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

Subject: Bristol Myers Squibb—Update on supply for BMS Product

Bristol Myers Squibb™

Dear Healthcare Professional,

The purpose of this communication is to provide information on supply for ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) since our last update sent on February 25, 2022.

BMS has resumed its manufacturing operations and ABRAXANE is no longer on allocation in the United States.

For the latest information on product inventory, please contact your wholesaler/distributer. You may contact Medical Information at 1-800-321-1335 if you have any questions about the safe and effective use of ABRAXANE.

This letter is not intended as a complete description of the benefits and risks related to the use of ABRAXANE. Please refer to the IMPORTANT SAFETY INFORMATION on pages 2-8 and Full Prescribing Information including Boxed WARNING.

If there is any change to the supply situation, we will proactively communicate with you in a timely and transparent manner.

Sincerely,

Adam Lenkowsky

General Manager and Head, U.S., Oncology, Immunology, Cardiovascular

Bristol Myers Squibb

INDICATIONS

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

IMPORTANT SAFETY INFORMATION

WARNING – SEVERE MYELOSUPPRESSION

- **Do not administer ABRAXANE therapy to patients who have baseline neutrophil counts of less than 1500 cells/mm^3**
- **Monitor for neutropenia, which may be severe and result in infection or sepsis. Perform frequent complete blood cell counts on all patients receiving ABRAXANE**

CONTRAINDICATIONS

- Baseline neutrophil counts of <1500 cells/mm^3
- A history of severe hypersensitivity reactions to ABRAXANE

WARNINGS AND PRECAUTIONS

Severe Myelosuppression

- Severe myelosuppression (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), 47% of patients with non–small cell lung cancer (NSCLC), and 38% of patients with pancreatic cancer
- Monitor for severe neutropenia and thrombocytopenia by performing complete blood cell counts frequently, including prior to dosing on Day 1 (for MBC) and Days 1, 8, and 15 (for NSCLC and for pancreatic cancer)
- Do not administer ABRAXANE to patients with baseline absolute neutrophil counts (ANC) of less than 1500 cells/mm^3
- In the case of severe neutropenia (<500 cells/mm^3 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
- In patients with MBC, resume treatment with every-3-week cycles of ABRAXANE after ANC recovers to a level >1500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3
- 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 1500 cells/mm^3 and platelet count of at least 100,000 cells/mm^3 on Day 1 or to an ANC of at least 500 cells/mm^3 and platelet count of at least 50,000 cells/mm^3 on Days 8 or 15 of the cycle
- In patients with adenocarcinoma of the pancreas, withhold ABRAXANE and gemcitabine if the ANC is less than 500 cells/mm^3 or platelets are less than 50,000 cells/mm^3 and delay initiation of the next cycle if the ANC is less than 1500 cells/mm^3 or platelet count is less than 100,000 cells/mm^3 on Day 1 of the cycle. Resume treatment with appropriate dose reduction if recommended

Severe Neuropathy

- Sensory neuropathy is dose- and schedule-dependent
- If ≥ Grade 3 sensory neuropathy develops, withhold ABRAXANE treatment until resolution to Grade 1 or 2 for MBC or until resolution to ≤ Grade 1 for NSCLC and pancreatic cancer followed by a dose reduction for all subsequent courses of ABRAXANE

Sepsis

- Sepsis occurred in 5% of patients with or without neutropenia who received ABRAXANE in combination with gemcitabine
- Biliary obstruction or presence of biliary stent were risk factors for severe or fatal sepsis
- If a patient becomes febrile (regardless of ANC), initiate treatment with broad-spectrum antibiotics
- For febrile neutropenia, interrupt ABRAXANE and gemcitabine until fever resolves and ANC ≥1500 cells/mm^3, then resume treatment at reduced dose levels

Pneumonitis

- Pneumonitis, including some cases that were fatal, occurred in 4% of patients receiving ABRAXANE in combination with gemcitabine
- Monitor patients for signs and symptoms and interrupt ABRAXANE and gemcitabine during evaluation of suspected pneumonitis
- Permanently discontinue treatment with ABRAXANE and gemcitabine upon making a diagnosis of pneumonitis

Severe Hypersensitivity

- Severe and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, have been reported
- Do not rechallenge patients who experience a severe hypersensitivity reaction to ABRAXANE with this drug
- Cross-hypersensitivity between ABRAXANE and other taxane products has been reported and may include severe reactions such as anaphylaxis. Closely monitor patients with a previous history of hypersensitivity reaction to ABRAXANE with this drug

Use in Patients With Hepatic Impairment

- The exposure and toxicity of paclitaxel can be increased in patients with hepatic impairment. Closely monitor patients with hepatic impairment for severe myelosuppression
- ABRAXANE is not recommended in patients who have a total bilirubin >5 x ULN or AST >10 x ULN
- For MBC and NSCLC, the starting dose should be reduced for patients with moderate or severe hepatic impairment
- For pancreatic adenocarcinoma, ABRAXANE is not recommended for patients with moderate to severe hepatic impairment (total bilirubin >1.5 x ULN and AST ≤10 x ULN)

Albumin (Human)

ABRAXANE contains albumin (human), a derivative of human blood

Embryo-Fetal Toxicity

- Based on mechanism of action and findings in animals, ABRAXANE can cause fetal harm when administered to a pregnant woman
- Advise females of reproductive potential of the potential risk to a fetus
- Advise females of reproductive potential to use effective contraception and avoid becoming pregnant during treatment with ABRAXANE and for at least six months after the last dose of ABRAXANE
- Advise male patients with female partners of reproductive potential to use effective contraception and avoid fathering a child during treatment with ABRAXANE and for at least three months after the last dose of ABRAXANE

ADVERSE REACTIONS

Randomized Metastatic Breast Cancer (MBC) Study

- The most common adverse reactions (≥20%) with single-agent use of ABRAXANE vs paclitaxel injection in the MBC study are alopecia (90%, 94%), neutropenia (all cases 80%, 82%; severe 9%, 22%), sensory neuropathy (any symptoms 71%, 56%; severe 10%, 2%), abnormal ECG (all patients 60%, 52%; patients with normal baseline 35%, 30%), fatigue/asthenia (any 47%, 39%; severe 8%, 3%), myalgia/arthralgia (any 44%, 49%; severe 8%, 4%), AST elevation (any 39%, 32%), alkaline phosphatase elevation (any 36%, 31%), anemia (any 33%, 25%; severe 1%, <1%), nausea (any 30%, 22%; severe 3%, <1%), diarrhea (any 27%, 15%; severe <1%, 1%), and infections (24%, 20%), respectively
- Sensory neuropathy was the cause of ABRAXANE discontinuation in 7/229 (3%) patients
- Other adverse reactions of note with the use of ABRAXANE vs paclitaxel injection included vomiting (any 18%, 10%; severe 4%, 1%), fluid retention (any 10%, 8%; severe 0%, <1%), mucositis (any 7%, 6%; severe <1%, 0%), hepatic dysfunction (elevations in bilirubin 7%, 7%), hypersensitivity reactions (any 4%, 12%; severe 0%, 2%), thrombocytopenia (any 2%, 3%; severe <1%, <1%), neutropenic sepsis (<1%, <1%), and injection site reactions (<1%, 1%), respectively. Dehydration and pyrexia were also reported
- Renal dysfunction (any 11%, severe 1%) was reported in patients treated with ABRAXANE (n=229)
- In all ABRAXANE-treated patients (n=366), ocular/visual disturbances were reported (any 13%; severe 1%)
- 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 Cancer (NSCLC) Study

- The most common adverse reactions (≥20%) of ABRAXANE in combination with carboplatin are anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue
- The most common serious adverse reactions of ABRAXANE in combination with carboplatin for NSCLC are anemia (4%) and pneumonia (3%)
- The most common adverse reactions resulting in permanent discontinuation of ABRAXANE are neutropenia (3%), thrombocytopenia (3%), and peripheral neuropathy (1%)
- The most common adverse reactions resulting in dose reduction of ABRAXANE are neutropenia (24%), thrombocytopenia (13%), and anemia (6%)
- The most common adverse reactions leading to withholding or delay in ABRAXANE dosing are 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
- Adverse reactions with a difference of ≥2%, Grade 3 or higher, with combination use of ABRAXANE and carboplatin vs combination use of paclitaxel injection and carboplatin in NSCLC are anemia (28%, 7%), neutropenia (47%, 58%), thrombocytopenia (18%, 9%), and peripheral neuropathy (3%, 12%), respectively

- Adverse reactions with a difference of ≥5%, Grades 1-4, with combination use of ABRAXANE and carboplatin vs combination use of paclitaxel injection and carboplatin in NSCLC are anemia (98%, 91%), thrombocytopenia (68%, 55%), peripheral neuropathy (48%, 64%), edema peripheral (10%, 4%), epistaxis (7%, 2%), arthralgia (13%, 25%), and myalgia (10%, 19%), respectively

- Neutropenia (all grades) was reported in 85% of patients who received ABRAXANE and carboplatin vs 83% of patients who received paclitaxel injection and carboplatin

Pancreatic Adenocarcinoma Study

- Among the most common (≥20%) adverse reactions in the phase III study, those with a ≥5% higher incidence in the ABRAXANE/gemcitabine group compared with the gemcitabine group are neutropenia (73%, 58%), fatigue (59%, 46%), peripheral neuropathy (54%, 13%), nausea (54%, 48%), alopecia (50%, 5%), peripheral edema (46%, 30%), diarrhea (44%, 24%), pyrexia (41%, 28%), vomiting (36%, 28%), decreased appetite (36%, 26%), rash (30%, 11%), and dehydration (21%, 11%)

- Of these most common adverse reactions, those with a ≥2% higher incidence of Grade 3-4 toxicity in the ABRAXANE/gemcitabine group compared with the gemcitabine group, respectively, are neutropenia (38%, 27%), fatigue (18%, 9%), peripheral neuropathy (17%, 1%), nausea (6%, 3%), diarrhea (6%, 1%), pyrexia (3%, 1%), vomiting (6%, 4%), decreased appetite (5%, 2%), and dehydration (7%, 2%)
- Thrombocytopenia (all grades) was reported in 74% of patients in the ABRAXANE/gemcitabine group vs 70% of patients in the gemcitabine group

- The most common serious adverse reactions of ABRAXANE (with a ≥1% higher incidence) are pyrexia (6%), dehydration (5%), pneumonia (4%), and vomiting (4%)

- The most common adverse reactions resulting in permanent discontinuation of ABRAXANE were peripheral neuropathy (8%), fatigue (4%), and thrombocytopenia (2%)

- The most common adverse reactions resulting in dose reduction of ABRAXANE are neutropenia (10%) and peripheral neuropathy (6%)

- The most common adverse reactions leading to withholding or delay in ABRAXANE dosing are neutropenia (16%), thrombocytopenia (12%), fatigue (8%), peripheral neuropathy (15%), anemia (5%), and diarrhea (5%)

- Other selected adverse reactions with a ≥5% higher incidence for all-grade toxicity in the ABRAXANE/gemcitabine group compared to the gemcitabine group, respectively, are asthenia (19%, 13%), mucositis (10%, 4%), dysgeusia (16%, 8%), headache (14%, 9%), hypokalemia (12%, 7%), cough (17%, 7%), epistaxis (15%, 3%), urinary tract infection (11%, 5%), pain in extremity (11%, 6%), arthralgia (11%, 3%), myalgia (10%, 4%), and depression (12%, 6%)

- Other selected adverse reactions with a ≥2% higher incidence for Grade 3-4 toxicity in the ABRAXANE/gemcitabine group compared to the gemcitabine group are thrombocytopenia (13%, 9%), asthenia (7%, 4%), and hypokalemia (4%, 1%)

Postmarketing Experience With ABRAXANE and Other Paclitaxel Formulations

- Severe and sometimes fatal hypersensitivity reactions. Cross-hypersensitivity between ABRAXANE and other taxanes has been reported

- Congestive heart failure, left ventricular dysfunction, and atrioventricular block. Most patients were previously exposed to cardiotoxic drugs, such as anthracyclines, or had underlying cardiac history

- Extravasation. Closely monitor 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

USE IN SPECIFIC POPULATIONS

Pregnancy

- Based on the mechanism of action and findings in animals, ABRAXANE can cause fetal harm when administered to a pregnant woman. Advise females of the potential risk to a fetus and to avoid becoming pregnant while receiving ABRAXANE

Lactation

- Paclitaxel and/or its metabolites were excreted into the milk of lactating rats. Nursing must be discontinued when receiving treatment with ABRAXANE and for two weeks after the last dose

Females and Males of Reproductive Potential

- Based on animal studies and mechanism of action, ABRAXANE can cause fetal harm when administered to a pregnant woman
- Verify the pregnancy status of females of reproductive potential prior to starting treatment with ABRAXANE
- Advise females of reproductive potential to use effective contraception and avoid becoming pregnant during treatment with and for at least six months after the last dose of ABRAXANE [*see Warnings and Precautions*]
- Advise males with female partners of reproductive potential to use effective contraception and avoid fathering a child during treatment with ABRAXANE and for at least three months after the last dose of ABRAXANE [*see Warnings and Precautions*]
- Based on findings in animals, ABRAXANE may impair fertility in females and males of reproductive potential

Pediatric

- The safety and effectiveness of ABRAXANE in pediatric patients have not been established

Geriatric

- A higher incidence of epistaxis, diarrhea, dehydration, fatigue, and peripheral edema was found in patients 65 years or older who received ABRAXANE for MBC in a pooled analysis of clinical studies
- Myelosuppression, peripheral neuropathy, and arthralgia were more frequent in patients ≥65 years of age treated with ABRAXANE and carboplatin in NSCLC
- Diarrhea, decreased appetite, dehydration, and epistaxis were more frequent in patients 65 years or older compared with patients younger than 65 years old who received ABRAXANE and gemcitabine in adenocarcinoma of the pancreas

Renal Impairment

- There are insufficient data to permit dosage recommendations in patients with severe renal impairment or end stage renal disease (estimated creatinine clearance <30 mL/min)

DOSAGE AND ADMINISTRATION

- DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS
- Dose reductions or discontinuation may be needed based on severe hematologic, neurologic, cutaneous, or gastrointestinal toxicity

Please see full Prescribing Information, including Boxed WARNING.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Bristol Myers Squibb™

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