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

Dear State Society:

Celgene Corporation is pleased to announce that ABRAXANE is now approved for the first-line treatment of locally advanced or metastatic non–small cell lung cancer (NSCLC), in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.

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

Dosage and Administration

The recommended dosing regimens for ABRAXANE in combination with carboplatin for advanced NSCLC and as a single agent in metastatic breast cancer are as follows:

Advanced NSCLC

• 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.

Metastatic breast cancer

• After failure of combination chemotherapy for metastatic breast cancer or relapse within 6 months of adjuvant chemotherapy, the recommended regimen of ABRAXANE is 260 mg/m² administered intravenously over 30 minutes every 3 weeks.

Important Dosing Information

• Dose adjustment is recommended for patients with moderate and severe hepatic impairment and patients who experience severe neutropenia or severe sensory neuropathy during treatment with ABRAXANE.
• Withhold ABRAXANE if AST >10 x ULN or bilirubin >5 x ULN.
• Dose reductions or discontinuation may be needed based on severe hematologic or neurologic toxicities.
• ABRAXANE contains albumin (human), a derivative of human blood.
• ABRAXANE can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant while receiving ABRAXANE.
• Men should be advised not to father a child while receiving ABRAXANE.

Please see Important Safety Information on page 3 and full Prescribing Information, including Boxed WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS, enclosed.
Extended Payment

Orders of ABRAXANE® placed before December 31, 2012 will be eligible to receive 90-day extended payment terms through the specialty/authorized distributors listed below.

<table>
<thead>
<tr>
<th>Distributor</th>
<th>Phone Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardinal Health Specialty Distribution*</td>
<td>866-476-1340</td>
</tr>
<tr>
<td>CuraScript Specialty Distribution</td>
<td>866-844-0148</td>
</tr>
<tr>
<td>Florida Infusion</td>
<td>727-942-1829</td>
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<tr>
<td>McKesson Specialty Health*</td>
<td>877-321-6626</td>
</tr>
<tr>
<td>Oncology Supply</td>
<td>334-983-9578</td>
</tr>
</tbody>
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*Please note: extended payment terms will only be available for orders placed through the specialty division of Cardinal Health and McKesson (extended payment terms will not be available for orders placed outside of the specialty divisions of those wholesalers).

Drug NDC and Coding

The National Drug Code (NDC) for ABRAXANE is 68817-134-50. The HCPCS J-code for ABRAXANE is J9264.

The ICD-9 diagnostic codes for the approved indications of ABRAXANE in advanced NSCLC and metastatic breast cancer are as follows:

**Advanced NSCLC**

162.2-162.9 Malignant neoplasm of bronchus and/or lung

**Metastatic breast cancer**

174.0-174.9 Malignant neoplasm of female breast

175.0-175.9 Malignant neoplasm of male breast

Packaging Information and Storage

ABRAXANE is supplied in a single-use vial, individually packaged in a carton. Each vial contains 100 mg of paclitaxel.

ABRAXANE vials should be stored in their original cartons at 20°C to 25°C (68°F to 77°F). Retain in the original package to protect from bright light.

Patient Assistance for ABRAXANE

Celgene Patient Support® can offer assistance with access to ABRAXANE for both insured and uninsured patients. This includes co-pay assistance or free drug to those patients who qualify, as well as assistance with obtaining insurance coverage. For more information or to participate, please contact Celgene Patient Support® at 1-800-931-8691.

For more information, or if you have any questions about the recent approval of ABRAXANE in NSCLC, visit www.abraxane.com or contact your Account Manager.

Please see Important Safety Information on page 3 and full Prescribing Information, including Boxed WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS, enclosed.
ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) 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.

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.

Important Safety Information

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.

- 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

CONTRAINDICATIONS

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

Hypersensitivity
- Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be rechallenged with the drug

WARNINGS AND PRECAUTIONS

Hematologic Effects
- Bone marrow suppression (primarily neutropenia) is dose-dependent and a dose-limiting toxicity of ABRAXANE
- Monitor for myelotoxicity by performing complete blood cell counts frequently, including prior to dosing on Day 1 for metastatic breast cancer (MBC) and Days 1, 8, and 15 for non-small cell lung cancer (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 7 days or more) during a course of ABRAXANE therapy, reduce the dose of ABRAXANE in subsequent courses in patients with either MBC or NSCLC

Please see full Prescribing Information, including Boxed WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS, enclosed.
Important Safety Information (continued)

- 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 >100,000 cells/mm³
- In patients with NSCLC, resume treatment if recommended at permanently reduced doses for both weekly ABRAXANE and every-3-week carboplatin after ANC recovers to at least 1,500 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

Nervous System
- Sensory neuropathy is dose- and schedule-dependent
- 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 MBC or until resolution to ≤ Grade 1 for NSCLC followed by a dose reduction for all subsequent courses of ABRAXANE

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

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

Albumin (Human)
- ABRAXANE contains albumin (human), a derivative of human blood

Use in Pregnancy: Pregnancy Category D
- 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

Use in Men
- Men should be advised not to father a child while receiving ABRAXANE

ADVERSE REACTIONS

Randomized Metastatic Breast Cancer (MBC) Study
- The most common adverse reactions (≥20%) with single-agent use of ABRAXANE in the MBC study were alopecia (90%), neutropenia (all cases 80%; severe 9%), sensory neuropathy (any symptoms 71%; severe 10%), abnormal ECG (all patients 60%; patients with normal baseline 35%), fatigue/asthenia (any 47%; severe 8%), myalgia/arthritis (any 44%; severe 8%), AST elevation (any 39%), alkaline phosphatase elevation (any 36%), anemia (all cases 33%; severe 1%), nausea (any 30%; severe 3%), diarrhea (any 27%; severe <1%) and infections (24%)
- Sensory neuropathy was the cause of ABRAXANE discontinuation in 7/229 (3%) patients

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Other adverse reactions of note included vomiting (any 18%; severe 4%), renal dysfunction (any 11%; severe 1%), fluid retention (any 10%; severe 0%); mucositis (any 7%; severe <1%), hepatic dysfunction (elevations in bilirubin 7%), hypersensitivity reactions (any 4%; severe 0%), thrombocytopenia (any 2%; severe <1%), and injection site reactions (<1%). In all ABRAXANE treated patients (n=366) ocular/visual disturbances were reported (any 13%; severe 1%). Dehydration and pyrexia were also reported.

Severe cardiovascular events possibly related to single-agent ABRAXANE occurred in approximately 3% of patients and 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.

Non-Small Cell Lung (NSCLC) Cancer Study

Adverse reactions with a difference of ≥2%, Grade 3 or higher, with combination use of ABRAXANE and carboplatin in NSCLC were anemia (28%); neutropenia (47%); thrombocytopenia (18%), and peripheral neuropathy (3%).

The most common adverse reactions (≥20%) of ABRAXANE in combination with carboplatin for NSCLC were anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue.

The most common serious adverse reactions of ABRAXANE in combination with carboplatin for NSCLC were 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%).

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).

Post-marketing Experience With ABRAXANE and Other Paclitaxel Formulations

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

There have been reports of congestive heart failure and left ventricular dysfunction with ABRAXANE, primarily among individuals with underlying cardiac history or prior exposure to cardiotoxic drugs.

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.

DRUG INTERACTIONS

Caution should be exercised when administering ABRAXANE concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4.

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Important Safety Information (continued)

USE IN SPECIFIC POPULATIONS

Nursing Mothers
• It is not known whether paclitaxel is excreted in human milk. 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

Pediatric
• The safety and effectiveness of ABRAXANE in pediatric patients have not been evaluated

Geriatric
• No toxicities occurred notably more frequently among patients ≥65 years of age who received ABRAXANE for MBC
• Myelosuppression, peripheral neuropathy, and arthralgia were more frequent in patients ≥65 years of age treated with ABRAXANE and carboplatin in NSCLC

Renal Impairment
• The use of ABRAXANE has not been studied in patients with renal impairment

DOSAGE AND ADMINISTRATION
• Dose adjustment is recommended for patients with moderate and severe hepatic impairment and patients who experience severe neutropenia or severe sensory neuropathy during treatment with ABRAXANE
• Withhold ABRAXANE if AST >10 x ULN or bilirubin >5 x ULN
• Dose reductions or discontinuation may be needed based on severe hematologic or neurologic toxicities
• Monitor patients closely

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Sincerely,

Gordon Willcox
Senior Director, National Accounts
US Hematology & Oncology
Celgene Corporation