Abraxis Oncology

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Paclitaxel (protein-bound particles) for injectable suspension

Abraxane®
for Injectable Suspension

(Patient Information Enclosed)

WARNING

ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

ABRAXANE® therapy should not be administered to patients with metastatic breast cancer 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.

DESCRIPTION

ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. 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 and approximately 900 mg of human albumin. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. ABRAXANE® is free of solvents.

The active agent in ABRAXANE® is paclitaxel, a natural product with antitumor activity. Paclitaxel is obtained from Taxus media. The chemical name for paclitaxel is β,20-Epoxy- 1,2a,4,7β,10ß,13a hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)- N-benzoyl-3-phenylisoserine.

Paclitaxel is a white to off-white crystalline powder with the empirical formula C47H51NO14 and a molecular weight of 853.91. It is highly lipophilic, insoluble in water, and melts at approximately 216°C to 217°C.

CLINICAL PHARMACOLOGY

Mechanism of Action

ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is an antimicrotubule agent 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.

Human Pharmacokinetics

The pharmacokinetics of total paclitaxel following 30 and 180-minute infusions of ABRAXANE® at dose levels of 80 to 375 mg/m^2 were determined in clinical studies. Dose levels of mg/m^2 refer to mg of paclitaxel in ABRAXANE®. Following intravenous administration of ABRAXANE®, paclitaxel plasma concentrations declined in a biphasic manner, the initial rapid decline representing distribution to the peripheral compartment and the slower second phase representing drug elimination. The terminal half-life was about 27 hours.

The drug exposure (AUCs) was dose proportional over 80 to 375 mg/m^2 and the pharmacokinetics of paclitaxel for ABRAXANE® were independent of the duration of administration. At the recommended ABRAXANE® clinical dose, 260 mg/m^2, the mean maximum concentration of paclitaxel, which occurred at the end of the infusion, was 18,741 ng/mL. The mean total clearance was 15 L/hr/m^2. The mean volume of distribution was 632 L/m^2; the large volume of distribution indicates extensive extravascular distribution and/or tissue binding of paclitaxel.

The pharmacokinetic data of 260 mg/m^2 ABRAXANE® administered over 30 minutes was compared to the pharmacokinetics of 175 mg/m^2 paclitaxel injection over 3 hours. The clearance of ABRAXANE® was larger (43%) than for the clearance of paclitaxel injection and the volume of distribution of ABRAXANE® was also higher (53%). Differences in Cmax and Cmax corrected for dose reflected differences in total dose and rate of infusion. There were no differences in terminal half-lives.

In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 µg/mL, indicate that between 89% to 98% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

After a 30-minute infusion of 260 mg/m^2 doses of ABRAXANE® , the mean values for cumulative urinary recovery of unchanged drug (4%) indicated extensive non-renal clearance. Less than 1% of the total administered dose was excreted in urine as the metabolites 6a-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel. Fecal excretion was approximately 20% of the total dose administered.

In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6a-hydroxypaclitaxel by CYP2C8; and to two minor metabolites, 3'-p-hydroxypaclitaxel and 6a, 3'-p-dihydroxypaclitaxel, by CYP3A4. In vitro, the metabolism of paclitaxel to 6a-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, 17a-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6a-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 PRECAUTIONS: Drug Interactions). The effect of renal or hepatic dysfunction on the disposition of ABRAXANE® has not been investigated.

Possible interactions of paclitaxel with concomitantly administered medications have not been formally investigated.

CLINICAL STUDIES

Metastatic Breast Carcinoma:

Data from 106 patients accrued in two single arm open label studies and from 460 patients enrolled in a randomized comparative study were available to support the use of ABRAXANE® in metastatic breast cancer.

Single Arm Open Label Studies- In one study, ABRAXANE® was administered as a 30-minute infusion at a dose of 175 mg/m^2 to 43 patients with metastatic breast cancer. The second trial utilized a dose of 300 mg/m^2 as a 30 minute infusion in 63 patients with metastatic breast cancer. Cycles were administered at 3 week intervals. Objective responses were observed in both studies.

Randomized Comparative Study-This multicenter trial was conducted in 460 patients with metastatic breast cancer. Patients were randomized to receive ABRAXANE® at a dose of 260 mg/m^2 given as a 30-minute infusion, or paclitaxel injection at 175 mg/m^2 given as a 3-hour infusion. Sixty-four percent of patients had impaired performance status (ECOG 1 or 2) at study entry; 79% had visceral metastases; and 76% had > 3 sites of metastases. Fourteen percent of the patients had not received prior chemotherapy; 27% had received chemotherapy in the adjuvant setting, 40% in the metastatic setting and 19% in both metastatic and adjuvant settings. Fifty- nine percent received study drug as second or greater than second-line therapy. Seventy-seven percent of the patients had been previously exposed to anthracyclines.

In this trial, patients in the ABRAXANE® treatment arm had a statistically significantly higher reconciled target lesion response rate (the trial primary endpoint) of 21.5% (95% CI: 16.2% to 26.7%), compared to 11.1% (95% CI: 6.9% to 15.1%) for patients in the paclitaxel injection treatment arm. See Table 1. There was no statistically significant difference in overall survival between the two study arms.

Table 1: Efficacy Results from Randomized Trial

		ABRAXANE® 260mg/m^2	Paclitaxel Injection 175mg/m^2
Reconciled Target Lesion Response Rate (primay endpoint)[a]			
All randomized patients	ResponseRate [95%CI]	50/233(21.5%) [16.19%–26.73%]	25/227(11.1%) [6.94%–15.09%]
	P-value[b]	0.003	
Patients whohad 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

INDICATION

ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

CONTRAINDICATIONS

ABRAXANE® should not be used in patients who have baseline neutrophil counts of < 1,500 cells/mm^3.

WARNINGS

Bone marrow suppression (primarily neutropenia) is dose dependent and a dose limiting toxicity. ABRAXANE® should not be administered to patients with baseline neutrophil counts of < 1,500 cells/mm^3. Frequent monitoring of blood counts should be instituted during ABRAXANE® treatment. Patients should not be retreated with subsequent cycles of ABRAXANE® until neutrophils recover to a level >1,500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3.

The use of ABRAXANE® has not been studied in patients with hepatic or renal dysfunction. In the randomized controlled trial, patients were excluded for baseline serum bilirubin >1.5 mg/dL or baseline serum creatinine >2 mg/dL.

Pregnancy – Teratogenic Effects: Pregnancy Category D:

ABRAXANE® can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel protein-bound particles to rats 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 embryo- and fetotoxicity, as indicated by intrauterine mortality, increased resorptions (up to 5-fold), reduced numbers of litters and live fetuses, reduction in fetal body weight and increase in fetal anomalies. Fetal anomalies included soft tissue and skeletal malformations, such as eye bulge, folded retina, microphthalmia, and dilation of brain ventricles. A lower incidence of soft tissue and skeletal malformations were also exhibited at 3 mg/m^2 (approximately 1% of the daily maximum recommended human dose on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women using 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 treatment with ABRAXANE®.

Use in Males: Men should be advised to not father a child while receiving treatment with ABRAXANE® (see PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility for discussion of effects of ABRAXANE® exposure on male fertility and embryonic viability).

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

PRECAUTIONS

Drug Interactions: No drug interaction studies have been conducted with ABRAXANE®.

The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering ABRAXANE® (paclitaxel protein-bound particles for injectable suspension) concomitantly with known substrates or inhibitors of CYP2C8 and CYP3A4 (see CLINICAL PHARMACOLOGY).

Potential interactions between paclitaxel, a substrate of CYP3A4, and protease inhibitors (such as ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials.

Hematology: ABRAXANE® therapy should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm^3. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving ABRAXANE®. Patients should not be retreated with subsequent cycles of ABRAXANE® until neutrophils recover to a level >1,500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3. In the case of severe neutropenia (<500 cells/mm^3 for seven days or more) during a course of ABRAXANE® therapy, a dose reduction for subsequent courses of therapy is recommended (see DOSAGE and ADMINISTRATION).

Nervous System: Sensory neuropathy occurs frequently with ABRAXANE®. The occurrence of grade 1 or 2 sensory neuropathy does not generally require dose modification. If grade 3 sensory neuropathy develops, treatment should be withheld until resolution to grade 1 or 2 followed by a dose reduction for all subsequent courses of ABRAXANE® (see DOSAGE and ADMINISTRATION).

Injection Site Reaction: Injection site reactions occur infrequently with ABRAXANE® and were mild in the randomized clinical trial. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

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

Paclitaxel has been shown to be clastogenic in vitro (chromosome aberrations in human lymphocytes) and in vivo (micronucleus test in mice). ABRAXANE® was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay.

Administration of paclitaxel protein-bound particles to male rats at 42 mg/m^2 on a weekly basis (approximately 16% of the daily maximum recommended human exposure on a mg/m^2 basis) for 11 weeks prior to mating with untreated female rats resulted in significantly reduced fertility accompanied by decreased pregnancy rates and increased loss of embryos in mated females. A low incidence of skeletal and soft tissue fetal anomalies was also observed at doses of 3 and 12 mg/m^2/week in this study (approximately 1 to 5% of the daily maximum recommended human exposure on a mg/m^2 basis). Testicular atrophy/degeneration has also been observed in single-dose toxicology studies in rodents administered paclitaxel protein-bound particles at 54 mg/m^2 and dogs administered 175 mg/m^2 (see WARNINGS).

Pregnancy: Teratogenic Effects: Pregnancy Category D: (See WARNINGS section).

Nursing Mothers: It is not known whether paclitaxel is excreted in human milk. Following intravenous administration of carbon-14 labeled paclitaxel to rats on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving ABRAXANE® therapy.

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

Geriatric use: Of the 229 patients in the randomized study who received ABRAXANE®, 11% were at least 65 years of age and < 2% were 75 years or older. No toxicities occurred notably more frequently among elderly patients who received ABRAXANE®.

Information for Patients: (See Patient Information Leaflet).

ADVERSE REACTIONS:

The following table shows the frequency of important adverse events in the randomized comparative trial for the patients who received either single-agent ABRAXANE® or paclitaxel injection for the treatment of metastatic breast cancer.

Table 2: Frequencya of Important Treatment Emergent Adverse Events in the Randomized Study on an Every-3-Weeks Schedule

	Percentage of Patients	
	ABRAXANE® 260/30minb (n=229)	Paclitaxel Injection 175/3hc,d (n=225)
Bone Marrow		
Neutropenia		
< 2.0 x 109/L	80	82
< 0.5 x 109/L	9	22
Thrombocytopenia		
< 100 x 109/L	2	3
< 50 x 109/L	<1	<1
Anemia		
< 11 g/dL	33	25
< 8 g/dL	1	<1
Infections	24	20
Febrile Neutropenia	2	1
Bleeding	2	2
Hypersensitivity Reaction[e]		
All	4	12
Severe[f]	0	2
Cardiovascular		
Vital Sign Changes[g]		
Bradycardia	<1	<1
Hypotension	5	5
Severe Cardiovascular Events[f]	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[f]	10	2
Myalgia / Arthralgia		
Any Symptoms	44	49
Severe Symptoms[f]	8	4
Asthenia		
Any Symptoms	47	39
Severe Symptoms[f]	8	3
Fluid Retention/Edema		
Any Symptoms	10	8
Severe Symptoms[f]	0	<1
Gastrointestinal		
Nausea		
Any symptoms	30	22
Severe symptoms[f]	3	<1
Vomiting		
Any symptoms	18	10
Severe Symptoms[f]	4	1
Diarrhea		
Any Symptoms	27	15
Severe Symptoms[f]	<1	1
Mucositis		
Any Symptoms	7	6
Severe Symptoms[f]	<1	0
Alopecia	90	94
Hepatic (Patients with		
Normal Baseline)		
Bilirubin Elevations	7	7
Alkaline Phosphatase Elevations	36	31
AST (SGOT) Elevations	39	32
Injection Site Reaction	<1	1

[a] Based on worst grade
[b] ABRAXANE dose in mg/m^2/duration in minutes
[c] paclitaxel injection dose in mg/m/duration in hours
[d] paclitaxel injection pts received premedication Includes treatment-related events related to hypersensitivity (e.g., flushing, dyspnea, chest pain, hypotension) that began on a day of dosing.
[f] Severe events are defined as at least grade 3 toxicity
[g] During study drug dosing.

form. In some instances, rare severe events observed with paclitaxel injection may be expected to occur with ABRAXANE®.

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

In the randomized metastatic breast cancer study, infectious episodes were reported in 24% of the patients treated with a dose of 260 mg/m^2 given as a 30-minute infusion. Oral candidiasis, respiratory tract infections and pneumonia were the most frequently reported infectious complications. Febrile neutropenia was reported in 2% of patients in the ABRAXANE® arm and 1% of patients in the paclitaxel injection arm.

Thrombocytopenia was uncommon. In the randomized metastatic breast cancer study, bleeding episodes were reported in 2% of the patients in each treatment arm.

Anemia (Hb <11 g/dL) was observed in 33% of patients treated with ABRAXANE® in the randomized trial and was severe (Hb <8 g/dL) in 1% of the cases. Among all patients with normal baseline hemoglobin, 31% became anemic on study and 1% had severe anemia.

Hypersensitivity Reactions (HSRs): In the randomized controlled metastatic breast cancer study, 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 in the randomized metastatic breast cancer trial. 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 in the randomized trial. These events included 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 rarely.

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 in the metastatic breast cancer randomized trial. 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: Reports of dyspnea (12%) and cough (6%) were reported after treatment with ABRAXANE® in the randomized trial. Rare reports (<1%) of pneumothorax were reported after treatment with ABRAXANE®. Rare reports of interstitial pneumonia, lung fibrosis, and pulmonary embolism have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE® treatment. Rare reports of radiation pneumonitis have been received in paclitaxel injection patients receiving concurrent radiotherapy. There is no experience with the use of ABRAXANE® with concurrent radiotherapy.

Neurologic: The frequency and severity of neurologic manifestations were influenced by prior and/or concomitant therapy with neurotoxic agents.

In general, the frequency and severity of neurologic manifestations were dose-dependent in patients receiving single-agent ABRAXANE®. In the randomized trial, sensory neuropathy was observed in 71% of patients (10% severe) in the ABRAXANE® arm and in 56% of patients (2% severe) in the paclitaxel injection arm. The frequency of sensory neuropathy increased with cumulative dose. Sensory neuropathy was the cause of ABRAXANE® discontinuation in 7/229 (3%) patients in the randomized trial. In the randomized comparative study, 24 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.

In general, the frequency and severity of neurologic manifestations were dose-dependent in patients receiving single-agent ABRAXANE®. In the randomized trial, sensory neuropathy was observed in 71% of patients (10% severe) in the ABRAXANE® arm and in 56% of patients (2% severe) in the paclitaxel injection arm. The frequency of sensory neuropathy increased with cumulative dose. Sensory neuropathy was the cause of ABRAXANE® discontinuation in 7/229 (3%) patients in the randomized trial. In the randomized comparative study, 24 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 incidences of grade 4 sensory neuropathies were reported in the clinical trial. Only one incident of motor neuropathy (grade 2) was observed in either arm of the controlled trial.

Cranial nerve palsies have been reported during postmarketing surveillance of ABRAXANE®. Because these events have been reported during clinical practice, true estimates of frequency cannot be made and a causal relationship to the events has not been established.

Reports of autonomic neuropathy resulting in paralytic ileus have been received as part of the continuing surveillance of paclitaxel injection safety.

Ocular/visual disturbances occurred in 13% of all patients (n=366) treated with ABRAXANE® in single arm and randomized trials and 1% were severe. The severe cases (keratitis and blurred vision) were reported in patients in a single arm study who received higher doses than those recommended (300 or 375 mg/m2). These effects generally have been reversible. However, rare reports in the literature of abnormal visual evoked potentials in patients treated with paclitaxel injection have suggested persistent optic nerve damage.

Arthralgia/Myalgia: Forty-four percent of patients treated in the randomized trial experienced arthralgia/myalgia; 8% experienced severe symptoms. The symptoms were usually transient, occurred two or three days after ABRAXANE® administration, and resolved within a few days.

Hepatic: Among patients with normal baseline liver function treated with ABRAXANE® in the randomized trial, 7%, 36%, and 39% had elevations in bilirubin, alkaline phosphatase, and AST (SGOT), respectively. 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.

Rare 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.

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

Gastrointestinal (GI): Nausea/vomiting, diarrhea, and mucositis were reported by 33%, 27%, and 7% of ABRAXANE® treated patients in the randomized trial.

Rare reports of intestinal obstruction, intestinal perforation, pancreatitis, and ischemic colitis have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE® treatment. Rare reports of neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, were observed in patients treated with paclitaxel injection alone and in combination with other chemotherapeutic agents.

Injection Site Reaction: Injection site reactions have occurred infrequently with ABRAXANE® and were mild in the randomized clinical trial. 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 rarely.
Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been received 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.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Asthenia: Asthenia was reported in 47% of patients (8% severe) treated with ABRAXANE® in the randomized trial. Asthenia included reports of asthenia, fatigue, weakness, lethargy and malaise.

Other Clinical Events: Rare cases of cardiac ischemia/infarction and thrombosis/embolism possibly related to ABRAXANE® treatment have been reported. Alopecia was observed in almost all of the patients. Nail changes (changes in pigmentation or discoloration of nail bed) were uncommon. Edema (fluid retention) was infrequent (10% of randomized trial patients); no patients had severe edema.

The following rare adverse events have been reported as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE® treatment: skin abnormalities related to radiation recall as well as reports of Stevens-Johnson syndrome, toxic epidermal necrolysis, conjunctivitis, and increased lacrimation. As part of the continuing surveillance of ABRAXANE®, skin reactions including generalized or maculo-papular rash, erythema, and pruritis have been observed. Additionally, there have been case reports of photosensitivity reactions, radiation recall phenomenon, and in some patients previously exposed to capecitabine, reports of palmar-plantar erythrodysaesthesiae. Because these events have been reported during clinical practice, true estimates of frequency cannot be made and a causal relationship to the events has not been established.

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.

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

After failure of combination chemotherapy for metastatic breast cancer or relapse within 6 months of adjuvant chemotherapy, the recommended regimen for ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is 260 mg/m2 administered intravenously over 30 minutes every 3 weeks.

Hepatic Impairment: The appropriate dose of ABRAXANE® for patients with bilirubin greater than 1.5 mg/dL is not known.

Dose Reduction: 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/m^2 for subsequent courses of ABRAXANE®. For recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m^2. For grade 3 sensory neuropathy hold treatment until resolution to grade 1 or 2, followed by a dose reduction for all subsequent courses of ABRAXANE®.
Preparation and Administration Precautions: ABRAXANE® is a cytotoxic anticancer 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 PRECAUTIONS: Injection Site Reaction).

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

Preparation for Intravenous Administration: ABRAXANE® is supplied as a sterile lyophilized powder for reconstitution before use. AVOID ERRORS, READ ENTIRE PREPARATION INSTRUCTIONS PRIOR TO RECONSTITUTION.

1. Aseptically, reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP.
2. Slowly inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of 1 minute, using the sterile syringe to direct the solution flow onto the INSIDE WALL OF THE VIAL.

3. DO NOT INJECT the 0.9% Sodium Chloride Injection, USP, directly onto the lyophilized cake as this will result in foaming.
4. Once the injection is complete, allow the vial to sit for a minimum of 5 minutes to ensure proper wetting of the lyophilized cake/powder.
5. Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs. Avoid generation of foam.
6. If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.

Each mL of the reconstituted formulation will contain 5 mg/mL paclitaxel.

Calculate the exact total dosing volume of 5 mg/mL suspension required for the patient: Dosing volume (mL) = Total dose (mg)/5 (mg/mL)

The reconstituted suspension should be milky and homogenous without visible particulates. If particulates or settling are 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 IV bag (plasticized polyvinyl chloride (PVC) containers, PVC or non-PVC type IV bag). The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer ABRAXANE® infusions. The use of an in-line filter is not recommended.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

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

Stability of Reconstituted Suspension in the Vial
Reconstituted ABRAXANE® should be used immediately, but may be refrigerated at 2ºC to 8ºC (36ºF to 46ºF) for a maximum of 8 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion.

Stability of Reconstituted Suspension in the Infusion Bag
The suspension for infusion prepared as recommended in an infusion bag should be used immediately, but may be stored at ambient temperature (approximately 25ºC) and lighting conditions for up to 8 hours.

HOW SUPPLIED

ABRAXANE® is available as 100 mg of paclitaxel in a single use vial, individually packaged in a carton.

Storage: Store the vial in original carton at controlled room temperature 20°C to 25°C (68°F to 77°F) (see USP Controlled Room Temperature). Store reconstituted suspension in the original carton at 2°C to 8°C (36°F to 46°F) to protect from bright light. Use reconstituted suspension within 8 hours. Discard any unused portion.

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.1-8 There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

REFERENCES

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8. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and Recommendations for Practice Pittsburgh, Pa: Oncology Nursing Society; 1999:32-41.

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Abraxis

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2020, Ruby Street, Melrose Park, Illinois,
USA, 60160.

Biocon

Imported and Marketed by :
Biocon Limited
20th KM, Hosur Road,
Electronics City,
Bangalore - 560 100. India

For any further information please contact:

Medical Advisor
Biocon Limited
Tower II, Semicon Park
Electronics city Phase II
Bangalore - 560100 India.