

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, 6.3)
- DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS.**

RECENT MAJOR CHANGES

- Indications and Usage (1.3) 09/2013
- Dosage and Administration (2.3, 2.5) 09/2013
- Warnings and Precautions, Hematologic Effects (5.1), Nervous System (5.2), Sepsis (5.3), Pneumonitis (5.4) 09/2013

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)
 - Metastatic adenocarcinoma of the pancreas as first-line treatment, in combination with gemcitabine. (1.3)

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; administer carboplatin on Day 1 of each 21-day cycle immediately after ABRAXANE. (2.2)
- Adenocarcinoma of the Pancreas: Recommended dosage of ABRAXANE is 125 mg/m² intravenously over 30-40 minutes on Days 1, 8 and 15 of each 28-day cycle; administer gemcitabine on Days 1, 8 and 15 of each 28-day cycle immediately after ABRAXANE. (2.3)
- 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. (2.4)
- Dose Reductions: Dose reductions or discontinuation may be needed based on severe hematologic, neurologic, cutaneous, or gastrointestinal toxicities. (2.5)
- Use caution when handling cytotoxic drugs. Closely monitor the infusion site for extravasation and infiltration. No premedication is required prior to administration. (2.6)

DOSAGE FORMS AND STRENGTHS

- For injectable suspension: lyophilized powder containing 100 mg of paclitaxel in single-use vial for reconstitution. (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)
- Sepsis occurred in patients with or without neutropenia who received ABRAXANE in combination with gemcitabine; interrupt ABRAXANE and gemcitabine until sepsis resolves, and if neutropenic, until neutrophils are at least 1500 cells/mm³, then resume treatment at reduced dose levels. (5.3)
- Pneumonitis occurred with the use of ABRAXANE in combination with gemcitabine; permanently discontinue treatment with ABRAXANE and gemcitabine. (5.4)
- Severe hypersensitivity reactions with fatal outcome have been reported. Do not re-challenge with this drug. (5.5)
- Exposure and toxicity of paclitaxel can be increased in patients with hepatic impairment; therefore administer with caution. (5.6)
- ABRAXANE contains albumin derived from human blood, which has a theoretical risk of viral transmission. (5.7)
- Fetal harm may occur when administered to a pregnant woman. Advise women of childbearing potential to avoid becoming pregnant while receiving ABRAXANE. (5.8)
- Advise men not to father a child while on ABRAXANE. (5.9)

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 are anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue. (6.2)
- The most common (≥ 20%) adverse reactions of ABRAXANE in adenocarcinoma of the pancreas are neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration. (6.3)

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.

Revised: October 2013

WARNING: NEUTROPENIA

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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, 6.3)*].
- 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.

1.3 Adenocarcinoma of the Pancreas

ABRAXANE is indicated for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

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. Administer carboplatin on Day 1 of each 21 day cycle immediately after ABRAXANE [see *Clinical Studies (14.2)*].

2.3 Adenocarcinoma of the Pancreas

The recommended dose of ABRAXANE is 125 mg/m² administered as an intravenous infusion over 30-40 minutes on Days 1, 8 and 15 of each 28-day cycle. Administer gemcitabine immediately after ABRAXANE on Days 1, 8 and 15 of each 28-day cycle [see *Clinical Studies (14.3)*].

2.4 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 (5.6), 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 ^c | Pancreatic Adenocarcinoma ^c |
| Mild | < 10 x ULN | AND | > ULN to ≤ 1.25 x ULN | 260 mg/m ² | 100 mg/m ² | 125 mg/m ² |
| Moderate | < 10 x ULN | AND | 1.26 to 2 x ULN | 200 mg/m ² | 75 mg/m ² | not recommended |
| Severe | < 10 x ULN | AND | 2.01 to 5 x ULN | 130 mg/m ² ^b | 50 mg/m ² | not recommended |
| | > 10 x ULN | OR | > 5 x ULN | not recommended | not recommended | not recommended |

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 Patients with bilirubin levels above the upper limit of normal were excluded from clinical trials for pancreatic or lung cancer.

2.5 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°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 | |

Adenocarcinoma of the Pancreas

Dose level reductions for patients with adenocarcinoma of the pancreas, as referenced in Tables 4 and 5, are provided in Table 3.

Table 3: Dose Level Reductions for Patients with Adenocarcinoma of the Pancreas

| Dose Level | ABRAXANE (mg/m ²) | Gemcitabine (mg/m ²) |
|---------------------------------------|-------------------------------|----------------------------------|
| Full dose | 125 | 1000 |
| 1 st dose reduction | 100 | 800 |
| 2 nd dose reduction | 75 | 600 |
| If additional dose reduction required | Discontinue | Discontinue |

Recommended dose modifications for neutropenia and thrombocytopenia for patients with adenocarcinoma of the pancreas are provided in Table 4.

Table 4: Dose Recommendation and Modifications for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or within a Cycle for Patients with Adenocarcinoma of the Pancreas

| Cycle Day | ANC (cells/mm ³) | | Platelet count (cells/mm ³) | ABRAXANE / Gemcitabine |
|---|------------------------------|----|---|---------------------------------|
| Day 1 | < 1500 | OR | < 100,000 | Delay doses until recovery |
| Day 8 | 500 to < 1000 | OR | 50,000 to < 75,000 | Reduce 1 dose level |
| | < 500 | OR | < 50,000 | Withhold doses |
| Day 15: IF Day 8 doses were reduced or given without modification: | | | | |
| | 500 to < 1000 | OR | 50,000 to < 75,000 | Reduce 1 dose level from Day 8 |
| | < 500 | OR | < 50,000 | Withhold doses |
| Day 15: IF Day 8 doses were withheld: | | | | |
| | ≥ 1000 | OR | ≥ 75,000 | Reduce 1 dose level from Day 1 |
| | 500 to < 1000 | OR | 50,000 to < 75,000 | Reduce 2 dose levels from Day 1 |
| | < 500 | OR | < 50,000 | Withhold doses |

Abbreviations: ANC = Absolute Neutrophil Count

Recommended dose modifications for other adverse drug reactions in patients with adenocarcinoma of the pancreas are provided in Table 5.

Table 5: Dose Modifications for Other Adverse Drug Reactions in Patients with Adenocarcinoma of the Pancreas

| Adverse Drug Reaction | ABRAXANE | Gemcitabine |
|--|---|-------------------|
| Febrile Neutropenia: Grade 3 or 4 | Withhold until fever resolves and ANC ≥ 1500; resume at next lower dose level | |
| Peripheral Neuropathy: Grade 3 or 4 | Withhold until improves to ≤ Grade 1; resume at next lower dose level | No dose reduction |
| Cutaneous Toxicity: Grade 2 or 3 | Reduce to next lower dose level; discontinue treatment if toxicity persists | |
| Gastrointestinal Toxicity: Grade 3 mucositis or diarrhea | Withhold until improves to ≤ Grade 1; resume at next lower dose level | |

2.6 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.

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