trial should demonstrate superior overall response rate for the Abraxane-containing regimen compared to the paclitaxel injection-containing regimen. The major efficacy trial was not designed to establish claims of lesser toxicity or better adverse reaction profile for protein (albumin)-bound paclitaxel over that of paclitaxel injection.

Safety and confirmation of activity were established in a single, multicenter, open-label, randomized (1:1) trial (CA031) conducted in 1052 patients with stage IIIB or IV non-small cell lung cancer (NSCLC). Patients received Abraxane 100 mg/m² as an intravenous infusion over 30 minutes on Days 1, 8, and 15 of each 21-day cycle or paclitaxel injection 200 mg/m² as an intravenous infusion over 3 hours. Both treatment arms received carboplatin at an AUC of 6 mg•min/mL intravenously on Day 1 of each 21-day cycle, following the paclitaxel infusion.

The primary objective of Protocol CA031, demonstration of superior overall response rate for the Abraxane-containing arm, as determined by an independent review committee masked to treatment assignment, was met. The odds ratio for comparison of the overall response rate was 1.31 (overall response rates were 33% and 25%, $p = 0.005$, Chi square test). Responses appeared to be equally durable in both treatment arms with median durations of response were 9.6 and 9.5 months in the Abraxane- and paclitaxel injection-containing arms, respectively. The trial failed to meet the two key secondary objectives of demonstration of superior progression-free survival [HR 0.93 (95% CI: 0.79, 1.09); $p = 0.38$, unstratified log-rank test] and superior overall survival [HR 0.93 (95% CI: 0.81, 1.08); $p = 0.34$, unstratified log-rank test] for the Abraxane-containing arm.

The size of the safety database was adequate for a supplemental application with 7 years of post-marketing experience. The primary evaluation of safety was based on data obtained in 1038

patients in Protocol CA031 who received at least one dose of protocol-specified treatment, which included 514 Abraxane-treated patients and 524 paclitaxel injection-treated patients. It is noted that the Protocol CA031 was not designed (open-label trial using different doses and schedules of paclitaxel administration; not described in analysis plan) to support claims of comparative safety. The following adverse reactions occurred more frequently in protein (albumin)-bound paclitaxel-treated patients than in the paclitaxel injection-treated patients: anemia (98%), hypoalbuminemia (82%), thrombocytopenia (68%), hypocalcemia (57%), hyperkalemia (37%), peripheral edema (10%), and epistaxis (7%). The following labeled adverse reactions for paclitaxel injection reported/occurred in $\geq 20\%$ of protein (albumin)-bound paclitaxel-treated patients were: alopecia (56%), peripheral neuropathy (48%), nausea (27%), increased ALT (26%), increased AST (22%), and hyperbilirubinemia (20%).

The approval of this application is based on FDA's prior findings of safety and efficacy for Taxol[®], the listed drug, together with the results of Protocol CA031, which "bridge" the anti-tumor activity and rule out clinically important decrements in progression-free or overall survival of Abraxane, in combination with carboplatin, as compared to a paclitaxel injection/carboplatin regimen. The toxicity profile of Abraxane, in combination with carboplatin, is considered acceptable for the treatment of locally advanced or metastatic non-small cell lung cancer, and was similar to that observed in the control arm. All review team members recommended approval. Issues to be further discussed in this review are the acceptability of the control arm in the bridging study (b) (4)

2. Background

Proposed Indication

(b) (4)

Lung cancer¹ is the second most common cancer (excluding non-melanoma skin cancers) in both men and women and the leading cause of cancer deaths in men and women in the United States. According to SEER estimates, there will be an estimated 226,160 new cases of lung cancer and an estimated 160,340 deaths due to lung cancer in 2012. Lung cancer is classified by histologic features as small cell (14%) or non-small cell (85%), as an initial basis for treatment selection. Non-small cell lung cancer is generally further subdivided into histologic subtypes of adenocarcinoma or squamous cell carcinoma; screening of tumor specimens for anaplastic lymphoma kinase (ALK) or epidermal growth factor receptor (EGFR) gene mutations as an aid to treatment selection is also now a standard practice. Only 15% of all lung cancers are diagnosed at a localized, operable stage, leaving most patients with incurable cancers for which multimodality therapy and chemotherapy may modestly prolong life but not result in cure. The overall one-year and 5-year survival rates for all lung cancers are 43% and 16%, respectively.

¹ Cancer Facts & Figures 2012 accessed on September 27, 2012 at <http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-031941.pdf>

Thus, effective new drugs and effective alternative drugs are needed for the treatment of lung cancer.

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines (version 3, 04/11/12) recommend that “the drug regimen with the highest likelihood of benefit with toxicity deemed acceptable to both the physician and the patients should be given as initial therapy for advanced [non-small cell] lung cancer.” For patients with good performance status (ECOG PS 0 or 1), consistent with the eligibility requirements for Protocol CA031, the practice guidelines identify chemotherapy alone or in combination with bevacizumab as acceptable first-line treatments; treatment with single-agent crizotinib is recommended only for patients with ALK-positive lung cancer. The guidelines further note that platinum-based (cisplatin or carboplatin) doublets which include paclitaxel, docetaxel, gemcitabine, etoposide, vinblastine, vinorelbine, or pemetrexed are effective for first-line treatment in patients with good performance status. Of these combinations, paclitaxel is FDA-approved for use, in combination with cisplatin for the first-line treatment of non-small cell lung cancer, as discussed below.

June 30, 2008: An efficacy supplement for Taxol® (paclitaxel, Bristol Myers Squibb) was approved for the indication “TAXOL, in combination with cisplatin, is indicated for the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy”, based on the following data

A randomized (1:1:1), 3-arm, open-label trial conducted by the Eastern Cooperative Oncology Group (ECOG), which enrolled 599 patients with chemotherapy-naïve, non-small cell lung cancer to were randomized to either

- Taxol 135 mg/ m² as a 24-hour infusion in combination with cisplatin 75 mg/m² on day 1 of a 21-day cycle (Arm 1, n=198)
- Taxol 250 mg/ m² as a 24-hour infusion in combination with cisplatin 75 mg/ m² on day 1 of a 21-day cycle with G-CSF support (Arm 2, n=201)
- cisplatin 75 mg/ m² on day 1 followed by etoposide 100 mg/ m² on days 1, 2, and 3 of each 21-day cycle [Arm 3 (control) n=200]

Based on these data, product labeling states that, for patients with non-small cell lung carcinoma, the recommended regimen, given every 3 weeks, is TAXOL administered intravenously over 24 hours at a dose of 135 mg/m² followed by cisplatin, 75 mg/m².

Efficacy Results for Trial Supporting Approval of Taxol for 1 st -line Treatment of NSCLC				
Efficacy Endpoint	Arm 1 Taxol 125 cisplatin 75	Arm 3 etoposide 100 x 3 cisplatin 75	Arm 2 Taxol 250 cisplatin 75	Arm 3 etoposide 100 x 3 cisplatin 75
Overall response rate	25%	12%	23%	12%
p-value	0.001		<0.001	
Time-to-Progression (mos)	4.3	2.7	4.9	2.7
p-value	0.05		0.004	
Overall Survival (months)	9.3	7.4	10.0	7.4
p-value	0.12		0.08	

Data supporting control arm for Protocol CA031

The paclitaxel regimen utilized as the control regimen in Protocol CA031 was not that used to support that approval of Taxol for the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy, as discussed above. As stated in the background section of Protocol CA031 (amendment 4), the selection of the control arm in the CA031 trial was based on current standard of care in the United States and the results of a 4-arm, randomized trial demonstrating similar outcomes for three alternative regimens to the cisplatin/paclitaxel treatment regimen supporting approval of the NSCLC indication for Taxol.

The four treatment arms compared in this trial are briefly summarized below

- Cisplatin plus paclitaxel (control), consisting of paclitaxel, 135 mg/m² over 24-hr period on day 1 and cisplatin, 75 mg/m² on day 2 of each 21-day cycle
- Cisplatin plus gemcitabine, consisting of gemcitabine, 1000 mg/m² on days 1, 8, and 15 and cisplatin, 100 mg/m² on day 1 of each 28-day cycle
- Cisplatin plus docetaxel, consisting of docetaxel, 75 mg/m² on day 1 and cisplatin, 75 mg/m² on day 1 of each 21-day cycle
- Carboplatin plus paclitaxel consisting of paclitaxel, 225 mg/m² over 3-hr period on day 1 and carboplatin, AUC 6.0 mg/ml/min on day 1 of each 21-day cycle

Specifically, the rationale for the control arm used in the CA031 protocol is characterized in the protocol, as follows: “The most commonly used chemotherapy regimen for first-line therapy in the US is carboplatin/Taxol. A recent Phase III study comparing carboplatin/Taxol to other doublets (cisplatin/Taxol vs. cisplatin/gemcitabine vs. cisplatin/docetaxel vs. carboplatin/Taxol) demonstrated that all the combinations have similar efficacy.² However, because of its more

² Schiller JH, Harrington D, Belani CP, et al: Comparison of Four Chemotherapy Regimens for Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 346:92-98, 2002.

favorable safety profile, the Eastern Collaborative Oncology Group (ECOG) selected carboplatin/Taxol as its reference regimen for future studies.”

Regulatory History for NDA 21660

January 7, 2005: Abraxane (paclitaxel protein-bound particles, for injection) (albumin-bound) was approved 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.”

This application was approved under the provisions of 505(b)(2) of the Food, Drug, and Cosmetic Act, relying on FDA’s prior finding of safety and effectiveness for the listed drug, Taxol, for the same indication. Safety and demonstration of clinical activity were primarily supported by a single randomized (1:1) trial conducted in 460 patients with metastatic breast cancer. The trial was designed to establish that single agent Abraxane, dosed at 260 mg/m² as a 30 minute intravenous infusion, preserved at least 75% of the treatment effect on overall response rate observed in patients receiving Taxol at a dose of 175 mg/m² as a 3-hour intravenous infusion. The trial demonstrated superior overall response rate (21.5% vs. 11.1%, p<0.003 stratified CMH test) for Abraxane-treated patients. The application was approved with post-marketing commitments to provide mature overall survival results, as follows: “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.”

February 15, 2007: An efficacy supplement with clinical data (SE8) was submitted fulfilling the post-marketing commitment to an analysis of overall survival. At the time of the analysis, 74% of the patients in the Abraxane arm and 77% of the patients in the Taxol arm had died. There was no statistically significant difference in overall survival between the two arms [HR 0.90 (95% CI: 0.73, 1.12), p=0.35]. Product labeling was amended to include a statement that there was no statistically significant difference in overall survival between the two arms for the major efficacy trial.

Regulatory History for NDA 21660/S031

November 4, 2005: An EOP2 meeting was held to discuss the adequacy of the proposed development program to support claims for (b) (4) first-line treatment of unresectable or metastatic NSCLC. The proposed program supporting treatment of metastatic NSCLC would rely on three single-arm trials, two phase 1 trials that included an expansion cohort at the recommended Phase 2 dose and Protocol CA028 entitled, “An Open-Label Phase II Trial of Increasing Doses of ABI-007 (a Cremaphor-Free, Protein Stabilized, Nanoparticle Paclitaxel) and Carboplatin in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC)”. (b) (4)

FDA provided the following advice:

- The proposed single arm phase 2 studies to support the approval of Abraxane in first-line metastatic lung cancer (b) (4) would not provide adequate information for a complete evaluation of safety and efficacy.
- A comparative trial or trials would be required in a setting where paclitaxel has an approved indication.
- Time to event endpoints, such as progression-free survival and overall survival, are not interpretable in single-arm trials.
- (b) (4)
- The pharmacokinetics of Abraxane when co-administered with carboplatin in NSCLC patients should be assessed given the 33% decrease in paclitaxel clearance when TAXOL was administered following cisplatin.

February 23, 2006: SPA non-agreement letter issued. The primary areas of disagreement were:

- The SPA request was premature since the dose and schedule of Abraxane had not been determined and the request did not include the statistical analysis plan (SAP).
- A non-inferiority approach was not acceptable because the contribution of paclitaxel to the efficacy of the combination cannot be determined for response rate, progression free survival or overall survival. Therefore, a superiority design would be necessary for approval with response rate as the primary endpoint and overall survival and progression free survival as secondary endpoints. The study will need to be powered for survival to demonstrate that overall survival is not worse than the control arm.
- Analyses of tumor-related endpoints should be based on an independent central, blinded review of radiological studies and an effort should be made to have a complete record of tumor measurements.
- Since a superiority trial design is required, differences in schedule between treatment arms were not problematic.

May 25, 2007: SPA non-agreement letter issued. The primary areas of disagreement were:

- The proposed Taxol dose for the control arm is 200 mg/m² over 3 hours. Justify this dose since it is different from the approved Taxol dose (135 mg/m² over 24 hrs) and the recommended community standard dose (225 mg/m²) in combination with carboplatin.
- Include a plan to provide PFS and survival analysis at the time of final tumor response analysis.
- Patients without baseline target lesions should not be eligible for the trial.
- The plan for sample size adjustment was acceptable however any increase sample size would increase the chances of detecting a smaller effect size which may be statistically significant but not clinically meaningful.
- The results of secondary endpoints will be considered only if the primary analysis of the primary endpoint was positive.
- The censoring method for PFS should be pre-specified. For the PFS analysis, patients who change therapy before progression should be censored at the last assessment. Patients with two or more missing assessments immediately prior to the next visit with a documented progression should be censored at the last assessment with documentation of no progression.

- PFS is a complex endpoint. The analysis results may be influenced by any imbalance in assessment dates or missing data between treatment arms. Several sensitivity analyses of PFS should be performed, taking these concerns into account and a detailed plan of how missing PFS assessments will be handled should be included in the final protocol/analysis plan.

August 30, 2007- SPA agreement letter issued for Protocol CA031.

August 11, 2010- Applicant requested that the technical (content & format) pre-sNDA meeting to discuss this supplement be cancelled based upon receipt of FDA's preliminary responses. In their responses, FDA noted that the safety and efficacy results had not been provided in the pre-meeting package. FDA's responses noted

- FDA agreed that the final Statistical Analysis Plan (SAP) for study CA031 submitted January 7, 2010, which the applicant stated was not substantially different from the SAP submitted September 19, 2008, was acceptable.
- The analyses to be provided in the ISS and ISE appeared acceptable and the proposed content/format for the SAS transport files were acceptable
- FDA agreed that the supplement could be supported primarily by a single trial (CA 031)
- Narrative summaries were to be provided in the efficacy supplement for patients with the following adverse events: death on study treatment or within 30 days of discontinuing study treatment, serious adverse events, and adverse events resulting in discontinuation of study treatment.
- The contents and analyses for population pharmacokinetic evaluation.

NDA 21660/S-031

The application was received on December 12, 2011 and amended on January 13, 2012; February 17, 2012; March 2, 2012; March 9, 2012; March 30, 2012; May 9, 2012; July 12, 2012; August 2, 2012; August 13, 2012; August 15, 2012; August 23, 2012; September 28, 2012; October 5, 2012; and October 11, 2012.

Abraxis Bioscience LLC requested priority designation based upon the criteria listed below. FDA's assessment of each criterion follows, in italics. Based on FDA's assessment, the request for priority designation was not granted.

- "Abraxane treatment demonstrated superior efficacy benefit of overall response rate (ORR) in patients with advanced NSCLC."

Assessment: Evidence of an 8% absolute increase in overall response rates (33% vs. 25%) is not sufficient to establish superior efficacy, given the small magnitude of the incremental effect and that Taxol was approved based on evidence of improved overall survival. The applicant's reported results for Trial CA031 demonstrate no significant improvement in progression-free or overall survival.

- "Abraxane treatment demonstrated significant reductions in the frequency, severity, and duration of the taxane-related treatment-limiting toxicity of severe peripheral neuropathy. In

addition, Abraxane treatment lacks the severe solvent-related drug hypersensitivity/hypersensitivity reactions that are treatment-limiting drug reactions for paclitaxel injection formulations.”

Assessment: *Data contained in this application are not sufficient to support a conclusion of superior safety. These are post-hoc, exploratory comparisons. The trial was not designed to obtain data that would support comparisons of comparative toxicity.*

- “There has been a drug shortage reported with paclitaxel as of mid-2011.”

Assessment: *This is not a criterion for review designation.*

3. CMC

I concur with the conclusions reached by the chemistry reviewer that, given the absence of new CMC information, the proposed new indication does not require changes to Sections 2 (Dosage and Administration), 3 (Dosage Forms and Strength), 11 (Description), or 16 (How Supplied/Storage and Handling). I also concur that facilities inspections were not required for this supplement as there were no proposed changes to the manufacturing site or process. The CMC and DMEPA reviewers arrived at agreed-upon carton and container labeling changes with Celgene, to enhance safe use. The CMC reviewer granted the applicant’s request for categorical exclusion from environmental assessment. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

Not applicable.

5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval. The application contained data from two clinical pharmacology studies evaluating the pharmacokinetics of a single dose of ABRAXANE in dose-escalating (Phase 1) trials in Japan, a substudy of Protocol CA031 evaluating the pharmacokinetics of a single-dose (cycle 1, day 1) of ABRAXANE in combination with carboplatin in White Americans and Europeans, and an additional substudy of Protocol CA031, evaluating for pharmacokinetic effects of carboplatin on ABRAXANE as well as the pharmacokinetics of a single- and multiple-dose (cycle 1, days 1, 8, & 15) of ABRAXANE in combination with carboplatin in Japanese patients.

The clinical pharmacology reviewer concluded that there was no evidence of clinically important drug interactions between paclitaxel and carboplatin and that the pharmacokinetics of paclitaxel in ABRAXANE-treated patients was similar between Japanese and White Europeans/Americans.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

This efficacy supplement relies on FDA's prior findings of safety and effectiveness for the listed drug, Taxol. The ability to rely on these prior findings is based on the same active pharmaceutical ingredient (paclitaxel) in both Taxol and Abraxane and demonstration of comparable clinical activity (higher overall response rate) with the absence of a clinically meaningful decrement in overall survival) in a randomized open-label trial comparing a clinically tolerable Abraxane plus carboplatin combination chemotherapy regimen to a paclitaxel injection/carboplatin combination regimen administered as first-line treatment for locally advanced or metastatic non-small cell lung cancer. The trial was designed to demonstrate superiority of the Abraxane-containing arm over the paclitaxel injection arm and not to evaluate non-inferiority of the two treatment arms. A non-inferiority trial would have been difficult to conduct since the magnitude of the treatment effect attributable to paclitaxel injection, when administered in combination with carboplatin at the doses and schedule used in Protocol CA031, has not been established.

The efficacy supplement also contained the pharmacokinetic, safety, and efficacy (overall response rate) data from Protocols CA018 and CA028, which were single-arm trials. The response data is inadequate to support efficacy in a first-line treatment setting, given available therapy or to "bridge" to the prior findings of efficacy for Taxol, since these trials were uncontrolled.

Protocol CA031 - Design

This trial was a randomized (1:1), open-label, active-controlled, multi-center trial conducted in patients receiving first-line therapy for non-small cell lung cancer (NSCLC). Patients who were candidates for potentially curative surgery or radiation therapy were ineligible. The randomization was stratified by disease stage (IIIb versus IV), age (< 70 versus ≥ 70 years), gender (male versus female), histology (adenocarcinoma versus squamous cell versus other), and geographic region. The primary endpoint was objective response rate (complete plus partial response rate) per independent review committee (IRC) assessment based on RECIST v 1.0 response criteria. The key secondary endpoints were progression-free survival (PFS) and overall survival (OS).

Patients were randomized to

- Abraxane 100 mg/m² weekly (days 1, 8 and 15), intravenously over 30 minutes, and carboplatin at a predicted AUC of 6, intravenously, on Day 1 of each 21-day cycle
- Paclitaxel injection 200 mg/m², intravenous infusion of 3 hours, followed by carboplatin at a predicted AUC of 6, intravenously, on Day 1 of each 21-day cycle

Note: In the clinical study report, the applicant discusses the basis for the selection of the dosing in the experimental arm and treatment arm as follows

- *In support of the Abraxane dose and schedule, the applicant states that Phase 1 and 2 studies CA015, CA018, and CA028 demonstrated a higher response rate in NSCLC and lower toxicity with a weekly Abraxane dosing schedule as compared to an every three-week schedule.*
- *In support of the dose of paclitaxel injection used in Protocol CA031, the applicant states that the control treatment was based on the results of Schiller, et al, with modifications to the paclitaxel dose based on the advice of the Protocol Steering Committee, which “strongly recommended that a Taxol dose of 225 mg/m² was not appropriate for the control arm due to the toxicity associated with this dose and 200 mg/m² is the dose most commonly administered.”*

The protocol was vague regarding the duration of treatment, stating that “[I]n general, assuming adequate tolerability of the regimen, it is encouraged that patients receive at least 6 cycles of treatment to permit adequate evaluation of the treatment regimen”, however “patients may continue on treatment in the absence of progressive disease and unacceptable toxicity as long as their treating physician feels it is in their best interests to do so.”

Tumor imaging studies were to be obtained every 6 weeks until investigator-determined disease progression or initiation of alternative anti-cancer therapy. Patients were evaluated for survival by phone or record review at monthly intervals for 6 months, then every 3 months thereafter for 12 months (a total of 18 months), per the final version of the protocol (amendment 4).

The sample size assumptions for Protocol CA031 included the following assumptions: 525 patients per arm were needed to detect an absolute increase in overall response rate of 7% (from 17% to 24%) in the experimental arm with 80% power and two-sided alpha of 0.05. This sample size was sufficient to detect a hazard ratio of 0.8, with 85% power and two-sided alpha of 0.05 after 735 progression-free survival events and 735 deaths.

The analysis plan included one planned interim analysis for overall response rates in 200 evaluable patients per arm, with alpha allocation of 0.001 and 0.049 to the interim and final efficacy analyses for the primary endpoint. Interim analyses of progression-free survival and overall survival were to be conducted at the time of the final analysis of overall response rate. The analysis plan also specified a hierarchical testing procedure for analysis of secondary efficacy endpoints, requiring testing of progression-free survival first and then overall survival, at an overall alpha of 0.05 two-sided.

Results

Study CA031 was conducted at 102 centers within 6 countries. A total of 1052 patients were randomized to Abraxane plus carboplatin (n=521) or paclitaxel injection plus carboplatin (n=531). The data cut-off date for the primary efficacy endpoint, overall response rate, was October 12, 2009, when the last patient enrolled had completed their second response assessment. The data cut-off date for all other efficacy endpoints was January 31, 2011.

The intent-to-treat (all randomized) patient population was generally well-balanced for demographic and prognostic variables occurring in more than 2% of the study population. The efficacy population had a median age of 59 years, with 344 patients (33%) aged 65 years or older, 75% were male, 81% were White, 15% were Asian, 2% were Black and 2% were White Hispanics. The majority (69%) of patients enrolled at Eastern European sites, with 16% enrolled in North America, 14% enrolled at sites in the Asia/Pacific region, and 1% enrolled at site in Australia/New Zealand. The majority of patients had an Eastern Cooperative Group (ECOG) performance status (PS) of 1 (76%), with 23.4 % having an ECOG PS of 0 and less than 1% having an ECOG PS of 2 at study entry. The majority had Stage IV disease (64%), while 24% had Stage IIb disease and 12% had another stage (not IV or IIb). The most common histologic subtype was adenocarcinoma/carcinoma (49%), followed by squamous cell carcinoma (43%), “other” (6%), and large cell carcinoma (2%).

The trial appeared to be well-controlled and well-conducted. Because this is a supplement rather than the original NDA and results are consistent with the findings for the listed drug, Taxol, clinical study site audits were not requested.

As noted in the statistical review, there were minor differences between the protocol-specified statistical analysis plan and those used in the clinical study report submitted in the supplement with regard to stratification variables included in the stratified analyses of the primary and key secondary efficacy endpoints. The analyses conducted by the statistical reviewer, presented below, demonstrate that the results are similar regardless of stratification variables used.

The primary objective of Protocol CA031, demonstration of superior overall response rate for the Abraxane-containing arm, was met. Responses appeared to be equally durable in both treatment arms (analyses generated by the statistical reviewer but not presented in her review). The trial failed to meet the two key secondary objectives of demonstration of superior progression-free survival and superior overall survival for the Abraxane-containing arm.

As noted by the statistical reviewer, “[D]ue to high censoring rate in the PFS [analysis using IRC-determined events], there was less than planned number of PFS event by the PFS and OS cut-off date [January 31, 2011]. However, there was more than the planned number of OS events by the PFS and OS cut-off date. Therefore, all the efficacy analyses in the CSR were final analyses.

An additional issue noted by the statistical reviewer was that the majority of PFS events in the IRC-determined PFS analysis were based on deaths rather than disease progression [232 of 297 (78%) and 257 of 312 (82%) PFS events in the Abraxane-containing and the paclitaxel injection-containing arms, respectively, were deaths]. This finding appears to primarily result from higher

censoring in the IRC analysis due to discrepancies in classifying disease progression between investigators and IRC.

Primary Efficacy Analysis and exploratory Analyses of Overall Response rate in Protocol CA031		
Efficacy Endpoints (based on IRC-assessment)	ABRAXANE (100 mg/m ² weekly) plus carboplatin (N=521)	Paclitaxel injection (200 mg/m ² q 3 weeks) plus carboplatin (N=531)
Overall Response Rate		
Number of patients with confirmed CR or PR	170	132
Overall response rate (95% CI)	33% (29%, 37%)	25% (21%, 29%)
P-value (Chi-Square test)	0.005	
Response Duration (in months)		
Median (95% CI)	6.9 (5.6, 8.0)	6.0 (5.6, 7.1)
Overall Response Rate by Histology		
Carcinoma/Adenocarcinoma	66/254 (26%)	71/264 (27%)
Squamous Cell Carcinoma	94/229 (41%)	54/221 (24%)
Large Cell Carcinoma	3/9 (33%)	2/13 (15%)
Other	7/29 (24%)	5/33 (15%)

Protocol-Specified Secondary Endpoint and Exploratory Analyses in Protocol CA031		
	ABRAXANE (100 mg/m ² weekly) plus carboplatin n=521	Paclitaxel injection (200 mg/m ² q 3 weeks) plus carboplatin n=531
IRC-determined Progression-Free Survival (PFS) – 1st secondary endpoint per analysis plan		
Total PFS events	297 (57.0%)	312 (58.8%)
Disease progression events	65 (12.5%)	55 (10.4%)
Deaths	232 (44.5%)	257 (48.4%)
Median PFS (in months)	6.3 months	5.8 months
Stratified HR [(95% CI) p-value]†	0.90 [(0.77, 1.06); p=0.21]	
Stratified HR [(95% CI) p-value] ‡	0.87 [(0.73, 1.04); p=0.13]	
Un-Stratified HR [(95% CI) p-value]	0.93 [(0.79, 1.09). p= 0.38]	
Investigator-determined Progression-free Survival (PFS) – Exploratory analysis		
Total PFS events	423 (81.0%)	413 (78%)
Disease progression events	106 (20.3%)	92 (17.3%)
Deaths	317 (60.8%)	321 (60.5%)
Median PFS (in months)	5.5 months	5.4 months
Stratified HR [(95% CI) p-value]†	0.94 [(0.82, 1.04); p=0.39]	
Stratified HR [(95% CI) p-value] ‡	0.90 [(0.78, 1.04); p=0.16]	
Un-Stratified HR [(95% CI) p-value]	0.96 [(0.84, 1.10). p= 0.56]	
Overall Survival (OS) – 2nd secondary endpoint per analysis plan		
Deaths	360 (69%)	384 (72%)
Median Survival (in months)	12.1	11.2
Stratified HR [(95% CI) p-value]†	0.92 [(0.80, 1.07) p=0.27]	
Stratified HR [(95% CI) p-value] ‡	0.94 [(0.81, 1.10) p=0.45]	
Un-Stratified HR [(95% CI) p-value]	0.93 [(0.81, 1.08) p=0.34]	
Duration of Response Per IRC assessment		
Number evaluable for response	N=170	N=132
Died or Progressed	85 (50%)	78 (59%)
Median DoR (months), 95%CI	9.6 (8.3, 10.8)	9.5 (8.1, 10.9)
Duration of Response per investigator assessment		
Number evaluable for response	n=200	N=160
Died or Progressed	155 (78%)	124 (78%)
Median DoR (months), 95%CI	8.3 (7.7, 9.5)	7.1 (7.0, 8.3)
†Stratified by CSR defined strata: Region, histology		
‡Stratified by SAP defined strata: Region, histology, stage, age, gender		

The data from Protocol CA031, as presented in the tables above, are sufficient to establish that the anti-tumor activity of paclitaxel injection is preserved when Abraxane, at 100 mg/m² administered as a weekly infusion, is substituted for paclitaxel injection in a combination chemotherapy regimen which has similar efficacy outcomes to that for which paclitaxel injection was approved. The determination is based on the statistically significant increase in overall response rates, similar durability of those responses, and

observed hazard ratios (and their 95% confidence intervals) for comparison of progression-free and overall survival between the two treatment arms. Due to the absence of data quantifying the treatment effect contributed by paclitaxel injection to the combination regimen employed as the control arm of CA031, it is not possible to determine the proportion of treatment effect preserved. (b) (4)

[REDACTED]

8. Safety

The size of the safety database was adequate for a supplemental application with 7 years of post-marketing experience. The primary evaluation of safety was based on data obtained in 1038 patients in Protocol CA031 who received at least one dose of protocol-specified treatment, which included 514 Abraxane-treated patients and 524 paclitaxel injection-treated patients. (b) (4)

[REDACTED]

The demographics and baseline characteristics of the safety population is likely to be similar or identical to the efficacy (as randomized) population, since 99% of the efficacy population also received at least one dose of study treatment. The median number of treatment cycles administered in both treatment groups was 6 cycles. No new safety signals were identified in safety analysis of Protocol CA031.

The incidence of permanent discontinuation of paclitaxel (Abraxane or paclitaxel injection) treatment for adverse drug reactions was similar in the two treatment groups (16% in each group). The most common adverse drug reactions resulting in permanent discontinuation of Abraxane were neutropenia (3%), thrombocytopenia (3%) and peripheral sensory neuropathy (1%) as compared to peripheral neuropathy (4%), peripheral sensory neuropathy (2%) and neutropenia (2%) for the paclitaxel injection-treated group. The incidence of adverse drug reactions leading to dose reduction of paclitaxel (Abraxane or paclitaxel injection) was higher in the Abraxane-treated group compared to the paclitaxel injection-treated group (46% vs. 23%). The most common adverse drug reactions leading to paclitaxel dose reduction in the Abraxane-treated group were neutropenia (24%), thrombocytopenia (approximately 13%), and anemia (6%) as compared to neutropenia (9%), peripheral sensory neuropathy (5%), and thrombocytopenia (4%) in the paclitaxel injection-treated group. The incidence of paclitaxel dose delays or doses held for adverse drug reactions was also higher in the Abraxane-treated group (71% vs. 41%). The most common adverse drug reactions resulting in delay or withholding of the paclitaxel dose were neutropenia (41%), thrombocytopenia (30%), and anemia (16%) as compared to neutropenia (12%), thrombocytopenia (12%), and peripheral sensory neuropathy (5%) for the paclitaxel injection-treated group.

The most common adverse reactions identified clinically and by laboratory testing are listed in the following tables. Those occurring at a higher rate in the Abraxane-treated group (bolded in the tables below) were anemia (98%), hypoalbuminemia (82%), thrombocytopenia (68%), hypocalcemia (57%), hyperkalemia (37%), peripheral edema (10%), and epistaxis (7%).

Per-Patient Incidence (≥ 5%) of Adverse Reactions in Abraxane-Treated Patients					
System Organ Class*	Preferred Term	ABRAXANE (100 mg/m ² weekly) plus carboplatin n=514		Paclitaxel injection (200 mg/m ² q 3 weeks) plus carboplatin n=524	
		All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Skin/subcutaneous tissue disorders	Alopecia	56	<1	60	0
	Rash	10	0	8	<1
Nervous system disorders	Peripheral neuropathy**	48	3	64	12
	Peripheral neuropathy*	26	2	40	5
	Dysgeusia	7	0	6	0
	Headache	7	<1	4	<1
	Dizziness	6	0	4	<1
General disorders and administration site conditions	Fatigue	25	4	23	4
	Asthenia	16	3	15	4
	Edema peripheral	10	0	4	<1
	Pyrexia	9	0	8	0
	Chest pain	5	<1	4	<1
Gastrointestinal disorders	Nausea	27	<1	25	<1
	Constipation	16	<1	13	<1
	Diarrhea	15	<1	11	0
	Vomiting	12	<1	12	<1
	Stomatitis	6	0	4	0
Respiratory thoracic and mediastinal disorders	Dyspnea	12	3	12	3
	Cough	9	<1	7	0
	Epistaxis	7	0	2	0
	Hemoptysis	4	<1	5	0
Investigations	Weight decreased	8	1	6	<1
Musculoskeletal and connective tissue disorders	Arthralgia	13	<1	25	2
	Myalgia	10	<1	19	2
Metabolic and nutrition disorders	Decreased appetite	17	2	18	<1
Infections and infestations	Pneumonia	5	2	3	2
Psychiatric disorders	Insomnia	5	0	8	<1
* MedDRA version 12.1 except for SMQ of peripheral neuropathy					
** MedDRA 14.0 SMQ Neuropathy (Broad Scope)					

Per-Patient Incidence (≥ 5%) of Laboratory-Detected Abnormalities in Abraxane-Treated Patients				
Laboratory Abnormality	ABRAXANE (100 mg/m² weekly) plus carboplatin		Paclitaxel injection (200 mg/m² q 3 weeks) plus carboplatin	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Anemia	98% (496/508)	28% (140/508)	91% (466/514)	7% (35/514)
Neutropenia	85% (430/508)	47% (239/508)	83% (424/513)	58% (296/513)
Thrombocytopenia	68% (344/508)	18% (92/508)	55% (284/513)	9% (47/513)
Lymphopenia	51% (257/508)	8% (40/508)	47% (242/513)	10% (53/513)
Elevated alanine aminotransferase (SGPT)	26% (128/492)	1% (5/492)	23% (113/498)	<1% (4/498)
Elevated aspartate aminotransferase (SGOT)	22% (110/492)	1% (5/492)	21% (103/498)	<1% (4/498)
Elevated alkaline phosphatase	20% (96/491)	1% (5/491)	25% (126/498)	<1% (4/498)
Hypoalbuminemia	82% (58/71)	3% (2/71)	72% (54/75)	0
Elevated creatinine	9% (45/490)	0	10% (52/497)	0
Hypocalcemia	57% (38/67)	1% (1/67)	51% (37/73)	1% (1/73)
Hypokalemia	11% (8/71)	3% (2/71)	9% (7/75)	3% (2/75)
Hyperkalemia	37% (26/71)	0	29% (22/75)	3% (2/75)
Hyponatremia	34% (24/71)	4% (3/71)	40% (30/75)	5% (4/75)
Hypernatremia	3% (2/71)	0	1% (1/75)	0
Hyperglycemia	60% (296/491)	2% (8/491)	58% (286/495)	3% (16/495)

9. Advisory Committee Meeting

This efficacy supplement was not referred to the Oncologic Drugs Advisory Committee because this is not the first drug approved in this class, the safety profile is acceptable for the first-line treatment of non-small cell lung cancer, the approach to support approval (bridging study to support reliance on prior findings of safety and efficacy) is similar to that use for the original approval for ABRAXANE, the application did not raise significant safety that were unexpected for paclitaxel, thus outside expertise was not necessary since there were no controversial issues that would benefit from advisory committee discussion.

10. Pediatrics

This efficacy supplement contained a request for a full waiver from the requirements of the Pediatric Research and Equity Act (PREA). The PeRC reviewed this request at its August 29, 2012 meeting and agreed with the Division to grant a full waiver in pediatric patients because studies are impossible or highly impractical because the disease/condition does not exist in the pediatric population. In considering this request, the PeRC also noted that the parent compound has been studied and has no activity in pediatric cancers, thus use for this product is not anticipated in pediatric patients (and a WR is not appropriate).

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: Not applicable for this efficacy supplement
- Physician labeling: All major issues have been resolved.
- General: The labeling was revised to replace the newly proposed sub-header “Breast Cancer” with “Metastatic Breast Cancer” throughout labeling for consistency with the previously approved indication. The schedule (weekly or every three weeks) has been included with recommendations for Dose Modifications (section 2) and Warnings and Precautions (section 5) to minimize confusion regarding potential risks and dosing modification directions.
- Indications and Usage: Editorial change for clarity from the applicant’s proposed wording for NSCLC; (b) (4)
[REDACTED]
- Dosage and Administration: Added recommended dose (2.2) and dose modifications (2.3, 2.4) for the NSCLC dosing regimen. (b) (4)
[REDACTED]

(b) (4)

- Warnings and Precautions: Sections 5.1 and 5.2 modified to include incidence information based on results of Protocol CA031, to include specific recommendations for dosing related to the weekly regimen. Editorial changes to replace directions made in “passive voice” to “command” language. Editorial correction to second sentence in section 5.4 (from “moderate **and** severe hepatic impairment” to moderate **or** severe hepatic impairment”).

- Adverse Reactions

A tabular listing of adverse reactions was limited to those in which between-arm differences ($\geq 5\%$ for overall incidence, $\geq 2\%$ for Grade 3-4 adverse reactions) were observed. (b) (4)

(b) (4)

Inclusion of laboratory-based adverse drug reactions in a separate table, distinct from clinically-documented adverse drug reactions.

In section 6.3, modified wording under Hypersensitivity Reactions to include “and sometimes fatal” for consistency with recent changes in section 5.3.

- Drug Interactions: removed statement that “no drug interactions studies have been conducted with Abraxane” and provided information on lack of drug interactions between carboplatin and Abraxane.

- Use in Specific Populations: added information on Geriatric Use (8.5) based on data from Protocol CA031; deleted section sentence from section 8.7 as unnecessary information.
- Clinical Pharmacology: Modified section 12.3 to include new pharmacokinetic information submitted under this supplement.
- Clinical Studies: Addition of a new subsection to describe the results of Protocol CA031. (b) (4)

- Carton and immediate container labels: Labeling modified to include updates for company name and address, text format (e.g. typography, layout, contrast), art work/logo, revising “100 mg” to “100 mg per vial”, expiration dating, and other editorial changes. All changes were agreed-upon between FDA and the applicant.
- Patient labeling: added required statement “These are not all the possible side effects of ABRAXANE. For more information, ask your doctor or pharmacist.” (b) (4)

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval
- Risk Benefit Assessment: All review disciplines recommended approval of this application. This efficacy supplement relies on FDA’s prior finding of safety and effectiveness for the listed drug, Taxol, which received approval for the treatment of locally advanced or metastatic non-small cell lung cancer in 2008. The results of the bridging study, Protocol CA031, provide adequate evidence that the anti-tumor activity of paclitaxel injection is preserved when paclitaxel is administered as Abraxane, in combination with carboplatin, at the proposed doses and schedules. In addition, the adverse reaction profile of Abraxane, in combination with carboplatin, at the proposed doses and schedules is acceptable given the seriousness of the condition and the adverse reaction profile of the alternative therapy (paclitaxel injection in combination with carboplatin).
- Recommendation for Post-marketing Risk Evaluation and Mitigation Strategies: I concur with the review team that a REMS is not required to ensure safe and effective use of Abraxane for the expanded indication.
- Recommendation for other Postmarketing Requirements and Commitments: None

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/s/

PATRICIA KEEGAN
10/11/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-660/S-031

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: sNDA 21660/31

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Monica Hughes
LaShawn Griffiths
Barbara Fuller
Kun He
Hong Zhao
Patricia Keegan
Shakun Malik
Jibril Abdus-Samad
Karen Jones
Todd Bridges
Lillian Zhang
Ted Chang
Rajeshwari Sridhara
Huanyu Chen

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-660/S-031

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505(b)(2)
Application Number(s)	021660/ 31
Priority or Standard	Standard
Submit Date(s)	12/12/2011
Received Date(s)	12/12/2011
PDUFA Goal Date	10/12/2012
Division / Office	OHOP/DOP2
Reviewer Name(s)	Shakun Malik, M.D.
Review Completion Date	09/06/2012
Established Name	ABI-007/Abraxane®
(Proposed) Trade Name	Abraxane
Therapeutic Class	Cytotoxic- microtubule inhibitor (paclitaxel protein-bound particles {albumin-bound})
Applicant	Abraxis Bioscience / Celgene Corporation
Formulation(s)	Injectable Suspension
Dosing Regimen	ABI-007 combination use in Non-Small Cell Lung Cancer (NSCLC) 100 mg/m ² intravenous over 30 min on Days 1, 8, and 15 of each 21-day cycle in combination with carboplatin AUC=6mg/min/mL intravenous on Day 1 only of each 21-day cycle beginning immediately after ABI-007 administration.
Indication(s)	Abraxane® (ABI-007) is indicated in combination with carboplatin for the first-line treatment of patients with locally advanced or metastatic NSCLC who are not candidates for potentially curative surgery and/or radiation therapy
Intended Population(s)	Adult population with advanced non-small cell lung cancer

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of the drug Abraxane[®] (ABI-007) in combination with carboplatin for the first-line treatment of patients with locally advanced or metastatic (Non-Small Cell Lung Cancer) NSCLC who are not candidates for potentially curative surgery and/or radiation therapy under 505 (b) (2)

My recommendation is based on evaluation of data from CA031 “ A Randomized, phase III trial of Abraxane[®] (ABI-007) and Carboplatin compared with Taxol and Carboplatin as first- line therapy in patients with NSCLC”.

The primary efficacy endpoint of this study was Over all Response Rate (ORR) defined as percentage of patients who achieved an objective confirmed CR or PR as determined by a blinded radiological review using RECIST Version 1.0 guideline.

Patients with advanced NSCLC treated with Abraxane[®] (ABI-007) in combination with carboplatin showed a statistically significantly increased ORR compared with patients treated with Taxol in combination with carboplatin (33% vs 25%) The OR was 1.31 (95% CI: 1.08, 1.59). The lower boundary of 95% CI of OR per IRC assessment was great than 1, which supports superiority of ABI-007 with respect to OR. In addition, the ORR analysis demonstrated a statistically significant difference in ORR for the treatment based on χ^2 test (P value=0.005).

Overall response rate, assessed in a blinded fashion by an independent radiology review, was regarded as an acceptable primary surrogate endpoint for this superiority trial because

- Paclitaxel is an active and effective chemotherapeutic agent in the treatment of NSCLC as evidenced by the global regulatory approvals for paclitaxel in the first-line treatment of advanced NSCLC and ,
- This study was designed as part of a 505(b)(2) registration strategy (FDA Guidance for Industry) under a Special Protocol Assessment in the US.

The study was powered assuming an ORR of 17% in the Taxol/carboplatin arm and 40% improvement (or an ORR of 24%) in the ABI-007/carboplatin arm.

The response rate of 25% in the Taxol/carboplatin arm in this study is better than that of the historical data from recent large phase 3 trials with Taxol/carboplatin arms reported by ECOG 1549 (ORR = 17%) (1) and ECOG 4599 (ORR = 10%) (2), but is similar to the response rate in a more recent study of Taxol/carboplatin +/- sorafenib (ESCAPE) of 24% to 27% (3).

1.2 Risk Benefit Assessment

Platinum doublet with taxane containing chemotherapy regimens are the standard first-line treatment in the majority of patients with advanced NSCLC in the United States (US). Taxol (paclitaxel) is prevalently used taxane in combination with carboplatin and is currently available in the proprietary product Taxol® (paclitaxel) Injection, manufactured by Bristol-Myers Squibb (b) (4) and by several other generic drug manufacturers.

Taxol consists of paclitaxel dissolved in a proprietary solvent, Cremophor® EL (BASF, (b) (4) and ethanol. In addition to its poor water solubility, Taxol administration requires routine premedication with corticosteroids, diphenhydramine, and H2 antagonists to reduce the incidence of hypersensitivity reactions and histamine release caused by a response to the formulation vehicle. In addition, Taxol must be administered over a period of either 3 hours or 24 hours, and requires the use of specialized infusion sets and in-line filters that do not contain di[2-ethylhexyl] phthalate (DEHP)]

Abraxane® (ABI-007) is paclitaxel (cytotoxic- microtubule inhibitor) that is protein-bound particles for injectable suspension (albumin-bound) and has been developed to possible reduce the toxicities associated with Taxol and the Cremophor EL/ethanol vehicle while maintaining the chemotherapeutic effect of the drug.

The Cremophor EL-free medium enables Abraxane® (ABI-007) to be given in a shorter duration with out the need for premedication to prevent solvent-related hypersensitivity reactions. In addition, standard tubing and intravenous (IV) bags may be used for the IV administration of ABI-007.

The pivotal study CA031 met its primary efficacy endpoint of RR, with no significant differences in secondary endpoints of PFS and OS.

The toxicities associated with ABI-007 are similar to Taxol and include alopecia, neutropenia, anemia, and thrombocytopenia. The Treatment Emergent Adverse Events (TEAEs) reported significantly more often with ABI-007/ carboplatin were anemia, thrombocytopenia, peripheral edema, epistaxis, and hemoglobin decreased ($p \leq 0.015$). Slightly lower incidences of Grade 3/4 neuropathy, neutropenia, arthralgia and myalgia were noted in ABI-007 arm.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

Abraxane® ABI-007 was approved in the US on 07 January 2005, in patients with metastatic breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy when prior therapy should have included an anthracycline unless clinically contraindicated.

This approval was based on results from the study CA012-0, under the New Drug Application (NDA) 021660. Study CA012-0 was a controlled, randomized, multicenter, open-label, Phase 3, non-inferiority study to evaluate the safety/tolerability and antitumor effect of ABI-007 (260 mg/m²) administered Intravenously (IV) over 30 minutes every 3 weeks compared with Taxol (175 mg/m²) given IV over 3 hours every 3 weeks in patients with metastatic breast cancer.

This application is in supports of a proposed new indication of non-small cell lung cancer for ABI-007 in combination with carboplatin, for the first-line treatment of NSCLC patients who are not candidates for potentially curative surgery and/or radiation therapy.

For the first-line treatment of non-small cell lung cancer, the recommended dose of ABI-007 is 100 mg/m² administered as an intravenous infusion over 30 minutes on Days 1, 8, and 15 of each 21-day cycle. The recommended dose of carboplatin is AUC = 6 mg•min/mL on Day 1 only of each 21-day cycle, beginning immediately after the end of ABI-007 administration. Day 1 is the only day of each 21-day cycle when carboplatin is used in combination with ABI-007.

Lung Cancer remains the number one cause of cancer deaths in United States (1) and the World (2). The 5 year survival rate for patients with lung cancer remains dismal around 15% (3). Tobacco smoke exposure is a known cause of this cancer in most of the cases, however 10% -15 % of the patients are never/light smokers defined as less than 100 cigarettes in their lifetime. NSCLC histology comprises about 85% of the lung cancer cases and although surgery remains the only curative modality for this disease, most of these patients (70%) present at advanced stage and thus are not surgical candidates.

Despite multiple subtypes of NSCLC per WHO Criteria (4) until recently first-line treatment for advanced disease was platinum-based doublet chemotherapy. With the discovery of molecular targets and targeted therapies, new treatment options for these patients are evolving.

Generally, current treatments lead to ORR of 25% to 35%, with time-to-progression of 4 to 6 months and a median survival of 8 to 10 months (1-year survival, 30% to 40% of patients; 2-year survival, 10% to 15% of patients) (5)

Bevacizumab a monoclonal antibody directed against vascular endothelial growth factor^{(b) (4)} (VEGF^{(b) (4)}) is approved, with carboplatin and paclitaxel, for first line treatment of unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer. Erlotinib, an Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitor, has been approved for

treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen and for maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.

On August 26, 2011, crizotinib received accelerated approval for the treatment of patients with locally advanced or metastatic anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer. This drug approval was in tandem with the approval of a test kit that detects the gene rearrangement in a patient's tumor that encodes ALK tyrosine kinase.

Platinum doublet with taxane containing chemotherapy regimens however remain the standard first-line treatment in the majority of patients with advanced NSCLC in the US

Taxol (paclitaxel) is prevalently used taxane in combination with carboplatin and consists of paclitaxel dissolved in a proprietary solvent, Cremophor® EL and ethanol.

Four clinical studies were conducted in patients with NSCLC. These studies include Study CA028 (ABI-007/carboplatin combination therapy), which included the optimal dose (100 mg/m² weekly) in NSCLC patients, 2 additional Phase 1/2 studies (CA015 and CA018) that evaluated ABI-007 (b) (4) in NSCLC patients and the pivotal randomized study CA031. (b) (4)

The approval of this NDA is based on the pivotal randomized study CA031.

Pivotal study CA031 was an open-label, controlled, randomized, multicenter, Phase 3 study evaluating the safety/tolerability and antitumor effect of ABI-007 /carboplatin combination therapy compared with that of Taxol/carboplatin combination therapy as first-line treatment in patients with advanced NSCLC. A total of 525 patients per treatment arm were planned to be enrolled for the intent-to-treat (ITT) analysis.

2.1 Product Information

Abraxane® (ABI-007) for Injectable Suspension is a solvent-free, protein stabilized formulation of paclitaxel, composed primarily of paclitaxel and human albumin and is supplied as a lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to IV infusion. Each single-use vial contains 100 mg of paclitaxel (bound to human albumin) and approximately 900 mg of human albumin with a mean particle size of approximately 130 nanometers, and is free of solvents. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. The dosage form is administered as an IV infusion over 30 minutes on Days 1, 8, and 15 of each 21-day cycle

ABI-007 is a microtubule inhibitor 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. The arrays render the cells dysfunctional, resulting ultimately in apoptosis and cell death.

Metabolism

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

Excretion

After a 30-minute infusion of 260 mg/m² doses of ABI-007, 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 6 α -hydroxypaclitaxel and 3'-p-hydroxypaclitaxel.

Fecal excretion was approximately 20% of the total dose administered.

2.2 Tables of Currently Available Treatments for Proposed Indications

All of the approved therapies for unresectable, locally advanced, recurrent or metastatic disease NSCLC have been based on improvement in overall survival compared to a comparator. Platinum-containing chemotherapy regimens are still the standard first-line treatment in the majority of patients, with taxanes and platinum-based agents used as the standard of care in the US and Japan. In the EU, a third-generation therapeutic agent (docetaxel, gemcitabine, paclitaxel, or vinorelbine), most commonly gemcitabine or vinorelbine, plus a platinum drug is used for advanced NSCLC (6). For first-line therapy in patients with Stage IV NSCLC and good performance status, the American Society of Clinical Oncology (ASCO) clinical practice guideline recommends treatment with a platinum-based two-drug combination of cytotoxic drugs (7). A trend that is becoming more prevalent is personalized NSCLC treatment based on tumor histology (squamous vs non-squamous), on molecular characteristics of the tumor, and on the patient's clinical status using agents targeting specific receptors and kinases and pathways (ie, epidermal growth factor receptor [EGFR], echinoderm microtubule-associated protein-like 4 [EML4] and anaplastic lymphoma kinase [ALK] fusion protein).

In advanced NSCLC, the prevalently used combination of solvent-based paclitaxel/carboplatin results in modest response rate, survival, and toxicity.

Table 1: Tables of Currently Available Treatments for Proposed Indications

Drug	Indication
Bevacizumab Non-squamous NSCLC	Initial treatment, in combination with carboplatin and paclitaxel
Docetaxel	Initial treatment, in combination with cisplatin
Gemcitabine	Initial treatment, in combination with cisplatin
Paclitaxel	Initial treatment, in combination with cisplatin
Pemetrexed Non-squamous NSCLC	Initial treatment in combination with cisplatin
Vinorelbine	single agent or in combination with cisplatin for the first-line treatment of ambulatory patients
Crizotinib	Anaplastic Lymphoma Kinase (ALK) positive locally advanced or metastatic NSCLC

2.3 Availability of Proposed Active Ingredient in the United States

ABI-007 has been approved for Metastatic breast cancer in 2005 and is available for commercial use.

2.4 Summary of Presubmission Regulatory Activity Related to Submission

End of Phase 2 Meeting

The clinical and regulatory development plan to support the approval of ABI-007 for the first-line treatment of NSCLC was discussed at a Type B Meeting with the FDA on 04 Nov 2005. The key elements from this meeting included:

- The proposed single arm Phase 2 studies to support the approval of ABI-007 in first-line metastatic NSCLC would not provide adequate information for a complete evaluation of safety and efficacy.
- A comparative trial or trials would be required in a setting where paclitaxel has an approved indication.

- A randomized trial would be required for the NSCLC setting. One possible design would be a randomized controlled trial (non-inferiority design) with response rate as the primary endpoint and PFS and OS as secondary endpoints.
- The independent assessment of response rate would be preferred, especially if the study was unblinded.
- The new protocol should be submitted for a SPA agreement.
- The PK of ABI-007 in NSCLC patients should be assessed when ABI-007 is co-administered with carboplatin because there was a 33% decrease in paclitaxel clearance when Taxol was administered following cisplatin

Special Protocol Assessment for Protocol CA031

The SPA procedure for protocol CA031 was initiated on 03 Feb 2006, and the SPA agreement with FDA was subsequently reached on 30 Aug 2007. The key agreements on the design and planned analysis of protocol CA031 to adequately address the objectives necessary to support a regulatory submission included the following:

- Superiority Study: One randomized superiority study with ORR as the primary endpoint is required for approval of the 505(b)(2) application.
- Treatment Arm: ABI-007 100 mg/m² administered IV over 30 minutes weekly on Days 1, 8, and 15 of each 3-week cycle followed by carboplatin (AUC = 6) administered IV on Day 1 only of each 3-week cycle.
- Comparator Arm: Taxol 200 mg/m² administered IV over 3 hours every-3-weeks immediately followed by carboplatin (AUC = 6) administered IV every-3-weeks (both drugs given on Day 1 of each 3-week cycle).
- Sample Size: Assuming a response rate of 24% for the ABI-007 /carboplatin arm (a relative improvement of approximately 40% over the Taxol/carboplatin), 525 patients per arm will provide 80% power with a two-sided Type 1 error of 0.049.
- Interim Analysis of ORR: Performed after 200 patients per arm have completed the second on-treatment response assessment. Study will not be stopped based on interim analysis of ORR. To preserve overall Type 1 error at 0.050, an alpha spending function allocates alpha of 0.001 and 0.049 at the interim and final analyses of ORR, respectively. The protocol includes an algorithm for re-estimating the sample size based on the outcome of the interim analysis.
- Secondary Efficacy Endpoints: Analyzed only if primary efficacy endpoint displays superiority of ABI-007 /carboplatin over Taxol/carboplatin. Key

secondary endpoints are PFS and OS. The final PFS analysis will be conducted once 70% of patients have had an event of disease progression or death (any cause). This is equivalent to 735 events which provides 85% power with a two-sided Type 1 error of 0.050 to detect an ABI-007/carboplatin to Taxol/carboplatin hazard ratio (HRA/T) of 0.80. Overall survival will be analyzed similarly when 70% of the patients have died. Interim PFS and OS data will be provided at final ORR analysis without penalty.

- PFS: Censoring methods for PFS are pre-specified. Sensitivity analyses of PFS will be performed.
- OS Follow-up: To obtain post-study survival data, patient status will be evaluated post-study by telephone contact monthly for 6 months, and then every-3-months thereafter for 12 months (total of 18 months follow-up).
- Independent Radiology Review: The analysis of tumor-related endpoints will be based on an independent, central, blinded review of radiological studies. The Imaging Charter includes two readers with one adjudicator.
- Imaging Schedule: Tumors will be assessed by imaging studies every-6-weeks during therapy (at any time during the sixth week). For patients who have not progressed by end-of-treatment, repeat imaging will be performed every-6-weeks until tumor progression is documented.

The FDA required that a superiority design would be necessary for approval with ORR as the primary endpoint, and PFS and OS as the secondary endpoints. The study would need to be powered for survival to demonstrate that OS is not worse than control arm. For the consideration of a 505(b)(2) application, the FDA wanted assurance that survival is not trending in the wrong direction. Furthermore, FDA recommended that the analyses on tumor-related endpoints should be based on an independent, central blinded review of radiological studies. This independent radiologic review of spiral Computed tomography (CT) scans followed a charter finalized and reviewed by the FDA as part of the SPA procedure prior to the first read.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

- Submission contained all components of e-CTD.
- The datasets submitted for the efficacy and safety data of the pivotal trial CA031 were resubmitted upon reviewer's requests with the documentations for the analysis. The FDA reviewers were then able to duplicate the analysis variable derivation and summary statistics. No further data resubmission was requested.

3.2 Compliance with Good Clinical Practices

The sponsor states that the clinical development of ABI-007 for the treatment of advanced NSCLC study was conducted according to Good Clinical Practice (GCP) guidelines.

The pivotal study was conducted in accordance with the regulations and guidelines of the US Food and Drug Administration (FDA), the Declaration of Helsinki and current amendments, local regulatory agencies, or International Conference on Harmonization (ICH), whichever afforded the greater protection to the patient and was applicable to the country of participation.

The protocol and informed consent form were approved prior to study initiation by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB) charged with oversight of the trial. All protocol amendments were also reviewed by an IEC/IRB prior to implementation. The IEC/IRB was organized in accordance with the United States (US) Code of Federal Regulations (CFR) (Title 21 CFR, Part 56).

Before a patient's participation in the study, written informed consent was obtained from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or study medications were administered. The IRB/IEC-approved informed consent form was personally signed and dated by the patient and the investigator or authorized personnel required by the center or IRB/IEC. The signed informed consent form was retained in accordance with institutional policy, and a copy of the signed consent form was provided to the patient.

Study CA031 was a multicenter study was conducted by investigators in 6 countries; Australia, Canada, Japan, Russia, Ukraine and the US.

A total of 102 study sites enrolled patients including 29 sites in Russia, 25 sites in the US, 21 sites in Japan, 16 sites in Ukraine, 6 sites in Canada, and 5 sites in Australia.

As per the sponsor, only investigators qualified to perform this study through experience and training were selected. Qualification criteria included hematology/oncology training and experience in the treatment of lung cancer patients, familiarity with human subject protection regulations and practices as well as Good Clinical Practice (GCP) regulations and standards for the conduct of clinical studies.

Blinded central imaging studies were performed by (b) (4).
(b) (4). Pharmacokinetic (PK) samples were analyzed by (b) (4).
(b) (4). Laboratory samples were analyzed by a central laboratory, (b) (4). However, in accordance with standard of care, local laboratory results were utilized to make treatment decisions. The electrocardiograms (ECGs) performed at baseline were evaluated locally. Medical monitoring, data management and statistical analyses for the clinical data were performed by Abraxis. The clinical study report (CSR) was prepared by Abraxis. Results from the PK portion of the study are presented in stand-alone reports.

Investigation of any particular site was not thought to be necessary as no one site results impacted the study results.

3.3 Financial Disclosures

FORM FDA 3455 – Disclosure: Financial Interests and Arrangements of Clinical Investigators were submitted only for Dr. (b) (6), who was a Sub-Investigator, Site (b) (6).

Dr. (b) (4) Abraxis BioScience (ABII) stock and Celgene Corporation (CELG) stock which exceeded \$50,000.00 during the time he carried out his duties as a sub-investigator under Study CA031.

On 30 March 2009, Dr. (b) (6) disclosed he owned (b) (6) shares of Abraxis BioScience stock, which had a market value exceeding \$50,000.00. On 12 October 2010, Dr. (b) (6) disclosed he no longer owned Abraxis BioScience stock.

Subsequently on 19 January 2011, Dr. (b) (6) disclosed he owned (b) (6) shares of Celgene Corporation stock, which had a market value exceeding \$50,000.00.

As per Abraxis BioScience's standard operating procedure, COP-136 – Financial Disclosure, Dr. (b) (6) participation as a sub-investigator under Study CA031 was approved based upon the following steps that were taken to minimize potential observer bias of the study results:

- The trial design of Study CA031 eliminated the introduction of bias by any primary investigator or sub-investigator. The investigators had no influence on the primary efficacy endpoint of overall response rate, defined as the percentage of patients who achieved an objective confirmed complete response or partial response. Assessment of the primary endpoint of patient response to treatment was evaluated by independent and central reviewers using Response Evaluation Criteria in Solid Tumors (RECIST) (Version 1.0) for computed tomography (CT) scans. The independent reviewers were blinded to the treatment assignment and to the investigator assessment of response.
- A key secondary efficacy endpoint in Study CA031 was progression-free survival (PFS). Assessment of the key secondary endpoint of PFS was also evaluated by independent and central reviewers using RECIST (Version 1.0) for CT scans. The independent reviewers were blinded to the treatment assignment and to the investigator assessment of response.
- Dr. (b) (6) one of fifteen (15) sub-investigators under Dr. (b) (6) at Site (b) (6) treated a small segment of the patients enrolled in Study CA031. Dr. (b) (6) site enrolled (b) (6) patients out of the total 1,052 patients enrolled in Study CA031. At this site, (b) (6) of the study patients were treated. Statistically, a site with less than (b) (6) has little impact on the reported outcomes.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Reviewed by the CMC

The Reviewer summarizes that this efficacy supplement proposes to add a new indication—NSCLC—and was submitted as PAS which is appropriate.

There are no CMC-related changes and the changes proposed in this supplement will not impact adversely identify, strength, purity and quality of the drug products.

The new NSCLC indication affects mainly the clinical sections in the package insert and did not raise CMC-related issues in the labeling review.

The reviewer concludes that from the CMC perspective this supplemental application, as amended, is recommended for APPROVAL.

4.2 Clinical Microbiology

This NDA supplement is recommended for approval from the standpoint of product quality microbiology (already an approved drug)

Refer to full Micro review

4.3 Clinical Pharmacology

This application was recommended for approval by clinical pharmacology

Refer to full clinical Pharmacology review

4.3.1 Mechanism of Action

ABI-007 is a microtubule inhibitor 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.

4.3.2 Pharmacokinetics

The pharmacokinetics (PK) profile of paclitaxel in NSCLC patients who received combination therapy of ABI-007 /carboplatin at the recommended dosing regimen (100 mg/m² for ABI-007 and AUC = 6 min•mg/mL for carboplatin) was similar to that observed in patients with solid tumors who received the same dose of ABI-007 alone. There was no clinically relevant PK drug-drug interactions observed between paclitaxel and carboplatin.

There was no difference in the PK of paclitaxel after ABI-007 administration between Japanese and non-Japanese patients.

5 Sources of Clinical Data

Table 2: Tables of Studies/Clinical Trials

Extrinsic Factor PK Study Reports

PK	08DA33	Investigate the effect on PK from the concomitant use of ABI-007 and carboplatin.	Open-label; Multicenter; Single-sequence; Within patient comparison; Uncontrolled.	ABI-007 100 mg/m ² IV over 30 min once a week (on Days 1, 8, 15) and carboplatin (AUC=6) IV over 60 min once every 3 weeks (on Day 1).	Treated: N=12	Advanced NSCLC.	Single-dose (carboplatin) Multiple-dose (ABI-007). PK during Cycle 1 Days 1 and 15.	Complete; Final Report.
Dose-escalation Safety PK	05DA11	Determine DLT and MTD. Investigate PK of ABI-007.	Phase 1; Open-label; Single-center; Parallel group; Dose-escalation; Uncontrolled.	ABI-007 80, 100, or 125 mg/m ² IV over 30 min once a week.	Treated: N=15	Advanced solid tumor.	Single ascending dose. PK during Cycle 1 Day 1.	Complete; Final Report.
Dose-escalation Safety PK	05DA13	Determine DLT and MTD. Investigate PK of ABI-007.	Phase 1; Open-label; Multicenter; Parallel group; Dose-escalation; Uncontrolled.	ABI-007 200, 260, or 300 mg/m ² IV over 30 min once every 3 weeks.	Treated: N=12	Advanced solid tumor.	Single ascending dose. PK during Cycle 1 Day 1.	Complete; Final Report.

Population PK Study Reports

PK	BIO-VT-5	Evaluate PK parameters of ABI-007 using a sparse PK sampling method.	Optional sparse PK sampling from study CA031 (only in the ABI-007/carboplatin arm).	<u>Dosing in Study CA031</u> ABI-007 100 mg/m ² IV over 30 min once a week (on Days 1, 8, 15) and carboplatin (AUC=6) IV once every 3 weeks (on Day 1) Taxol 200 mg/m ² IV over 3 hours and carboplatin (AUC=6) IV, both once every 3 weeks (on Day 1).	Planned: N=100 Actual: N=15 (insufficient sample size to support the planned population PK analysis)	First-line treatment of Stage IIIb/IV NSCLC.	PK during Cycle 1 at 0.25, 3.5 and 24 hours post-infusion.	Complete; Final Report.
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Patient PD and PK/PD Study Reports

PD	BIO-VT-6	Evaluate SPARC and other molecular biomarkers in tumor tissue and peripheral blood to determine the correlation with efficacy outcomes.	Optional tumor specimen-based molecular biomarker analyses in study CA031 (both arms).	<u>Dosing in Study CA031</u> ABI-007 100 mg/m ² IV over 30 min once a week (on Days 1, 8, 15) and carboplatin (AUC=6) IV once every 3 weeks (on Day 1) Taxol 200 mg/m ² IV over 3 hours and carboplatin (AUC=6) IV, both once every 3 weeks (on Day 1).	Total: N=71 ABI-007: N=35 Taxol: N=36	First-line treatment of Stage IIIb/IV NSCLC.	Samples collected within 2 weeks of starting treatment and then Day 1 of odd numbered cycles (Cycles 1, 3, 5, 7, etc.).	Complete; Final Report.
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Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

Efficacy Safety (Optional PK & PD)	CA031	Compare disease response and safety/tolerability of ABI-007/carboplatin to Taxol/carboplatin.	Phase 3; Randomized; Multicenter; Open-label; Active-Controlled; Superiority.	ABI-007 100 mg/m ² IV over 30 min once a week (on Days 1, 8, 15) and carboplatin (AUC=6) IV once every 3 weeks (on Day 1) Taxol 200 mg/m ² IV over 3 hours and carboplatin (AUC=6) IV, both once every 3 weeks (on Day 1).	Entered: N=1052 ABI-007: N=521 Taxol: N=531 Treated: N=1038 ABI-007: N=514 Taxol: N=524 Completed: N=1035 ABI-007: N=511 Taxol: N=524	First-line treatment of Stage IIIb/IV NSCLC.	Continued in absence of progressive disease and unacceptable toxicity.	Ongoing; Final CSR. (3 patients in ABI-007/carboplatin arm had therapy ongoing at the CSR cut-off date of 31Jan2011.)
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Study Reports of Uncontrolled Clinical Studies

Dose-escalation Safety Efficacy	CA028	Evaluate safety/tolerability and antitumor activity of ABI-007 in combination with carboplatin.	Phase 2: Multicenter; Open-label; Dose-escalation; Uncontrolled.	ABI-007 IV over 30 min once a week or once every 3 weeks and carboplatin (AUC=6) IV on Day 1 of cycle. ABI-007 every 3 weeks: Cohort 1: 225 mg/m ² ; Cohort 2: 260 mg/m ² ; Cohort 3: 300 mg/m ² ; Cohorts 4, 8: 340 mg/m ² . ABI-007 once a week: Cohort 5: 140 mg/m ² on Days 1 and 8; Cohort 6: 100 mg/m ² on Days 1, 8, and 15; Cohort 7: 125 mg/m ² on Days 1, 8, and 15.	Entered: N=254 Treated: N=251 Completed: N=251 N=25 each at 225, 260, 300, 140, 100, 125 mg/m ² , and N=101 at 340 mg/m ² .	First-line treatment of Stage IIIB/IV NSCLC.	Continued in absence of progressive disease and unacceptable toxicity.	Complete; Final CSR.
Dose-escalation Safety Efficacy	CA015	Phase 1: Determine MTD and DLT. Phase 2: Evaluate safety/tolerability and determine antitumor activity at once a week MTD.	Phase 1/2: Single-center; Open-label; Dose-escalation; Uncontrolled.	Phase 1: ABI-007 at 100, 125, 150, or 175 mg/m ² IV over 30 min once a week. Phase 2: ABI-007 at 125 mg/m ² (MTD) IV over 30 min once a week, and ABI-007 at 125 mg/m ² (MTD) IV over 2 hours once a week.	Entered: N=77 Treated: N=75 N=50 IV over 30 min: N=3 at 100 mg/m ² ; N=40 at 125 mg/m ² ; N=7 at 150 mg/m ² , and N=25 IV over 2 hours at 125 mg/m ² . Completed: N=75	First-line treatment of Stage IIIB/IV NSCLC.	Continued in absence of progressive disease and unacceptable toxicity.	Complete; Final CSR.
Safety Efficacy	CA018	Evaluate safety/tolerability and determine antitumor activity	Phase 2: Multicenter; Open-label; Uncontrolled.	ABI-007 260 mg/m ² IV over 30 min once every 3 weeks.	Entered: N=43 Treated: N=43 Completed: N=43	First-line treatment of Stage IIIB/IV NSCLC.	Continued in absence of progressive disease and unacceptable toxicity.	Complete; Final CSR.
Integrated Safety Analyses	ISS	Safety data from 5 studies: CA031, CA028, CA015, CA018, and CA016	NA	ABI-007/carboplatin combination therapy (CA031 and CA028). ABI-007 monotherapy (CA015 and CA018). ABI-007 IV dosing schedules of once a week or once every 3 weeks. ABI-007 doses were 75-340 mg/m ² .	Integrated Safety Based on Treated Populations ABI-007 NSCLC combination therapy: N=765 Once a week: N=589; Once every 3 weeks: N=176. ABI-007 NSCLC monotherapy: N=118 Once a week: N=75; Once every 3 weeks: N=43. ABI-007 MBC combination therapy: N=32 (Once a week).	First-line treatment of Stage IIIB/IV NSCLC (CA031, CA028, CA015, CA018). (b) (4)	Treatment in individual studies continued in absence of progressive disease and unacceptable toxicity.	Complete; Final Report.
Comparative Efficacy Analyses	SCE	Efficacy data from 4 NSCLC studies: CA031, CA028, CA015, CA018.	NA	ABI-007/carboplatin combination therapy (CA031 and CA028). (b) (4) ABI-007 IV dosing schedules of once a week or once every 3 weeks. ABI-007 doses were 100-340 mg/m ² .	Comparative Efficacy Based on: ITT Population: CA031: N=1052 Treated Populations: CA028: N=200* CA015: N=50** CA018: N=43 *N < 251 due to how cohorts were pooled. ** IV over 30 min.	First-line treatment of Stage IIIB/IV NSCLC.	Treatment in individual studies continued in absence of progressive disease and unacceptable toxicity.	Complete; Final Report.

Other Study Reports

(b) (4)

Dose-escalation Safety PK	DM97-123	Determine MTD, evaluate the PK profile, and evaluate the antitumor activity of ABI-007.	Phase 1/2; Single-center; Open-label; Dose-escalation; Uncontrolled.	ABI-007 135, 200, 300, or 375 mg/m ² IV once every 3 weeks over 180 min for the 1st dose for the 1st 3 subjects enrolled and over 30 min for subsequent infusions for these subjects and for all infusions in subjects subsequently enrolled.	Entered: N=19 Treated: N=19 PK Analyses: N=16	Advanced solid tumors.	Continued in absence of progressive disease and unacceptable toxicity.	Complete; Final CSR.
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Dose-escalation Safety PK	CA005-0	Determine MTD, safety/tolerability, and PK parameters of ABI-007.	Phase 1; Single-center; Open-label; Dose-escalation; Uncontrolled.	ABI-007 80, 100, 125, 150, 175, or 200 mg/m ² IV over 30 min once a week.	Entered: N=39 Treated: N=39 PK Analyses: N=23	Advanced non-hematologic malignancies.	Continued in absence of progressive disease and unacceptable toxicity.	Complete; Final CSR.
Safety Efficacy PK	CA012-0	Compare antitumor activity and evaluate safety/tolerability of ABI-007 versus Taxol. PK substudy.	Phase 3; Multicenter; Randomized; Open-label; Active-Controlled; Noninferiority.	ABI-007 260 mg/m ² IV over 30 min once every 3 weeks. Taxol 175 mg/m ² IV over 3 hours once every 3 weeks.	Entered: N=460 ABI-007: N=233 Taxol: N=227 Treated: N=454 ABI-007: N=229 Taxol: N=225 PK Analyses: N=12 (directly assigned to ABI-007 treatment)	MBC.	Continued in absence of progressive disease and unacceptable toxicity.	Complete; Final CSR.

Reports of Postmarketing Experience

Postmarketing safety	Lung Cancer AE Report	Identify ADRs in patients who were treated with ABI-007 for lung cancer.	Spontaneous adverse event reports for lung cancer postmarketing experience.	Commercial ABI-007.	N=116,527 exposed US: N=103,614 Outside US: N=12,913	Lung cancer.	NA	Complete; Final Report.
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5.2 Review Strategy

Clinical review is based on efficacy and toxicity data sets submitted by the sponsor for the pivotal study CA031, CSR's, CRF's, sponsor's presentation slides and literature review.

5.3 Discussion of Individual Studies/Clinical Trials

CA031 was "A Randomized, phase III trial of ABI-007 and Carboplatin compared with Taxol and Carboplatin as first-line therapy in patients with NSCLC". This was a superiority study evaluating Response Rate (RR) of ABI-007 /carboplatin to a comparator regimen of Taxol/carboplatin in patients with advanced NSCLC. Study CA031 was conducted at 102 centers within 6 countries.

A total of 1052 patients were randomized in a 1:1 allocation (ABI-007/carboplatin: 521 versus taxol/carboplatin: 531). The randomization was centralized and stratified by disease stage (IIIb versus IV), age (< 70 versus $\geq$ 70 years), gender (male versus female), histology (adenocarcinoma versus squamous cell versus other), and geographic region. The cut off date for the primary efficacy endpoint ORR was 10/12/2009 (patients completed the second response assessment). The cut-off date for all other efficacy endpoints was 1/31/2011.

Primary Objective

- To compare disease response of ABI-007 /carboplatin vs Taxol/carboplatin as first-line therapy in patients with advanced NSCLC.

Secondary Objectives

- To compare the frequency of toxicities
- To compare PFS;
- To compare overall survival;
- To compare duration of response in responding patients;
- To compare secreted protein, acidic and rich in cysteine (SPARC) and other molecular biomarkers in tumor tissue and peripheral blood and determine their possible correlation with efficacy outcomes ; and evaluate PK parameters

Randomization was stratified by disease stage (IIIb vs IV), age (< 70 vs $\geq$ 70 years), gender (male vs female), histology (adenocarcinoma vs squamous cell vs other), and geographic region.

Protocol Amendments

The study protocol was originally dated 21 Feb 2007, revised on 16 Jul 2007, and subsequently amended 4 times. The major changes were as follows:

Amendment 01 (01 Oct 2007)

- Addition of language defining the stratification of patient randomization.
- Clarification of reconstruction intervals for CT scanning

- Clarification regarding handling of patients who had radiotherapy or surgery while on study in the analysis of PFS.

Amendment 02 (12 Sep 2008)

- Addition of references to “Companion Protocol CA044” providing the details for sample collection and analysis for an additional optional biomarker study. This included SPARC testing of tumor tissue and blood in order to further study the correlation between expression of molecular biomarkers and clinical outcome.
- Addition of sparse PK sampling.

Amendment 03 (05 Mar 2009)

- Clarified that PK sampling was an optional procedure.
- To designate the biomarker sample collection and analysis a sub-study of the protocol rather than a separate companion protocol.

Amendment 04 (09 Jun 2009)

- Removed the retrospective measurement and quantitative assessment of nontarget lesions in the situation where progressive disease was assessed, based solely on progression of nontarget lesions.

Study Design and Plan

This was a controlled, randomized, multicenter, phase 3 study that planned to enroll a total of 525 patients per treatment arm for the intent-to-treat (ITT) analysis.

The data cut-off date for analysis of the primary efficacy endpoint of disease response assessed by independent blinded reviewers was 12 Oct 2009.

The study consisted of baseline assessments done within 28 days of randomization, a treatment phase, end-of-study (EOS) evaluations and follow-up. Eligible patients were randomized on Day 1 in a 1:1 ratio into 1 of 2 treatment arms and were required to start treatment within 7 days of randomization.

Treatment Arm A (ABI-007/carboplatin): Patients randomized to this arm received ABI-007 100 mg/m² administered weekly over 30 minutes without any steroid premedication followed by carboplatin at AUC = 6 on Day 1 of each cycle, repeated every 3 weeks.

A maximum of 2 dose reductions were allowed from the original dose:

- First dose reduction (25% reduction): Decrease ABI-007 to 75 mg/m² and carboplatin to an AUC = 4.5.
- Second dose reduction (50% reduction): Decrease ABI-007 to 50 mg/m² and carboplatin to an AUC = 3.0.

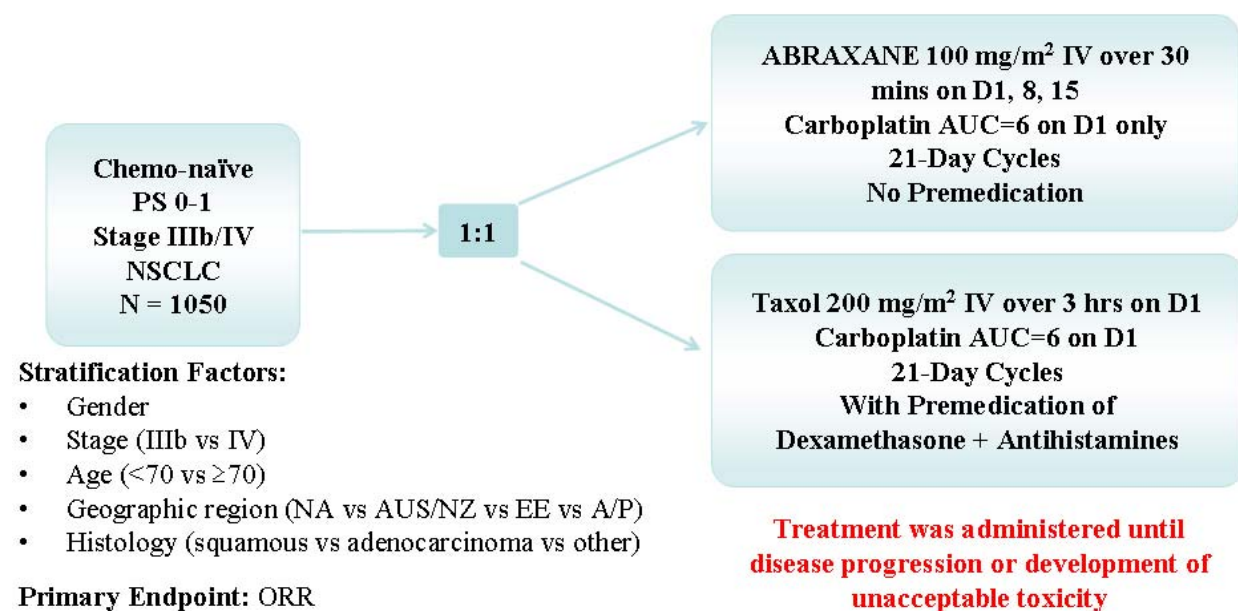
Treatment Arm B (Taxol/carboplatin): Patients randomized to this arm received Taxol 200 mg/m² administered over 3 hours with standard premedication (per the prescribing information) followed by carboplatin at AUC = 6, repeated every 3 weeks (both drugs given on Day 1 of each cycle).

A maximum of 2 dose reductions were allowed from the original dose.

- First dose reduction (25% reduction): Decrease Taxol to 150 mg/m² and carboplatin to an AUC = 4.5.
- Second dose reduction (50% reduction): Decrease Taxol to 100 mg/m² and carboplatin to an AUC = 3.0.

A patient could continue treatment at the investigator's discretion until disease progression, development of an unacceptable toxicity, or withdrawal of consent.

Figure 1: CA031: Study Design



Eligibility Criteria

Inclusion Criteria:

1. Patient with histologically or cytologically confirmed Stage IIIB or IV NSCLC.
2. Male or a non-pregnant and non-lactating female patients and ≥ 18 years of age.
 - If a female patient was of child-bearing potential, as evidenced by regular menstrual periods, she must have had a negative serum pregnancy test (beta human chorionic gonadotropin [β hCG]) documented within 72 hours of the first administration of study drug.
 - If sexually active, the patient must have agreed to utilize contraception considered adequate and appropriate by the investigator.
3. Patient had no other current active malignancy.

4. Radiographically documented measurable disease (defined by the presence of ≥ 1 radiographically documented measurable lesion).
5. Patient had received no prior chemotherapy for the treatment of metastatic disease. Adjuvant chemotherapy was permitted providing cytotoxic chemotherapy was completed 12 months prior to starting the study.
6. Patient had the following blood counts at baseline:
 - absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$;
 - platelets $\geq 100 \times 10^9/L$;
 - hemoglobin (Hgb) ≥ 9 g/dL.
7. Patient had the following blood chemistry levels at baseline:
 - aspartate transaminase (AST/serum glutamic oxaloacetic transaminase [SGOT]), alanine transaminase (ALT/serum glutamic pyruvic transaminase [SGPT]) $\leq 2.5 \times$ upper limit of normal range (ULN) or $\leq 5.0 \times$ ULN if liver metastases;
 - total bilirubin $\leq$ ULN;
 - creatinine ≤ 1.5 mg/dL.
8. Patient had expected survival of >12 weeks.
9. Patient had Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
10. Patient or his/her legally authorized representative or guardian had been informed about the nature of the study, had agreed to participate in the study, and had signed the informed consent form prior to participation in any study-related activities.

Exclusion Criteria

A patient was not eligible for inclusion in this study if any of the following criteria applied:

1. Patient had evidence of active brain metastases, including leptomeningeal involvement. Prior evidence of brain metastasis was permitted only if treated and stable and off therapy for ≥ 1 month.
2. The only evidence of disease was non-measurable.
3. Patient had preexisting peripheral neuropathy of grade 2, 3, or 4 (per CTCAE, Version 3.0).
4. Patient had received radiotherapy in the preceding 4 weeks, except if to a nontarget lesion only. Prior radiation to a target lesion was permitted only if there had been clear progression of the lesion since radiation was completed.
5. Patient had a clinically significant concurrent illness.
6. Patient had received treatment with any investigational drug within the previous 4 weeks.
7. Patient had a history of allergy or hypersensitivity to any of the study drugs.
8. Patient had serious medical risk factors involving any of the major organ systems such that the investigator considered it unsafe for the patient to receive an experimental research drug.
9. Patient was enrolled in any other clinical protocol or investigational trial that involved administration of experimental therapy and/or therapeutic devices.

Patients enrolled in the trial were to be naïve to chemotherapy; however, adjuvant chemotherapy was permitted, providing cytotoxic chemotherapy was completed 12 months prior to starting the study.

Response was determined according to RECIST guidelines, Version 1.0. Tumors were assessed by imaging studies every 6 weeks during therapy (at any time during the sixth week). For patients who had not progressed by the end of treatment, repeat imaging was performed every 6 weeks until tumor progression was documented or a new anticancer therapy was initiated. Patients were followed for 18 months post-study to monitor survival. The follow-up consisted of telephone interviews or review of records done on a monthly basis for 6 months and every 3 months thereafter for 12 months.

A Data Monitoring Committee (DMC) was used to provide recommendations for potentially increasing sample size and continuing or stopping the study based on review of interim safety data. The study used a central laboratory except for patients enrolled in Japan where local laboratory facilities were used.

A blinded central imaging review was used for all patients with at least one post-baseline response assessment. The central imaging reviewers were blinded to treatment and to the investigator assessment of response and provided an independent assessment of response and progression. Patients were considered responders if they achieved an objective CR or PR according to RECIST guidelines, Version 1.0, confirmed by repeat assessments performed no less than 4 weeks after the criteria for response were first met. Patients who discontinued early from the study prior to a post-baseline response assessment or who were randomized but did not receive treatment were considered to be non-responders.

An optional sparse PK study was conducted as an optional study in Russia, Ukraine, the US, and Canada only.

Removal of Patients from Therapy or Assessment

A patient could voluntarily discontinue study participation at any time. The investigator may have also, at his/her discretion, discontinued the patient's study participation at any time. In the event of discontinuation, the patient was to return to the study site as soon as feasible to have the EOS assessments performed.

1. Patients were to be withdrawn from study treatment if any of the following occurred:
2. Progressive disease (PD).
3. Development of toxicity that was unacceptable in the opinion of the investigator.
4. Patient declined to continue therapy (ie, withdrew consent).
5. If, following the second dose reduction, there was a recurrence of grade 4 neutropenia, or any other hematologic toxicity that was grade 3 or 4, or any grade 3 or 4 non-myelosuppressive AE, unless, at the discretion of the investigator, there was evidence of continuing benefit to the patient that outweighed the risk of recurrent toxicity.
6. Initiation of other anticancer therapy.
7. In the investigator's judgment, it was in the patient's best interest to discontinue the study.

Patients who were withdrawn from this study secondary to a laboratory abnormality or AE were to be followed. Patients whose treatment was discontinued prior to disease progression were followed every 6 weeks with repeat tumor imaging to document continued remission or disease progression.

6 Review of Efficacy

Efficacy Summary

The primary endpoint of superiority of ABI-007/carboplatin arm in the pivotal trial (CA 031), ORR as determined by independent radiologic review and confirmed at east 4 weeks after the initial response criterion compared to Taxol/carboplatin arm was met.

6.1 Indication:

ABI-007 is indicated in combination with carboplatin for the first-line treatment of patients with locally advanced or metastatic NSCLC who are not candidates for potentially curative surgery and/or radiation therapy

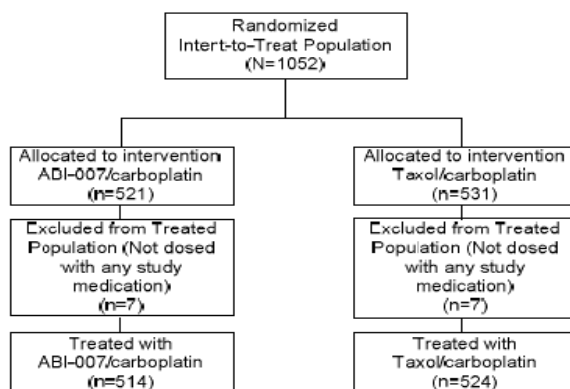
6.1.1 Methods

All efficacy analyses were performed using the Intent To Treat (ITT) population, which includes all randomized patients regardless of whether the patient received any study drug or had any efficacy assessments collected.

There were 521 patients in the ITT population in the ABI-007 /carboplatin arm and 531 patients in the ITT population in the Taxol/carboplatin arm (1052 patients' total).

The Treated population, which included all randomized patients who received at least 1 dose of study drug, was the analysis population for all safety analyses. Only patients with clear documentation that no study drug was administered were to be excluded from the Treated population. In the Treated population, there were 514 ABI-007 /carboplatin patients and 524 Taxol/carboplatin patients (1038 patients' total).

Figure 2: Patient Flow Diagram for Study CA031



6.1.2 Demographics

Demographics were comparable between the 2 treatment arms and representative of the targeted study population.

Table 3: Baseline Characteristics (ITT)

	ABI-007 + carboplatin (N=521)	Taxol + carboplatin (N=531)
Age (years)		
Median (range)	60.0 (28,81)	60.0 (24,84)
< 65 years, n (%)	360 (69%)	348 (66%)
≥ 65 years, n (%)	161 (31%)	183 (34%)
Gender: Male/Female	75% / 25%	75% / 25%
Origin, n (%)		
White, Non-Hispanic and Non-Latino	416 (80%)	433 (82%)
Asian	79 (15%)	80 (15%)
Black, of African Heritage	12 (2%)	8 (2%)
White, Hispanic or Latino	11 (2%)	5 (< 1%)
Other	2 (< 1%)	5 (< 1%)
North American Indian or Alaskan	1 (< 1%)	0 (0%)
Stage at Randomization: IIIb/Stage IV	21% / 79%	21% / 79%
Histology of Primary Diagnosis, n (%)		
Carcinoma/Adenocarcinoma	254 (49%)	264 (50%)
Squamous Cell Carcinoma	229 (44%)	221 (42%)
Large Cell Carcinoma	9 (2%)	13 (2%)
Other	29 (6%)	33 (6%)
ECOG PS: 0/1	26% / 74%	21% / 78%
Smoking Status, N	519	526
Ever/Never Smoked (%)	74%/26%	73%/27%

The median age was 60 years old for both arms. The majority of the patients were < 65 years old; male, White with ECOG performance status of 1.

6.1.3 Subject Disposition

Fourteen patients were randomized but were not dosed; 7 due to investigator discretion, 3 due to adverse events, 3 due to protocol deviations and 1 due to withdrawal of consent.

The proportion of treated patients in the ITT populations was the same for each treatment arm (99%). As of the 31 Jan 2011 cut-off date, > 99% of patients had completed the study treatment and 3 patients in the ABI-007/carboplatin arm had therapy ongoing.

Table 4: Subject Disposition

Variable / Category	ABI-007/ carboplatin (N=521)	Taxol/ carboplatin (N=531)	All Patients (N=1052)
Intent-to-treat Patients, N	521	531	1052
Patients Treated, n (%)	514 (99%)	524 (99%)	1038 (99%)
Therapy Ongoing, n (%)	3 (< 1%)	0	3 (<1%)
Therapy Discontinued, n (%)	511 (> 99%)	524 (100%)	1035 (>99%)
Reason for Therapy Discontinuation, N	511	524	1035
Progressive Disease, n (%)	275 (54%)	265 (51%)	540 (52%)
Unacceptable Toxicity, n (%)	61 (12%)	62 (12%)	123 (12%)
Adverse Event, n (%)	20 (4%)	24 (5%)	44 (4%)
Investigator Discretion, n (%)	86 (17%)	99 (19%)	185 (18%)
Protocol Deviation, n (%)	3 (<1%)	4 (<1%)	7 (<1%)
Lost to Follow-up, n (%)	1 (<1%)	1 (<1%)	2 (<1%)
Patient Discretion, n (%)	65 (13%)	67 (13%)	132 (13%)
Other ^a , n (%)	0 (<1%)	2 (<1%)	2 (<1%)

^a The "Other" category included GCP deviation, study drug Taxol not available, Taxol no longer available, and high bilirubin.

In both treatment arms, the most common reason for discontinuation was progressive disease (52% overall). The other reasons for discontinuation (reported in $\geq 10\%$ of patients) were similar for the 2 treatment arms (investigator discretion [18% overall], patient discretion [13% overall], and unacceptable toxicity [12% overall]).

The most common reasons provided for discontinuation for both treatment arms due to investigator discretion included "patient's interest/benefit," "6 cycles completed," and "further treatment is no longer beneficial for the patient". The most frequent reason provided for discontinuation due to patient discretion was that the patient had withdrawn consent from the study.

Protocol Deviation: A total of 7 patients discontinued due to protocol deviations; the majority of these patients discontinued due to lack of compliance.

In general, the distribution of reasons for discontinuation by site reflected the overall patient distribution.

A total of 62 patients were randomized via the IVR system with an inaccurate stratification factor: one date of birth error resulting in mis-stratification by age, one gender error, 32 disease stage errors, and 31 histology errors.

The sponsor claims that the information in the IVR system was compared with patient information in the clinical database and that all inaccurate stratification factor information was corrected in the clinical database, which was used for all stratified and subgroup analyses.

6.1.4 Analysis of Primary Endpoint(s)

In this study, 1052 patients with advanced NSCLC were randomized 1:1 to receive either ABI-007 (100 mg/m²) weekly without premedication followed by carboplatin (AUC=6) every 3 weeks (n=521) or Taxol (200 mg/m²) every 3 weeks with premedication (n=531) followed by carboplatin (AUC=6) every 3 weeks (n=531) as first-line therapy.

The primary objective was to compare disease response (using RECIST [Version 1.0] guidelines) between the ABI-007 /carboplatin and the Taxol/carboplatin treatment arms. The secondary objectives included comparisons of the frequency of AEs, PFS, OS, and duration of response in responding patients.

The randomization stratified by disease stage (IIIb vs IV), age (< 70 vs ≥ 70 years), gender (male vs female), histology (adenocarcinoma vs squamous cell vs other), and geographic region (North America vs Asia/Pacific vs Eastern Europe) resulted in well balanced treatment arms, overall and within the strata.

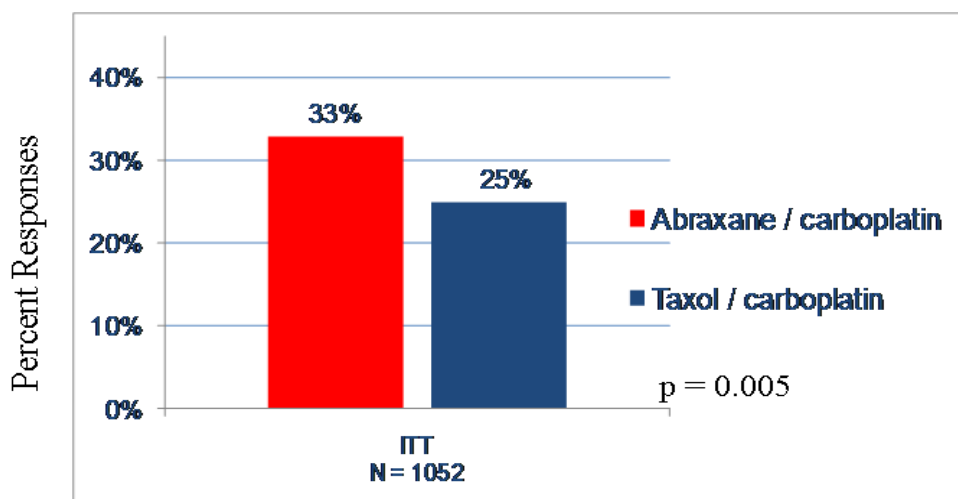
Table 5 presents the primary analysis results of ORR per IRC assessment as well as per INV assessment at the time of the final ORR analysis. There were 170 (33%) and 132 (25%) response in the ABI-007/carboplatin arm and taxol/carboplatin arm, respectively. The OR was 1.31 (95% CI: 1.08, 1.59). The lower boundary of 95% CI of OR per IRC assessment was great than 1, which supports superiority of ABI-007 with respect to OR. In addition, the ORR analysis demonstrated a statistically significant difference in ORR for the treatment based on χ^2 test (P value=0.005).

Table 5: ORR Results by IRC and INV Assessment in the ITT Population

	IRC		INV	
	ABI-007/ carboplatin N=521	Taxol/ carboplatin N=531	ABI-007/ carboplatin N=521	Taxol/ carboplatin N=531
ORR, n (%)	170 (32.6%)	132 (24.9%)	200 (38.4%)	160 (30.1%)
95% CI	(28.6, 36.8)	(21.2, 28.8)	(34.2, 42.6)	(26.2, 34.0)
CR, n(%)	0	1(0.2%)	2 (0.3%)	4(0.7%)
PR, n(%)	170 (32.6%)	131 (24.7%)	198 (38%)	156 (29%)
OR (95% CI)	1.31 (1.08, 1.59)		1.27 (1.08, 1.51)	
χ^2 test p-value	0.005		0.005	

The independent radiologic review of spiral CT scans involved an independent assessment by two radiologists and, if discrepant, an adjudicator reviewed each independent radiologist assessment and selected the appropriate final radiology assessment

Figure 3: ORR by Independent Radiological Review



The radiologists were blinded to treatment arm assignment, treatment duration, histology of the primary tumor, geographic location of the study site, and treatment outcome. The review followed a charter finalized and reviewed by the FDA as part of a Special Protocol Assessment prior to the first read. All readers were trained in the charter and the reading algorithms.

6.1.5 Analysis of Secondary Endpoints(s)

According to the SAP, the final analysis for PFS was planned to be conducted once 70% of patients had an event of disease progression or death (any cause), equivalent to 735 events. Due to a higher than expected rate of censoring, the final PFS analysis was performed with 609 events.

The median PFS was 6.3 months for the ABI-007/carboplatin arm and 5.8 months for the taxol/carboplatin arm. The un-stratified hazard ratio was 0.93 with 95% CI (0.79, 1.09).

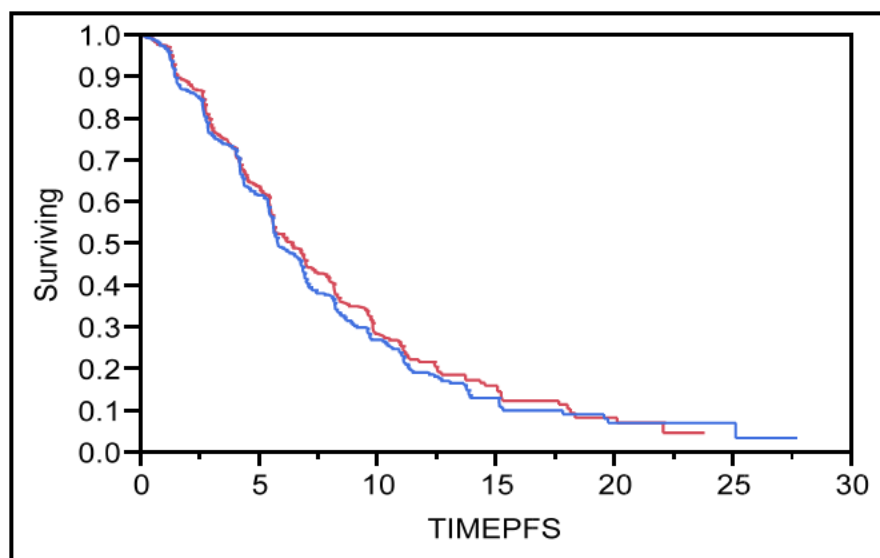
Table 6: IRC PFS Analysis Results in the ITT Population

	ABI-007/carboplatin N=521	Taxol/carboplatin N=531
PFS	297 (57.0%)	312 (58.8%)
PD	65 (12.5%)	55 (10.4%)
Death	232 (44.5%)	257 (48.4%)
Median PFS (months), 95%CI	6.3 (5.6, 7.0)	5.8 (5.6, 6.7)
Stratified HR (95% CI) [p-value] [†]	0.90 (0.77, 1.06) [0.21]	
Stratified HR (95% CI) [p-value] [‡]	0.87 (0.73, 1.04) [0.13]	
Un-Stratified HR (95% CI) [p-value]	0.93 [0.79, 1.09] 0.38]	

[†]Stratified by CSR defined strata: Region, histology

[‡]Stratified by SAP defined strata: Region, histology, stage, age, gender

Figure 4; Progression Free Survival Plot



Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.8281	1	0.3628
Wilcoxon	0.8290	1	0.3625

Table 7 : Overall Response Rate by Histology

Carcinoma/Adenocarcinoma	66/254 (26%)	71/264 (27%)
Squamous Cell Carcinoma	94/229 (41%)	54/221 (24%)
Large Cell Carcinoma	3/9 (33%)	2/13 (15%)
Other	7/29 (24%)	5/33 (15%)

6.1.6 Other Endpoints

Overall Survival (OS) According to the SAP, the final analysis for OS was planned to be conducted once 70% of patients had died (any cause), equivalent to 735 death events. The actual final OS analysis was performed with 744 (71%) death events.

The median OS was 12.1 months for the ABI-007/carboplatin arm and 11.2 months for the taxol/carboplatin arm. The un-stratified hazard ratio was 0.93 with 95% CI (0.79, 1.09).

Table 8 : OS Analysis Results in ITT Population

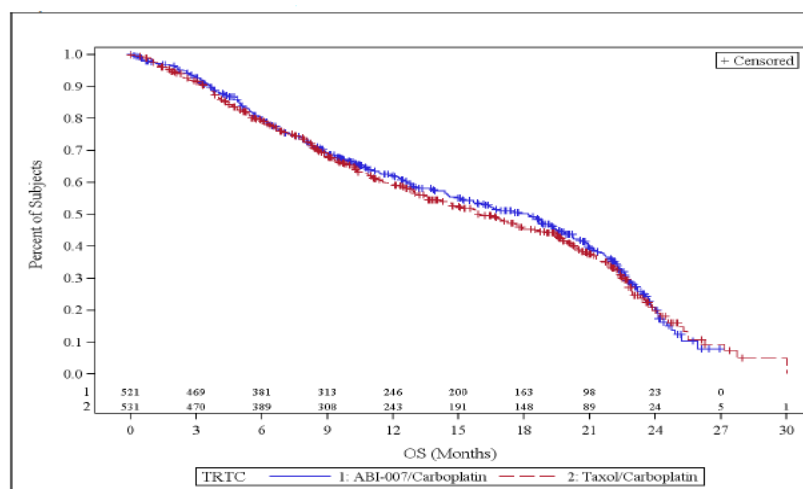
	ABI-007/carboplatin N=521	Taxol/carboplatin N=531
Death Events	360(69.1%)	384 (72.3%)
Median OS (months), 95%CI	12.1 (10.8, 12.9)	11.2 (10.2, 12.6)
Stratified HR (95% CI) [p-value] †*	0.92 (0.80, 1.07) [0.27]	
Stratified HR (95% CI) [p-value] ‡*	0.94 (0.81, 1.10) [0.45]	
Un-Stratified HR (95% CI) [p-value]*	0.93 (0.81, 1.08) [0.34]	

†Stratified by CSR defined strata: Region, histology

‡Stratified by SAP defined strata: Region, histology, stage, age, gender

*Nominal P value

Figure 5: K-M Curves for OS



7 Review of Safety

Safety Summary

A total of 1038 patients received at least 1 dose of study drug and were included in the Treated population. A median of 6.0 cycles was administered for both arms.

A median of 6.0 cycles was administered for both arms. The median number of carboplatin doses administered was 6.0 for both treatment regimens.

Table 9; Number of Cycles and Study Drug Doses Administered (Treated Population)

Variable Category / Statistic	ABI-007/ carboplatin (N=514)	Taxol/ carboplatin (N=524)
Number of Cycles Administered		
Mean (SD)	6.3 (4.57)	6.1 (4.30)
Median (Min, Max)	6.0 (1, 31)	6.0 (1, 30)
Number of Taxane Doses Administered		
Mean (SD)	17.3 (13.03)	6.1 (4.30)
Median (Min, Max)	15.0 (1, 85)	6.0 (1, 30)
Number of Carboplatin Doses Administered		
Mean (SD)	6.2 (4.40)	6.1 (4.26)
Median (Min, Max)	6.0 (1, 28)	6.0 (1, 30)

The toxicities associated with ABI-007 are similar to Taxol and include alopecia, neutropenia, anemia, and thrombocytopenia. The Treatment Emergent Adverse Events (TEAEs) reported significantly more often with ABI-007/ carboplatin were anemia, thrombocytopenia, peripheral edema, epistaxis, and hemoglobin decreased ($p \leq 0.015$). Slightly lower incidences of Grade 3/4 neuropathy, neutropenia, arthralgia and myalgia were noted in ABI-007 arm.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

In addition to the analysis of the data sets submitted by the sponsor for the Pivotal NSCLC Study (Study CA031), an Integrated Summary of Safety (ISS) included the following

1. Pivotal NSCLC study CA031 (ABI-007 + carboplatin).

Phase III, randomized, open-label, comparative study of following treatment regimens as First-line therapy in patients with advanced NSCLC:

- ABI-007 100 mg/m² administered over 30 minutes weekly plus carboplatin at area under the curve (AUC)=6 every 3 weeks (q3w).
- Taxol 200 mg/m² administered over 3 hours q3w with standard premedication plus carboplatin at AUC=6 q3w.

521 patients were randomized to ABI-007 100 mg/m² weekly + carboplatin; 532 patients were randomized to Taxol 175 mg/m² q3w + carboplatin.

Safety endpoints: Treatment-emergent adverse events (AEs) and serious adverse events (SAEs), laboratory abnormalities including myelosuppression, dose modifications, and premature discontinuation of study drug.

2. Primary supportive NSCLC study CA028 (ABI-007 + carboplatin).

An Open-Label, Phase II Trial of Increasing Doses of ABI-007 and Carboplatin in patients with Advanced NSCLC.

Phase II, non-randomized, open-label, study evaluating the following increasing dose cohorts of ABI-007 administered over 30 minutes plus carboplatin at AUC=6 q3w as first-line therapy in patients with advanced NSCLC.

Following the initial experience with the q3w dosing cohorts, an additional 75 patients were enrolled in the optimal q3w dose cohort.

25 patients were enrolled per dose cohort; an additional 75 patients were enrolled in the optimal q3w dose cohort. Multi-center study conducted in Eastern Europe.

Safety endpoints: Treatment-emergent AEs and SAEs, laboratory abnormalities including myelosuppression, dose modifications, and premature discontinuation of study drug.

3. Other supportive NSCLC studies CA015 and CA018 (b) (4)

- **Study CA015** (An Open-Label, Phase I/II Trial of ABI-007 : Phase I/II, non-randomized, open-label, study evaluating ABI-007 administered over 30 minutes weekly for 3 weeks followed by 1 week of rest as first-line therapy in patients with stage IV NSCLC.

The study included Exploratory cohort of 25 patients dosed at the MTD over 2 hours weekly for 3 weeks followed by 1 week of rest.

- **Study CA018:** (An Open-Label, Phase II Trial of ABI-007 in Patients with Advanced NSCLC). Open-label, study evaluating ABI-007 260 mg/m² administered over 30 minutes q3w as first-line therapy in patients with advanced NSCLC.

43 patients enrolled. Multi-center study conducted in Eastern Europe.

(b) (4)

7.1.2 Categorization of Adverse Events

- Treatment-emergent AEs and SAEs.
- Laboratory abnormalities (hematology and clinical chemistry).
- Dose modifications (dose reductions, dose delays, and dosing interruptions).
- Premature discontinuation of study drug.

7.2 Adequacy of Safety Assessments

In general, safety assessments were adequate. In addition to the clinical trials data the sponsor submitted Postmarket data of safety since the approval for the breast cancer indication.

In the pivotal trial CA031, a total of 1038 patients received at least 1 dose of study drug and were included in the ITT population.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics

The proportion of patients receiving a given number of cycles was comparable between the treatment arms throughout the duration of treatment; ie, all patients in both treatment arms received 1 cycle per-protocol; approximately 75% received ≥ 4 cycles; approximately 50% received 6 cycles; and approximately 10% received 12 cycles.

Treatment exposure was tested for patients < 65 years vs ≥ 65 years, for patients < 70 years vs ≥ 70 years and for patients < 75 years vs ≥ 75 years.

In general, the mean number of cycles administered was slightly lower in the elderly patient arms as compared with the overall population.

- For patients ≥ 65 years of age, the median number of cycles administered was 5.0 in the ABI-007/carboplatin arm and 6.0 in the Taxol/carboplatin arm.
- In the ≥ 70 age subgroup, the median number of cycles given was 5.0 in the ABI-007/carboplatin arm and 6.0 in the Taxol/carboplatin arm.
- patients in the ≥ 75 year age subgroup received a median of 5.5 cycles in the ABI-007/carboplatin arm and 6.0 cycles in the Taxol/carboplatin arm.

Drug-demographic interaction that could be analyzed and noted in the current pivotal trial was age and histological subtypes of NSCLC.

7.2.2 Special Animal and/or In Vitro Testing

This sNDA does not include information in Module 4 (Nonclinical Study Reports) using the Electronic Common Technical Document (eCTD) format. No additional nonclinical pharmacology and toxicology studies were conducted to support the proposed NSCLC indication for ABI-007. The sponsor cross references to the Item 5 Nonclinical Pharmacology and Toxicology documentation submitted to the ABI-007 original NDA 021660 for ABI-007 that was submitted on 04 Nov 2004 and was approved on 07 Jan 2005.

7.2.3 Routine Clinical Testing

In the safety analyses, taxane-related hematologic toxicities were summarized both as the events reported by the investigators as AEs and the hematological laboratory values graded per NCI CTCAE, Version 3.0. This analysis approach was used to ensure these events were not under-reported. AEs were analyzed using the categories listed in the SAP.

Hematology

The maximal degree of myelosuppression was evaluated by summarizing the most severe NCI CTCAE (Version 3.0) grade for ANC, white blood cell (count) (WBC), lymphocytes, platelet count, and Hgb in each treatment cycle and by the most severe grade overall (ie, anytime after first dose of study drug).

Clinical Chemistry

Hepatic and renal function was summarized using the NCI CTCAE (Version 3.0) grade for alkaline phosphatase, ALT (SGPT), AST (SGOT), total bilirubin, and creatinine. The most severe NCI CTCAE grade was summarized for the first cycle and overall.

7.3 Major Safety Results

7.3.1 Deaths

The proportion of patient deaths was 4% for both arms. Events that led to death were mostly cardiac disorders and respiratory, thoracic, and mediastinal disorders. Deaths reported for more than 1 patient were due to cardiac arrest, pulmonary embolism, and pulmonary hemorrhage for both treatment arms.

Table 10: Treatment-emergent Adverse Events with Outcome of Death

	ABI-007/ carboplatin (N=514)	Taxol/ carboplatin (N=524)
	n (%)	n (%)
Patients with at Least 1 AE with Outcome of Death	18 (4%)	19 (4%)
Patient with at Least 1 AE with Outcome of Death by MedDRA (Version 12.1) System Organ Class and Preferred Term		
Cardiac disorders	6 (1%)	5 (<1%)
Cardiac arrest	2 (<1%)	1 (<1%)
Arrhythmia	1 (<1%)	0
Cardiac failure acute	1 (<1%)	0
Cardiopulmonary failure	1 (<1%)	1 (<1%)
Myocardial infarction	1 (<1%)	1 (<1%)
Acute coronary syndrome	0	1 (<1%)
Cardio-respiratory arrest	0	1 (<1%)
Respiratory, thoracic and mediastinal disorders	6 (1%)	10 (2%)
Pulmonary embolism	4 (<1%)	4 (<1%)
Pulmonary haemorrhage	2 (<1%)	3 (<1%)
Dyspnoea	0	1 (<1%)
Pulmonary oedema	0	1 (<1%)
Respiratory failure	0	1 (<1%)
General disorders and administration site conditions	2 (<1%)	1 (<1%)
Disease progression	1 (<1%)	0
Multiorgan failure	1 (<1%)	0
Sudden death	0	1 (<1%)
Infections and infestations	1 (<1%)	1 (<1%)
Pneumonia	1 (<1%)	1 (<1%)
Injury, poisoning and procedural complications	1 (<1%)	0
Alcohol poisoning	1 (<1%)	0
Nervous system disorders	1 (<1%)	0
Cerebrovascular accident	1 (<1%)	0
Vascular disorders	1 (<1%)	0
Hypertension	1 (<1%)	0
Blood and lymphatic system disorders	0	1 (<1%)
Disseminated intravascular coagulation	0	1 (<1%)
Gastrointestinal disorders	0	1 (<1%)
Gastrointestinal haemorrhage	0	1 (<1%)

There were 2 treatment-related adverse events with an outcome of death; one in each arm. Patient 368-0031 in the ABI-007/carboplatin arm had an event of multiorgan failure, suspected by the investigator to be possibly related to ABI-007 and carboplatin. Patient 376-0005 in the Taxol/carboplatin arm had a gastrointestinal hemorrhage considered to be possibly related to Taxol and carboplatin.

7.3.2 Nonfatal Serious Adverse Events

Treatment-emergent Serious Adverse Events were comparable overall with frequencies of SAEs in both treatment arms (18% in the ABI-007/carboplatin arm and 15% in the Taxol/carboplatin arm).

A higher percentage of patients in the ABI-007/carboplatin treatment arm experienced an SAE of anemia (4%) compared to the Taxol/carboplatin arm (< 1%). All other SAEs were observed in similar percentages.

Table 11: Treatment-emergent Serious Adverse Events

	ABI-007/ carboplatin (N=514)	Taxol/ carboplatin (N=524)
	n (%)	n (%)
Patients with at Least 1 Serious AE	93 (18%)	80 (15%)
Patients with SAEs by MedDRA (Version 12.1) System Organ Class and Preferred Term		
Blood and lymphatic system disorders	26 (5%)	12 (2%)
Anemia	19 (4%)	3 (<1%)
Infections and infestations	21 (4%)	16 (3%)
Pneumonia	14 (3%)	11 (2%)
Respiratory, thoracic and mediastinal disorders	18 (4%)	26 (5%)
Dyspnoea	4 (<1%)	6 (1%)
Pulmonary embolism	4 (<1%)	8 (2%)

7.3.3 Dropouts and/or Discontinuations

The proportion of patients with ≥ 1 TEAE resulting in discontinuation was comparable for the 2 treatment arms for discontinuation of both taxane arms.

The most common events resulting in taxane and carboplatin discontinuation in the ABI-007/carboplatin arm were neutropenia (3% for both) and thrombocytopenia (3% for both), and in the Taxol/carboplatin arm was peripheral sensory neuropathy (4% and 3%, respectively). All other such events were reported in $\leq 2\%$ of patients in either treatment arm for discontinuation of both taxane and carboplatin.

Taxane and Carboplatin Dose Modifications

The proportion of patients and the number of doses with a taxane dose reduction were higher with ABI-007 (46% and 33%, respectively) relative to Taxol (23% and 13%, respectively). Similar percentages to these were observed in the incidence of carboplatin dose reductions.

The majority of both taxane and carboplatin dose reductions were due to AE/toxicity in both treatment arms; ABI-007/carboplatin (> 99% for both treatments) and Taxol/carboplatin (> 99% and 98%, respectively).

The overall incidence of dose reductions in the ABI-007/carboplatin arm vs the Taxol/carboplatin arm is due to the hematologic AEs of neutropenia/decreased neutrophil count, thrombocytopenia/decreased platelet count, and anemia/decreased Hgb. The sponsor hypothesizes that this is most likely due to the weekly dosing schedule of ABI-007 compared with the every three week Taxol dosing schedule, providing a higher chance of dose delays or reductions due to myelosuppression in the ABI-007/carboplatin arm.

Interruptions in taxane or carboplatin dosing, defined as interruptions at the time of infusion, were uncommon, occurring in < 1% of patients and < 1% of cycles for both treatment regimens. The reason for the taxane dose interruptions was “other” (3 patients) in the ABI-007 arm and hypersensitivity reaction (4 patients) or “other” (1 patient) in the Taxol arm.

Delayed and missed taxane and carboplatin doses were more common in ABI-007/carboplatin arm (82% and 72% of patients, respectively) relative to the Taxol/carboplatin arm (54% of patients for each). The reason for dose delay/missed dose was most commonly AE/toxicity for both treatment arms. The 3 most often reported AEs that led to taxane dose delays in the ABI-007/carboplatin arm were neutropenia (41%), thrombocytopenia (30%), and anemia (16%). The 3 most often reported in the Taxol/carboplatin arm were neutropenia (12%), thrombocytopenia (12%), and peripheral sensory neuropathy (5%)

7.3.4 Significant Adverse Events

Table 8 provides the frequency and severity of adverse events (AEs) that have been reported in $\geq 5\%$ incident rate using MedDRA System Organ Class and Preferred Term, Version 12.1.

Table 12: Incidence of Adverse Reactions Reported in $\geq 5\%$ of Patients

System Organ Class	Preferred Term	ABI-007 (100 mg/m ² weekly) + carboplatin (N=514)		Solvent-based paclitaxel (200 mg/m ² every 3 weeks) + carboplatin (N=524)	
		All Grades ^b Toxicity (%)	Grade 3 or >Toxicity (%)	All Grades Toxicity (%)	Grade 3 or > Toxicity (%)
Blood and lymphatic system disorders ^c	Anemia	98	28	91	7
	Leukopenia	89	24	83	24
	Neutropenia	85	47	83	58
	Thrombocytopenia	68	18	55	9
Skin and subcutaneous tissue disorders	Alopecia	56	<1	60	0
	Rash	10	0	8	<1
Nervous system disorders	Peripheral neuropathy	48	3	64	12
	Dysgeusia	7	0	6	0
	Headache	7	<1	4	<1
	Dizziness	6	0	4	<1
General disorders and administration site conditions	Fatigue	25	4	23	4
	Asthenia	16	3	15	4
	Edema peripheral	10	0	4	<1
	Pyrexia	9	0	8	0
Gastrointestinal disorders	Chest pain	5	<1	4	<1
	Nausea	27	<1	25	<1
	Constipation	16	<1	13	<1
	Diarrhea	15	<1	11	0
	Vomiting	12	<1	12	<1
Respiratory thoracic and mediastinal disorders	Stomatitis	6	0	4	0
	Dyspnea	12	3	12	3
	Cough	9	<1	7	0
	Epistaxis	7	0	2	0
Investigations	Hemoptysis	4	<1	5	0
	Alanine aminotransferase increase	9	2	9	<1
	Weight decreased	8	1	6	<1
	Aspartate aminotransferase increase	8	<1	6	<1
Musculoskeletal and connective tissue disorders	Arthralgia	13	<1	25	2
	Myalgia	10	<1	19	2
Metabolic and nutrition disorders	Decreased appetite	17	2	18	<1
Infections and infestations	Pneumonia	5	2	3	2
Psychiatric disorders	Insomnia	5	0	8	<1

7.4 Supportive Safety Results

7.4.1 Laboratory Findings

The incidence of clinical chemistry values of NCI CTCAE grade 3 or 4 that occurred after the first dose of study drug was summarized and listed.

Table 13: Incidence of Abnormal Lab Test $\geq$ 5% NCI CTCAE Results

Laboratory tests	LAB Name	ABI-007 (100 mg/m ² weekly) + carboplatin (N=514)		Solvent-based paclitaxel (200 mg/m ² every 3 weeks) + carboplatin (N=524)	
		All Grades Toxicity (%)	Grade 3/4 Toxicity (%)	All Grades Toxicity (%)	Grade 3/4 Toxicity (%)
Bone marrow function	WBC decrease	89	24	83	24
	Neutrophil decrease	85	47	83	58
	Lymphocyte decrease	51	8	47	10
	Hemoglobin decrease	98	28	91	7
	Platelet decrease	68	18	55	9
Electrolyte abnormalities	Sodium	37	4	41	5
	Potassium	45	3	37	5
	Glucose	61	2	58	3
	Calcium	57	1	51	1
Hepatic function	Alanine Aminotransferase increase	26	1	23	<1
	Aspartate Aminotransferase increase	22	1	21	<1
	Total Bilirubin increase	4	0	5	<1
	Albumin decrease	82	3	72	0
Renal function	Creatinine increase	9	0	10	0

7.5 Other Safety Explorations

Peripheral Neuropathy: The physician assessed peripheral neuropathy using the NCI CTCAE of “Neuropathy –Sensory.” The frequency of physician assessment of peripheral neuropathy grade (0 – 5) at baseline, Day 1 of each cycle, and final evaluation was presented. The frequency of worst peripheral neuropathy grade overall (ie, anytime after the first dose of study drug) was also Tested.

Additionally, peripheral neuropathy events were captured as AEs.

Time to first occurrence and to improvement in peripheral neuropathy was evaluated as:

- Time to first occurrence of peripheral neuropathy of any grade;
- Time to first occurrence of grade 2 or higher peripheral neuropathy;
- Time to first occurrence of grade 3 or higher peripheral neuropathy;
- Time to improvement of grade 3 or higher peripheral neuropathy by at least one grade;
- Time to improvement of grade 2 or higher peripheral neuropathy by at least one grade;
- Time to improvement of grade 3 or higher peripheral neuropathy to grade 1;
- Time to improvement of grade 2 or higher peripheral neuropathy to grade 1.

The sponsor concluded that the Neuropathy AEs were reported significantly less often in the ABI-007/carboplatin arm as compared with the Taxol/carboplatin arm. The majority (64%) of Taxol/carboplatin-treated patients and fewer than half of ABI-007/carboplatin-treated patients (48%) developed neuropathy during the study. Most of these events were considered treatment-related. These results however could not be verified by the FDA.

7.5.2 Drug-Demographic Interactions

Drug-demographic interaction that could be analyzed and noted in the current pivotal trial was age and histological subtypes of NSCLC.

Of the 514 patients in the randomized study who received ABI-007 and carboplatin for the first-line treatment of non-small cell lung cancer, 31% were 65 years or older and 3.5% were 75 years or older. Myelosuppression events, peripheral neuropathy events, and arthralgia were more frequent in patients 65 years or older compared to patients younger than 65 years old.

Patients received a median of 15.0 doses of taxane with the ABI-007 weekly regimen relative to 6.0 doses with the every 3 week Taxol regimen.

Sensitivity analysis done by histological subtype showed ORR 26% versus 27% in patients with Adenocarcinoma, 41% versus 24% with Squamous cell carcinoma and 33% versus 15% Large Cell Carcinoma.

7.5.3 Drug-Drug Interactions

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 ABI-007 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.

There are no clinically important pharmacokinetic drug-drug interactions between carboplatin and paclitaxel when administered as ABI-007. Administration of carboplatin immediately after the completion of ABI-007 infusion to patients with non-small cell lung cancer reduced paclitaxel AUC_{inf} and C_{max} by 18% and 16%, respectively. These changes in paclitaxel exposure are not considered to be clinically important. The observed mean AUC_{inf} of free carboplatin was approximately 23% higher than the targeted value (6 min*mg/mL) but its mean half life and clearance were consistent with those reported in the absence of paclitaxel.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The carcinogenic potential of ABI-007 has not been studied.

Paclitaxel was clastogenic in vitro (chromosome aberrations in human lymphocytes) and in vivo (micronucleus test in mice). ABI-007 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 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/m²/week in this study (approximately 1 to 5% of the daily maximum recommended human exposure on a mg/m² 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/m² in rodents and 175 mg/m² in dogs.

7.6.2 Human Reproduction and Pregnancy Data

ABI-007 is Pregnancy Category D

There are no adequate and well-controlled studies in pregnant women using ABI-007. Based on its mechanism of action and findings in animals, ABI-007 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 will be apprised of the potential hazard to the fetus. Women of childbearing potential will be advised to avoid becoming pregnant while receiving ABI-007.

Administration of paclitaxel protein-bound particles to rats during pregnancy, 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 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/m² (approximately 1% of the daily maximum recommended human dose on a mg/m² basis).

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.

7.6.3 Pediatrics and Assessment of Effects on Growth

Pediatric patients were not included in these clinical studies with ABI-007. Studies required that patients be more than 18 years of age to meet eligibility criteria. Therefore, the safety of ABI-007 in pediatric patients has not been established.

Pursuant to 21 CFR §314.55(c)(2)(ii), a formal request for a waiver of pediatric studies for the use of ABI-007, in combination with carboplatin, for the first-line treatment of advanced non-small cell lung cancer was submitted to the Investigational New Drug (IND) Application 055974 on 27 May 2011 (eCTD Sequence #0061).

Non-small cell lung cancer is an indication that has extremely limited applicability to pediatric patients because the pathophysiology of this disease occurs, for the most part, in the adult population. Because non-small cell lung cancer is an adult-related condition, the Sponsor requests that the Agency grant a full waiver of the pediatric assessment as required under PREA for this Supplemental New Drug Application (sNDA).

In accordance with Section VI(B) of the Guidance for Industry entitled, “How to Comply with the Pediatric Research Equity Act” (Draft Guidance, September 2005, Procedural), the Sponsor is requesting a full waiver based on the following criterion for full waiver (section 505B(a)(4)(A) of the Act): Necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed) (section 505B(a)(4)(A)(i) of the Act).

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No reports of accidental exposure to ABI-007 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.

8 Postmarket Experience

As of 19 September 2011, ABI-007 is approved in 42 countries as monotherapy for metastatic breast cancer. The recommended dose of single-agent ABI-007 for patients with metastatic breast cancer is 260 mg/m² administered intravenously over 30 minutes every 3 weeks. As per the sponsor as of 07 January 2005 up to the most recent Periodic Safety Update Report cut-off date of 06 July 2011 cumulatively, approximately (b) (4) patients have been exposed to commercial ABI-007 globally, including (b) (4) patients from the United States (US) and (b) (4) patients in territories outside the US. During this period, 2,611 adverse events from 1,645 unique adverse event reports have been received from (a) contract pharmacies; (b) spontaneous sources; (c) regulatory authorities; and (d) scientific literature.

Of the 1,645 unique case reports, 11 reports with a total of 20 ADRs were for patients who were treated with ABI-007 for the unlabeled indication of lung cancer. The most frequently reported events in the subset of lung cancer patients were fatigue and decreased appetite.

Paclitaxel is an active pharmaceutical ingredient in ABI-007. The major risks associated with the use of ABI-007 for the treatment of patients with metastatic breast cancer (an approved indication) reflect the known toxicities of paclitaxel. These risks include alopecia, hematologic toxicities (neutropenia and anemia), peripheral sensory neuropathy, myalgia/arthralgia, fatigue/asthenia, hypersensitivity reactions, gastrointestinal events (nausea and diarrhea), infections, elevated aspartate aminotransferase and alkaline phosphatase, and abnormal electrocardiogram.

In the postmarketing setting where patients were treated with ABI-007 for the unlabeled indication of lung cancer, there are insufficient data to suggest a safety profile that is different from the one established for patients with metastatic breast cancer treated with ABI-007. However, the ADRs reported in the patients treated with ABI-007 for the unlabeled indication of lung cancer are consistent with the safety profile established for ABI-007 in the treatment of metastatic breast cancer.

The following adverse reactions have been identified during post-approval use of ABI-007.

Hypersensitivity Reactions

Severe and sometimes fatal hypersensitivity reactions have been reported with ABI-007.

Cardiovascular

There have been reports of congestive heart failure and left ventricular dysfunction with ABI-007. Most of the individuals were previously exposed to cardiotoxic drugs, such as anthracycline, or had underlying cardiac history.

Respiratory

There have been reports of interstitial pneumonia and pulmonary embolism in patients receiving ABI-007 and reports of radiation pneumonitis in patients receiving concurrent radiotherapy. Reports of lung fibrosis have been received as part of the continuing surveillance of solvent-based paclitaxel safety and may also be observed with ABI-007.

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 solvent-based paclitaxel suggest persistent optic nerve damage. These may also be observed with ABI-007.

Hepatic

Reports of hepatic necrosis and hepatic encephalopathy leading to death have been received as part of the continuing surveillance of solvent-based paclitaxel safety and may occur following ABI-007 treatment.

Gastrointestinal (GI)

There have been reports of intestinal obstruction, intestinal perforation, pancreatitis, and ischemic colitis following ABI-007 treatment. There have been reports of neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, occurring in patients treated with solvent-based paclitaxel alone and in combination with other chemotherapeutic agents.

Injection Site Reaction

There have been reports of extravasation of ABI-007.

Severe events such as phlebitis, cellulitis, induration, necrosis, and fibrosis have been reported as part of the continuing surveillance of solvent-based paclitaxel safety. In some cases the onset of the injection site reaction in solvent-based paclitaxel 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 solvent-based paclitaxel 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 ABI-007. There has 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 solvent-based paclitaxel.

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 solvent-based paclitaxel may be expected to occur with ABI-007.

9 Appendices

9.1 Literature Review/References

1. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med*. 2002;346: 92-98.
2. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small cell lung cancer. *N Engl J Med*. 2006;355:2542-2550
3. Scagliotti GV, Novello S, vonPawel J, et al. Phase III study of carboplatin and paclitaxel alone or with sorafenib in advanced non-small-cell lung cancer. *J Clin Oncol*. 2010;28(11):1835-1842.
4. American Cancer Society: Cancer Facts and Figures 2011. Atlanta, Ga: American cancer Society, 2011.
5. Jemal A, Siegel R, Ward E, et al. (2009) Cancer statistics, 2009. *CA Cancer J Clin* 59:225–249
6. Ries L, Eisner M, Kosary C, et al., eds.: Cancer Statistics Review, 1975-2002. Bethesda, Md: National Cancer Institute, 2005
7. Beasley MB, Brambilla E, Travis WD The 2004 World Health Organization classification of lung tumors. *Semin Roentgenol* 40:90–97(2005)
8. Scagliotti GV, De Marinis F, Rinaldi M, et al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. *J Clin Oncol*.;20:4285-4291(2002).
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10. Azzoli CG, Baker Jr. S, Temin S, et al. American Society of Clinical Oncology clinical practice guideline update on chemotherapy for Stage IV non–small-cell lung cancer. *Am Soc of Clin Onc*. 2009:1-26.

9.2 Labeling Recommendations

The FDA ABRAXANE Review Team has completed the review and revision of this label and the FDA has submitted this revised label to the sponsor for the approval. FDA approval of this Application is contingent on achieving agreement with the Applicant on the FDA revised label

9.3 Advisory Committee Meeting

An advisory committee meeting was not held.

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

/s/

SHAKUNTALA M MALIK
09/07/2012

JOHN R JOHNSON
09/07/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

sNDA: 21660:31

Applicant: CELGENE CORP

Stamp Date: 12/12/2011

Drug Name: Abraxane

NDA Type: (Supplement)

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			electronic
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	505 (b)2			Approved drug Abraxane
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	ranging studies)?				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			This trial was conducted as per SPA agreement
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	This is an approved drug
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all		X		

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	of the raw data needed to derive these endpoints included?				
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	The FDA may request additional data this if deemed necessary
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE?

Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Shakun Malik, MD	January 19, 2012
Reviewing Medical Officer	Date
John Johnson, MD	January 19, 2012
Clinical Team Leader	Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

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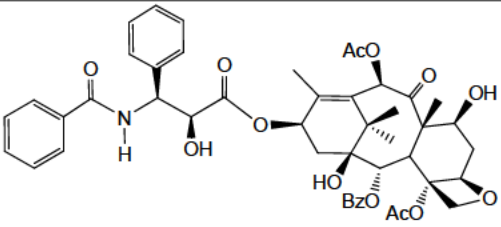
/s/

SHAKUNTALA M MALIK
01/26/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-660/S-031

CHEMISTRY REVIEW(S)

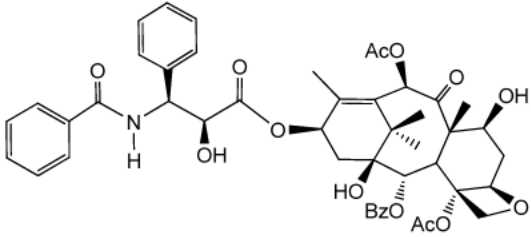
QUALITY (CMC) REVIEW #2		1. ORGANIZATION ONDQA Div 1, Branch 3 HFD-150	2. NDA NUMBER 021-660
3. NAME AND ADDRESS OF APPLICANT Abraxis BioScience, LLC c/o Celgene Corporation 86 Morris Avenue Summit, NJ 07901		4. COMMUNICATION, DATE S-031 (SDN 371) PAS PDUFA Date: Oct. 12, 2012	
5. PROPRIETARY ABRAXANE® for Injectable Suspension	6. NAME OF THE DRUG paclitaxel protein-bound particles for injectable suspension	7. AMENDMENT, REPORT, DATE N/A	
8. COMMUNICATION PROVIDES FOR: Efficacy supplement to add a new indication—advanced non-small cell lung cancer (NSCLC).			
9. PHARMACO. CATEGORY Anti-cancer	10. HOW DISPENSED Rx only	11. RELATED IND, NDA, DMF N/A	
12. DOSAGE FORM Lyophilized cake	13. POTENCY 100 mg/vial (5 mg/mL)		
14. CHEMICAL NAME AND STRUCTURE 5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine			
Company Code: ABI-007 Empirical Formula: C ₄₇ H ₅₁ NO ₁₄ Molecular Weight: 853.91 CASRN: 33069-62-4		Chemical Structure: 	
Indication: Metastatic breast cancer (approved) and non-small cell lung cancer (proposed).			
15. COMMENTS This efficacy supplement proposed to add non-small cell lung cancer to the approved indication of metastatic breast cancer. The total amount of active ingredient to be introduced into the environment in the US is estimated to be ~ (b) (4) ppb per year— about (b) (4) fold less than the <i>de minimus</i> level (1 ppb) established by FDA. A categorical exclusion for environmental assessment is therefore granted. Establishment evaluation is not necessary because no site changes are involved. The changes proposed in this supplement will not impact adversely identify, strength, purity and quality of the drug products.			
16. CONCLUSION AND RECOMMENDATION From the CMC perspective the recommendation for this supplemental application remains APPROVAL—the same as in CMC Review #1.			
17. REVIEWER NAME Huai T. (Ted) Chang	18. REVIEWERS SIGNATURE See appended electronic signature sheet	19. DATE COMPLETED Sep. 17, 2012	
DISTRIBUTION: ORIGINAL JACKET, CSO, REVIEWER, DIVISION FILE			

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/s/

HUAI T CHANG
09/17/2012

HASMUKH B PATEL
09/17/2012

QUALITY (CMC) REVIEW #1	1. ORGANIZATION	2. NDA NUMBER
	ONDQA Div 1, Branch 3 HFD-150	021-660
3. NAME AND ADDRESS OF APPLICANT		4. COMMUNICATION, DATE
Abraxis BioScience, LLC		S-031 (SDN 371)
c/o Celgene Corporation		PAS
86 Morris Avenue		PDUFA Date: Oct. 12, 2012
Summit, New Jersey 07901		
5. PROPRIETARY	6. NAME OF THE DRUG	7. AMENDMENT, REPORT, DATE
ABRAXANE® for Injectable Suspension	paclitaxel protein-bound particles for injectable suspension	N/A
8. COMMUNICATION PROVIDES FOR:		
Efficacy supplement to add a new indication for the first-line treatment of advanced non-small cell lung cancer (NSCLC) in patients.		
9. PHARMACO. CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Anti-cancer	Rx only	N/A
12. DOSAGE FORM	13. POTENCY	
Lyophilized cake	100 mg/vial (5 mg/mL)	
14. CHEMICAL NAME AND STRUCTURE		
5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine		
Company Code:	ABI-007	Chemical Structure: 
Empirical Formula:	C ₄₇ H ₅₁ NO ₁₄	
Molecular Weight:	853.91	
CASRN:	33069-62-4	
Indication: Treatment of breast cancer and non-small cell lung cancer.		
15. COMMENTS		
This efficacy supplement proposed to add a new indication—NSCLC—and was submitted as a PAS which is appropriate. The new NSCLC indication affects mainly the clinical sections in the package insert and did not raise CMC-related issues in the labeling review. There are no CMC-related changes. The changes proposed in this supplement will not impact adversely identify, strength, purity and quality of the drug products.		
16. CONCLUSION AND RECOMMENDATION		
From the CMC perspective this supplemental application, as amended, is recommended for APPROVAL.		
17. REVIEWER NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
Huai T. (Ted) Chang	See appended electronic signature sheet	Aug. 30, 2012
DISTRIBUTION: ORIGINAL JACKET, CSO, REVIEWER, DIVISION FILE		

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08/30/2012

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08/30/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-660/S-031

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 #: 21660
Supplement # 31
Drug Name: Abraxane[®] for Injection Suspension (ABI-007)
Indication(s): First line local advanced or metastatic NSCLC
Applicant: Celgene Corp.
Date(s): Submission: 12/9/2011
PDUFA: 10/9/2012

Review Priority: Standard

Biometrics Division: Division of Biometrics V
Statistical Reviewer: Huanyu (Jade) Chen
Concurring Reviewers: Kun He, Team Leader
Rajeshwari Sridhara, Division Director

Medical Division: Division of Oncology Products 2
Clinical Team: Shakun Malik, M.D., Clinical Reviewer
Johnson Johnson, M.D., Team Leader
Patricia Keegen, M.D., Division Director
Project Manager: Monica Hughes

Keywords: chi-squared test, log-rank test, relative risk ratio

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1. EXECUTIVE SUMMARY

Abraxane[®] (ABI-007) is a novel, solvent-free, albumin-bound, microtubule inhibitor and paclitaxel particle. In this supplemental New Drug Application (sNDA), the applicant is seeking a regulatory approval of the use of abraxane[®] (ABI-007) in combination with carboplatin (ABI-007/carboplatin) when compared with the taxol and carboplatin combination (taxol/ carboplatin) for the first line therapy of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who are not candidates for potentially curative surgery or radiation therapy.

The pivotal study CA031 was a randomized, open-label, active-controlled, multi-center Phase III trial. This study was designed as part of a 505(b) (2) registration strategy under a special protocol assessment (SPA). The primary endpoint was objective response rate (ORR: CR/PR) per independent review committee (IRC) assessment based on Response Evaluation Criteria in Solid Tumors guidelines 1.0. The key secondary endpoints were progression-free survival (PFS) and overall survival (OS). A total of 1052 patients were randomized in a 1:1 allocation (ABI-007/carboplatin: 521 versus taxol/carboplatin: 531).

The data and analyses from the study CA031 demonstrated that the ABI-007/carboplatin arm had statistically significant difference in the ORR when compared with the taxol/carboplatin arm (33% versus 25%, relative risk ratio or odds ratio ($P_{ABI-007}/P_{taxol}$) = 1.31 [95% CI: 1.082, 1.593]) over taxol/ carboplatin. However, ABI-007/carboplatin failed to demonstrate statistically significant improvement in either PFS or OS.

Whether the data and analyses from the current submission demonstrated an overall favorable risk-benefit profile is deferred to the clinical team reviewing this submission.

2. INTRODUCTION

Abraxane[®] (ABI-007) is a novel, solvent-free, albumin-bound, microtubule inhibitor and paclitaxel particle. In this supplemental New Drug Application (sNDA), the applicant is seeking a regulatory approval of the use of abraxane[®] (ABI-007) in combination with carboplatin (ABI-007/carboplatin) when compared with the taxol and carboplatin combination (taxol/ carboplatin) for the first line therapy of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who are not candidates for potentially curative surgery or radiation therapy. The pivotal study CA031 included in the submission was a randomized, open-label, active-controlled, multi-center Phase III trial, which was designed as part of a 505(b) (2) registration strategy under a special protocol assessment (SPA).

2.1 Overview

Lung cancer is the leading cause of cancer-related deaths worldwide, with 1.2 million new cases diagnosed each year. NSCLC is the most common type of lung cancer, accounting for 80% of all new cases. Platinum-containing chemotherapy regimens are the standard first-line treatment in the majority of patients, with taxanes and platinum-based agents used as the standard of care in the US. In the advanced NSCLC, the prevalently used combination of solvent-based paclitaxel/carboplatin results in modest response rate, survival, and toxicity.

ABI-007 was approved in 2005 for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. ABI-007 in combination with carboplatin was evaluated as a first line therapy for NSCLC patients who were not candidates for potentially curative surgery and/or radiation therapy in the pivotal study CA031. This study was a randomized, multi-center, open-label, active -controlled phase III trial comparing the efficacy and safety of ABI-007/carboplatin to taxol/carboplatin.

Study CA031 was conducted at 102 centers within 6 countries. A total of 1052 patients were randomized in a 1:1 allocation (ABI-007/carboplatin: 521 versus taxol/carboplatin: 531). The randomization was centralized and stratified by disease stage (IIIb versus IV), age (< 70 versus ≥ 70 years), gender (male versus female), histology (adenocarcinoma versus squamous cell versus other), and geographic region. The cut off date for the primary efficacy endpoint ORR was 10/12/2009 (patients completed the second response assessment). The cut-off date for all other efficacy endpoints was 1/31/2011.

Reviewer's Comments:

The applicant also submitted supportive efficacy data from two non-randomized open-label phase II studies CA018 and CA028 and can not evaluate efficacy based on the ORR due to non-randomized design. Therefore, this reviewer will focus only on the randomized study CA031. Please refer to the clinical review of this application for the evaluation of studies CA018 and CA028.

2.2 Data Sources

The electronic submission including protocols, statistical analysis plan, study reports, and analysis datasets for the original NDA submission are located on the network with network path: \\CDSESUB1\EVSPROD\NDA021660\0208. Per the reviewer's request, the updated documents and datasets are located on the network path: \\CDSESUB1\EVSPROD\NDA021660\0219.

3. STATISTICAL EVALUATION OF STUDY CA031

Part of the text, tables and figures presented in this section are adapted from the Applicant's Clinical Study Report (CSR).

3.1 Data and Analysis Quality

At the original submission, the applicant did not submit SAS programs. In addition, when the .xpt format datasets were transferred to SAS format, most of the datasets have different names in .xpt and SAS format.

Upon this reviewer's request, the applicant resubmitted the documentations for the analysis datasets with analysis programs. This reviewer was able to duplicate the analysis variable derivation and summary statistics. No further data resubmission was requested.

3.2 Evaluation of Efficacy

3.2.1 Objective

The primary efficacy objective of study CA031 was to compare the objective response rate (ORR: CR/PR) via independent review committee (IRC) assessment based on Response Evaluation Criteria in Solid Tumors (RECIST) guidelines 1.0 when treated with ABI-007/carboplatin versus taxol/carboplatin. The secondary efficacy objectives included progression-free survival (PFS), overall survival (OS), and duration of response in responding patients.

Reviewer's Comments:

This reviewer focuses on the evaluation of efficacy results on the primary endpoint ORR and the key secondary endpoints PFS and OS.

3.2.2 Study Design

Study CA031 was designed to evaluate the efficacy and safety of ABI-007/carboplatin relative to taxol/carboplatin for the first line therapy of patients with advanced NSCLC. There were baseline evaluations, treatment, on treatment response assessments, end of study evaluations, AE resolution follow up evaluations, and post-study follow up phases. During the treatment phase, patients randomized to ABI-007/carboplatin received ABI-007 100 mg/m² weekly (Days 1, 8 and 15 of each 3-weeks cycle) IV over approximately 30 minutes without steroid premedication and without granulocyte colony-stimulating factor prophylaxis followed by carboplatin at AUC = 6 on Day 1 per cycle. Treatment could continue for at least 6 cycles until progressive disease (PD) or unacceptable toxicity. Following discontinuation, patient status continued to be

evaluated monthly for 6 months and every 3 months thereafter for 18 months (a total of 24 months).

Approximately 1050 patients were planned to be randomized in an open-label fashion via IVRS system in a 1:1 ratio to observe superior of ABI-007/carboplatin in ORR (17% versus 24%) in the intent to treat (ITT) population. The randomization was centralized and stratified by the stratification factors by disease stage (IIIb versus IV), age (< 70 versus ≥ 70 years), gender (male versus female), histology (adenocarcinoma versus squamous cell versus other), and geographical region (North America versus Australia/New Zealand versus Eastern Europe versus Asia/Pacific).

The main inclusion criteria were patients aged 18 years or older with a histologically/cytologically confirmed stage IIIb/IV NSCLC; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; measurable disease per RECIST1.0 guidelines; adequate hematologic, hepatic, and renal function; expected survival of > 12 weeks; and no prior treatment for metastatic disease (adjuvant therapy was allowed if it was completed 12 months prior to study entry). Patients were ineligible with active brain metastases including leptomeningeal involvement (prior evidence of metastasis was allowed if it was treated and stable, off-therapy for ≥ 1 month) or baseline peripheral neuropathy ≥ Grade 2.

Reviewer’s Comments:
Table 1 presents discordances between SAP and CSR for the stratification factors.

Table 1. Discordance in Stratification Factors' Classification between SAP and CSR

	SAP	CSR
Disease stage	IIIb versus IV	I, II, IIIa, IIIb, IV, unknown carcinoma / adenocarcinoma,
Histology of primary diagnosis	adenocarcinoma versus squamous cell versus other	large cell carcinoma, squamous cell carcinoma, and other

3.2.3 Efficacy Endpoints

3.2.3.1 ORR

The primary efficacy endpoint ORR was the percentage of patients who achieved an objective confirmed complete response (CR) or partial response (PR) and confirmed by repeat assessments performed no less than 4 weeks after the criteria for response were first met. The radiographic results were evaluated by independent blinded radiological reviewers (IRC) according to RECIST 1.0.

Tumors were assessed by imaging studies every 6 weeks during therapy (at any time during the 6th week). For patients who had not progressed by the end-of-treatment, repeat imaging was performed every 6 weeks until tumor progression was documented or a new anticancer therapy was initiated.

3.2.3.2 PFS

PFS was defined as the time from the day of randomization to the start of disease progression or death (any cause), whichever occurred first, based on the IRC assessment.

3.2.3.3 OS

OS was defined as the time from the day of randomization to death (any cause) as assessed by post-study follow-up performed monthly for 6 months and every 3 months thereafter for 12 months.

3.2.4 Sample Size Considerations

Study CA031 was designed to have 80% power with a two-sided alpha of 0.05 in 525 patients per arm to detect an ORR increase from 17% in the taxol/carboplatin response rate (P_A) to 24% in the ABI-007/carboplatin response rate (P_T) through the date that the last randomized patient completes the second response assessment.

Sample size increase was planned when the interim analyses ORR (detailed in section 3.2.5) difference was lower than assumed 7% ORR increase. Table 2 summarizes the sample size re-estimation algorithm.

Table 2. Sample Size Re-estimation Algorithm

	ABI-007/carboplatin	Taxol/carboplatin	Sample Size
Initial assumed treatment difference	24%	17%	525 patients/arm
Minimum treatment difference of interest	22%	17%	990 patients/arm
Interim observed treatment difference	R_1	R_2	N' patients/arm

Source: SAP Section 2.4 P 11 of 40

- If $N' < 525$, then no sample size adjustment;
- If $525 < N' < 990$, then adjust sample size to N' patients/arm; or
- If $N' \geq 990$, then adjust sample size to 990 patients/arm

Reviewer's Comments:

Based on the interim ORR results, sample size increase was not adjusted.

Secondary efficacy endpoints were to be analyzed only if ORR demonstrated superiority of ABI-007/carboplatin. A hierarchical procedure in controlling multiple comparisons between the key secondary endpoints PFS and OS were pre-specified in the order of PFS and OS at $\alpha = 0.05$. Both PFS and OS analyses were planned to have 85% power to detect a hazard ratio (HR) of 0.8 with a two-sided alpha of 0.05. It was estimated that 735 (70%) PFS and OS events were needed for the final PFS and OS analyses.

3.2.5 Interim Analysis

According to SAP, an interim analysis of ORR was planned after enrolling 200 patients per arm have completed the 2nd response assessment. The Haybittle JL (1971) and Peto et al. (1977) alpha spending function was used to allocate alpha of 0.001 and 0.049 at the interim and final analyses of response rate, respectively.

At the time of the final ORR analysis, the interim analyses of PFS and OS were planned with projected 513 PFS and OS events. The Haybittle JL (1971) and Peto et al. (1977) alpha spending function was used to allocate alpha of 0.001 and 0.049 at the interim and final analyses of response rate, respectively.

Reviewer's Comments:

Table 3 compares the planned study design to the actual conducted analyses in the CSR. Due to high censoring rate in the PFS, there was less than planned number of PFS event by the PFS and OS cut-off date. However, there was more than the planned number of OS events by the PFS and OS cut-off date. Therefore, all the efficacy analyses in the CSR were final analyses.

Table 3. Planned Study Design in SAP and Actual Conducted Analysis in the CSR

Endpoint (Assumption)	Planned		Actual
	Interim	Final	
ORR (17% versus 24%)	400 Patients	All completed 2nd assessment	by 10/12/09
PFS (HR=0.8)	513 events	735 events	609 PFS events by 1/31/11
OS (HR=0.8)	513 events	735 events	744 OS events by 1/31/11

3.2.6 Statistical Methodologies

Intent-to-Treat (ITT) was defined as the population of all randomized patients who have been randomized to receive study treatment. The ITT population was the primary analysis population for all efficacy analyses.

Efficacy Analysis Method for ORR

The superiority of ABI-007/carboplatin to taxol/carboplatin would be established if the lower bound of the 95.1% CI of relative risk ratio or odds ratio (OR) (P_A / P_T) > 1.0 . Treatment comparison of response rates was planned to use the chi-square test. An ORR analysis using the investigative (INV) determination of response was evaluated as a secondary analysis of ORR.

Reviewer's Comments:

Although the terminology relative risk ratio was used in the protocol and SAP, OR will be used in the label.

Efficacy Analysis Methods for PFS and OS

The planned primary analysis for PFS and OS was a stratified log-rank test. The median PFS or OS and survival curves were estimated using the Kaplan-Meier (K-M) method. The hazard ratio (HR) with 95% confidence interval (CI) of treatment arm was estimated by a stratified Cox regression procedure.

Reviewer's Comments:

The stratification factor used for the stratified log-rank test was unspecified in the final SAP.

3.2.7 Applicant's Results and FDA Statistical Reviewer's Findings/ Comments

3.2.7.1 Patient Population and Disposition

Table 4 presents the patient disposition.

Table 4. Patient Disposition in the ITT Population

Patient Disposition	Treatment Arm	
	ABI-007/carboplatin N=521	Taxol/carboplatin N=531
Not Treated	7 (1%)	7 (1%)
Ongoing	3 (<1%)	0
Discontinued	511 (>99%)	524 (100%)
Progressive Disease	275 (54%)	265 (51%)
Unacceptable Toxicity	61 (12%)	62 (12%)
Investigator Discretion	86 (17%)	99 (19%)
Patient Discretion	65 (13%)	67 (13%)
Adverse Event	20 (4%)	24 (5%)
Completed 6 Cycles Therapy	21 (4%)	28 (5%)

Reviewer's Comments:

Disease progression (51%), investigator and patient discretions (30%), and toxicity (12%) were the primary reasons for treatment discontinuation. Although appears to be balanced between treatment arms, there were more than 99% patients discontinued, and 30% patients discontinued due to "investigator discretion" or "patients' discretion", which may cause loss of information and impact on protocol adherence.

3.2.7.2 Baseline Demographics and Disease Characteristics

Table 5 presents the patient demographics and baseline characteristics.

Table 5. Demographics and Baseline Disease Characteristics in the ITT Population

			Treatment Arm N (%)	
			ABI-007/ carboplatin N=521	Taxol/ carboplatin N=531
Age (yr)	Mean (SD) [Median (min - max)]		59.5 (9.1) [60.0 (28-81)]	59.7 (9.5) [60 (24-84)]
	≥ 65		161 (31%)	183 (34%)
	≥70		74 (14%)	82 (15%)
Female			129 (25%)	134 (25%)
Race	Non-Hispanic White		416 (80%)	433 (82%)
	Hispanic White		11 (2%)	5 (<1%)
	Asian		79 (15%)	80 (15%)
	Black		12 (2%)	8 (2%)
Region	Asia/Pacific		74 (14%)	75 (14%)
	Australia/New Zealand		5 (1%)	9 (2%)
	Eastern Europe		358 (69%)	366 (69%)
	North American		84 (16%)	81 (15%)
Disease Stage	IIIb		135 (26%)	116 (22%)
	IV		325 (62%)	344 (65%)
	Other		61 (12%)	71 (13%)
Histology	Squamous carcinoma		229 (44%)	221 (42%)
	Carcinoma/Adenocarcinoma		254 (48%)	264 (50%)
	Large Cell Carcinoma		9 (2%)	13 (2%)
	Other		29 (6%)	33 (6%)
CSR Used Histology	Non-Squamous Carcinoma		292 (56%)	310 (58%)
	Squamous Carcinoma		229 (44%)	221 (42%)
ECOG	0		133 (26%)	113 (21%)
	1		385 (74%)	416 (78%)
	2		3 (<1%)	2 (<1%)
Smoking Status	Never Smoked		137 (26%)	144 (27%)
	Current		214 (41%)	234 (44%)
	Quit		168 (32%)	148 (28%)
	Missing		2 (<1%)	5 (<1%)
Time from Date of Primary Diagnosis to Date of Study Entry:	<1 months		347 (67%)	345 (65%)
	1-3 months		116 (22%)	118 (22%)
	≥ 3 months		58 (11%)	19 (13%)

Reviewer's Comments:

There were slightly more patients in the ABI-007/carboplatin arm for baseline stage IIIB, ECOG 0, and quit smoking status than those in the taxol/Carboplatin arm.

Table 6 presents the CRF stratification factors and the stratification misclassification at interactive voice response system (IVRS).

Table 6. Baseline Stratification Factors Miss-classification Discordance between CRF and SAP

	Treatment Arm N (%)	
	ABI-007/carboplatin N=521	Taxol/carboplatin N=531
Misclassification on Stratification Factors	33 (6%)	32 (6%)

Reviewer's Comments:

Overall, the discordance rate between IVRS and CRF was 6% (65) in the classification for age (1), gender (1), stage (32) or histology (31). Patients were reclassified based on the CRF documents, which appeared balanced between treatment arms. The applicant did not provide IVRS defined stratification factors dataset. Therefore, this reviewer did not conduct sensitivity analysis based IVRS stratification factors.

3.2.7.3 Primary Efficacy Endpoint – ORR

Table 7 presents the primary analysis results of ORR per IRC assessment as well as per INV assessment at the time of the final ORR analysis. There were 170 (33%) and 132 (25%) response in the ABI-007/carboplatin arm and taxol/carboplatin arm, respectively. The OR was 1.31 (95% CI: 1.08, 1.59). The lower boundary of 95% CI of OR per IRC assessment was great than 1, which supports superiority of ABI-007 with respect to OR. In addition, the ORR analysis demonstrated a statistically significant difference in ORR for the treatment based on χ^2 test (P value=0.005).

Table 7. ORR Results by IRC and INV Assessment in the ITT Population

	IRC		INV	
	ABI-007/ carboplatin N=521	Taxol/ carboplatin N=531	ABI-007/ carboplatin N=521	Taxol/ carboplatin N=531
ORR, n (%)	170 (32.6%)	132 (24.9%)	200 (38.4%)	160 (30.1%)
95% CI	(28.6, 36.8)	(21.2, 28.8)	(34.2, 42.6)	(26.2, 34.0)
CR, n(%)	0	1(0.2%)	2 (0.3%)	4(0.7%)
PR, n(%)	170 (32.6%)	131 (24.7%)	198 (38%)	156 (29%)
OR (95% CI)	1.31 (1.08, 1.59)		1.27 (1.08, 1.51)	
χ^2 test p-value	0.005		0.005	

3.2.7.4 Key Secondary Efficacy Endpoint – PFS

According to the SAP, the final analysis for PFS was planned to be conducted once 70% of patients had an event of disease progression or death (any cause), equivalent to 735 events. Due to a higher than expected rate of censoring, the final PFS analysis was performed with 609 events.

Table 8 and Figure 1 present the efficacy analysis for PFS with a total of 120 (11%) progressive diseases and 489 (46%) death events. ABI-007/carboplatin failed to demonstrate a statistically significant difference in PFS compared with the taxol/carboplatin (un-stratified log-rank test p-value: 0.38). The median PFS was 6.3 months for the ABI-007/carboplatin arm and 5.8 months for the taxol/carboplatin arm. The un-stratified hazard ratio was 0.93 with 95% CI (0.79, 1.09).

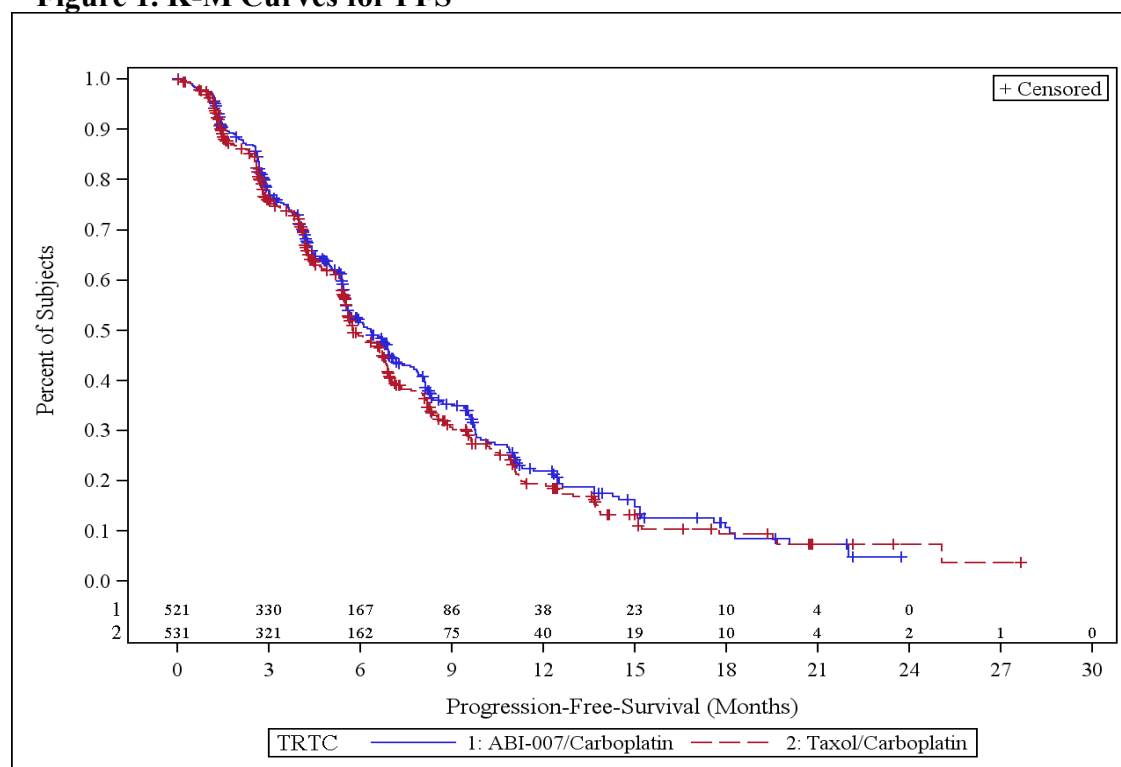
Table 8. IRC PFS Analysis Results in the ITT Population

	ABI-007/carboplatin N=521	Taxol/carboplatin N=531
PFS	297 (57.0%)	312 (58.8%)
PD	65 (12.5%)	55 (10.4%)
Death	232 (44.5%)	257 (48.4%)
Median PFS (months), 95%CI	6.3 (5.6, 7.0)	5.8 (5.6, 6.7)
Stratified HR (95% CI) [p-value]†	0.90 (0.77, 1.06) [0.21]	
Stratified HR (95% CI) [p-value] ‡	0.87 (0.73, 1.04) [0.13]	
Un-Stratified HR (95% CI) [p-value]	0.93 [0.79, 1.09] 0.38]	

†Stratified by CSR defined strata: Region, histology

‡Stratified by SAP defined strata: Region, histology, stage, age, gender

Figure 1. K-M Curves for PFS



Reviewer's Comments:

1. As discussed in sections 3.2.2 and 3.2.6, the analyses for PFS and OS were stratified log-rank test. However, the stratification factors were unspecified in the final SAP. Instead of five strata at the randomization, the applicant used histology and region for the stratified log-rank test in the CSR. In addition, the histology had different classification in the CSR than the SAP. Furthermore, there exist IVRS misclassifications than CSR. Therefore, this reviewer used un-stratified log-rank test results for PFS analysis.
2. Within PFS events, the most events were death events instead of progression.
3. This reviewer also conducted sensitivity analyses of stratified log-rank on PFS using SAP defined strata as well as CSR defined strata. As shown in Table 8, ABI-007/carboplatin failed to demonstrate a statistically significant difference in PFS compared with the taxol/carboplatin in neither of these sensitivity analyses.
4. Due to high censoring rate (42%), this reviewer also evaluated the censoring reasons on PFS. The most common reasons for censoring were discontinuation of scanning by the investigator for progressive disease (28% and 25%, respectively), new anticancer therapy or lesion site surgery (8% for both arms), and two or more consecutive missing response assessment followed by PFS event (3% for both arm). The median follow-up time for PFS in censored patients was approximately 4 months for both arms.

Table 9. Summary of Censoring in PFS per IRC Assessment

	ABI- 007/carboplatin N=521	Taxol/carboplatin N=531
Number of Patients Censored	224 (43%)	219 (41%)
Reason for Censoring		
Completed 18 Months Follow-up	0	4 (<1%)
Lost to Follow-up	10 (2%)	12 (2%)
Scanning Discontinued per PD by Investigator	144 (28%)	134 (25%)
New Anticancer Therapy or Lesion Site Surgery	40 (8%)	44 (8%)
≥ 2 Consecutive Missing tumor assessments	15 (3%)	14 (3%)
PFS Follow-up Ongoing	15 (3%)	11 (2%)

5. The PFS results were not reliable due to inadequate follow-up and missing data.

3.2.7.5 Secondary Efficacy Endpoint – OS

According to the SAP, the final analysis for OS was planned to be conducted once 70% of patients had died (any cause), equivalent to 735 death events. The actual final OS analysis was performed with 744 (71%) death events. Table 10 and Figure 2 present the final analysis results for OS. The median OS was 12.1 months for the ABI-007/carboplatin arm and 11.2 months for the taxol/carboplatin arm. The un-stratified hazard ratio was 0.93 with 95% CI (0.79, 1.09).

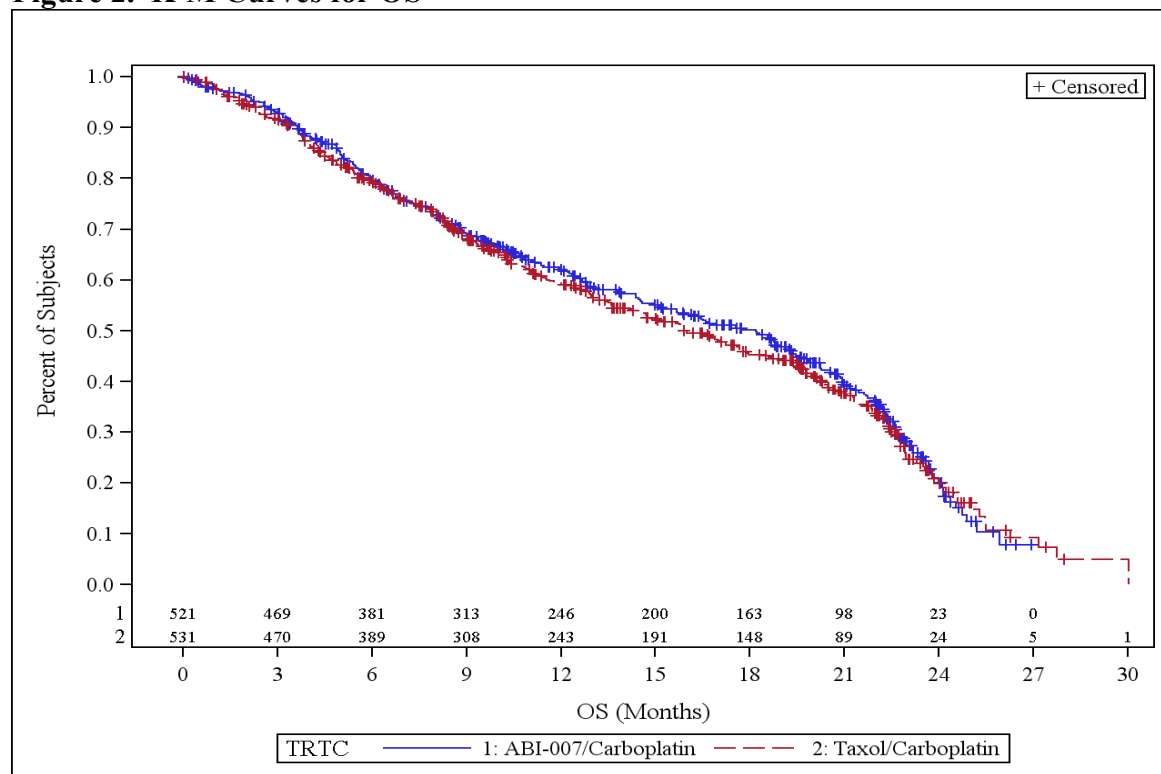
Table 10. OS Analysis Results in ITT Population

	ABI-007/carboplatin N=521	Taxol/carboplatin N=531
Death Events	360(69.1%)	384 (72.3%)
Median OS (months), 95%CI	12.1 (10.8, 12.9)	11.2 (10.2, 12.6)
Stratified HR (95% CI) [p-value] †*	0.92 (0.80, 1.07) [0.27]	
Stratified HR (95% CI) [p-value] ‡*	0.94 (0.81, 1.10) [0.45]	
Un-Stratified HR (95% CI) [p-value]*	0.93 (0.81, 1.08) [0.34]	

†Stratified by CSR defined strata: Region, histology

‡Stratified by SAP defined strata: Region, histology, stage, age, gender

*Nominal P value

Figure 2. K-M Curves for OS

Reviewer's Comments:

1. Due to the hierarchical procedure design and failure on the PFS, alpha was not reserved in OS analysis. All the p values are nominal p value.
2. Due to the same reasons as discussed on section 3.2.7.4, this reviewer used un-stratified log-rank test results as primary analysis for OS.
3. As shown in Table 10, neither the primary nor the sensitivity analyses on OS demonstrated statistically significant difference on the ABI-007/carboplatin arm compared with the taxol/carboplatin arm.

3.3 Evaluation of Safety

Table 11 provides the frequency and severity of adverse events (AEs) that have been reported in $\geq 5\%$ incident rate using MedDRA System Organ Class and Preferred Term, Version 12.1.

Table 11. AEs with $\geq 5\%$ Incident Rate in the As-Treated Population Based on MedDRA V12.1

System Organ Class	Preferred Term	ABI-007/carboplatin N=514		Taxol/carboplatin N=524	
		All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Blood and lymphatic system disorders	Anemia	98	28	91	7
	Leukopenia	89	24	83	24
	Neutropenia	85	47	83	58
	Thrombocytopenia	68	18	55	9
Skin and subcutaneous tissue disorders	Alopecia	56	<1	60	0
	Rash	10	0	8	<1
Nervous system disorders	Peripheral neuropathy	26	2	40	5
	Dysgeusia	7	0	6	0
	Headache	7	<1	4	<1
	Dizziness	6	0	4	<1
General disorders and administration site conditions	Fatigue	25	4	23	4
	Asthenia	16	3	15	4
	Edema peripheral	10	0	4	<1
	Pyrexia	9	0	8	0
	Chest pain	5	<1	4	<1
Gastrointestinal disorders	Nausea	27	<1	25	<1
	Constipation	16	<1	13	<1
	Diarrhea	15	<1	11	0
	Vomiting	12	<1	12	<1
	Stomatitis	6	0	4	0
Respiratory thoracic and mediastinal disorders	Dyspnea	12	3	12	3
	Cough	9	<1	7	0
	Epistaxis	7	0	2	0
	Hemoptysis	4	<1	5	0
Investigations	Alanine aminotransferase increased	9	2	9	<1
	Weight decreased	8	1	6	<1
	Aspartate aminotransferase increased	8	<1	6	<1
Musculoskeletal and connective tissue disorders	Arthralgia	13	<1	25	2
	Myalgia	10	<1	19	2
Metabolic and nutrition disorders	Decreased appetite	17	2	18	<1

Infections and infestations	Pneumonia	5	2	3	2
Psychiatric disorders	Insomnia	5	0	8	<1

Table 12 provides the frequency and severity of adverse events (AEs) that have been reported in $\geq 5\%$ incident rate using the MedDRA 14.0 SMQ neuropathy (broad scope) for Peripheral neuropathy.

Table 12. AEs with $\geq 5\%$ Incident Rate in the As-Treated Population Based on MedDRA 14.0 SMQ Neuropathy (Broad Scope) and Laboratory Test

System Organ Class	Preferred Term	ABI-007/carboplatin N=514		Taxol/carboplatin N=524	
		All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Nervous system disorders	Peripheral neuropathy*	48	3	64	12

Table 13 provides the frequency and severity of adverse events (AEs) that have been reported in $\geq 5\%$ incident rate using the laboratory assessments.

Table 13. AEs with $\geq 5\%$ Incident Rate in the As-Lab-Tested Population Based on Laboratory Tests

Lab Test	ABI-007/carboplatin (N=514)				Taxol/carboplatin (N=524)			
	GL1_4	GL3_4	GH1_4	GH3_4	GL1_4	GL3_4	GH1_4	GH3_4
Neutrophils (ANC)	430/508 (85%)	239/508 (47%)			424/513 (83%)	296/513 (58%)		
WBC	451/508 (89%)	121/508 (24%)			425/514 (83%)	121/514 (24%)		
Hemoglobin	496/508 (98%)	140/508 (28%)			466/514 (91%)	35/514 (7%)		
Platelet Count	344/508 (68%)	92/508 (18%)			284/513 (55%)	47/513 (9%)		
Lymphocytes	257/508 (51%)	40/508 (8%)			242/513 (47%)	53/513 (10%)		
Alkaline Phosphatase			96/491 (20%)	5/491 (1%)			126/498 (25%)	4/498 (<1%)
ALT (SGPT)			128/492 (26%)	5/492 (1%)			113/498 (23%)	4/498 (<1%)
AST (SGOT)			110/492 (22%)	5/492 (1%)			103/498 (21%)	4/498 (<1%)
Total Bilirubin			21/492 (4%)				23/498 (5%)	2/498 (<1%)
Albumin	58/71 (82%)	2/71 (3%)			54/75 (72%)			
Creatinine			45/490 (9%)				52/497 (10%)	
Calcium	38/67 (57%)	1/67 (1%)	1/67 (1%)		37/73 (51%)	1/73 (1%)		

Lab Test	ABI-007/carboplatin (N=514)				Taxol/carboplatin (N=524)			
	GL1_4	GL3_4	GH1_4	GH3_4	GL1_4	GL3_4	GH1_4	GH3_4
Glucose	6/491 (1%)		296/491 (60%)	8/491 (2%)	4/495 (<1%)	1/495 (<1%)	286/495 (58%)	16/495 (3%)
Potassium	8/71 (11%)	2/71 (3%)	26/71 (37%)		7/75 (9%)	2/75 (3%)	22/75 (29%)	2/75 (3%)
Sodium	24/71 (34%)	3/71 (4%)	2/71 (3%)		30/75 (40%)	4/75 (5%)	1/75 (1%)	

Reviewer's Comments:

1. *Per medical review team's request, this reviewer conducted safety analyses. This reviewer duplicated the safety results proposed in the Table 5 of the label except the blood and lymphatic system disorder. FDA's results on blood and lymphatic system disorder were confirmed by the applicant to be used in the label. In addition, this reviewer performed further analyses and provided Table 13.*
2. *Please refer the clinical review of this application for further discussion.*

3.4 Benefit/Risk Ratio

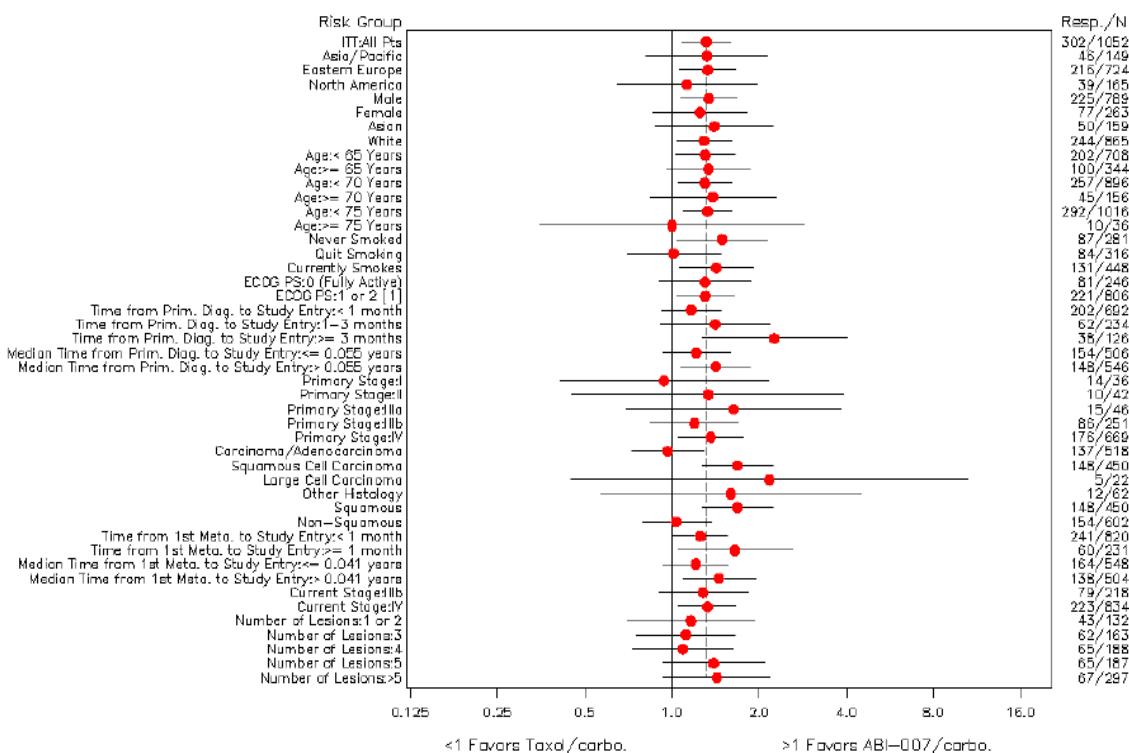
ABI-007/carboplatin arm demonstrated a statistically significant improvement in the primary endpoint ORR, but failed to demonstrate any improvement on either PFS or OS. Whether the submission demonstrated an overall favorable risk-benefit profile on ABI-007/carboplatin arm is deferred to the clinical team reviewing this submission.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 ORR Subgroup Analysis

Figure 3 summarizes ORR subgroup analysis results, which were considered as exploratory.

Figure 3. Subgroup Analysis Results of IRC ORR in the ITT Population



Note: The horizontal axis uses a logarithmic scale.

Note: The Australia/New Zealand region (N = 14 patients) is not shown.

[1] ECOG PS: 1 (Restrictive but Ambulatory) or 2 (Ambulatory but Unable to Work)

Source: Figure 3.0

Source: CSR Figure 5 P 94 of 6164

Reviewer's Comments:

Per subgroup analyses by histology, only squamous cell subgroup demonstrated clinical benefit on the treatment. The histology subgroup analysis results should be included in the label.

5. SUMMARY AND CONCLUSIONS

In this NDA, the applicant is seeking a regulatory approval of the use of abraxane[®] (ABI-007) in combination with carboplatin when compared with the taxol and carboplatin combination for the first line therapy of patients with locally advanced or metastatic NSCLC who were not candidates for potentially curative surgery or radiation therapy. The pivotal study CA031 was a randomized, open-label, active-controlled, multi-center Phase III trial as part of a 505(b) (2) registration strategy under a SPA.

5.1 Statistical Issues

The following are some statistical issues in the submission:

1. Per SAP, the applicant's efficacy analysis for either PFS or OS was stratified log-rank test. As discussed in sections 3.2.2, 3.2.6, and 3.2.7.4, due to the discordance between

SAP and CSR, the un-stratified log-rank test was used as the efficacy analysis for the PFS and OS.

2. The PFS results were not reliable due to inadequate follow-up and missing data.
3. There were more than 99% patients discontinued, and 30% patients discontinued due to “investigator discretion” or “patients’ discretion”, which may cause loss of information and impact on protocol adherence.
4. Regarding to the ORR histology subgroup analyses, only squamous patients demonstrated clinical benefit on the treatment arm.

5.2 Collective Evidence

The data and analyses from the study CA031 demonstrated that the ABI-007/carboplatin arm had statistically significant difference in the ORR (33% versus 25%, relative risk ratio ($P_{ABI-007}/P_{taxol}$) = 1.31 [95% CI = 1.082, 1.593]).

However, the trial failed to demonstrate statistically significant improvement in either PFS or OS for ABI-007/carboplatin arm. The un-stratified log-rank test p-values were 0.38 and 0.34, respectively. The median PFS was 6.3 months for the ABI-007/carboplatin arm and 5.8 months for the taxol/carboplatin arm with HR 0.93 and 95% CI (0.79, 1.09). The median OS was 12.1 months for the ABI-007/carboplatin arm and 11.2 months for the taxol/carboplatin arm; the un-stratified Cox proportional HR was 0.93 with 95% CI (0.81, 1.08).

5.3 Conclusions and Recommendations

Based on the data and analyses from the study CA031, ABI-007/carboplatin arm demonstrated a statistically significant improvement in the primary endpoint ORR, but failed to demonstrate any improvement on either PFS or OS. Whether the data and analyses of the submission demonstrated an overall favorable risk-benefit profile on ABI-007/carboplatin arm is deferred to the clinical team reviewing this submission.

5.4 Labeling recommendations

1. The subgroup analysis of ORR by histology should be included in the label.
2. (b) (4)
3. (b) (4)
4. In the Table 5 of the label, the blood and lymphatic system disorder AE ($\geq 5\%$) results should be updated based on this reviewer’s calculation.

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

/s/

HUANYU CHEN
08/22/2012

KUN HE
08/22/2012
Accepted as a complete review.

RAJESHWARI SRIDHARA
08/22/2012

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 21660

Applicant: Celgene Corp.

Stamp Date: 12/12/2011

Drug Name: Abraxane

NDA/BLA Type: Standard

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	√			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	√			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	√			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	√			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	√			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	√			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.		√		The DSMB meeting minutes and data are unavailable
Appropriate references for novel statistical methodology (if present) are included.	√			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	√			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	√			

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

/s/

HUANYU CHEN
01/20/2012

KUN HE
01/20/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-660/S-031

CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	21-660 / SE31 (SDN 371)
Submission Type	Efficacy Supplement
Submission Dates	12/09/2011; 03/08/2012
Review Classification	Standard
PDUFA Due Date	10/12/2012
Brand Name	ABRAXANE® for Injectable Suspension
Generic Name	Paclitaxel protein-bound particles for injectable suspension
Proposed Indication	Non-small cell lung cancer (NSCLC)
Formulation	Single use vial containing 100 mg of lyophilized power of paclitaxel (bound to human albumin)
Dosing Regimen	100 mg/m ² IV over 30 min on Days 1, 8, and 15 of each 21-day cycle in combination with carboplatin AUC=6 min•mg/mL IV on Day 1 only of each 21-day cycle
Related IND	55,974
Sponsor	Celgene Corporation
OCP Reviewer	Lillian H. Zhang, Ph.D.
OCP Team Leader	Hong Zhao, Ph.D.
OCP Division	Division of Clinical Pharmacology 5 (DCP5)
Clinical Division	Division of Oncology Products 2 (DOP2)

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1 EXECUTIVE SUMMARY

ABRAXANE[®], a microtubule inhibitor, is an albumin-bound form of paclitaxel. The original NDA 21,660 was submitted under the 505(b)(2) using TAXOL[®] (paclitaxel) as a reference listing drug (RLD) and was approved by the FDA in 2005 for the treatment of advanced breast cancer (BC).

The current 505(b)(2) efficacy supplemental NDA (sNDA) for Abraxane is to seek approval for a proposed new indication: in combination with carboplatin as the first-line treatment of non-small cell lung cancer (NSCLC) in patients who are not candidates for potentially curative surgery and/or radiation therapy. The recommended dosing regimen of Abraxane for the newly proposed indication is 100 mg/m² administered as an intravenous (IV) infusion over 30 minutes on Days 1, 8, and 15 of each 21-day cycle which is different from the approved dosing regimen (260 mg/m² administered IV over 30 minutes Q3W) for the BC indication. The recommended dose of carboplatin is AUC = 6 mg•min/mL on Day 1 only of each 21-day cycle, beginning immediately after the completion of Abraxane administration.

Clinical efficacy of Abraxane in patients with NSCLC was evaluated in a registration trial (Study CA031) in which Abraxane/carboplatin demonstrated superiority over the control arm (Taxol/carboplatin) for the primary efficacy endpoint of Objective Response Rate (ORR) (33% versus 25%, p = 0.005; pA/pT = 1.31 [95.1% CI = 1.08, 1.59]). Increases of Grade 3/4 thrombocytopenia and anemia and slightly lower incidences of Grade 3/4 neuropathy, neutropenia, arthralgia and myalgia were seen with the Abraxane/carboplatin arm compared to the Taxol/carboplatin arm. The most common adverse reactions (≥ 20%) when Abraxane is used in combination with carboplatin are anemia, leukopenia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue.

The pharmacokinetics (PK) profile of paclitaxel in NSCLC patients who received combination therapy of Abraxane/carboplatin at the recommended dosing regimen (100 mg/m² for Abraxane and AUC = 6 min•mg/mL for carboplatin) was similar to that observed in patients with solid tumors who received the same dose of Abraxane alone. There was no clinically relevant PK drug-drug interactions observed between paclitaxel and carboplatin.

1.1 RECOMMENDATIONS

This sNDA is acceptable from a clinical pharmacology perspective provided that the Applicant and the Agency come to an agreement regarding the labeling language.

1.2 PHASE 4 REQUIREMENTS AND COMMITMENTS

There are no clinical pharmacology requested PMRs or PMCs.

Signatures:

Lillian H. Zhang, Ph.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 5

Hong Zhao, Ph. D.
Clinical Pharmacology Team Leader
Division of Clinical Pharmacology 5

Cc: DOP2: CSO – **M Hughes**; MTL – **J Johnson**; MO – **S Malik**
DCP5: Reviewers – **LH Zhang**; TL – **H Zhao**
Division Deputy Director – **B Booth**; Division Director - **A Rahman**

1.3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Registration Trial Design: Study CA031 was a controlled, randomized, open-label, Phase 3 trial to compare the efficacy and safety of Abraxane in combination with carboplatin to Taxol in combination with carboplatin for the treatment of NSCLC. A total of 1,052 patients with advanced NSCLC were randomized 1:1 to the following treatment arms:

- Arm A: Abraxane 100 mg/m² weekly (QW) + carboplatin (AUC = 6 min•mg/mL) every 3 weeks (Q3W)
- Arm B: Taxol 200 mg/m² Q3W + carboplatin (AUC = 6 min•mg/mL) Q3W

Dose Selection: The dose and dosing regimen of Abraxane used in the pivotal trial CA031 (100 mg/m² administered IV over 30 minutes QW on Days 1, 8, and 15 of each 21-day cycle, followed by carboplatin (AUC = 6 min•mg/mL) IV administered on Day 1 only of each 21-day cycle) was primarily based upon the clinical observation in supporting Phase 2 trial CA028 in which acceptable tolerability and efficacy of Abraxane was demonstrated in the patients with advanced NSCLC.

Efficacy Results: The primary efficacy endpoint of Study CA031 is overall response rate (ORR) defined as the proportion of patients with a confirmed complete or partial overall response based on the blinded radiological assessment. Patients with advanced NSCLC treated with Abraxane/carboplatin showed a statistically significantly higher ORR compared to patients treated with Taxol/carboplatin (33% vs. 25%, p = 0.005; pA/pT = 1.31 [95.1% CI = 1.02, 1.59]).

Pharmacokinetics: The PK profile of paclitaxel in patients with advanced NSCLC who received the combination therapy of Abraxane/carboplatin at the recommended dosing regimens (100 mg/m² QW for Abraxane and AUC = 6 min•mg/mL for carboplatin Q3W) was similar to that observed in patients with solid tumors who received the same dose of Abraxane alone. No clinically relevant PK drug-drug interactions were observed between paclitaxel and carboplatin in Japanese patients with advanced NSCLC who received the Abraxane/carboplatin combination therapy. There was no difference in the PK of paclitaxel after Abraxane administration between Japanese and non-Japanese patients.

Safety profile: The most common adverse reactions (≥ 20%) when Abraxane is used in combination with carboplatin were anemia, leukopenia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue. Patients in the Abraxane/carboplatin arm showed an increased incidence of anemia and thrombocytopenia and a decreased incidence of peripheral neuropathy, peripheral sensory neuropathy, and arthralgia versus the Taxol/carboplatin arm.

2 QUESTION BASED REVIEW

For brevity only QBR questions related to the current sNDA submission are addressed below. For additional details please refer to the clinical pharmacology reviews in DAARTS:

- NDA 21-660 (S-000) for BC (SDN 1, submission date: 19-March-2004);

(b) (4)

2.1 GENERAL ATTRIBUTES

What pertinent regulatory background or history regarding the study drug?

Abraxane is a solvent-free and an albumin-bound form of paclitaxel. It has been developed with the objective of eliminating Cremophor-EL and alcohol from Taxol (paclitaxel) to overcome problems associated with these solvents, such as hypersensitivity. The original NDA was submitted under 505(b)(2) using Taxol as a RLD and was approved by the FDA on January 7, 2005 for the treatment of BC after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. The recommended dosing regimen for Abraxane is 260 mg/m² administered IV over 30 minutes every 3 weeks (Q3W).

2.1.1 What are the proposed mechanisms of action and therapeutic indications?

Abraxane is a microtubule inhibitor 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. The proposed indication for this sNDA is the use of Abraxane in combination with carboplatin for the treatment of NSCLC who are not candidates for potentially curative surgery and/or radiation therapy.

2.1.2 What are the proposed dosage and route of administration?

ABRAXANE[®] is supplied as a lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to IV infusion. Each single-use vial contains 100 mg of paclitaxel (bound to human albumin) and approximately 900 mg of human albumin with a mean particle size of approximately 130 nanometers, and is free of solvents. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. The dosage form is administered as an IV infusion over 30 minutes on Days 1, 8, and 15 of each 21-day cycle.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical trials used to support dosing or claims?

Efficacy and safety for Abraxane in combination with carboplatin for the first-line treatment of patients with advanced NSCLC were primarily supported by data from the registration Phase 3 Study CA031. Data from three supportive Phase 2 trials conducted in NSCLC patients, CA028 (Abraxane/carboplatin combination therapy), and CA015 and CA018 (b) (4) provided additional support.

Study CA031 was a controlled, randomized, open-label, Phase 3 superiority trial to compare Abraxane/carboplatin vs. Taxol/carboplatin as first-line therapy in a total of 1,052 patients with advanced NSCLC. Eligible patients were randomized 1:1 to one of the two treatment arms:

- Arm A: ABI-007 100 mg/m² administered IV weekly on Days 1, 8, and 15 of each 21-day cycle, immediately followed by carboplatin (AUC = 6 min•mg/mL) IV administered on Day 1 only of each 21-day cycle
- Arm B: Taxol 200 mg/m² Q3W + carboplatin (AUC = 6 min•mg/mL) Q3W

Randomization was stratified by factors known to be prognostic in NSCLC, i.e. disease stage (IIIb vs IV), age (< 70 vs ≥ 70 years), gender, histology (adenocarcinoma vs squamous cell vs other), and geographic region.

Key features of Study CA031 and the other three supportive trials are summarized in Table 1:

Table 1 Trials to Support Efficacy and Safety of Abraxane in NSCLC Patients

Study	Objectives of the study	Design	Doses	Patient Number of Patients
Pivotal				
CA031	Compare disease response and safety/tolerability of Abraxane/carboplatin to Taxol/carboplatin	Phase 3; Randomized; Multicenter; Open-label; Active-Controlled; Superiority.	Abraxane 100 mg/m ² IV over 30 min QW and carboplatin (AUC=6) IV Q3W (on Day 1) Taxol 200 mg/m ² IV over 3 hours and carboplatin (AUC=6) IV, both Q3W (on Day 1).	Abraxane: N=521 Taxol: N=531
Supportive				
CA028	Safety and efficacy of Abraxane in combination with carboplatin	Phase 2; Multicenter; Open-label; Dose-escalation; Uncontrolled.	Abraxane IV over 30 min QW or Q3W and carboplatin (AUC=6) IV on Day 1 of cycle. Abraxane Q3W: Cohort 1: 225 mg/m ² ; Cohort 2: 260 mg/m ² ; Cohort 3: 300 mg/m ² ; Cohorts 4,8: 340 mg/m ² Abraxane QW: Cohort 5: 140 mg/m ² on Days 1 and 8; Cohort 6: 100 mg/m ² on Days 1, 8, and 15; Cohort 7: 125 mg/m ² on Days 1, 8, and 15	N = 25 each at 225, 260, 300, 140, 100, 125 mg/m ² ; and N = 101 at 340 mg/m ²
CA018	Safety and efficacy	Phase 2; Multicenter; Open-label; Uncontrolled.	Abraxane 260 mg/m ² IV over 30 min Q3W.	N = 43
CA015	Phase 1: MTD and DLT. Phase 2: safety and efficacy	Phase 1/2; Open-label; Dose-escalation; Uncontrolled.	<u>Phase 1</u> Abraxane at 100, 125, 150, or 175 mg/m ² IV over 30 min QW. <u>Phase 2</u> Abraxane at 125 mg/m ² (MTD) IV over 30 min QW. and Abraxane at 125 mg/m ² IV over 2 hrs QW	IV over 30 min: N = 3, 100 mg/m ² ; N = 40, 125 mg/m ² ; N = 7, 150 mg/m ² ; IV over 2 hours: N = 25, 125 mg/m ²

Additional Clinical Trials

Table 2 summarizes additional trials pertaining clinical pharmacology and study reports that provide data on PK and drug interactions of paclitaxel in the Abraxane/carboplatin combination therapy.

Table 2 Clinical Pharmacology Studies Contributing Data to the sNDA

Report No	Study description, Population	Objectives	Treatment	No. of Patients
BIO-VT-5	Sub-study of trial CA031 NSCLC (White)	Sparse PK	Same as in trial CA031: Abraxane/carboplatin combination therapy	N = 15
08DA33	Sub-study of trial CA031 NSCLC (Japanese)	Drug-drug interaction between Abraxane and carboplatin	Same as in trial CA031: Abraxane/carboplatin combination therapy	N = 12
05DA11	Study J0101 Advanced solid tumors (Japanese)	Safety, PK	Single ascending dose: Abraxane: 80 – 125 mg/m ² Cycle 1 Day 1	N = 15
05DA13	Study J0100 Advanced solid tumors (Japanese)	Safety, PK	Single ascending dose: Abraxane: 200 – 300 mg/m ² Cycle 1 Day 1	N = 12

2.2.2 What is the basis for selecting the clinical endpoint or surrogate and how are they used to assess efficacy in the pivotal clinical study? What is the clinical outcome in terms of efficacy and safety?

Primary Efficacy Endpoint: The primary efficacy endpoint for Study CA031 was overall response rate (ORR) defined as the proportion of patients with a confirmed complete or partial overall response based on the blinded radiological assessment according to RECIST guidelines.

Abraxane/carboplatin combination demonstrated superiority over the control arm for the primary efficacy endpoint ($p < 0.005$) in patients with advanced NSCLC (see Table 2).

Table 3 Summary of the Primary Efficacy Result

	Abraxane (100 mg/m ² QW) + carboplatin (N=521)	Taxol (200 mg/m ² Q3W) + carboplatin (N=531)
ORR		
Confirmed complete or partial overall response, n (%)	170 (33%)	132 (25%)
95% CI	28.6, 36.7	21.2, 28.5
Odds Ratio (Abraxane/Taxol) (95% CI)	1.31 (1.08, 1.59)	

Secondary Efficacy Endpoints: The key secondary endpoints for Study CA031 were progress free survival (PFS) and overall survival (OS). There was no statistically significant improvement in the Abraxane/carboplatin arm compared to Taxol/carboplatin arm for both PFS and OS. Median PFS was 6.3 months (95% CI = 5.6, 7.0 months) in the Abraxane/carboplatin arm and 5.8 months (95% CI = 5.6, 6.7 months) in the Taxol/carboplatin arm. Median OS was 12.1 months (95% CI = 10.8, 12.9 months) in the Abraxane/carboplatin arm and 11.2 months (95% CI = 10.3, 12.6 months) in the Taxol/carboplatin arm.

Safety: According to the Applicant, the Abraxane/carboplatin treatment regimen was generally better tolerated than the Taxol/carboplatin treatment regimen, with clinically and statistically significant reductions in frequency and duration of severe peripheral neuropathy, arthralgia and myalgia, and neutropenia. The most common adverse reactions ($\geq 20\%$) when Abraxane is used in combination with carboplatin were anemia, leukopenia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue. Patients in the Abraxane/carboplatin arm showed an increased incidence of anemia and thrombocytopenia versus the Taxol/carboplatin arm.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. The plasma concentrations of total paclitaxel of Abraxane were determined by a validated liquid chromatography atmospheric pressure ionization tandem mass spectrometry method (LC-API/MS/MS). The concentrations of platinum in plasma and in the protein-free ultrafiltered plasma were determined by a validated inductively coupled plasma-mass spectrometry method. The performance of the bioanalytical method is reviewed in Section 2.5.

2.2.4 Pharmacokinetic (PK) characteristics of the drug and its major metabolites

2.2.4.1 What are the PK characteristics of paclitaxel in patients with NSCLC? Is the PK profile of paclitaxel in NSCLC patients similar to that in solid tumors?

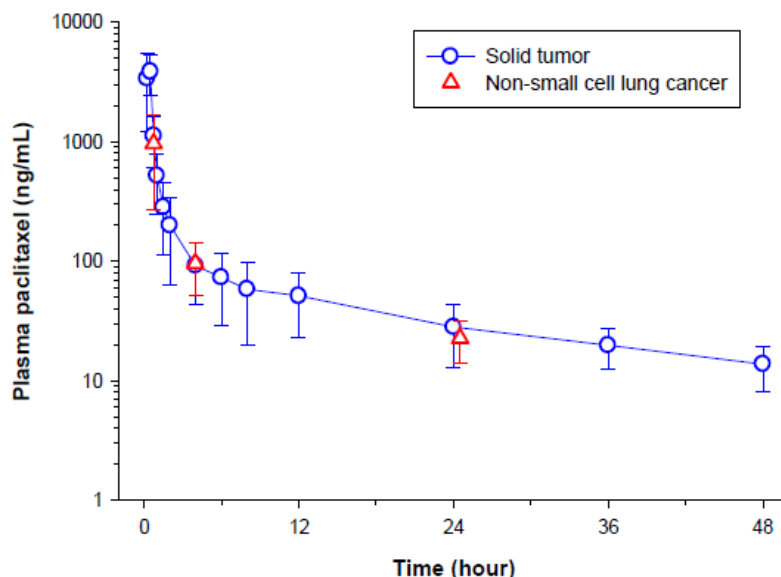
In the pivotal trial CA031, blood samples for paclitaxel PK analysis were collected on Day 1 of Cycle 1 at 0.75, 4, and 24.5 hours after the start of Abraxane infusion in 15 patients, 13 from Europe and 2 from US. Due to the limited number of sampling time points available, a reliable PK analysis could not be performed. Instead only the comparative concentration data are summarized and presented in Table 4 and Figure 1.

Table 4 Plasma Concentrations of Paclitaxel in Patients with NSCLC Receiving Abraxane/Carboplatin and in Patients with Solid Tumors Receiving Abraxane Alone (Cycle 1, Day 1)

Time after the Start of Abraxane Infusion (h)	Plasma Paclitaxel Conc.* (ng/mL)	
	NCSCl ¹ (n = 15)	Solid Tumors ² (n = 6)
0.75	966 (699)	1117 (519)
4.0	96.3 (44.5)	91.7 (48.7)
24	--	28.1 (15.4)
24.5	22.6 (8.5)	--

* Mean (SD); ¹trial CA031; ²trial CA005-0 excluding 1 patient who had severe obstructive liver disease

Figure 1 Mean (SD) Plasma Concentrations of Paclitaxel between Patients with NSCLC and Solid Tumors (Cycle 1, Day 1)



The impact of the type of tumors on PK of paclitaxel was explored by comparing the single-dose PK data observed in patients with NSCLC in trial CA031 to the historical data (trial CA005-0 submitted in the original NDA) in patients with solid tumors. As presented in Table 4 and in Figure 1, the mean concentrations of paclitaxel observed at 0.75, 4, and 24.5 hours after the start of the infusion in patients with NSCLC in Study CA031 were comparable with the historical data observed in patients with solid tumors who received the same dose of Abraxane (100 mg/m²) without concomitant carboplatin. Based on this similarity, tumor type would not expect to have a significant effect on the PK of paclitaxel after Abraxane administration.

2.3 INTRINSIC FACTORS

2.3.1 Hepatic Impairment

A dedicated hepatic impairment study, CA037, was conducted in patients with advanced solid tumors and hepatic impairment. In the trial, Abraxane was administered as an IV infusion over 30 min Q3W. Based on the study results, in the currently approved label for the breast cancer indication, no dosage reduction is recommended for patients with mild hepatic impairment and the recommended dose reduction for patients with moderate and severe hepatic impairment are approximately 25% and 50%, respectively, of the recommended starting dose, 260 mg/m². Please refer to the sNDA 21-660 (Submission Date: 01-August-2008) for more details. As tumor type would not expect to have a significant effect on the PK of paclitaxel after Abraxane administration, the same dose adjustment recommendation will be applied to patients with advanced NSCLC and with moderate or severe hepatic impairment.

2.4 EXTRINSIC FACTORS

2.4.1 Drug-drug interactions

2.4.1.1 Are there any *in vivo* drug-drug interaction (DDI) studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

(b) (4) paclitaxel is metabolized primarily in liver by cytochrome P450 (CYP) 2C8 and CYP 3A4 and urinary excretion of the unchanged drug only accounts for approximately 4% of the dose (260 mg/m²). For carboplatin, the major route of elimination is renal excretion of the unchanged drug, with approximately 71% of the dose excreted in urine within 24 hours (PARAPLATIN[®] PI). So far, there have been no reports indicating that carboplatin is an inhibitor or inducer of any CYP enzymes.

The potential PK drug-drug interaction (DDI) between paclitaxel and carboplatin was investigated as a sub-study of trial CA031 in 12 Japanese patients with advanced NSCLC. This was an open-label, multicenter, single-sequence, within patient PK comparison in which Abraxane and carboplatin were administered at the recommended dose and dosing regimen: Abraxane on Days 1, 8, and 15 of Cycle 1 by IV infusion over 30 minutes at a dose of 100 mg/m²; carboplatin with an targeted AUC of 6 min•mg/mL administered by IV infusion over 60 minutes on Day 1 following the completion of Abraxane infusion. Serial blood sampling was performed for 72 hours after the start of Abraxane infusion on Days 1 and 15 for the determination of paclitaxel concentrations in plasma, and for 23.5 hours after the start of carboplatin infusion on Day 1 for the determination of platinum concentration in plasma and ultrafiltrate.

The mean (±SD) plasma concentration profiles for paclitaxel administered as Abraxane in the absence and presence of carboplatin are presented in Figure 2. Selected PK parameters and their statistical comparisons in ten patients who had blood samples available on both Day 1 and Day 15 are summarized in Table 5.

Figure 2 Mean (SD) Plasma Concentrations of Paclitaxel in Japanese NSCLC Patients Receiving Abraxane with or without Subsequent Carboplatin

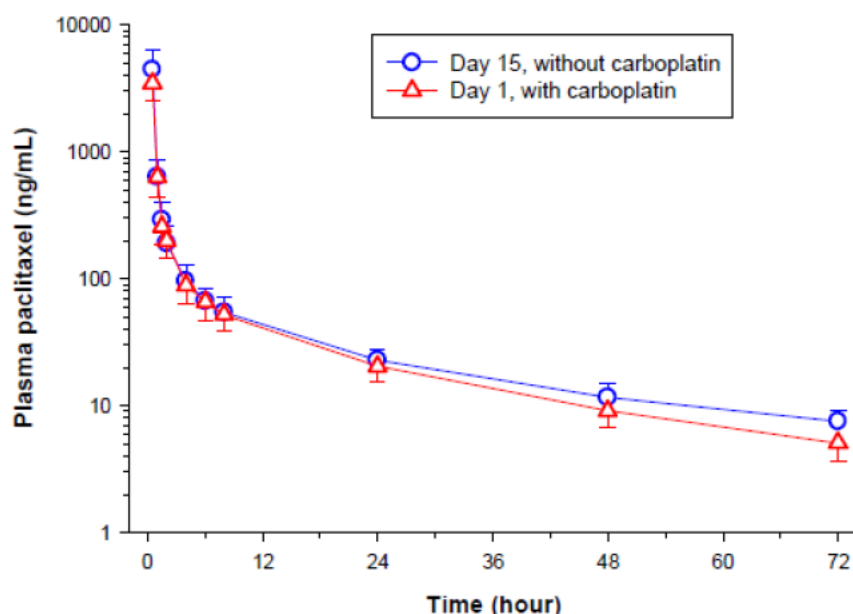


Table 5 Plasma PK Parameters of Paclitaxel in Japanese NSCLC Patients Receiving Abraxane with or without Subsequent Carboplatin

Parameters*	Day 1 Abraxane + Carboplatin (n = 10)	Day 15 Abraxane alone (n = 10)	Geo-mean ratio (day 1/day 15) (90% CI)
C _{max} (ng/mL)	3366 (22.6)	4009 (54.2)	0.84 (0.76 – 0.92)
AUC _t (h*ng/mL)	3866 (20.0)	4388 (28.9)	0.88 (0.83 – 0.93)
AUC _∞ (h*ng/mL)	4041 (19.5)	4908 (25.4)	0.82 (0.78 – 0.87)

*geometric mean (CV%)

By comparing the PK parameters for plasma paclitaxel between Day 1 (in the presence of carboplatin) and Day 15 (in the absence of carboplatin), results indicated that administration of carboplatin immediately after the completion of Abraxane infusion to Japanese patients with advanced NSCLC reduced paclitaxel AUC_{inf} and C_{max} by 18% and 16%, respectively. However, these changes in paclitaxel exposure are not considered to be clinically important.

In trial CA031, carboplatin dosing was based on the Calvert formula: carboplatin dose (mg) = (Target AUC) x (glomerular filtration rate [GFR] + 25) where GFR was replaced with the creatinine clearance (CLcr) estimated by the Cockcroft-Gault formula. Sites were permitted to use local laboratory values for creatinine or CLcr. Table 4 summarizes plasma carboplatin PK parameters for total and free carboplatin. The observed mean AUC_∞ for free carboplatin in plasma was 7.4 mg•min/mL, approximately 23% higher than the targeted value (6 mg•min/mL). However, the mean t_{1/2} and CL for total and free carboplatin were consistent with those reported in the absence of paclitaxel. The observed higher than targeted carboplatin AUC was probably at least partially due to the difference in the methodology (CLcr vs GFR) used to estimate the carboplatin dose.

Table 6 PK Parameters of Carboplatin in Japanese Patients with NSCLC Receiving Abraxane/Carboplatin Combination Therapy

Parameters*	Total carboplatin	Free carboplatin
AUC _∞ (h*ng/mL)	10.7 (1.2)	7.4 (0.7)
CL (mL/min)	62.7 (9.8)	93.4 (16.2)
t _{1/2} (h)	12 (1.4)	4.0 (0.2)

*Mean (SD)

2.4.1.2 Are the PK of paclitaxel similar between Japanese and Non-Japanese patients?

Across-study comparisons were conducted to compare the PK of paclitaxel between Japanese and non-Japanese patients who received Abraxane at 100 mg/m². Table 7 summarizes the demographics and the PK data of paclitaxel observed from the sub-DDI study of trial CA031 in Japanese patients with NSCLC, data from trial J-0101 in Japanese patients with solid tumors, and the historical data from trial CA005-0 in non-Japanese patients with solid tumors.

Table 7 Comparison of PK Parameters of Paclitaxel between Japanese and Non-Japanese Patients

Parameters*	Abraxane 100 mg/m ² , blood sampling Cycle 1 Day 1		
	Japanese NSCLC (CA031)	Japanese Solid Tumors (J-0101)	Non-Japanese Solid Tumors (CA005-0)
N	12	6	6
Age	63 (37-72)	59 (49-73)	57 (38-74)
Body Surface Area (m2)	1.6 (1.4 – 1.8)	1.6 (1.5 – 1.8)	1.90 (1.6 – 2.1)
C _{max} (ng/mL)	3460 (905)	4253 (518)	4513 (2002)
AUC _t (h*ng/mL)	3893 (897)	3937 (516)	3950 (1335)
AUC _∞ (h*ng/mL)	4073 (929)	4141 (538)	4311 (1557)
t _{1/2} (h)	24.2 (3.0)	26.1 (7.3)	18.2 (3.0)
CL (L/h/m2)	25.9 (6.6)	24.5 (3.2)	25.7 (8.3)

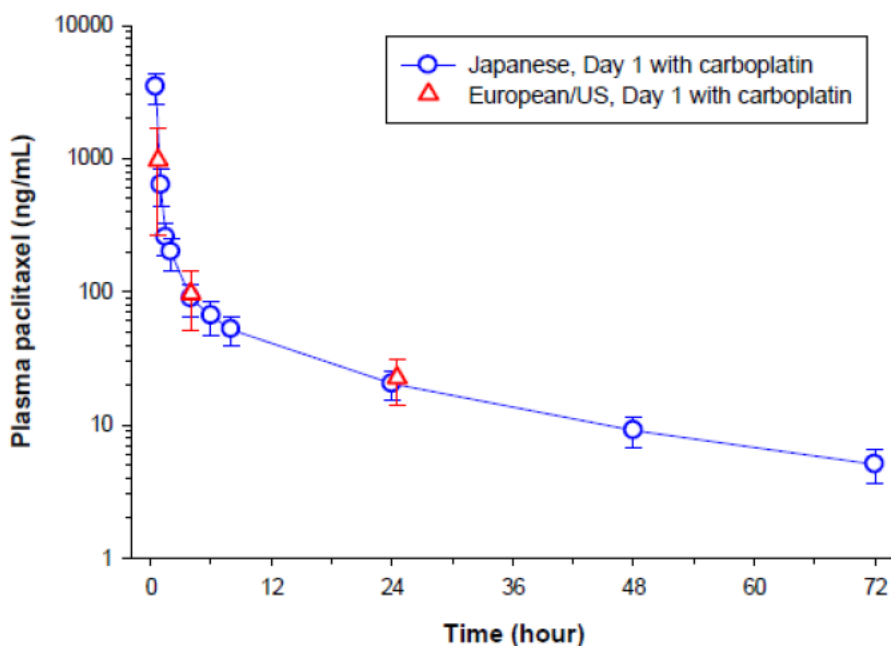
* Mean (SD) for PK parameters

As results indicated, the single-dose PK parameters of paclitaxel were comparable among Japanese patients with NSCLC receiving 100 mg/m² Abraxane in combination with carboplatin, Japanese patients with solid tumors as well as non-Japanese patients with solid tumors receiving the same dose of Abraxane alone.

In addition, as illustrated in Figure 3 comparing the concentration profile of plasma paclitaxel between Japanese (sub-DDI study of trial CA031) and non-Japanese patients with NSCLC (sub-PK study of CA031) who received the same Abraxane (100 mg/m²)/carboplatin (AUC = 6 min•mg/mL) combination therapy on Day 1 of Cycle 1, the mean concentrations of paclitaxel

from non-Japanese patients with NSCLC at 0.75, 4, and 24.5 hours after Abraxane dosing were superimposed with the mean concentration-time profile from Japanese patients with NSCLC, suggesting a similarity of the paclitaxel PK profile between Japanese and non-Japanese patients with NSCLC.

Figure 3 Mean (SD) Plasma Concentrations of Paclitaxel between Japanese and Non-Japanese NSCLC Patients (Cycle 1, Day 1)



In conclusion, the PK of paclitaxel after Abraxane administration are similar between Japanese and non-Japanese patients and administration of Abraxane followed immediately by a subsequent administration of carboplatin is not likely to result in clinically important PK interactions between paclitaxel and carboplatin.

2.5 ANALYTICAL SECTION

2.5.1 Was the active moiety identified and measured in the clinical trials?

Yes. Total human plasma concentrations of paclitaxel were determined using a validated liquid chromatography atmospheric pressure ionization tandem mass spectrometry (LC-API/MS/MS) method. (b) (4)

3 DETAILED LABELING RECOMMENDATIONS

FDA recommended clinical pharmacology labeling modifications are presented below. The Applicant proposed labeling changes are in **RED** and modifications made by the Agency are in **BLUE**.

4 Pages Immediately Following Withheld - b(4) Draft Labeling

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

/s/

LILLIAN H ZHANG
08/30/2012

HONG ZHAO
08/30/2012
I concur.

Office of Clinical Pharmacology				
New Drug Application Filing and Review Form				
General Information About the Submission				
NDA Number	21-660/S31	Brand Name	ABRAXANE® for Injectable Suspension	
DCP Division (I, II, III, IV, V)	V	Generic Name	Paclitaxel protein-bound particles for injectable suspension	
Medical Division	Oncology/DOP2	Drug Class	Microtubule inhibitor	
OCP Reviewer	Lillian H. Zhang, Ph.D.	Indication	Breast cancer (BC) and non-small cell lung cancer (NSCLC)	
OCP Team Leader	Hong Zhao, Ph.D.	Dosage Form	Single use vial containing 100 mg of lyophilized powder of paclitaxel (bound to human albumin)	
Date of Submission	December 9, 2011	Dosing Regimen	- BC: 260 mg/m² IV over 30 min every 3 weeks - NSCLC: 100 mg/m² IV over 30 min on Days 1, 8, and 15 of each 21-day cycle in combination with carboplatin AUC=6 mg•min/mL IV on Day 1 only of each 21-day cycle	
Due Date of OCP Review	September 7, 2012	Route of Administration	IV	
Priority Classification	Standard	Sponsor	Celgene	
PDUFA Due Date	October 12, 2012			
Clinical Pharmacology Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	4		4 bioanalytical study reports
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	X	2		05DA11 and 05DA13
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1		08DA33 (DDI between ABRAXANE and carboplatin)
In-vivo effects of primary drug:				

In-vitro:				
in-silico				
Subpopulation studies -				
ethnicity:	X	2		05DA11 and 05DA13 Japanese subjects
gender:				
geriatrics:				
renal impairment:				
hepatic impairment:				
pediatrics:				
PD:				
Phase 2:	X	3		CA028, CA015, and CA018
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	2		CA031 (Report BIO-VT-5 for PK and Report BIO-VT-6 for PD)
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
QTC studies:				
In-Vitro Release BE				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Biliary Elimination				
Pediatric development plan				
Literature References				
Total Number of Studies				
Filability and QBR comments				
	"X" if yes	Comments		
Application fileable?	X			

Comments sent to firm?		For studies BIO-VT-5, 08DA33, 05DA11 and 05DA13, please submit the following: • bioanalytical method validation reports • individual concentration vs. time data, and corresponding pharmacokinetic parameters. Submit the dataset as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the original analysis should be flagged and maintained in the datasets
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date	Lillian H. Zhang, Ph.D.	
Secondary reviewer Signature and Date	Hong Zhao Ph.D.	

CC: HFD-150 (CSO – **M Hughes**; MTL – **J Johnson**; MO – **S Malik**)
HFD-860 (Reviewer - **LH Zhang**; TL - **H Zhao**; DDD - **B Booth**; DD - **A Rahman**)

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	To-be-marketed product was used in the pivotal clinical trial
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	IV formulation
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	x			
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		x		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	

1 6	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
1 7	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
General					
1 8	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
1 9	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

_____ **Yes** _____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

For studies BIO-VT-5, 08DA33, 05DA11 and 05DA13, please submit the following:

- bioanalytical method validation reports
- individual concentration vs. time data, and corresponding pharmacokinetic parameters. Submit the dataset as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the original analysis should be flagged and maintained in the datasets.

Lillian H. Zhang, Ph.D.

09-January-2012

Reviewing Clinical Pharmacologist

Date

Hong Zhao, Ph.D.

10-January-2012

Team Leader/Supervisor

Date

Clinical Pharmacology - sNDA Filing Memo

NDA: 21-660/S31 (Efficacy Supplement)
IND: 55974
Product: ABRAXANE® (Paclitaxel protein-bound particles for injectable suspension);
Sponsor: Celgene
Filing Date: January 12, 2012
Reviewer: Lillian H. Zhang, Ph.D.

Background: ABRAXANE®, a microtubule inhibitor, is an albumin-bound form of paclitaxel. The original NDA 21,660 was submitted through the 505(b)(2) approach using TAXOL® (paclitaxel) as a reference listing drug (RLD) and was approved by the FDA on January 7, 2005 for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. The recommended regimen for ABRAXANE is 260 mg/m² administered intravenously (IV) over 30 minutes every 3 weeks.

The Applicant states that ABRAXANE has been developed to improve the therapeutic index of paclitaxel, by reducing the toxicities associated with the RLD and the Cremophor® EL and ethanol vehicle in the RLD formulation while improving the chemotherapeutic effect of the drug, which is achieved by taking advantage of endogenous transport pathways to deliver higher doses of paclitaxel to the tumor

The current application is an 505(b)(2) efficacy supplemental NDA (sNDA) for ABRAXANE for a proposed new indication as listed below:

(b) (4)

The recommended dose of ABRAXANE for the newly proposed indication is 100 mg/m² administered as an IV infusion over 30 minutes on Days 1, 8, and 15 of each 21-day cycle. The recommended dose of carboplatin is AUC = 6 mg•min/mL on Day 1 only of each 21-day cycle, beginning immediately after the completion of ABRAXANE administration.

Formulation: The active agent in ABRAXANE (ABI-007) is paclitaxel (bound to human albumin). ABRAXANE is supplied as a sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to IV 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 mL of reconstituted suspension contains 5 mg paclitaxel.

Clinical Studies: This application contains data/results from 4 clinical trials to support the efficacy and safety of ABRAXANE for the newly proposed indication. These trials include the pivotal, randomized Study CA031 and 3 supportive trials, CA028, CA015, and CA018. A summary of these trials is presented in Table 1.

TABLE 1. Study to Support Efficacy and Safety of ABRAXANE in NSCLC Patient Population

Study	Objectives of the study	Design	Doses	Number of Patients
Pivotal				
CA031 (optional PK/PD)	Compare disease response and safety/ tolerability of ABI-007/ carboplatin to Taxol/carboplatin	Phase 3; Randomized; Multicenter; Open-label; Active-Controlled; Superiority.	ABI-007 100 mg/m ² IV over 30 min once a week (on Days 1, 8, 15) and carboplatin (AUC=6) IV once every 3 weeks (on Day 1) Taxol 200 mg/m ² IV over 3 hours and carboplatin (AUC=6) IV, both once every 3 weeks (on Day 1).	Treated: N=1038 ABI-007: N=514 Taxol: N=524 Completed: N=1035 ABI-007: N=511 Taxol: N=524
Supportive				
CA028	Evaluate safety and efficacy of ABI-007 in combination with carboplatin	Phase 2; Multicenter; Open-label; Dose-escalation; Uncontrolled.	ABI-007 IV over 30 min once a week or once every 3 weeks and carboplatin (AUC=6) IV on Day 1 of cycle. ABI-007 every 3 weeks: Cohort 1: 225 mg/m ² ; Cohort 2: 260 mg/m ² ; Cohort 3: 300 mg/m ² ; Cohorts 4,8: 340 mg/m ² ABI-007 once a week: Cohort 5: 140 mg/m ² on Days 1 and 8; Cohort 6: 100 mg/m ² on Days 1, 8, and 15; Cohort 7: 125 mg/m ² on Days 1, 8, and 15	Treated: N=251 Completed: N=251 N=25 each at 225, 260, 300, 140, 100, 125 mg/m ² ; and N=101 at 340 mg/m ²
CA018	Safety and efficacy	Phase 2; Multicenter; Open-label; Uncontrolled.	ABI-007 260 mg/m ² IV over 30 min once every 3 weeks.	Treated: N=43 Completed: N=43
CA015	Phase 1: Determine MTD and DLT. Phase 2: Evaluate safety and efficacy	Phase 1/2; Open-label; Dose-escalation; Uncontrolled.	<u>Phase 1</u> ABI-007 at 100, 125, 150, or 175 mg/m ² IV over 30 min once a week. <u>Phase 2</u> ABI-007 at 125 mg/m ² (MTD) IV over 30 min once a week. and ABI-007 at 125 mg/m ² IV over 2 hrs once a week	Treated: N=75 N=50 IV over 30 min: N=3 at 100 mg/m ² ; N=40 at 125 mg/m ² ; N=7 at 150 mg/m ² ; N=25 IV over 2 hrs at 125 mg/m ² . Completed: N=75

Dose selection

According to the Applicant, the dose of ABRAXANE 100 mg/m² administered IV over 30 minutes weekly on Days 1, 8, and 15 of each 3-week cycle, followed by carboplatin (AUC = 6) IV administered on Day 1 only of each 3-week cycle used in the pivotal trial CA031 was based on the results from the Phase 1 and Phase 2 studies CA015, CA018 and CA028.

Efficacy

In the pivotal trial CA031, the primary efficacy endpoint was ORR (the proportion of patients

who achieved an objective confirmed complete or partial overall response). The Applicant states that patients with advanced NSCLC treated with ABRAXANE/carboplatin showed a significantly higher ORR compared to patients treated with Taxol/carboplatin (33% versus 25%, $p = 0.005$; $pA/pT = 1.313$ [95.1% CI = 1.082, 1.593]). For the key secondary endpoints of PFS and OS, there was no statistically significant improvement in the ABI-007/carboplatin arm compared to Taxol/carboplatin arm.

Safety

According to the Applicant, the most common adverse reactions ($\geq 20\%$) when ABRAXANE is used in combination with carboplatin are anemia, leukopenia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue.

Clinical Pharmacology

The sponsor has submitted study reports for the following clinical pharmacology related studies:

TABLE 2. Clinical Pharmacology Study Reports

Report No. (Study Code)	Description of PK Analysis	ABI-007 Dose	Study Population (Race)	No. of Patients (M/F)
BIO-VT-5 (CA031 sub-study)	Single-dose sparse PK, in combination with carboplatin	100 mg/m ² Cycle 1 Day 1	NSCLC (White ^a)	15 (10/5)
08DA33 (J-0103) (CA031 sub-study)	Single and multiple-dose PK Drug-drug interaction between ABI-007 and carboplatin	100 mg/m ² Cycle 1 Days 1, 8, 15	NSCLC (Japanese)	12 (9/3)
05DA11 (J-0101)	Single ascending dose PK	80-125 mg/m ² Cycle 1 Day 1	Advanced solid tumor (Japanese)	15 (6/9)
05DA13 (J-0100)	Single ascending dose PK	200-300 mg/m ² Cycle 1 Day 1	Advanced solid tumor (Japanese)	12 (10/2)

According to the sponsor, Report BIO-VT-5 and Report 08DA33 provide data from two PK sub-studies of the pivotal trial CA031. These two reports evaluated PK of paclitaxel in the targeted NSCLC patients who received the ABRAXANE /carboplatin combination therapy at the proposed dosing regimen. For Report BIO-VT-5, the Applicant states that due to the small sample size ($N = 15$), the population PK analysis was not conducted; but the noncompartmental PK analysis was attempted for each patient.

Report 05DA11 and Report 05DA13 evaluated the PK of paclitaxel when administered as ABRAXANE at various dose levels in Japanese patients with advanced solid tumors. Data from Report 05DA11 and Report 05DA13 were used by the Applicant in across-study comparisons to demonstrate the dose proportionality of ABRAXANE and to exclude the racial difference in the PK of paclitaxel after ABI-007 administration.

In addition, this application contains CA031 SPARC Biomarker Report (BIO-VT-6) summarizing results from the biomarker/PD portion of the pivotal trial CA031.

Recommendation: The Office of Clinical Pharmacology/Division of Pharmaceutical Evaluation 5 finds that 21-660/S31 is fileable.

Comments:

For studies BIO-VT-5, 08DA33, 05DA11 and 05DA13, please submit the following:

- bioanalytical method validation reports
- individual concentration vs. time data, and corresponding pharmacokinetic parameters. Submit the dataset as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the original analysis should be flagged and maintained in the datasets

Action:

1. A pharmacogenomics consult was submitted on January 10, 2012.

Signatures

Lillian H. Zhang, Ph.D.

Reviewer

Division of Clinical Pharmacology 5

Hong Zhao, Ph.D.

Team Leader

Division of Clinical Pharmacology 5

Cc: DHP: CSO –**M Hughes**; MTL – **J Johnson**; MO – **S Malik**

DCP-5: Reviewer – **LH Zhang**; TL – **H Zhao**; Deputy DD - **B Booth**

DD - **A Rahman**

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/s/

LILLIAN H ZHANG
01/13/2012

HONG ZHAO
01/13/2012
I concur.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-660/S-031

OTHER REVIEW(S)

**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**

Label and Labeling Review

Date:	September 19, 2012
Reviewer:	Jibril Abdus-Samad, PharmD Division of Medication Error Prevention and Analysis
Team Leader	Todd Bridges, RPh Division of Medication Error Prevention and Analysis
Associate Director	Scott Dallas, RPh Division of Medication Error Prevention and Analysis
Deputy Director	Kellie Taylor, PharmD, MPH Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Abraxane (Paclitaxel Protein-Bound Particles for Injectable Suspension) (Albumin-Bound) 100 mg per vial
Application Type/Number:	NDA 021660
Submission Number:	S-031
Applicant:	Abraxis BioScience, LLC, a wholly-owned subsidiary of Celgene Corporation
OSE RCM #:	2012-59

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1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling for Abraxane submitted with S-031 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

Abraxane was originally approved on January 7, 2005, for the treatment of metastatic breast cancer. On December 9, 2011 the Applicant submitted an efficacy supplement (S-031) to support the safety and efficacy of Abraxane, (b) (4)

On May 23, 2012, DMEPA completed a labeling review for Abraxane (OSE review 2012-780) associated with an Office of New Drug Quality and Assessment supplement (S-033). Recommendations from OSE review 2012-780 have been included in this review (see Appendix F) since S-033 received a Complete Response. The comments in Section 4.2 and Appendix F of this review will be communicated to the Applicant.

1.2 PRODUCT INFORMATION

The following product information is provided in the December 9, 2011 submission.

- Active Ingredient: Paclitaxel Protein-Bound Particles
- Indication of Use:
 - Breast Cancer (approved)
 - NSCLC (proposed)
- Route of Administration: Intravenous
- Dosage Form: For Injection
- Strength: 100 mg per vial
- Dose and Frequency:
 - Breast Cancer: 260 mg/m² intravenously infused over 30 minutes every 3 weeks.
 - Hepatic Impairment: 130 mg/m² to 200 mg/m²
 - Neutropenia or Neuropathy: 180 mg/m² to 220 mg/m²
 - NSCLC: 100 mg/m² intravenously infused over 30 minutes on Days 1, 8, and 15 of each 21-day cycle
 - Hematologic and Non-hematologic Toxicity: 50 mg/m² to 75 mg/m²
- How Supplied: 100 mg in single use vial individually packaged in a carton (NDC #68817-134-50)

- 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.
- Container and Closure System: Amber glass bottles, closed with a polyethylene undercap and a plastic screw cap.

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (AERS) database for Abraxane medication error reports as well as PubMed and the ISMP publications. We also reviewed DMEPA's previous review of Abraxane as well as the Abraxane label and labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA AERS database using the strategy listed in Table 1. The search date of May 1, 2012 was used because our last search covered the time period prior to that date in OSE Review 2012-780, dated May 23, 2012. The AERS Search Strategy yielded zero reports.

Table 1: AERS Search Strategy	
Date	May 1, 2012 to July 3, 2012
Drug Names	(Abraxane) (Abrax%) (Paclitaxel Pro%)
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

2.2 LITERATURE SEARCH

We searched PubMed and the ISMP publications on August 6, 2012 for additional cases and actions concerning Abraxane since our last review of Abraxane (OSE Review 2012-780, dated May 23, 2012). The searches yielded zero cases or actions.

2.3 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Container Labels submitted December 9, 2011 (Appendix B)
- Carton Labeling submitted December 9, 2011 (Appendix C)
- Insert Labeling submitted December 9, 2011

2.4 PREVIOUSLY COMPLETED REVIEWS

DMEPA previously reviewed Abraxane in OSE Review 2012-780, and we looked at the review to ensure the Applicant implemented all our recommendations.

3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

3.1 PROPOSED DOSES RESULT IN SMALLER VOLUMES TO INFUSE

The proposed indications and respective dose reductions (50 mg/m^2 to 75 mg/m^2) of Abraxane result in smaller volumes (less than 30 mL) to be infused over 30 minutes. Healthcare practitioners are familiar with infusing larger volumes of Abraxane because the approved doses (130 mg/m^2 to 260 mg/m^2) are larger. The Applicant proposes to maintain the approved preparation and administration instructions in the labeling for the new doses of Abraxane. The approved instructions indicate Abraxane is to be prepared by reconstituting with 20 mL of 0.9 % Sodium Chloride Injection, resulting in a concentration of 5 mg/mL. The appropriate volume, based on the patient's dose, is then injected into an empty intravenous infusion bag and administered to the patient over 30 minutes. For example, a patient with BSA 1.5 m^2 receiving Abraxane 50 mg/m^2 results in a 75 mg (15 mL) of reconstituted Abraxane to be infused via infusion bag over 30 minutes (see Appendix D for a complete illustration of Abraxane doses and infusion volumes). Due to the smaller doses resulting in smaller infusion volumes, DMEPA is concerned with the following:

- The smaller, proposed dose infusion volumes may lead to confusion because healthcare practitioners are used to the larger approved doses and infusion volumes for this product.
- Are infusion pumps capable of accurately delivering the smaller volume minibag because typically, commercially available small intravenous bags contain a minimum of 50 mL?
- A significant portion of the smaller doses be lost in the intravenous infusion set tubing considering the total infusion volume could potentially be 15 mL.

DMEPA considered the option of preparing and administering the smaller volumes in a syringe via syringe pump. However, placing the smaller volume of Abraxane in a syringe may put patients at risk for inadvertent administration via slow intravenous push injection. Additionally, healthcare practitioners are familiar with the approved preparation and administration instructions for Abraxane, which the Applicant proposes to maintain for this efficacy supplement. Different preparation and administration instructions for Abraxane for a similar adult population may introduce opportunities for confusion and wrong administration technique errors, such as administering Abraxane via

intravenous push injection. We note that our medication error searches did not retrieve any errors with the approved preparation and administration instructions.

The second option we considered was to modify the preparation instructions for toxicity-related dose reductions and their respective smaller final volume infusions by adding additional 0.9% Sodium Chloride to the intravenous bag to a typical final volume of 50 mL to be infused over 30 minutes. DMEPA discussed this issue with the DOP2 clinical team and ONDQA during a labeling meeting on July 18, 2012. The team agreed with DMEPA's preliminary proposal.

On July 31, 2012, during a meeting with ONDQA, it was clarified that if we decide to recommend further dilution of the intravenous bag, the Applicant would have to submit stability data, which should only take approximately 1 or 2 weeks for the Applicant to complete. Therefore, upon further discussion with DOP2, we agreed to ask the Applicant for data regarding how the lower doses of Abraxane were being prepared and administered during the clinical trials and if any medication errors occurred. The Information Request (IR) is detailed in Appendix E.

On August 22, 2012, the Applicant's response to the IR indicated the clinical trials preparation and administration instructions were identical to the approved insert labeling. In the pivotal clinical trial, there were no medication error reports, product complaints, or preparation and administration difficulties related among the 100 patients that received the toxicity-related dose reduction of 50 mg/m².

DMEPA also obtained data from an intravenous infusion pump manufacturer, Hospira^{***} that verified the following:

- infusion pumps can accurately delivery a range of 0.1 mL/hr to 999 mL/hr for volumes ranging from (b) (4) to 9,999.9 mL (a worst case scenario would require Abraxane 15 mL infused at a rate of 30 mL/hr)
- these infusion pumps are widely used in oncology centers

Therefore, based on the fact that these small volume doses were delivered in clinical trials without issues and that infusion pumps to deliver these smaller doses are widely used, DMEPA finds the Applicants proposed instructions for preparation and administration acceptable.

Additionally, we evaluated whether a significant portion of the smaller doses would be lost in the intravenous infusion set tubing upon completion of Abraxane infusion. Due to the small final volume (e.g., 15 mL) of the dose, any remaining solution in the intravenous line may represent a clinically significant amount of reconstituted Abraxane solution not delivered to the patient. However, the standard practice of flushing the intravenous line once a drug infusion is complete will help to ensure patients receive the complete dose.

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3.2 PREVIOUSLY COMPLETED REVIEWED

Recommendations from OSE Review 2012-780 have been included in this review (see Appendix F) since S-033 received a Complete Response. The comments in Section 4.2 and Appendix F of this review will be communicated to the Applicant.

4 CONCLUSIONS

DMEPA concludes that the proposed label and labeling can be improved by (b) (4)



4.1 COMMENTS TO THE DIVISION

DMEPA recommends the following be revised in the Dosage and Administration - Highlights of Prescribing Information section of the insert labeling prior to approval of this supplement.

(b) (4)



If you have questions or need clarifications, please contact Frances Fahnbulleh, OSE project manager, at 301-796-0942.

4.2 COMMENTS TO THE APPLICANT

A. Container Label and Carton Labeling

(b) (4)



² <http://www.ismp.org/Tools/errorproneabbreviations.pdf> Last accessed August 30, 2012

B. Carton Labeling

Add the lot number and expiration date.

REFERENCE

1. DeFronzo, Kimberly. OSE Review 2012-780, Abraxane Label and Labeling Review. May 23, 2012

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

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Appendix D: Abraxane Preparation Calculations

Abraxane Preparation Calculations												
Breast Cancer (approved)							NSCLC (proposed)					
BSA (m ²)	Dose 260 mg/m ²	Infusion Volume (mL)	Dose 200 mg/m ²	Infusion Volume (mL)	Dose 130 mg/m ²	Infusion Volume (mL)	Dose 100 mg/m ²	Infusion Volume (mL)	Dose 75 mg/m ²	Infusion Volume (mL)	Dose 50 mg/m ²	Infusion Volume (mL)
1.4	364	73	280	56	182	36	140	28	105	21	70	14
1.5	390	78	300	60	195	39	150	30	113	23	75	15
1.6	416	83	320	64	208	42	160	32	120	24	80	16
1.7	442	88	340	68	221	44	170	34	128	26	85	17
1.8	468	94	360	72	234	47	180	36	135	27	90	18
1.9	494	99	380	76	247	49	190	38	143	29	95	19
2	520	104	400	80	260	52	200	40	150	30	100	20
2.1	546	109	420	84	273	55	210	42	158	32	105	21
2.2	572	114	440	88	286	57	220	44	165	33	110	22
2.3	598	120	460	92	299	60	230	46	173	35	115	23
2.4	624	125	480	96	312	62	240	48	180	36	120	24

* volume rounded to nearest whole number

Appendix E: IR for Preparation and Administration Instructions

DMEPA is currently reviewing the preparation instructions in the insert labeling for the proposed NSCLC indication. We are concerned that preparing the recommended dosage and toxicity-related dose reductions results in volumes less than the typical minimum volume (50 mL) used for 30 minute intravenous bag infusions. For example, a patient with BSA 1.5 m² receiving Abraxane 50 mg/m² will result in a 75 mg dose or 15 mL of reconstituted Abraxane to be infused via infusion bag over 30 minutes. Therefore, we request the following to address our concerns:

1. Provide the preparation and administration instructions used in the clinical trials for all doses (recommended dose and toxicity-related dose reductions).
2. Discuss any medication errors, product complaints, or preparation and administration difficulties experienced during the clinical trials. This discussion should include the type of error, outcome, and causality.

Appendix F: Label and Labeling Recommendations from OSE Review 2012-780

(b) (4)



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/s/

JIBRIL ABDUS-SAMAD
09/19/2012

SCOTT M DALLAS
09/20/2012

KELLIE A TAYLOR
09/21/2012

CAROL A HOLQUIST
09/21/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: September 21, 2012

To: Monica Hughes, Lead Regulatory Project Manager
Division of Oncology Products 2 (DOP-2)
Office of Hematology Oncology Drug Products

From: Carole Broadnax, PharmD, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
Office of Prescription Drug Promotion (OPDP)

Cc: Karen Munoz, Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP), OPDP

Subject: NDA 21660/31
Abraxane for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound)
OPDP Labeling Comments

OPDP/DPDP has reviewed the proposed labeling (Package Insert (PI) and carton/container) as requested in your consult dated January 6, 2012. OPDP/DCDP comments for the proposed patient package insert (PPI) were provided in a separate consult response dated September 20, 2012.

DPDP's comments are based on the substantially complete version of the proposed PI titled, "9-6-12 FDA Proposed Revisions Abraxane Labeling NDA 21660.31 (NSCLC).doc," sent via electronic mail to OPDP (Carole Broadnax) from DOP 2 (Monica Hughes) on September 6, 2012. OPDP's comments are provided directly in the attached document. Please note that for the PI, OPDP hid deletions and formatting changes so that OPDP comments are easier to read.

DPDP reviewed the proposed revised carton and container labeling sent via electronic mail to OPDP (Carole Broadnax) from DOP 2 (Monica Hughes) on September 18, 2012. OPDP does not have comments on the carton and container labeling at this time.

Thank you for your consult. If you have any questions, please contact Carole Broadnax at (301) 796-0575 or Carole.Broadnax@fda.hhs.gov.

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/s/

CAROLE C BROADNAX
09/21/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Consumer Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: September 20, 2012

To: Monica Hughes, Lead Regulatory Project Manager
Division of Oncology Products 2 (DOP-2)
Office of Hematology Oncology Drug Products

From: Karen Munoz-Nero, BSN, RN, Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)
Office of Prescription Drug Promotion (OPDP)

CC: Carole Broadnax, R.Ph., Pharm.D., Regulatory Review Officer
Division of Professional Drug Promotion (DPDP), OPDP

Subject: NDA 021660
Abraxane (paclitaxel protein-bound particles) for injection
OPDP Comments on proposed patient package insert

In response to the Division of Oncology Products 2 (DOP-2) January 6, 2012, consult request, DCDP has reviewed the proposed patient package insert (PPI) for Abraxane (paclitaxel protein-bound particles) for injection. Comments for the proposed Package Insert (PI) will be provided under separate cover by Carole Broadnax.

DCDP's comments on the PPI are based on the following documents:

- The completed Division of Medical Policy Programs (DMPP) revised labeling entitled, "paclitaxel protein-bound particles for injectable suspension (ABRAXANE) sNDA 21660-31 PPI Sep-2012 clean.docx" sent via electronic mail from Nathan Caulk, MS, BSN, RN, Patient Labeling Reviewer on September 19, 2012.
- The PI entitled, "NSCLC Celgene responses 14Sep2012.doc" sent via electronic mail from Monica Hughes on September 17, 2012.

DCDP's comments are provided directly in the attached document.

Thank you for the opportunity to comment on this proposed labeling. If you have any questions regarding this consult review, please contact Karen Munoz-Nero at 301-796-3274 or Karen.Munoz@fda.hhs.gov.

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/s/

KAREN MUNOZ-NERO
09/20/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: September 19, 2012

To: Patricia Keegan, MD
Director
Division of Oncology Products 2 (DOP2)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nathan Caulk, MS, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name) Dosage Form and Route: ABRAAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound)

Application Type/Number: NDA 21-660

Supplement Number: S-031

Applicant: Celgene Corporation

1 INTRODUCTION

On December 12, 2011, Celgene Corporation submitted for the Agency's review an Efficacy Supplement (S-031) to their approved New Drug Application (NDA) 21-660 for ABRAXANE (paclitaxel protein-bound particles for injectable suspension) (albumin-bound). The purpose of this submission is to provide for a new indication for the first-line treatment of locally advanced or metastatic Non-Small Cell Lung Cancer, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy. On January 6, 2012, the Division of Oncology Products 2 (DOP2) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for ABRAXANE.

This review is written in response to a request by DOP2 for DMPP to review the Applicant's proposed Patient Package Insert (PPI) for ABRAXANE.

2 MATERIAL REVIEWED

- Draft ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) Patient Package Insert (PPI) received on December 12, 2011.
- Draft ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) Prescribing Information (PI) received on December 12, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on September 7, 2012.

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)
- 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)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI is appended to this memorandum. Consult DMPP 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.

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REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 21660 (31) SE1

Name of Drug: Abraxane for Injectable Suspension

Applicant: Abraxis Bioscience a wholly owned subsidiary of Celgene Corporation

PI Labeling Reviewed

Submission Date: December 9, 2011, revised labeling submitted January 13, 2012.

Receipt Date: December 12, 2011, revised labeling submitted January 13, 2012.

Background and Summary Description

This supplement provides for a proposed new indication of “First Line Treatment of NSCLC in Combination with Carboplatin.”

Provides for updates to the following sections of the PI: Highlights and Prescribing Information, Indications and Usage (Section 1), Dosage and Administration (Section 2), Warnings and Precautions (Section 5), Adverse Reactions (Section 6), Use in Specific Population (Section 8), Clinical Pharmacology (Section 12), Clinical Studies (Section 14), Patient Counseling Information (Section 17).

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement. **Additional labeling comments are noted at the bottom of this review.**

Conclusions/Recommendations

We identified the noted labeling deficiencies during a preliminary review of the package insert and requested that the sponsor submit revised labeling to address our comments by February 24, 2012.

Monica Hughes

Regulatory Project Manager

2/10/12

Date

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**

- ☐ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- ☐ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- ☐ There is no redundancy of information.
- ☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- ☐ A horizontal line must separate the HL and Table of Contents (TOC).
- ☐ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- ☐ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- ☐ Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading – if no contraindications are known, it must state “None”)
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)

• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

- **Highlights Limitation Statement**

- ☐ Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

- **Product Title**

- ☐ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

- ☐ The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

- ☐ All text in the boxed warning is **bolded**.
- ☐ Summary of the warning must not exceed a length of 20 lines.
- ☐ Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- ☐ Must have the verbatim statement “***See full prescribing information for complete boxed warning.***” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

- ☐ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- ☐ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
- ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
- ☐ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
- ☐ Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- ☐ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- ☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- ☐ All contraindications listed in the FPI must also be listed in HL.
- ☐ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- ☐ For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- ☐ Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- ☐ For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- ☐ Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”).**”

- **Revision Date**

- ☐ A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- ☐ The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- ☐ The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- ☐ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- ☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- ☐ If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

- **General Format**

- ☒ A horizontal line must separate the TOC and FPI.
- ☐ The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- ☐ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- ☐ Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.

- ☐ Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- ☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- ☐ Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.
- ☐ For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of 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 clinical practice.”
- ☐ For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). 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.”

- **Use in Specific Populations**

- ☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- ☐ This section is required and cannot be omitted.
- ☒ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:
 - “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

We noted the following additional labeling deficiencies during our preliminary review. These were documented in the filing letter:

1 Page Immediately Following Withheld - b(4) Draft Labeling

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

/s/

MONICA L HUGHES
02/10/2012

KAREN D JONES
02/10/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-660/S-031

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21660

SUPPL # 31

HFD # 107

Trade Name Abraxane

Generic Name paclitaxel protein-bound particles for injectable suspension) (albumin-bound)

Applicant Name Abraxis BioScience, LLC, a wholly-owned subsidiary of Celgene Corporation

Approval Date, If Known October 11, 2012

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

505(b)(2) SE1

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.

N/A

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:

N/A

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3 years

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?

N/A

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# 21660

Abraxane

NDA# NDA 20262

Taxol® (paclitaxel) for injection

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:

CA031 " A Randomized, phase III trial of Abraxane® (ABI-007) and Carboplatin compared with Taxol and Carboplatin as first-line therapy in patients with NSCLC".

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:

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:

N/A

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 # 55974 and 114882 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 ☐
Explain:

!
! NO ☐
! Explain:

Investigation #2

YES ☐
Explain:

!
!
! 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: Monica Hughes
Title: Lead Regulatory Health Project Manager
Date: October 11, 2012

Name of Office/Division Director signing form: Patricia Keegan, M.D.
Title: Division Director, DOP2/OHOP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

MONICA L HUGHES
10/11/2012

PATRICIA KEEGAN
10/11/2012

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

APPLICATION INFORMATION ¹		
NDA # 21660	NDA Supplement # 31	If NDA, Efficacy Supplement Type: SE1
Proprietary Name: Abraxane Established/Proper Name: paclitaxel protein-bound particles for injectable suspension) (albumin-bound) Dosage Form: For Injectable Suspension		Applicant: Abraxis BioScience, LLC, a wholly-owned subsidiary of Celgene Corporation Agent for Applicant (if applicable): N/A
RPM: Monica Hughes		Division: DOP2
<u>NDA and NDA Efficacy Supplements:</u> NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☒ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.) <u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)): NDA 02062: Taxol (paclitaxel) Provide a brief explanation of how this product is different from the listed drug. It contains Taxol that is bound in protein (albumin) particles. ☐ This application does not rely upon a listed drug. ☐ This application relies on literature. ☐ This application relies on a final OTC monograph. ☒ This application relies on (explain) Clinical Study CA031 <u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u> <u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u> ☒ No changes ☐ Updated Date of check: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.		
❖ Actions		
- Proposed action - User Fee Goal Date is <u>October 12, 2012</u>		☒ AP ☐ TA ☐ CR
Previous actions (<i>specify type and date for each action taken</i>)		☒ None

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received						
❖ Application Characteristics ³							
Review priority: ☒ Standard ☐ Priority Chemical classification (new NDAs only): <table border="0"> <tr> <td>☐ Fast Track</td> <td>☐ Rx-to-OTC full switch</td> </tr> <tr> <td>☐ Rolling Review</td> <td>☐ Rx-to-OTC partial switch</td> </tr> <tr> <td>☐ Orphan drug designation</td> <td>☐ Direct-to-OTC</td> </tr> </table> NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies REMS: ☐ MedGuide ☐ Communication Plan ☐ ETASU ☐ MedGuide w/o REMS ☐ REMS not required Submitted in response to a PMR Submitted in response to a PMC Submitted in response to a Pediatric Written Request Comments:		☐ Fast Track	☐ Rx-to-OTC full switch	☐ Rolling Review	☐ Rx-to-OTC partial switch	☐ Orphan drug designation	☐ Direct-to-OTC
☐ Fast Track	☐ Rx-to-OTC full switch						
☐ Rolling Review	☐ Rx-to-OTC partial switch						
☐ Orphan drug designation	☐ Direct-to-OTC						
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates						
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	☐ Yes ☐ No						
❖ Public communications (<i>approvals only</i>)							
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No						
• Press Office notified of action (by OEP)	☒ Yes ☐ No						
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other ASCO Burst						

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i>	☒ No ☐ Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) ☒ Verified 21 CFR 314.50(i)(1) ☒ (ii) ☐ (iii)
[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire _____
[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i>	☒ N/A (no paragraph IV certification) ☐ Verified

• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner’s receipt of the applicant’s notice of certification? (Note: The date that the patent owner received the applicant’s notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)). <i>If “Yes,” skip to question (4) below. If “No,” continue with question (2).</i> (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant’s notice of certification, as provided for by 21 CFR 314.107(f)(3)? <i>If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.</i> <i>If “No,” continue with question (3).</i> (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). <i>If “No,” the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.</i> (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? <i>If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i> <i>If “No,” continue with question (5).</i>	Not Applicable ☐ Yes ☐ No ☐ Yes ☐ No ☐ Yes ☐ No ☐ Yes ☐ No
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(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). <i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i> <i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i>	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist ⁴	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Approval Letter and Approved Labeling: October 11, 2012
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	October 11, 2012
Original applicant-proposed labeling	December 12, 2011
Example of class labeling, if applicable	N/A

⁴ Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Attached to the PI, see PI section
Original applicant-proposed labeling	
Example of class labeling, if applicable	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
Most-recent draft labeling	October 11, 2012
❖ Proprietary Name - Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) - Review(s) (<i>indicate date(s)</i>) - Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.	N/A
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	☒ RPM February 10, 2012 ☒ DMEPA September 20, 2012 ☒ DMPP/PLT (DRISK) September 19, 2012 ☒ ODPD (DDMAC) Professional: September 21, 2012 Consumer: September 20, 2012 ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte: ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment: September 5, 2012	February 10, 2012 ☐ Not a (b)(2) ☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
Applicant is on the AIP	☐ Yes ☒ No
- This application is on the AIP - If yes, Center Director's Exception for Review memo (<i>indicate date</i>) - If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Pediatrics (<i>approvals only</i>) - Date reviewed by PeRC: August 29, 2012 If PeRC review not necessary, explain: _____ - Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	☒ Verified, statement is acceptable
❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	October 10, 2012 (uploaded October 11, 2012) October 9, 2012 October 3, 2012 September 6, 2012 August 22, 2012 August 9, 2012 August 7, 2012 August 1, 2012 July 5, 2012 May 3, 2012 Filing letter: February 9, 2012 ACK letter: December 21, 2011
❖ Internal memoranda, telecons, etc.	October 2, 2012 (uploaded October 5, 2012) October 1, 2012 (uploaded October 5, 2012) September 24, 2012 (uploaded October 5, 2012) August 30, 2012 (uploaded August 29, 2012) August 27, 2012 (uploaded September 18, 2012) July 18, 2012 (uploaded August 29, 2012) July 16, 2012 (uploaded August 29, 2012) July 2, 2012 (uploaded August 29, 2012) May 14, 2012, Mid-Cycle Meeting (uploaded August 29, 2012) January 6, 2012 (Review Designation Memo) January 4, 2012 Initial Planning Meeting: Held, uploaded February 9, 2012)
❖ Minutes of Meetings	
Regulatory Briefing (<i>indicate date of mtg</i>)	☒ No mtg
If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A or no mtg
Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☐ No mtg August 9, 2010 email (uploaded March 25, 2011)
EOP2 meeting (<i>indicate date of mtg</i>)	☐ No mtg November 4, 2005 (uploaded December 5, 2005)

Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	SPA not accepted: March 23, 2006, May 25, 2007. SPA accepted: August 30, 2007
❖ Advisory Committee Meeting(s)	☒ No AC meeting
- Date(s) of Meeting(s) 48-hour alert or minutes, if available <i>(do not include transcript)</i>	
Decisional and Summary Memos	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	☒ None
Division Director Summary Review <i>(indicate date for each review)</i>	☐ None October 11, 2012
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	☒ None
PMR/PMC Development Templates <i>(indicate total number)</i>	☒ None
Clinical Information⁶	
❖ Clinical Reviews	
Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	Concurred, September 7, 2012
Clinical review(s) <i>(indicate date for each review)</i>	September 7, 2012 Filing Review: January 26, 2012
Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	Page 14 of clinical review: September 7, 2012 (Dr. Malik)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	☒ Not applicable
❖ Risk Management - REMS Documents and Supporting Statement <i>(indicate date(s) of submission(s))</i> - REMS Memo(s) and letter(s) <i>(indicate date(s))</i> - Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i>	☒ None
❖ DSI Clinical Inspection Review Summary(ies) <i>(include copies of DSI letters to investigators)</i>	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	☐ None
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	☐ None Concurred, August 22, 2012
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	☐ None Concurred, August 22, 2012
Statistical Review(s) <i>(indicate date for each review)</i>	☐ None August 22, 2012

⁶ Filing reviews should be filed with the discipline reviews.

		Filing Review: January 20, 2012
Clinical Pharmacology ☐ None		
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	☒ None	
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☐ None Concurred, August 30, 2012	
Clinical Pharmacology review(s) (indicate date for each review)	☐ None August 30, 2012 Filing Review: January 13, 2012	
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	☒ None	
Nonclinical ☒ None		
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (indicate date for each review)	☐ None	
• Supervisory Review(s) (indicate date for each review)	☐ None	
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	☐ None	
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	☐ None	
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	☐ No carc	
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page	
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	☐ None requested	
Product Quality ☐ None		
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	☒ None	
• Branch Chief/Team Leader Review(s) (indicate date for each review)	☐ None Concurred, September 17, 2012 Concurred, August 30, 2012	
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	☐ None September 17, 2012 August 30, 2012	
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review) ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)	☒ Not needed	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	☒ None	
❖ Environmental Assessment (check one) (original and supplemental applications)		
☒ Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	Review begins on Page 3 of the September 17, 2012, product quality review.	
☐ Review & FONSI (indicate date of review)		
☐ Review & Environmental Impact Statement (indicate date of each review)		

❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>	Date completed: ☐ Acceptable ☐ Withhold recommendation ☒ Not applicable
☐ BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

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

/s/

MONICA L HUGHES
10/11/2012

INTERNAL MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 10, 2012
TIME: 11:00AM-11:30AM
LOCATION: Teleconference; WO 22, Room 3376
APPLICATION: sNDA 21660/31 (NSCLC)
DRUG NAME: Abraxane

FDA ATTENDEES:

Patricia Keegan - Division Director
Shakun Malik- Clinical Reviewer
John Johnson-Clinical TL
Huanyu (Jade) Chen-Statistical reviewer
Kun He-Statistical TL
Monica Hughes-Lead RPM

CELGENE ATTENDEES:

Gad Soffer
Markus Renschler
Paul Bhar
(b) (6)
Richard Pilot
Trushna Shah
(b) (4), (b) (6)
Renu Vaish
Debbie Tady

BACKGROUND: The purpose of this teleconference was to discuss outstanding labeling issues as part of the review of sNDA 21660/31. FDA sent Celgene revised labeling on October 9, 2012, requesting a response this morning in advance of this scheduled teleconference to discuss any outstanding issues. Celgene provided revised labeling via email communication on October 10, 2012, in advance of this teleconference. This teleconference was to discuss outstanding labeling issues.

DISCUSSION: [REDACTED] (b) (4)

1 Page Immediately Following Withheld - b(4) Draft Labeling

October 10, 2012

Teleconference with Celgene: Outstanding Labeling Issues as part of sNDA 21660/31

(b) (4)

Celgene agreed to review the data and provide additional information to FDA regarding the 7/17 patients who did not resume treatment.

POST-MEETING FOLLOW-UP: Celgene provided additional information and proposed the following (b) (4) “For the ABRAXANE plus carboplatin treated group, 17/514 (3%) patients developed Grade 3 peripheral neuropathy and no patients developed Grade 4 peripheral neuropathy. Grade 3 neuropathy improved to Grade 1 or resolved in 10/17 patients (59%) following interruption or discontinuation of ABRAXANE.” FDA agreed.

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

/s/

MONICA L HUGHES
10/11/2012

505(b)(2) ASSESSMENT

Application Information		
NDA # 21660	NDA Supplement #: S- 031	Efficacy Supplement Type SE- 1
Proprietary Name: Abraxane for Injectable Suspension Established/Proper Name: paclitaxel protein-bound particles for injectable suspension (albumin based) Dosage Form: For Injectable Suspension Strengths: Single Use vial containing 100 mg paclitaxel		
Applicant: Celgene Corporation, a wholly owned subsidiary of Abraxis Bioscience		
Date of Receipt: December 12, 2011		
PDUFA Goal Date: October 12, 2012		Action Goal Date (if different): N/A
Proposed Indication(s): NSCLC		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☒ NO ☐

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Taxol (paclitaxel)	Efficacy and Safety Data

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

This efficacy supplement relies on FDA’s prior findings of safety and effectiveness for the listed drug, Taxol. The ability to rely on these prior findings is based on the same active pharmaceutical ingredient (paclitaxel) in both Taxol (solvent-based paclitaxel) and Abraxane (albumin-bound paclitaxel) and demonstration of comparable clinical activity (higher overall response rate) with the absence of a clinically meaningful decrement in overall survival in a randomized open-label trial comparing a clinically tolerable Abraxane plus carboplatin combination chemotherapy regimen to a solvent-based paclitaxel/carboplatin combination regimen administered as first-line treatment for locally advanced or metastatic non-small cell lung cancer.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☐ NO ☒

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

If “NO”, proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Taxol® (paclitaxel) for injection	NDA 20262	Yes (356h)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☐ YES ☒ NO ☐

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES ☐ NO ☒

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES ☐ NO ☒

If “YES”, please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☒ NO ☐

If “YES”, please list which drug(s) and answer question d) i. below.

If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing: NDA 020262 (Taxol, paclitaxel)

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If (a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

This application provides for a new indication, non-small cell lung cancer (NSCLC).

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES ☐ NO ☒

If “**NO**” to (a) proceed to question #11.
If “**YES**” to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

If “**YES**” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES ☐ NO ☐

If “**NO**”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☐ NO ☐

If “**YES**” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS
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- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Exclusivity Data: There is no unexpired exclusivity for this product.

No patents listed ☒ proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- ☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- ☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- ☒ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
- ☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- ☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- ☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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/s/

MONICA L HUGHES
10/11/2012

PATRICIA KEEGAN
10/11/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 9, 2012
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: sNDA 21660/31: FDA Proposed Labeling

Please find attached FDA's counter proposal to your revised package insert (PI) and patient insert, as submitted on October 5, 2012.

If you agree with our proposed changes, please accept those changes. In your reply to us, please include in track changes, any outstanding labeling issues that we need to reach agreement on.

Please submit your clean and redlined version of the proposed labeling via email communication to me by 9:00 AM tomorrow, October 10, 2012. In addition to submitting your revised labeling to me via email communication, please also submit a formal copy to your NDA.

Please let me know if you have any questions.

Regards,

Monica Hughes, M.S.
Lead Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9225
Fax: 301-796-9849

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/s/

MONICA L HUGHES
10/09/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 2, 2012
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: sNDA 21660/31: Internal Labeling Meeting

FDA discussed Celgene's revised labeling sent via email communication on September 17, 2012, and the recently approved labeling from the CBE supplements 034 and 035 with DOP1.

Attendees: Monica Hughes, Shakun Malik, John Johnson, Patricia Keegan, Frank Cross, Patricia Cortazar, Nancy Scher, Amna Ibrahim

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/s/

MONICA L HUGHES
10/05/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 1, 2012
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: sNDA 21660/31: Internal Labeling Meeting

FDA continued to review and discuss Celgene's revised labeling sent via email communication on September 17, 2012.

Attendees: Monica Hughes, Shakun Malik, John Johnson, Patricia Keegan, Ted Chang

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/s/

MONICA L HUGHES
10/05/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 24, 2012
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: sNDA 21660/31: Internal Labeling Meeting

FDA reviewed and discussed Celgene's revised labeling sent via email communication on September 17, 2012.

Attendees: Monica Hughes, Patricia Keegan, Shakun Malik, John Johnson, Huanyu (Jade) Chen, Kun He, Lillian Zhang, Karen Munoz, John Johnson, Jibril Abdus-Samad, Nathan Caulk, Barbara Fuller, Carole Broadnax, Ted Chang

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/s/

MONICA L HUGHES
10/05/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 3, 2012
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: sNDA 21660/31: Abraxane NSCLC

Please find attached our proposed labeling (PI/PPI) in response to your proposed revised labeling submitted via email communication on September 14, 2012.

Please note that we have incorporated our proposed revisions to the Abraxane labeling approved by DOP1 on September 28, 2012. Please also note that we are working internally with DOP1 on the review of this package insert and additional comments may follow.

1. [REDACTED] (b) (4)
2. Please include a vertical line for all of the recent major changes sections in the Full Prescribing Information for your recent approval of supplements 034 and 035.
3. Please note, we do not agree with your proposed change [REDACTED] (b) (4)
4. Please ensure the table numbers are correct throughout the label.

If you agree with our proposed changes, please accept those changes. In your reply to us, please only include in track changes, any outstanding labeling issues that we need to reach agreement on.

Please submit your clean and redlined version of the proposed labeling by 1:00 PM on Friday, October 5, 2012. In addition to submitting your revised labeling to me via email communication, please also submit a formal copy to your NDA.

Please let me know if you have any questions.

Regards,

Monica Hughes, M.S.
Lead Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9225
Fax: 301-796-9849

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/s/

MONICA L HUGHES
10/03/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 1, 2012
From: Karen D. Jones, Chief Project Management Staff DOP2/OHOP
Subject: sNDA 21660: Information Request

The following email communication was sent to Dr. Wendy Corbett on August 1, 2012:

On behalf of Monica Hughes, the Regulatory Project Manager assigned to your NDA 21660, please find below an information request from the clinical/statistical team reviewing your supplement 031. Please respond via email within 24 hours and then follow that with a formal submission as an amendment to the supplement. Please confirm receipt of this communication by return email.

Please submit all the called macro(s) in SAS programs freqv3.sas and univv5e.sas ASAP.

Before your submission, please double check and re-run both programs. For example, you have the following comment in both programs:

```
%* NOTE: MACRO WORDS.SAS MUST BE INCLUDED FOR FREQ.SAS TO RUN  
*;
```

The reviewer could not find this macro in the previous or current NDA addendums.

Thank you.
Karen

Karen D. Jones
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products

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/s/

KAREN D JONES
09/19/2012

Meeting Summary:
Wrap-Up Meeting: August 27, 2012
sNDA 21660/31
Abraxane, NSCLC

Overview: Important Review Goal Dates

Primary review Completion Goal Date according to GRMP: September 7, 2012

Secondary review Completion Goal Date according to GRMP: September 14, 2012

PDUFA Goal Date: October 12, 2012

FDA Attendees: Monica Hughes, Carole Broadnax, Jibril Abdus-Samad, Ted Chang, Kun He, John Johnson, Patricia Keegan, Huanyu Chen, Lillian Zhang, Hong Zhao, Shakun Malik, Karen Jones, Frances Fahnbulleh, Nathan Caulk

Agenda Items and Discussion During Meeting:

1. Discipline Specific Reviews of Application

a. CMC: Ted Chang

Discussion During Meeting: Following a brief discussion regarding Celgene's response to our IR regarding infusion of small volumes, both DMEPA and CMC agreed that no further labeling changes were required. No additional CMC issues, a brief review of labeling will be completed shortly.

b. Clinical Pharmacology: Lillian Zhang

Discussion During Meeting: No issues to discuss; primary and secondary reviews to be completed shortly.

c. Clinical: Shakun Malik

Discussion During Meeting: No issues to discuss; primary and secondary reviews to be completed shortly.

d. Stats: Jade Chen

Discussion During Meeting: The statistics team found the inclusion of results for the primary endpoint of ORR to be acceptable, (b) (4)

The team will be meeting internally on August 30, and will discuss the changes further.

e. DMEPA: Jibril Abdus-Samad, discussion of the Celgene's response to our IR regarding infusion of small volumes

Discussion During Meeting: Following a brief discussion of Celgene's response to our IR regarding small volumes, DMEPA has no additional recommended labeling changes. Review will be completed shortly.

Meeting Summary:
Wrap-Up Meeting: August 27, 2012
sNDA 21660/31
Abraxane, NSCLC

2. Pending Consults

Discuss anticipated completion dates of outstanding consults:

- DMEPA

Discussion During Meeting: Review will be completed shortly.

- Patient Labeling Team

Discussion During Meeting: Review will be completed following receipt of substantially complete labeling from the division.

- OPDP

Discussion During Meeting: Review will be completed following receipt of substantially complete labeling from the division.

3. Discussion of Proposed Action To Be Taken: Clinical will lead discussion

Discussion During Meeting: All review disciplines recommended an approval action for this application.

4. Labeling Discussion: Clinical/Stat will lead discussion

- Discuss status of labeling review

- Meetings held: July 9, 16, and 17
- Additional meeting scheduled: August 30, 2012

*Anticipate sending draft labeling to the sponsor this week.

- Discuss any open items with input needed from other reviewers

Discussion During Meeting: An additional meeting will be set up during the second week of September to discuss Celgene's response to our labeling comments.

5. Discussion of Proposed Action To Be Taken:

Discussion During Meeting: The review team proposed an approval action for this application.

Meeting Summary:
Wrap-Up Meeting: August 27, 2012
sNDA 21660/31
Abraxane, NSCLC

6. Discussion of sign-off procedure and schedule: Clinical will lead discussion

a. Begin labeling/PMC/PMR discussions: September 21, 2012

Discussion During Meeting: Final primary and secondary reviews need to be completed (by end of first week of September) in order for the DD to complete the review within PDUFA action goal date. Sign-off process will continue with labeling, PMR/PMCs, and action letter.

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/s/

MONICA L HUGHES
09/18/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 30, 2012
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: sNDA 21660/31: Internal Labeling Meeting

FDA's proposed revisions as discussed during the August 30, 2012 labeling meeting.

Attendees: Monica Hughes, Shakun Malik, John Johnson, Huanyu (Jade) Chen, Kun He, Hong Zhao, John Johnson, Jibril Abdus-Samad, Nathan Caulk, Carole Broadnax

Sections covered include:

- Highlights
- Indications and Usage (Section 1)
- Review Adverse Reactions (Section 6)
- Division review of the Patient Package Insert, labeling will be sent to PLT and OPDP following this meeting.

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/s/

MONICA L HUGHES
09/07/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 18, 2012
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: sNDA 21660/31: Internal Labeling Meeting

FDA's proposed revisions as discussed during the July 18, 2012 labeling meeting.

Attendees: Monica Hughes, Shakun Malik, John Johnson, Huanyu (Jade) Chen, Hong Zhao, John Johnson, Jibril Abdus-Samad, Nathan Caulk, Ted Chang

Sections covered include:

- CMC (Sections 2, 3, and 16 (no proposed changes), and Section 11)
- Clinical Pharmacology (Section 12)
- Carton and Vial Labeling

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/s/

MONICA L HUGHES
08/29/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 16, 2012
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: sNDA 21660/31: Internal Labeling Meeting

FDA's proposed revisions as discussed during the July 16, 2012 labeling meeting.

Attendees: Monica Hughes, Shakun Malik, John Johnson, Huanyu (Jade) Chen, Hong Zhao, John Johnson, Jibril Abdus-Samad, Nathan Caulk,

Sections covered include:

- Section 2: Dosage and Administration
- Section 14: Clinical Studies
- Section 8: Use in Specific Populations, Geriatric Use, and Patients with Renal Impairment

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/s/

MONICA L HUGHES
08/29/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 2, 2012

From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP

Subject: sNDA 21660/31: Internal Labeling Meeting

FDA's proposed revisions as discussed during the July 2, 2012 labeling meeting.

Attendees: Mona Patel, Shakun Malik, John Johnson, Huanyu (Jade) Chen, Hong Zhao, John Johnson, Jibril Abdus-Samad, Nathan Caulk, Sharon Mills, Carol Broadnax, Anthony Murgio

Sections covered include:

- Section 1: Indications and Usage
- Section 2: Dosage and Administration
- Section 5: Warnings and Precautions
- Black Box Warning
- Section 6: Adverse Reactions
- Section 8: (Begin)Use in Specific Populations, Geriatric Use, and Patients with Renal Impairment

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/s/

MONICA L HUGHES
08/29/2012

Mid-Cycle Meeting Summary
Abraxane sNDA: 21660/31
Meeting Held: May 14, 2012

Attendees: Monica Hughes, Patricia Keegan, Joseph Gootenberg, Shakun Malik, Hong Zhao, Huanyu (Jade) Chen, Kun He, John Johnson, Shakun Malik, Ted Chang, Richard Pazdur, and additional members of OHOP staff.

Mid-Cycle Meeting Agenda and Discussion

1. Important Goal Dates

Primary review Completion Goal Date according to GRMP: September 7, 2012

PDUFA Goal Date: October 12, 2012

2. Discipline Specific Reviews of Application

- Presentations included a discussion of the applicable studies/information submitted
- Presentations discussed the status of review of the data
- Presentations discussed findings so far:

- a. Are there issues requiring resolution?

Discussion During Meeting: No issues have been identified, review is ongoing.

- b. Are there any major labeling issues?

Discussion During Meeting: Labeling meetings are scheduled to begin in July. Some labeling issues were discussed during the clinical presentation and are outlined in # 5 below.

- c. Are there PMC and Risk Management Plan Issues?

Discussion During Meeting: No issues have been identified, review is ongoing.

- Identification of need for additional input from review team or through additional consults (not already requested):

Discussion During Meeting: No additional consults were identified.

- Information requests to be sent to sponsor:

Discussion During Meeting: Request for information to be sent to sponsor as review issues are identified.

Mid-Cycle Meeting Summary
Abraxane sNDA: 21660/31
Meeting Held: May 14, 2012

- Review Discipline Presentations During Mid-Cycle Meeting:
 - a. Clinical: Shakun Malik
 - b. Clinical Pharmacology: Lillian Zhang, delivered by Hong Zhao
 - c. Statistical: Jade Chen

3. Pending Consults

- OPDP
- OSE/DMEPA
- Patient Labeling Team

4. Issues Requiring Resolution: To be determined and communicated to the sponsor during the review of this sNDA.

5. Labeling Issues:

(b) (4)

6. PMC and Risk Management Plan Issues:

- Need for Pre-Approval Safety Conference?

Discussion During Meeting: A pre-approval safety conference is not required.

7. Scheduled Meetings

Team Meetings: To be held as needed.

Wrap-Up: Scheduled for August 27, 2012

Labeling: Scheduled for July 9, 16, 18, and 30, 2012. Additional meetings will be scheduled.

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/s/

MONICA L HUGHES
08/29/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 6, 2012
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: sNDA 21660/31

Please find attached FDA's counter proposal to your revised package insert (PI), patient insert, and carton and container labeling as submitted on February 17, 2012, in response to our February 10, 2012, filing communication.

We also refer to your CMC prior approval supplement 21660/33, submitted on February 24, 2012, and subsequently issued a complete response letter on June 21, 2012. During the review of supplement 21660/33 and the March 6, 2012, annual report, the carton and container labeling was reviewed and comments were conveyed to Celgene.

We note that some of the comments noted below were communicated to Celgene on May 30, 2012, as part of the review of the revised carton and container labeling submitted under supplement 21660/33 and as part of the March 6, 2012, annual report. In response to FDA's comments Celgene submitted revised Carton and Container labeling on June 15, 2012, under supplement 21660/33. However, supplement 21660/33 was subsequently issued a complete response letter on June 21, 2012. Therefore, we would like to include the previously agreed upon changes to the carton and container labeling under this supplement.

Abraxane is supplied as a single use vial containing 100 mg of paclitaxel, individually packaged in a carton.

Please note these are our preliminary comments, this labeling is currently being reviewed by our counterparts in Office of Prescription Drug Promotion (OPDP) and the Patient Labeling Team (PLT) and additional comments will follow.

General Comments: As conveyed to Celgene as part of the review of sNDA 21660/33, the following proposed changes have been reviewed and determined to be acceptable and should be incorporated:

(b) (4)



1 Page Immediately Following Withheld - b(4)

As noted in Annual Report #7 dated March 6, 2012, and as provided as part of supplement 21660/33, Celgene made the following changes based on the change of NDA ownership from Abraxis BioScience LLC to Celgene Corporation.

15. Changed from: Abraxis Oncology A Division of American Pharmaceutical Partners, Inc.
Schaumburg, IL 60173

To:
“Manufactured for:
Celgene Corporation
Summit, NJ 07901

(b) (4)

ABRAXANE® is a registered trademark of Abraxis BioScience, LLC.
©2005-2012 Abraxis BioScience, LLC. All Rights Reserved.
Abraxis BioScience, LLC is a wholly owned subsidiary of Celgene Corporation
US 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”

Please let me know if you have any questions.

Regards,

Monica Hughes, M.S.
Lead Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9225
Fax: 301-796-9849

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/s/

MONICA L HUGHES
09/06/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 22, 2012
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: sNDA 21330/31

Please confirm the FDA updated Table 5 for the PI and Table 1 below via email communication by COB Aug 22, 2012. Please follow up with a subsequent formal submission to sNDA 21660/31.

(b) (4)

Table 1. Incidence of Abnormal Lab Test NCI CTCAE Results

Lab Test	ABI-007/carboplatin (N=514)				Taxol/carboplatin (N=524)			
	GL1_4	GL3_4	GH1_4	GH3_4	GL1_4	GL3_4	GH1_4	GH3_4
Neutrophils (ANC)	430/508 (85%)	239/508 (47%)			424/513 (83%)	296/513 (58%)		
WBC	451/508 (89%)	121/508 (24%)			425/514 (83%)	121/514 (24%)		
Hemoglobin	496/508 (98%)	140/508 (28%)			466/514 (91%)	35/514 (7%)		
Platelet Count	344/508 (68%)	92/508 (18%)			284/513 (55%)	47/513 (9%)		
Lymphocytes	257/508 (51%)	40/508 (8%)			242/513 (47%)	53/513 (10%)		
Alkaline Phosphatase			96/491 (20%)	5/491 (1%)			126/498 (25%)	4/498 (<1%)
ALT (SGPT)			128/492 (26%)	5/492 (1%)			113/498 (23%)	4/498 (<1%)
AST (SGOT)			110/492 (22%)	5/492 (1%)			103/498 (21%)	4/498 (<1%)
Total Bilirubin			21/492 (4%)				23/498 (5%)	2/498 (<1%)
Albumin	58/71 (82%)	2/71 (3%)			54/75 (72%)			
Creatinine			45/490 (9%)				52/497 (10%)	
Calcium	38/67 (57%)	1/67 (1%)	1/67 (1%)		37/73 (51%)	1/73 (1%)		
Glucose	6/491 (1%)		296/491 (60%)	8/491 (2%)	4/495 (<1%)	1/495 (<1%)	286/495 (58%)	16/495 (3%)
Potassium	8/71 (11%)	2/71 (3%)	26/71 (37%)	0	7/75 (9%)	2/75 (3%)	22/75 (29%)	2/75 (3%)
Sodium	24/71 (34%)	3/71 (4%)	2/71 (3%)	0	30/75 (40%)	4/75 (5%)	1/75 (1%)	0

SAS program used to calculate Table 1.

(b) (4)

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Please let me know if you have any questions.

Regards,

Monica Hughes, M.S.
Lead Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9225
Fax: 301-796-9849

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/s/

MONICA L HUGHES
08/22/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 9, 2012
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 21660/31: Information Request

We are in the process of reviewing your application and have the following comments and requests for additional information

1. In your MedDRA AE calculation, you used the number of patients in the as-treated population in the denominator, but in the calculation of AE based the lab test, you used the number of patients who received the lab tests. Please provide a rationale of using a different denominator.

For example, the ABI-007 Grade 1 anaemia incident rate is 25% = 125/508 using the number of patients who received the lab tests, and is 125/514=24% if using the number of as-treated population.
2. Please provide the inclusion and exclusion criteria in the calculation of the NCI CTCAE incident rate for the entire lab test terms.
3. FDA statistician calculated all NCI CTCAE incident rates based on the lab tests. The SAS programs and results are attached in this IR. Since the results differ than what you submitted, please comment on the SAS codes and datasets used which caused the difference.
4. Potassium, glucose, calcium, and sodium AE results had both low and high AEs. Please provide a document or comment so that the statistician can verify.
5. Please provide your SAS codes in deriving all incidence rates using the lab tests. The codes which can be read clearly (without so many calls of macros) would be really appreciated.

Please find the attached documents below: SAS codes and an Excel Spreadsheet.

Please submit your responses to our comments above along with the data by 2:00 PM ET August 13, 2012.

Please let me know if you have any questions.

Regards,

Monica Hughes, M.S.
Lead Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9225, Fax: 301-796-9849

2 Pages Immediately Following Withheld - b(4)

Lab Test	ABI-007				Taxol			
	High AE Grade		Low AE Grade		High AE Grade		Low AE Grade	
	G1-4	G3-4	G1-4	G3-4	G1-4	G3-4	G1-4	G3-4
ABS.LYMPHOCYTE COUNT			258 (50%)	41 (8%)			243 (46%)	54 (10%)
ABS.NEUTROPHIL COUNT			431 (84%)	239 (46%)			424 (81%)	296 (56%)
ALBUMIN			58 (11%)	2 (0%)			55 (10%)	0 (0%)
ALKALINE PHOSPHATASE	101 (20%)	6 (1%)			129 (25%)	5 (1%)		
ALT	130 (25%)	6 (1%)			117 (22%)	4 (1%)		
AST	111 (22%)	6 (1%)			106 (20%)	4 (1%)		
BILIRUBIN, TOTAL	22 (4%)	0 (0%)			23 (4%)	2 (0%)		
CALCIUM	1 (0%)		39 (8%)	1 (0%)			37 (7%)	1 (0%)
CREATININE	46 (9%)				52 (10%)			
GLUCOSE, RANDOM	300 (58%)	8 (2%)	6 (1%)		289 (55%)	17 (3%)	4 (1%)	1 (0%)
HGB			497 (97%)	141 (27%)			468 (89%)	36 (7%)
PLATELET COUNT			344 (67%)	93 (18%)			285 (54%)	48 (9%)
POTASSIUM	27 (5%)		8 (2%)	2 (0%)	22 (4%)	2 (0%)	7 (1%)	2 (0%)
SODIUM	2 (0%)		26 (5%)	5 (1%)	1 (0%)	(%)	31 (6%)	5 (1%)
WBC			452 (88%)	121 (24%)			425 (81%)	121 (23%)

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/s/

MONICA L HUGHES
08/09/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 7, 2012
From: Melanie Pierce, DOP2/OHOP/CDER
Subject: NDA 21660/31; Advice/Information request

We are in the process of reviewing your application and have the following comments and requests for additional information:

DMEPA is currently reviewing the preparation instructions in the insert labeling for the proposed NSCLC indication. We are concerned that preparing the recommended dosage and toxicity-related dose reductions results in volumes less than the typical minimum volume (50 mL) used for 30 minute intravenous bag infusions. For example, a patient with BSA 1.5 m² receiving Abraxane 50 mg/m² will result in a 75 mg dose or 15 mL of reconstituted Abraxane to be infused via infusion bag over 30 minutes. Therefore, we request the following to address our concerns:

1. Provide the preparation and administration instructions used in the clinical trials for all doses (recommended dose and toxicity-related dose reductions).
2. Discuss any medication errors, product complaints, or preparation and administration difficulties experienced during the clinical trials. This discussion should include the type of error, outcome, and causality.

We ask that you respond within 7 days of receipt.

If you have any questions, please do not hesitate to call me at 301-796-1273.

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/s/

MELANIE B PIERCE
08/07/2012

From: Patel, Mona
Sent: Thursday, July 05, 2012 3:28 PM
To: 'wcorbett@celgene.com'
Subject: FDA Inquiry: NDA 21660 (Supplement 31)
Dr. Corbett,

My name is Mona Patel. I am sending this request on behalf of Monica Hughes who is on leave this week.

We are not able to replicate the numbers in Table 5 of your proposed package insert submitted under Supplement 31. Please indicate what Table (s) in the database were used to generate Table 5 and provide the Proc File, so we can replicate your analysis.

Please email us a response by 3:30pm, Thursday, July 12, 2012 and follow-up with a formal submission.

Please acknowledge receipt of this email.

Thank you,

Mona

Mona Patel, PharmD | LCDR, USPHS | Regulatory Project Manager | Division of Oncology Products 2,
Office of Hematology & Oncology Products, CDER, FDA | White Oak Complex, Bldg. 22, Room 2328 |
10903 New Hampshire Avenue | Silver Spring, MD 20993

☎ 301.796.4236 (phone) • 301.796.9849 (fax) | mona.patel@fda.hhs.gov (email)



consider the environment before printing this e-mail

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/s/

MONA G PATEL
07/05/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 3, 2012
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: sNDA 21660/31

We have the following request for information:

Please provide the xpt.format data set and relevant SAS program for the response evaluation (investigator assessment), which contains one record per patient. Under the current submission, the dataset APSPINV.XPT has 3481 observations for 1053 patients.

We are requesting a response by noon on Wednesday, May 9, 2012.

Please let me know if you have any questions.

Regards,

Monica Hughes, M.S.
Lead Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9225
Fax: 301-796-9849

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/s/

MONICA L HUGHES
05/03/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting and Filing Meeting Minutes)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 21-660	NDA Supplement #:S- 31	Efficacy Supplement Type: SE- 1
Proprietary Name: Abraxane for Injectable Suspension Established/Proper Name: paclitaxel protein-bound particles for injectable suspension (albumin based) Dosage Form: For Injectable Suspension Strengths: Single Use vial containing 100 mg paclitaxel		
Applicant: Abraxis Bioscience a wholly owned subsidiary of Celgene Corporation Agent for Applicant (if applicable): N/A		
Date of Application: December 9, 2011 Date of Receipt: December 12, 2011		
PDUFA Goal Date: October 12, 2012	Action Goal Date (if different): N/A	
Filing Date: January 26, 2012	Date of Filing Meeting: January 12, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) N/A		
Proposed indication(s)/Proposed change(s): First Line Treatment of NSCLC in combination with carboplatin		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		☐ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☒ 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 55974				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system?	X			
<i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>				
Are the proprietary, established/proper, and applicant names correct in tracking system?	X			
<i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm	X			
<i>If no, ask the document room staff to make the appropriate entries.</i>				
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: ☒ Not in arrears ☐ In arrears			
505(b)(2)		YES	NO	NA	Comment
(NDAs/NDA Efficacy Supplements only)					
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].			X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?			X		
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm			X		
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm			X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 3 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?			X	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	X			

¹

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?		X		Sponsor amended supplement with this information on January 13, 2012.
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				

Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			X	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>			X	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?			X	
<i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?	X			
<i>If no, request in 74-day letter</i>				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>			X	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the DCRMSRMP mailbox</i>		X		
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ Not Applicable			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>			X	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>			X	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		X		Team is evaluating potential PRO data and a SEALD consult may be necessary.
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)?	X			

Date(s): November 4, 2005 <i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): August 9, 2010 <i>If yes, distribute minutes before filing meeting</i>	X			Meeting was cancelled upon receipt and review of FDA responses.
Any Special Protocol Assessments (SPAs)? Date(s): August 30, 2007 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 12, 2012

BLA/NDA/Supp #: 21-660, Supplement 31

PROPRIETARY NAME: Abraxane

ESTABLISHED/PROPER NAME: Paclitaxel protein-bound particles for injectable suspension (albumin based)

DOSAGE FORM/STRENGTH: For Injectable Suspension/ Single Use vial containing 100 mg paclitaxel

APPLICANT: Abraxis Bioscience a wholly owned subsidiary of Celgene Corporation

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): First Line Treatment of NSCLC in combination with carboplatin

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Monica Hughes	Y
	CPMS/TL:	Karen Jones	N
Cross-Discipline Team Leader (CDTL)	John Johnson		Y
Clinical	Reviewer:	Shakun Malik	Y
	TL:	John Johnson	Y

Clinical Pharmacology	Reviewer:	Lillian Zhang	Y
	TL:	Hong Zhao	N
Biostatistics	Reviewer:	Jade Chen	Y
	TL:	Kun He	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Margaret Brower	N
	TL:	Andrew McDougal	N
Product Quality (CMC)	Reviewer:	Ted Chang	Y
	TL:	Hasmukh Patel	N
CMC Labeling Review	Reviewer:	Ted Chang	Y
	TL:	Hasmukh Patel	N
Facility Review/Inspection	Reviewer:	Ted Chang	Y
	TL:	Hasmukh Patel	N

FILING MEETING DISCUSSION:

GENERAL 505(b)(2) filing issues? If yes, list issues:	☐ Not Applicable ☐ YES ☒ NO
Per reviewers, are all parts in English or English translation? If no, explain:	☒ YES ☐ NO
Electronic Submission comments List comments:	☐ Not Applicable
CLINICAL Comments: No filing issues discussed, asked the statistical reviewers to provide a break down of patients enrolled per site and to provide the ORR by site. The safety update will include only the 3 patients still enrolled.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

Clinical study site(s) inspections(s) needed? If no, explain: This is a multicenter global trial and clinical review found no specific site that could be driving the study results.	☐ YES ☒ NO
Advisory Committee Meeting needed?	☐ YES Date if known: ☒ NO ☐ To be determined Reason: The team agreed that an ODAC meeting will not be required because, based on the team's preliminary review: - Abraxane is not the first in its class - The clinical study design of Trial 301 is acceptable - The application does not raise significant safety or efficacy issues - The application does not raise significant public health questions on the role of Abraxane in the the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy.
If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL PHARMACOLOGY Comments to be conveyed to the sponsor in the filing letter: For studies BIO-VT-5, 08DA33, 05DA11 and 05DA13, the sponsor should submit the following: - bioanalytical method validation reports - individual concentration vs. time data, and corresponding pharmacokinetic parameters. The dataset as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the original analysis should be flagged and maintained in the datasets.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter

Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO									
BIOSTATISTICS Comments to be conveyed to the sponsor in the filing letter: - Sponsor should provide the DMC meeting minutes for the planned ORR, PFS, and OS interim analyses. - Sponsor should provide the SAS programs with adequate documentation to reproduce the results in CSR section 10 tables 4, 5, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 21, 22, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, and 35; and in Appendix tables 2.0, 3.0, 4.0, 5.0, and 6.0. - Sponsor should provide the SAS programs with adequate documentation to reproduce the figures 2, 5, 6, and 7 in CSR section 10. - After the statistical reviewer transferred the xpt format to SAS format, most of the dataset have different names in XPT and SAS format. Sponsor should provide a list of dataset names matching .xpt format and SAS format. For example, <table border="1" data-bbox="240 898 906 1029"> <thead> <tr> <th>Description</th><th>XPT format Name</th><th>SAS format Name</th></tr> </thead> <tbody> <tr> <td>Demographics</td><td>ADEMO</td><td>A_demo</td></tr> <tr> <td>...</td><td></td><td></td></tr> </tbody> </table> - The FDA statistical reviewer used arspind.sas program and got the dataset arspinv.sas7bdat with 4342 observations and 48 variables. The submitted dataset in XPT format has 1053 observations and 35 variables. Please see the attached SAS log file, and identify what caused the discrepancy. The sponsor should also resubmit the SAS programs if there are problems in the already submitted SAS programs.	Description	XPT format Name	SAS format Name	Demographics	ADEMO	A_demo	...			☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
Description	XPT format Name	SAS format Name								
Demographics	ADEMO	A_demo								
...										
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter									

PRODUCT QUALITY (CMC) Comments: No comments, no facility inspections will be required.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> - Establishment(s) ready for inspection? - Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? Comments: Per CMC reviewer, facility inspections will not be required.	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
<u>CMC Labeling Review</u> Comments: No comments discussed at the filing meeting.	☐ Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Patricia Keegan, MD 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments: The review team discussed the following during the filing meeting: 1. Team agreed that a standard review clock is appropriate because the data in this supplemental application do not establish that Abraxane is more effective than paclitaxel, based on the magnitude of the increased response rate of 8%, in the absence of an effect on progression-free or overall survival. In addition, the data in this application do not establish that Abraxane has superior safety based on unplanned exploratory comparisons analyses of some, but not all, taxane-related toxicities.	

2. A mid-cycle meeting was scheduled for May 14, 2012.
3. Standing monthly meetings were set up beginning in March 2012.
4. The team agreed that a SEALD consult was not required for this supplement; the FACT data proposed in section 6.2 will not be accepted.
5. The team discussed the need for DSI clinical site inspections, the statistical reviewer will look at the patient enrollment per site and will provide the information to the review team to determine if inspections are required. Following the filing meeting, the information was reviewed, and it was determined that DSI inspections were not required as this is a multicenter global trial and clinical review found no specific site that could be driving the study results.
6. The team agreed that labeling meetings should be scheduled in July/August and that at least 3 meetings (1.5 hours) should be scheduled for the clinical/stats team and 1 to review CMC labeling.

REGULATORY CONCLUSIONS/DEFICIENCIES

☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> ☒ Standard Review ☐ Priority Review
-------------------------------------	---

ACTIONS ITEMS

- | | |
|-------------------------------------|--|
| ☒ | Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug). |
| ☒ | Send review issues/no review issues by day 74 |
| ☒ | Conduct a PLR format labeling review and include labeling issues in the 74-day letter |

Monica Hughes

February 9, 2012

Regulatory Project Manager

Date

Karen Jones

February 9, 2012

Chief, Project Management Staff

Date

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/s/

MONICA L HUGHES
02/09/2012

KAREN D JONES
02/10/2012



NDA 21660/S-031

FILING COMMUNICATION

Abraxis BioScience, LLC, a wholly-owned subsidiary of Celgene Corporation
Attention: Wendy L. Corbett, Ph.D., MBA
Director, Global Regulatory Affairs-Oncology Solid Tumors
400 Connell Drive, Suite 7000
Berkeley Heights, NJ 07922

Dear Dr. Corbett:

Please refer to your Supplemental New Drug Application (sNDA) dated December 9, 2012, received December 12, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Abraxane® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension)(albumin-bound).

We also refer to your amendment dated January 13, 2012.

This supplemental application proposes to add the following new indication: Abraxane, in combination with carboplatin, for the first-line treatment of advanced NSCLC.

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this supplemental application is considered filed 60 days after the date we received your supplemental application. The review classification for this supplemental application is **Standard**. Therefore, the user fee goal date is October 12, 2012.

We are reviewing your supplemental application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 14, 2012.

During our filing review of your supplemental application, we identified the following potential review issues and are requesting you submit the following information:

Statistics:

1. Please provide the data monitoring committee (DMC) meeting minutes for the planned interim analyses of overall response rate, progression-free survival, and overall survival.
2. Please provide the SAS programs with adequate documentation to reproduce the results in CSR section 10 tables 4, 5, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 21, 22, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, and 35; and in Appendix tables 2.0, 3.0, 4.0, 5.0, and 6.0.
3. Please provide the SAS programs with adequate documentation to reproduce the figures 2, 5, 6, and 7 in the clinical study report, section 10.
4. When the .xpt format is transferred to SAS format, most of the datasets have different names in .xpt and SAS format. Please provide a list of dataset names which matching the .xpt format to the same dataset presented in SAS format. For example,

Description	XPT format Name	SAS format Name
Demographics	ADEMO	A demo
...		

5. The statistical reviewer used the arspind.sas program and got the dataset arspinv.sas7bdat with 4342 observations and 48 variables. The submitted dataset in .xpt format has 1053 observations and 35 variables. Please see the attached SAS log file, and identify what caused the discrepancy. Please also resubmit the SAS programs within 30 days if the SAS programs currently in the sNDA are corrupted or contain errors in format or content.

Clinical Pharmacology:

6. For studies BIO-VT-5, 08DA33, 05DA11 and 05DA13, please submit the following:
 - a. the bioanalytical method validation reports; and,
 - b. the individual concentration vs. time data, and corresponding pharmacokinetic parameters. Submit the dataset as a SAS transport file (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the original analysis should be flagged and maintained in the datasets.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the supplemental application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the supplemental application. If you respond

to these issues during this review cycle, we may not consider your response before we take an action on your application.

During our preliminary review of your submitted labeling, we have identified the following labeling issues:

(b) (4)



We request that you resubmit labeling that addresses these issues by February 24, 2012. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission 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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

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.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Monica Hughes, M.S., Senior Regulatory Health Project Manager, at (301) 796-9225.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Attachments: SAS log file

21 Pages Immediately Following Withheld - b(4)

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/s/

PATRICIA KEEGAN
02/09/2012

eCTD sNDA (21-660, Supplement 31)
Abraxane
Initial Planning Meeting Agenda/Meeting Minutes

Memorandum

Date: January 4, 2012
From: Monica Hughes, M.S., DOP2/OHOP/CDER
Subject: Initial Planning Meeting : NDA 21660/31

Efficacy Supplement: sNDA 21660/31

Product: Abraxane
Submission Date: December 9, 2011
Received Date: December 12, 2011
Sponsor: Abraxis Bioscience, LLC, a wholly owned subsidiary of Celgene Corporation
Proposed Indication: (b) (4)

Current Review Team for STN 21-660/31:

Patricia Keegan, M.D., Director DOP2	Attended Meeting
Monica Hughes, M.S., Senior Regulatory Health Project Manager	Attended Meeting
Karen Jones (CPMS)	Attended Meeting
Shakun Malik, M.D., Medical Officer	Attended Meeting
John Johnson, M.D., Medical (TL and CDTL)	Attended Meeting
Jade Chen, Ph.D., Statistics	Attended Meeting
Kun He, Ph.D., Statistics (TL)	
Lillian Zhang, Ph.D., Clinical Pharmacology	Attended Meeting
Hong Zhao, Ph.D, Clinical Pharmacology (TL)	Attended Meeting
Margaret Brower, Ph.D., Non-Clinical	Attended Meeting
Andrew McDougal, Ph.D., Non-Clinical (acting TL)	Attended Meeting
Ted Chiang, Ph.D., Product	
Hasmukh Patel, Ph.D., Product (TL)	
Deborah Mesmer, Product (RPM)	

A standard **reminder** that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss.

Agenda Items:

The following agenda was reviewed during this meeting. Discussion, agreement, and action items are noted below each section.

1. Review Status:

- Priority Review requested, discussion during the meeting as to grant a standard/priority review clock
- Note: Categorical Exclusion request included with this supplement
- Note: Request full waiver of pediatric studies included with this supplement
- Note: The clinical development of Abraxane has been conducted under IND 55974.

Discussion During Meeting: Team agreed that a standard review clock is appropriate because the data in this supplemental application do not establish that Abraxane is more effective than paclitaxel, based on the magnitude of the increased response rate of 8%, in the absence of an effect on progression-free or overall survival. In addition, the data in this application do not establish that Abraxane has superior safety based on unplanned exploratory comparisons analyses of some, but not all, taxane-related toxicities.

2. Dates Milestone Letters Must Issue (assuming a standard 10 month clock):

- **Acknowledgment letter Due Date:** Due: December 23, 2011
 - Issued December 21, 2011
- **Filing Action Letter Due Date:** February 10, 2012
 - Do we have any filing issues that we should discuss today?
 - If the filing issues are not identified by 2/10/12, we will need to send a “Notification of Review Status”

Discussion During Meeting: no issues were discussed during this meeting.

- **Deficiencies Identified Letter (74 day letter) Due Date:** February 24, 2012
- Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner’s Target date is September 14, 2012).
- Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant (Target Date: September 21, 2012).
- **Review Target due dates:**
Primary Review due: September 7, 2012 (5weeks before Action)

Secondary Review due: September 14, 2012 (4weeks before action)

- Compile and circulate Action Letter and Action Package: Target date- September 21, 2012.
- **Final Action Letter Due Date:** October 12, 2012

3. Potential Consults Needed:

a	OPDP (DDMAC) Reviewer	Marybeth Toscano- professional reviewer, Michelle Safarik- consumer reviewer, Olga Salis – RPM
b.	DSI	* Do we need clinical site inspections?
c.	OSE	Sue Kang-OSE RPM Sean Bradley-OSE RPM TL Jibril Abdus-Samad and his TL is Todd Bridges-DMEPA *DMEPA/CMC/DDMAC to review carton/container, PI and patient labeling
d.	Maternal Health	*No changes to these sections of the label, is consult needed?
e.	Facility/DMPQ	*Do we need facility inspections?
f.	QT-IRT Consult	*Do we need a QT-IRT consult?
g.	Pediatric Page/Perc Review:	***Requested a full waiver

Are there any additional consults we need?

Discussion During Meeting:

- (1) Regarding DSI inspections, the medical officer will review the submission to determine if DSI inspections are needed, we will discuss at the filing meeting.
- (2) The team agreed that a maternal health consult is not needed.
- (3) The team agreed that no facility inspections are needed.
- (4) The clinical pharmacology reviewer will review the submission to see if any additional QT information is required, but does not believe a QT-IRT consult will be required.
- (5) The medical officer will review the PRO data included to determine if a SEALD consult is needed, the team will discuss at the filing meeting.

4. Upcoming/TBD Internal Team Meetings:

- **Filing Meeting:** Scheduled for January 19, 2012
Please bring Filing review (TL signature) and Interim Deliverables
Please be prepared to identify significant filing issues for day 74 letter
- **Mid-Cycle Meeting:** Scheduled for May 14, 2012, during Monday Oncology Meeting.
Slides have to be sent to Dianne Spillman by TBD.

- **Labeling Meetings (suggested section groupings): When should we begin labeling meetings?**
 - a. (Clinical Sections: Adverse Reactions, Warnings and Precautions)
 - b. (Clinical Sections: Dosage and Strength, Clinical Studies)
 - c. (CMC, Nonclinical Sections, Clinical Pharmacology)
 - **Include OSE/CMC during this labeling meeting to review carton and container.
 - d. (Highlights, Indications and Usage)

Discussion During Meeting: The team agreed to group labeling meetings by review team sections. No meeting will be longer than 1.5 hours, meetings to be scheduled in the near future.

- **Team Meetings and PMR/PMC Working Meetings:**
 - Do we want to schedule monthly team meetings?
 - Do we want to schedule separate PMC/PMR meetings?

Discussion During Meeting: The team agreed to hold monthly meetings beginning in March. The team did not discuss PMC/PMR meetings, but those will be scheduled as needed.

- **Wrap- Up Meeting:** TBD, By September 7, 2012.

5. **Applicant Orientation Presentation:** Scheduled for February 17, 2012, during Friday clinical rounds.

Discussion During Meeting: This meeting will need to be re-scheduled to accommodate schedules.

6. **ODAC Needed/Not Needed:**
Target AC date: June-July 2012 (month 7-8.5)

Discussion During Meeting: The team agreed that an ODAC meeting will not be required because, based on the team's preliminary review:

- Abraxane is not the first in its class
- the clinical study design of Trial 301 is acceptable
- the application does not raise significant safety or efficacy issues
- the application does not raise significant public health questions on the role of Abraxane in the the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy.

7. **Miscellaneous Items or Issues:**

- a. Team was made aware that they need to bring their Filing Review Memos to the Filing Meeting scheduled for January 12, 2012. The template is available on the 21st Century website.
<http://inside.fda.gov:9003/ProgramsInitiatives/Drugs/21stCenturyReview/ucm034190.htm>
- b. CMC RPM/Deborah Mesmer will assist with the following:
 - **Establishment (EES)**
 - **Environmental Analysis: Request for Categorical Exclusion**

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/s/

MONICA L HUGHES
02/09/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

DATE: January 6, 2012

FROM: Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research

SUBJECT: Designation of NDA application review status
Sponsor: Celgene Corporation
Product: Abraxane
Indication: First Line Treatment of NSCLC in combination with carboplatin.

TO: NDA 21-660, Supplement 31

The review status of this file submitted as a NDA efficacy supplement is designated to be:

☒ Standard (10 Months)

☐ Priority (6 Months)

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

MONICA L HUGHES
01/06/2012

PATRICIA KEEGAN
01/06/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO (Office/Division): Patient Labeling Team			FROM (Name, Office/Division, and Phone Number of Requestor): Monica Hughes, RPM, DOP2/OHOP, 301-796-9225	
DATE 1/6/12	IND NO.	NDA NO. 21660/31	TYPE OF DOCUMENT Efficacy Supplement	DATE OF DOCUMENT 12/9/11
NAME OF DRUG Abraxane		PRIORITY CONSIDERATION No	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 8/15/12 (PDUFA Date 10/12/12)
NAME OF FIRM: Abraxis Bioscience a wholly owned subsidiary of Celgene				
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 2a MEETING ☐ END-OF-PHASE 2 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):				
II. BIOMETRICS				
☐ PRIORITY P NDA REVIEW ☐ END-OF-PHASE 2 MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW): ☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):				
III. BIOPHARMACEUTICS				
☐ DISSOLUTION ☐ BIOAVAILABILITY STUDIES ☐ PHASE 4 STUDIES ☐ DEFICIENCY LETTER RESPONSE ☐ PROTOCOL - BIOPHARMACEUTICS ☐ IN-VIVO WAIVER REQUEST				
IV. DRUG SAFETY				
☐ PHASE 4 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 ☐ NONCLINICAL				
COMMENTS / SPECIAL INSTRUCTIONS: This SE1 efficacy supplement provides labeling revisions for the First Line Treatment of NSCLC in combination with carboplatin. There is a package insert, patient package insert, and carton and vial labeling included. The changes to the PPI are minor, but are requesting a review from the patient labeling team. We are requesting a reviewer assignment to be included in to be scheduled labeling meetings. A mid-cycle meeting has been set up for May 14, 2012. Link to Supplement 31: EDR Location: \\CDSESUB1\EVSPROD\NDA021660\021660.enx DARRTS Supporting document 371 eCTD Sequence 0208				

SIGNATURE OF REQUESTOR Monica Hughes	METHOD OF DELIVERY (Check one) ☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

MONICA L HUGHES
01/06/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR DDMAC LABELING REVIEW CONSULTATION **Please send immediately following the Filing/Planning meeting**				
TO: CDER-DDMAC-RPM		FROM: (Name/Title, Office/Division/Phone number of requestor) Monica Hughes, RPM DOP2/OHOP, 301-796-9225				
REQUEST DATE 1/6/12	IND NO.	NDA/BLA NO. 21660/31	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)			
NAME OF DRUG Abraxane	PRIORITY CONSIDERATION No	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) 8/15/12			
NAME OF FIRM: Abraxis Bioscience a wholly owned subsidiary of Celgene		PDUFA Date: 10/12/12				
TYPE OF LABEL TO REVIEW						
<table border="0"> <tr> <td style="vertical-align: top;"> TYPE OF LABELING: (Check all that apply) ☒ PACKAGE INSERT (PI) ☒ PATIENT PACKAGE INSERT (PPI) ☒ CARTON/CONTAINER LABELING ☐ MEDICATION GUIDE ☐ INSTRUCTIONS FOR USE(IFU) </td> <td style="vertical-align: top;"> TYPE OF APPLICATION/SUBMISSION ☐ ORIGINAL NDA/BLA ☐ IND ☒ EFFICACY SUPPLEMENT ☐ SAFETY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ PLR CONVERSION </td> <td style="vertical-align: top;"> REASON FOR LABELING CONSULT ☐ INITIAL PROPOSED LABELING ☒ LABELING REVISION </td> </tr> </table>				TYPE OF LABELING: (Check all that apply) ☒ PACKAGE INSERT (PI) ☒ PATIENT PACKAGE INSERT (PPI) ☒ CARTON/CONTAINER LABELING ☐ MEDICATION GUIDE ☐ INSTRUCTIONS FOR USE(IFU)	TYPE OF APPLICATION/SUBMISSION ☐ ORIGINAL NDA/BLA ☐ IND ☒ EFFICACY SUPPLEMENT ☐ SAFETY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ PLR CONVERSION	REASON FOR LABELING CONSULT ☐ INITIAL PROPOSED LABELING ☒ LABELING REVISION
TYPE OF LABELING: (Check all that apply) ☒ PACKAGE INSERT (PI) ☒ PATIENT PACKAGE INSERT (PPI) ☒ CARTON/CONTAINER LABELING ☐ MEDICATION GUIDE ☐ INSTRUCTIONS FOR USE(IFU)	TYPE OF APPLICATION/SUBMISSION ☐ ORIGINAL NDA/BLA ☐ IND ☒ EFFICACY SUPPLEMENT ☐ SAFETY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ PLR CONVERSION	REASON FOR LABELING CONSULT ☐ INITIAL PROPOSED LABELING ☒ LABELING REVISION				
EDR link to submission: This SE1 efficacy supplement provides labeling revisions for the First Line Treatment of NSCLC in combination with carboplatin. There is a package insert, patient package insert, and carton and vial labeling included. Link to Supplement 31: EDR Location: \\CDSESUB1\EVSPROD\NDA021660\021660.enx Supporting document 371 eCTD Sequence 0208						
Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.						

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: May 14, 2012: 10:00 During the Standing Monday Oncology Meeting

Labeling Meetings: TBD

Wrap-Up Meeting: TBD

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

☒ eMAIL

☐ HAND

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/s/

MONICA L HUGHES
01/06/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO (Division/Office): Mail: OSE			FROM: Monica Hughes, RPM, DOP2/OHOP 301-796-9225	
DATE 1/6/11	IND NO.	NDA NO. 21660/31	TYPE OF DOCUMENT: SE1 Efficacy Supplement	DATE OF DOCUMENT: December 9, 2011
NAME OF DRUG: Abraxane		PRIORITY CONSIDERATION: No	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE: 8/15/2012
NAME OF FIRM: Abraxis Bioscience a wholly owned subsidiary of Celgene				
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):				
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 ☐ BIOAVAILABILITY 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: This SE1 efficacy supplement provides labeling revisions for the First Line Treatment of NSCLC in combination with carboplatin. Will provide labeling closer to the PDUFA Date of 10/12/12 There is a package insert, patient package insert, and carton and vial labeling included. Link to Supplement 31: EDR Location: \\CDSESUB1\EVSPROD\NDA021660\021660.enx Supporting document 371 eCTD Sequence 0208				

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

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/s/

MONICA L HUGHES
01/06/2012



NDA 21660/S-31

**ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT**

Abraxis BioScience, LLC, a wholly-owned subsidiary of Celgene Corporation
Attention: Wendy L. Corbett, Ph.D., MBA
Director, Global Regulatory Affairs-Oncology Solid Tumors
400 Connell Drive, Suite 7000
Berkeley Heights, NJ 07922

Dear Dr. Corbett:

We have received your December 9, 2011, Supplemental New Drug Application (sNDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 21660
SUPPLEMENT NUMBER: 31
PRODUCT NAME: Abraxane® for Injectable Suspension
DATE OF SUBMISSION: DECEMBER 9, 2011
DATE OF RECEIPT: DECEMBER 12, 2011

This supplemental application proposes the following change(s): Abraxane, in combination with carboplatin, for the first-line treatment of advanced NSCLC.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 10, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have questions, call me, at (301) 796-9225.

Sincerely,

{See appended electronic signature page}

Monica Hughes, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
Center for Drug Evaluation and Research

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/s/

MONICA L HUGHES
12/21/2011