PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] **ABRAXANE® for Injectable Suspension**

paclitaxel powder for injectable suspension

nanoparticle, albumin-bound (nab®) paclitaxel

Powder For Suspension, 100 mg paclitaxel/vial, Intravenous

Professed

Antineoplastic Agent

Bristol-Myers Squibb Canada
2344 Alfred-Nobel Blvd., Suite 300
Saint-Laurent, Québec
H4S 0A4

Date of Initial Authorization:
MAR 08, 2024

Submission Control Number: 283773

RECENT MAJOR LABEL CHANGES

4 Dosage and Administration, 4.5 Missing Dose	08/2023
7 Warnings and Precautions, Reproductive Health: Female and Male Potential	08/2023

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

RECENT MAJOR LABEL CHANGES 2

TABLE OF CONTENTS 2

PART I: HEALTH PROFESSIONAL INFORMATION 4

1 INDICATIONS 4

1.1 Pediatrics 4

1.2 Geriatrics 4

2 CONTRAINDICATIONS 4

3 SERIOUS WARNINGS AND PRECAUTIONS BOX 5

4 DOSAGE AND ADMINISTRATION 5

4.1 Dosing Considerations 5

4.2 Recommended Dose and Dosage Adjustment 5

4.3 Reconstitution 9

4.4 Administration 10

4.5 Missed Dose 11

5 OVERDOSAGE 11

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING 11

7 WARNINGS AND PRECAUTIONS 12

7.1 Special Populations 15

7.1.1 Pregnant Women 15

7.1.2 Breast-feeding 15

7.1.3 Pediatrics 15

7.1.4 Geriatrics 15

8 ADVERSE REACTIONS 16

8.1 Adverse Reaction Overview 16
8.2 Clinical Trial Adverse Reactions 16
8.3 Less Common Clinical Trial Adverse Reactions 23
8.5 Post-Market Adverse Reactions 25
9 DRUG INTERACTIONS 26
9.2 Drug Interactions Overview 26
9.4 Drug-Drug Interactions 27
9.5 Drug-Food Interactions 27
9.6 Drug-Herb Interactions 27
9.7 Drug-Laboratory Test Interactions 27
10 CLINICAL PHARMACOLOGY 27
10.1 Mechanism of Action 27
10.2 Pharmacodynamics 27
10.3 Pharmacokinetics 27
11 STORAGE, STABILITY AND DISPOSAL 30
12 SPECIAL HANDLING INSTRUCTIONS 30
PART II: SCIENTIFIC INFORMATION 30
13 PHARMACEUTICAL INFORMATION 30
14 CLINICAL TRIALS 31
14.1 Clinical Trials by Indication 31
Metastatic Breast Carcinoma 31
Metastatic Pancreatic Cancer 34
15 MICROBIOLOGY 39
16 NON-CLINICAL TOXICOLOGY 39
PATIENT MEDICATION INFORMATION 41

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ABRAXANE® for Injectable Suspension (paclitaxel powder for injectable suspension) (nanoparticle, albumin-bound [nab®] paclitaxel) is indicated for:

- the treatment of metastatic breast cancer.
- the first-line treatment of metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

ABRAXANE should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

Note: An albumin form of paclitaxel may substantially affect a drug's functional properties relative to those of drug in solution. **Do not substitute with or for other paclitaxel formulations.**

1.1 Pediatrics

Pediatrics (≤ 16 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Evidence from clinical studies in metastatic breast cancer suggests that use of ABRAXANE in patients over the age of 65 is associated with a higher incidence of epistaxis, diarrhea, dehydration, fatigue and peripheral edema. Evidence from the pivotal clinical study in metastatic pancreatic cancer suggest that patients 75 years or older who received ABRAXANE in combination with gemcitabine had a higher risk of serious adverse reactions and adverse reactions that led to treatment discontinuation. No survival benefit for the combination treatment of ABRAXANE and gemcitabine has been demonstrated for patients 75 years and older, however, clinical studies did not include sufficient number of patients with metastatic pancreatic cancer in this age group to determine whether they respond differently from younger patients (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

- ABRAXANE® is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing of ingredients, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- ABRAXANE for Injectable Suspension (paclitaxel powder for injectable suspension) (nanoparticle, albumin-bound [nab®] paclitaxel) is contraindicated in patients who have baseline neutrophil counts of < 1,500 cells/mm^3 on day 1 of each treatment cycle.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- ABRAXANE® for Injectable Suspension (paclitaxel powder for injectable suspension) (nanoparticle, albumin-bound [nab®] paclitaxel) should be administered under the supervision of a physician experienced in the use of anti-cancer chemotherapeutic agents (see 1 INDICATIONS).
- **Note:** An albumin form of paclitaxel may substantially affect a drug's functional properties relative to those of drug in solution. **Do not substitute with or for other paclitaxel formulations.** In the treatment of metastatic breast cancer, ABRAXANE has been evaluated as a single agent only.
- Bone marrow suppression (primarily neutropenia) is dose-dependent and a dose-limiting toxicity of ABRAXANE (see 2 CONTRAINDICATIONS and Hematologic section below).
- Sepsis with or without neutropenia occurred in patients who received ABRAXANE in combination with gemcitabine (see Infection section below).
- Pneumonitis, including some cases that were fatal, occurred in patients receiving ABRAXANE in combination with gemcitabine (see Respiratory section below).
- Patients ≥ 75 years of age treated with ABRAXANE in combination with gemcitabine experienced more toxicity and no demonstrated survival benefit (see 7.1.4 Geriatrics section).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

No premedication to prevent hypersensitivity reactions is required prior to administration of ABRAXANE® for Injectable Suspension (paclitaxel powder for injectable suspension) (nanoparticle, albumin-bound [nab®] paclitaxel).

The primary elimination pathway for ABRAXANE is hepatic metabolism followed by biliary excretion. The exposure to paclitaxel may be higher in patients with hepatic impairment than in patients with normal hepatic function. The starting dose of ABRAXANE should be reduced in patients with moderate to severe hepatic impairment (see 4.2 Recommended Dose and Dosage Adjustment). As renal excretion is a minor elimination pathway for ABRAXANE, increased exposure to paclitaxel is not expected in patients with mild to moderate renal impairment. Adjustment of the starting ABRAXANE dose is not required for patients with mild to moderate renal impairment (see 4.2 Recommended Dose and Dosage Adjustment).

Do not substitute for or with other paclitaxel formulations.

4.2 Recommended Dose and Dosage Adjustment

Metastatic Breast Cancer

The recommended regimen for ABRAXANE is 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks. Dose levels of mg/m^2 refer to mg of paclitaxel in ABRAXANE.

Dose Adjustment for Treatment of Breast Cancer: Patients who experience severe neutropenia (neutrophil < 500 cells/mm^3 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, an 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.

Metastatic Pancreatic Cancer

The recommended dose of ABRAXANE is 125 mg/m^2 administered as an intravenous infusion over 30-40 minutes on Days 1, 8 and 15 of each 28-day cycle. The recommended dose of gemcitabine is 1000 mg/m^2 as an intravenous infusion over 30-40 minutes beginning immediately after the completion of ABRAXANE administration on Days 1, 8 and 15 of each 28-day cycle.

Dose Adjustment for Treatment of Metastatic Pancreatic Cancer:

The recommended dose reductions for ABRAXANE and gemcitabine from the clinical trial are outlined in **Tables 1** to **3** below. When a dose reduction was required, no dose re-escalation was permitted during the trial (with the exception of Day 15, see **Table 2** below).

Due to dose-dependent and dose-limiting myelosuppression (primarily neutropenia) with ABRAXANE in combination with gemcitabine, more conservative dose modifications may be necessary based on clinical judgment and experience with chemotherapeutic drugs. Note that the gemcitabine dose modifications used in the clinical trial differ from the recommendations in the GEMZAR product monograph.

Table 1: Dose Level Reductions for Patients with Metastatic Pancreatic Cancer

Dose Level	ABRAXANE® Dose (mg/m^2)	Gemcitabine Dose (mg/m^2)
Full dose	125	1000[a]
1st dose level reduction	100	800[a]
2nd dose level reduction	75	600[a]
If additional dose reduction required	Discontinue treatment	Discontinue treatment[a]

a. dose modifications differ from the recommendations in the GEMZAR product monograph

Table 2: Dose Recommendation and Modifications for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or Within a Cycle for Patients with-Metastatic Pancreatic Cancer

Cycle Day	ANC count (cells/mm^3)		Platelet count (cells/mm^3)	ABRAXANE Dose	Gemcitabine Dose
Day 1	≥ 1500	AND	≥ 100,000	Treat on time at current dose levels	
	< 1500	OR	< 100,000	Delay doses until recovery	
Day 8	≥ 1000	AND	≥ 75,000	Treat on time at current dose levels	
	≥ 500 but < 1000	OR	≥ 50,000 but < 75,000	Reduce doses 1 dose level	
	< 500	OR	< 50,000	Withhold doses	
Day 15: IF Day 8 doses were given without modification:					
Day 15	≥ 1000	AND	≥ 75,000	Treat on time at current dose levels	
	≥ 500 but < 1000	OR	≥ 50,000 but < 75,000	Treat at current dose level and follow with WBC Growth Factors[a, b]	
	< 500	OR	< 50,000	Withhold doses	
Day 15: IF Day 8 doses were reduced:					
Day 15	≥ 1000	AND	≥ 75,000	Return to the Day 1 dose level and follow with WBC Growth Factors[a, b]	
	≥ 500 but < 1000	OR	≥ 50,000 but < 75,000	Treat with Day 8 dose level and follow with WBC Growth Factors[a, b]	
	< 500	OR	< 50,000	Withhold doses	
Day 15: IF Day 8 doses were withheld:					
Day 15	≥ 1000	AND	≥ 75,000	Return to Day 1 dose level and follow with WBC Growth Factors[a, b]	
	≥ 500 but < 1000	OR	≥ 50,000 but < 75,000	Reduce 1 dose level and follow with WBC Growth Factors[a, b]	
	< 500	OR	< 50,000	Withhold doses	

Abbreviations: ANC = Absolute Neutrophil Count; WBC GF = white blood cell growth factor.

a. In the clinical trials, G-CSF was optional if descent only affected platelets.
b. If WBC Growth Factors are not available, a reduction in dose levels is recommended. Although this option was not included in the clinical trial protocol this approach is consistent with clinical practice.

Table 3: Dose Modifications for Other Adverse Drug Reactions in Patients with-Metastatic Pancreatic Cancer

Adverse Drug Reaction	ABRAXANE Dose	Gemcitabine Dose
Febrile Neutropenia: Grade 3 or 4	Withhold doses until fever resolves and ANC ≥ 1500; resume at reduced dose levels.	
Peripheral Neuropathy: Grade 3 or 4	Withhold dose until improves to ≤ Grade 1; resume at reduced dose level	Treat with same dose
Cutaneous Toxicity: Grade 2 or 3	Reduce doses 1 level; discontinue treatment if ADR persists	
Gastrointestinal Toxicity: Grade 3 mucositis or diarrhea	Withhold doses until improves to ≤ Grade 1; resume at reduced dose levels	

Abbreviations: ADR = Adverse Drug Reaction

Hepatic Impairment

For patients with mild hepatic impairment (total bilirubin > 1 to ≤ 1.5 x ULN and aspartate aminotransferase [AST] ≤ 10 x ULN), no dose adjustments are required regardless of indication. Treat with same doses as patients with normal hepatic function.

For patients with moderate to severe hepatic impairment (total bilirubin > 1.5 to ≤ 5 x ULN and aspartate aminotransferase [AST] ≤ 10 x ULN), a 20% reduction in dose is recommended for metastatic breast cancer patients. The reduced dose may be escalated to the dose for patients with normal hepatic function if the patient is tolerating the treatment for at least two cycles. There are insufficient data to permit dosage recommendations for patients with metastatic pancreatic cancer that have moderate to severe hepatic impairment.

For patients with total bilirubin > 5 x ULN or AST > 10 x ULN, there are insufficient data to permit dosage recommendations regardless of indication.

Renal Impairment

Adjustment of the starting ABRAXANE dose is not required for patients with mild to moderate renal impairment (estimated creatinine clearance ≥ 30 to < 90 mL/min). 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).

Pediatrics (≤ 16 years of age)

Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics).

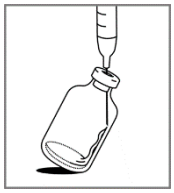
4.3 Reconstitution

ABRAXANE is supplied as a sterile lyophilized powder for reconstitution before use. **Avoid errors, read entire preparation instructions prior to reconstitution**.

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
50 mL	20 mL 0.9% Sodium Chloride Injection, USP	20 mL	5 mg/mL

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.**

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.

Neither freezing nor refrigeration adversely affects the stability of the product.

Stability of Reconstituted Suspension in the Vial

ABRAXANE reconstituted in the vial should be used immediately but may be refrigerated between 2 and 8°C 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 (see 11 STORAGE, STABILITY AND DISPOSAL). Discard any unused portion. Some settling of the reconstituted suspension may occur. 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.

Inject the appropriate amount of reconstituted ABRAXANE into an empty, sterile, i.v. bag (plasticized polyvinyl chloride (PVC) containers, PVC or non-PVC type i.v. bag). No further dilution is required. The use of specialized DEHP-free solution containers or administration sets may also be used but are not required to prepare or administer ABRAXANE infusions.

The use of medical devices containing silicone oil as a lubricant (ie, syringes and IV bags) to reconstitute and administer ABRAXANE may result in the formation of proteinaceous strands.

Visually inspect the reconstituted ABRAXANE suspension in the IV bag prior to administration. If strands are observed, administer reconstituted ABRAXANE suspension through a 15 µm filter. If strands are present and a 15 µm filter is not available, discard the product. Do not use a filter with a pore size less than 15 µm.

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 20 to 25°C) and ambient lighting conditions for up to 8 hours (see 11 STORAGE, STABILITY AND DISPOSAL).

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

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.

4.4 Administration

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 Injection Site Reactions).

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).

Slowly withdraw the dosing volume of the reconstituted ABRAXANE suspension from the vial(s) into a syringe. Inject the appropriate amount of reconstituted ABRAXANE into an empty, sterile, intravenous infusion bag (plasticized polyvinyl chloride (PVC) containers, PVC or non-PVC type i.v. bag). No further

dilution is required. The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer ABRAXANE infusions.
The use of medical devices containing silicone oil as a lubricant (ie, syringes and IV bags) to reconstitute and administer ABRAXANE may result in the formation of proteinaceous strands.

Visually inspect the reconstituted ABRAXANE suspension in the IV bag prior to administration. If strands are observed, administer reconstituted ABRAXANE suspension through a 15 µm filter. If strands are present and a 15 µm filter is not available, discard the product. Do not use a filter with a pore size less than 15 µm.

Do not mix any other drugs with the ABRAXANE infusion.

4.5 Missed Dose

If a planned dose of ABRAXANE is missed, it should be administered as soon as possible. The schedule of administration should be adjusted to maintain the prescribed dosing interval.

5 OVERDOSAGE

There is no known antidote for ABRAXANE® for Injectable Suspension (paclitaxel powder for injectable suspension) (nanoparticle, albumin-bound [nab®] paclitaxel) overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, sensory neurotoxicity, and mucositis.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 4: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	Lyophilized powder, 100 mg paclitaxel per single-use vial.	Human albumin

ABRAXANE® for Injectable Suspension (paclitaxel powder for injectable suspension) (nanoparticle, albumin-bound [nab®] paclitaxel) is supplied as a white to yellow, sterile, lyophilized cake for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Paclitaxel exists in the particle in a non-crystalline, amorphous state. 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.

ABRAXANE is available in a single-use glass vial with a stopper, individually packaged in a carton. The stopper is not made with natural rubber latex.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

General

Albumin (Human): ABRAXANE® for Injectable Suspension (paclitaxel powder for injectable suspension) (nanoparticle, albumin-bound [nab®] paclitaxel) contains albumin (human), a derivative of human blood and is a nanoparticle albumin-bound (nab) form of paclitaxel. 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.

Carcinogenesis and Mutagenesis

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). Paclitaxel injection was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay (see 16 NON-CLINICAL TOXICOLOGY).

Cardiovascular

AV block has been reported during treatment with paclitaxel as well as with the albumin-bound [nab] paclitaxel ABRAXANE. Clinical trial information estimates the incidence of atrioventricular block (AV block) in patients treated with ABRAXANE is 1/1310 (0.08%). In the post-market setting, one patient having no confounding risk factors required pacemaker placement (see 8.5 Post-Market Adverse Reactions). ECG abnormalities were noted in 60% of patients treated with ABRAXANE in the metastatic breast cancer randomized trial. Among patients with a normal ECG prior to study entry, 35% of patients treated with ABRAXANE developed an abnormal tracing while on study (see 8.2 Clinical Trial Adverse Reactions). ECG monitoring, particularly patients who are predisposed to cardiac risks from underlying malignancy, co-morbidities or concomitant use of chemotherapeutic drugs that may be cardiotoxic, should be considered during treatment with ABRAXANE. Patients exhibiting signs and symptoms of AV block should be further monitored and appropriate medical therapy administered.

Driving and Operating Machinery

Adverse events such as fatigue, weakness and malaise may affect the ability to drive and use machines.

Hematologic

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 and in 38% of patients with pancreatic cancer. ABRAXANE therapy should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm^3 and baseline platelet counts of less than 100,000 cells/mm^3 on day 1 of each treatment cycle. 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 (see 8 ADVERSE REACTIONS and 4 DOSAGE AND ADMINISTRATION).

Hepatic/Biliary/Pancreatic

In the randomized controlled trials, patients were excluded for elevated baseline serum bilirubin.

Exposure and toxicity of paclitaxel can increase with hepatic impairment. Patients with hepatic impairment may be at increased risk of toxicity, particularly from myelosuppression; such patients should be closely monitored for development of profound myelosuppression. ABRAXANE is not recommended in patients that have total bilirubin > 5 x ULN or AST > 10 x ULN. In addition, ABRAXANE is not recommended in patients with metastatic pancreatic cancer that have moderate to severe hepatic impairment (total bilirubin > 1.5 x ULN and AST < 10 x ULN). The starting dose should be reduced for patients with moderate or severe hepatic impairment (see 4 DOSAGE AND ADMINISTRATION).

Immune

Very rare occurrences of severe hypersensitivity reactions, including anaphylactic reactions with fatal outcome have been reported. Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be re-challenged with the drug. The use of ABRAXANE in patients exhibiting hypersensitivity to paclitaxel or human albumin has not been studied.

Infection

Sepsis was reported in 5% of patients with or without neutropenia who received ABRAXANE in combination with gemcitabine. Complications due to the underlying pancreatic cancer, especially biliary obstruction or presence of biliary stent, were identified as significant contributing factors. If a patient becomes febrile (regardless of neutrophil count), initiate treatment with broad spectrum antibiotics. For febrile neutropenia, withhold ABRAXANE and gemcitabine until fever resolves and ANC ≥ 1500, then resume treatment at reduced dose levels (see 4 DOSAGE AND ADMINISTRATION).

Injection Site Reactions

Injection site reactions can occur with ABRAXANE. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Monitoring and Laboratory Tests

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. 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 (see 4 DOSAGE AND ADMINISTRATION).

Neurologic

Sensory neuropathy occurs frequently with ABRAXANE. The occurrence of grade 1 or 2 sensory neuropathy does not generally require dose modification. When ABRAXANE is used as monotherapy, 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 4 DOSAGE AND ADMINISTRATION). For combination use of ABRAXANE and gemcitabine, if grade 3 or higher peripheral neuropathy develops, withhold ABRAXANE treatment until resolution to ≤ Grade 1 and resume at a reduced dose for all subsequent courses of ABRAXANE. The median time to first occurrence of Grade 3 peripheral neuropathy was 140 days, and the median time to improvement from Grade 3 peripheral neuropathy to Grade 0 or 1 was 29 days. Of the patients with treatment interrupted due to peripheral neuropathy, 44% (31/70 patients) were able to resume ABRAXANE at a reduced dose. No patients treated with ABRAXANE/gemcitabine had Grade 4 peripheral neuropathy (see 4 DOSAGE AND ADMINISTRATION).

Ophthalmologic

There have been reports of reduced visual acuity due to cystoid macular edema (CME) during treatment with ABRAXANE as well as with other taxanes. Most reports of CME have resolved after cessation of the taxane treatment (see 8.5 Post-Market Adverse Reactions). Patients with visual impairment during ABRAXANE treatment should seek a prompt and complete ophthalmologic examination. ABRAXANE should be discontinued if a CME diagnosis is confirmed.

Renal

The use of ABRAXANE has not been adequately studied in patients with severe renal impairment or end stage renal disease (estimated creatinine clearance <30 mL/min). In the randomized controlled trials, patients were excluded for elevated baseline serum creatinine.

Reproductive Health: Female and Male Potential

Men should be advised to use effective contraception and to avoid fathering a child while receiving treatment with ABRAXANE and up to six months after treatment. Advise females of reproductive potential to use effective contraception during treatment with ABRAXANE and for at least six months after the last dose.

- **Fertility**

  Animal studies with ABRAXANE showed irreversible, toxic effects on the male reproductive organs including testicular atrophy/degeneration and decreased germinal epithelial cells at clinically relevant exposure levels. ABRAXANE induced infertility in male rats. Administration of paclitaxel prior to and during mating produced impairment of fertility in male and female rats. Based on these findings in animals, ABRAXANE may impair fertility in females and males of reproductive potential**.**

  As ABRAXANE may decrease male fertility, preservation of sperm may be considered for the purpose of later fatherhood (see 16 NON-CLINICAL TOXICOLOGY).

- **Teratogenic Risk**

  Based on its mechanism of action and findings in animals, ABRAXANE can cause fetal harm when administered to a pregnant woman and male with reproductive potential (see 16 NON-CLINICAL TOXICOLOGY).

Respiratory

Pneumonitis, including some cases that were fatal, has been reported in 4% of patients treated with ABRAXANE in combination with gemcitabine. Of the 17 pneumonitis ADRs in the ABRAXANE/gemcitabine arm, 2 had a fatal outcome. Due to cases of pneumonitis seen in the clinical trial, patients with a history of interstitial lung disease, multiple allergies or progressive dyspnea and unproductive cough were excluded from further enrollment, and it is recommended that such patients not be treated with ABRAXANE. Monitor patients closely for signs and symptoms of pneumonitis and interrupt treatment during evaluation of suspected pneumonitis. If a diagnosis of pneumonitis is made, permanently discontinue treatment of ABRAXANE and gemcitabine (see 8 ADVERSE REACTIONS section and GEMZAR product monograph).

7.1 Special Populations

7.1.1 Pregnant Women

ABRAXANE can cause fetal harm when administered to a pregnant woman (see 16 NON-CLINICAL TOXICOLOGY).

There are no adequate and well-controlled studies in pregnant women using ABRAXANE. Females of reproductive potential should have a pregnancy test prior to starting treatment with 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.

There was no exposure in pregnancy in the clinical trials.

7.1.2 Breast-feeding

It is not known whether paclitaxel is excreted in human milk. In rats, following intravenous administration of carbon-14 labeled paclitaxel 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, nursing must be discontinued when receiving ABRAXANE therapy.

7.1.3 Pediatrics

Pediatrics (≤ 16 years of age): The safety and effectiveness of ABRAXANE in pediatric patients have not been evaluated.

7.1.4 Geriatrics

A pooled analysis conducted in 981 patients receiving ABRAXANE monotherapy for metastatic breast cancer, of which 15% were ≥ 65 years old and 2% were ≥ 75 years old, indicated a higher incidence of epistaxis, diarrhea, dehydration, fatigue and peripheral edema in patients ≥ 65 years. Of the 421 patients with metastatic pancreatic adenocarcinoma in the randomized study who received ABRAXANE and gemcitabine, 41% were 65 years or older and 10% were 75 years or older. Diarrhea, decreased appetite, dehydration and epistaxis were more frequent in patients 65 years or older compared with patients younger than 65 years old. In patients 75 years and older who received ABRAXANE and gemcitabine, there was a higher incidence of serious adverse reactions and adverse reactions that led to treatment discontinuation including hematologic toxicities, peripheral neuropathy, decreased appetite and dehydration, and no demonstrated survival benefit. Carefully assess patients 75 years and older for their ability to tolerate ABRAXANE in combination with gemcitabine. Give special consideration to performance status, co-morbidities and increased risk of infections.

Pharmacokinetic/pharmacodynamics modeling using data from 125 patients with advanced solid tumors indicates that patients ≥65 years of age may be more susceptible to development of neutropenia within the first treatment cycle.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In the phase III study of metastatic breast cancer, the adverse events which were very common were those expected for paclitaxel and included alopecia (90%), neutropenia (80%), leukopenia (72%), sensory neuropathy (71%), asthenia (47%), arthralgia/myalgia (44%), AST (SGPT) elevations (39%), alkaline phosphatase elevations (36%), abnormal ECG [all patients (60%) and patients with normal baseline (35%)], anemia in patients with normal baseline (20%), nausea (30%), vomiting (18%), infections (24%), diarrhea (27%), dyspnea (12%), and fluid retention/edema (10%). Approximately 27% of patients receiving ABRAXANE® for Injectable Suspension (paclitaxel powder for injectable suspension) (nanoparticle, albumin-bound [nab®] paclitaxel) on a 3 weekly regimen experienced serious adverse events (SAEs). The events occurring in greater than 10 patients were grade 4 neutropenia (9%), infection (3%), and increased GGT (3%).

In the phase III study of metastatic pancreatic cancer, the most common treatment emergent adverse events (≥ 20%) in patients receiving ABRAXANE in combination with gemcitabine were: fatigue (59%), nausea (54%), peripheral neuropathy SMQ (54%), alopecia (50%), peripheral edema (46%), diarrhea (44%), anemia (42%), neutropenia (42%), pyrexia (41%), vomiting (36%), decreased appetite (36%), constipation (30%), thrombocytopenia (30%), rash (28%), abdominal pain (23%), and dehydration (21%). Approximately 50% of patients receiving ABRAXANE and gemcitabine experienced serious adverse events, including pyrexia, vomiting, dehydration and pneumonia. Adverse reactions resulting in death within 30 days of the last dose of study drug were reported for 4% of patients in the ABRAXANE and gemcitabine group and for 4% of patients in the gemcitabine group.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying and approximating rates of adverse drug reactions in real-world use.

Metastatic Breast Cancer

The following table shows the frequency of common important adverse events for the patients who received single-agent ABRAXANE® for Injectable Suspension (paclitaxel powder for injectable suspension) (nanoparticle, albumin-bound [nab®] paclitaxel) or Paclitaxel Injection for the treatment of metastatic breast cancer in the randomized comparative phase III trial.

Table 5: Frequency[a] of Common Important Treatment Emergent Adverse Events in the Randomized Study (by MedDRA System Organ Class and Preferred Term)

System Organ Class / Preferred Term	ABRAXANE® for Injectable Suspension[b] 260 mg/m^2/30 minutes n = 229 (%)	Paclitaxel Injection[b] 175 mg/m^2/3 hours n = 225 (%)
Blood and lymphatic system disorders		
Neutropenia < 2.0 x 10^9/L < 0.5 x 10^9/L	80 9	82 22
Leukopenia < 4.0 x 10^9/L < 1.0 x 10^9/L	72 0	79 1
Thrombocytopenia 100 x 10^9/L < 50 x 10^9/L	2 < 1	3 < 1
Anaemia (normal at baseline) <110g/L < 80g/L	33 1	25 < 1
Febrile neutropenia	2	1
Cardiac disorders		
Vital sign changes[e]		
Bradycardia	< 1	< 1
Hypotension	5	5
Acute cardiac event[d]	3	4
Gastrointestinal disorders		
Nausea	30	22
Vomiting	18	10
Diarrhea	27	15
Gastrointestinal mucosal disorder	7	6
General disorders and administration site conditions		
Generalised oedema	10	8
Severe Generalised oedema[d]	0	< 1

Injection site reaction	< 1	1
Asthenia	47	39
Severe Asthenia[d]	8	3
Immune system disorders[c]		
Hypersensitivity	4	12
Severe Hypersensitivity[d]	0	2
Infections and infestations		
Infection	24	20
Investigations		
Electrocardiogram abnormal	60	52
Electrocardiogram abnormal with normal baseline[f]	35	30
Blood bilirubin increased	7	7
Blood alkaline phosphatase increased	36	31
Aspartate aminotransferase increased	39	32
Musculoskeletal and connective tissue disorders		
Myalgia/Arthralgia	44	49
Severe Myalgia/Arthralgia[d]	8	4
Nervous system disorders		
Neurological symptom	71	56
Severe Neurological symptom[d]	10	2
Respiratory, thoracic and mediastinal disorders		
Cough	7	6
Dyspnea	12	9
Skin and subcutaneous tissue disorders		
Alopecia	90	94
Nail Disorder	1	0
Vascular disorders		
Haemorrhage	2	2

a. Based on worst grade.
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.

e. During study drug dosing. Bradycardia defined as pulse < 50 bpm and hypotension defined as diastolic blood pressure < 40 mmHg or decrease in systolic blood pressure of ≥ 30 mmHg.
f. Out of the 60 patients, 35 patients had a normal baseline ECG.

Adverse Event Experiences by Body System: Unless otherwise noted, the following discussion refers to the primary safety database of 229 patients with metastatic breast cancer treated with single-agent ABRAXANE in the randomized controlled trial. The frequency and severity of important clinically relevant adverse events for the study are presented above in tabular form. In some instances, rare severe events observed with paclitaxel injection may be expected to occur with ABRAXANE. Refer to the following section, 8.3 Less Common Clinical Trial Adverse Drug Reactions for the adverse events that occurred at a rate of less than 1%.

Hematologic: Neutropenia, the most important hematologic toxicity, was dose-dependent and generally rapidly 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 ABRAXANE at a dose of 260 mg/m^2 compared to 22% in patients receiving Cremophor®- based 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. Fever occurring at any time during the treatment course was reported in 14% of patients in the ABRAXANE arm.

Thrombocytopenia was almost never severe (< 50 x 10^9/L). Two percent of patients treated with ABRAXANE in the randomized trial experienced a decrease in their platelet count below 100 x 10^9/L at least once while on treatment. In the randomized metastatic breast cancer study, bleeding episodes were reported in 2% of the patients in each treatment arm.

Anemia (Hb <110g/L) in patients with normal baseline was observed in 20% of patients treated with ABRAXANE in the randomized trial and was severe (Hb < 80g/L) in 1% of the patients with normal baseline hemoglobin. Red cell transfusions were required in 2% of patients in the phase III study, and in 1% of those with normal baseline hemoglobin levels.

Hypersensitivity Reactions (HSRs): Hypersensitivity reactions to ABRAXANE were observed in 4% of all patients. No Grade 3 or 4 treatment-related hypersensitivity reactions occurred in the ABRAXANE treatment group. In the phase III study, the hypersensitivity reactions (i.e., those related to hypersensitivity and occurring on the day of dosing) consisted of dyspnea (1%) and flushing, hypotension, chest pain, and arrhythmia (all < 1%).

Cardiovascular: Hypotension, during the 30-minute infusion, occurred in 5% of patients treated with ABRAXANE in the randomized metastatic breast cancer trial. This vital sign change 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.

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 treated with ABRAXANE in the metastatic breast cancer randomized trial. Among patients with a normal ECG prior to study entry, 35% of patients treated with ABRAXANE 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%) and cough (7%) were reported after treatment with ABRAXANE in the randomized trial.

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 discontinuation in 7/229 (3%) patients receiving ABRAXANE in the randomized trial. Severe sensory symptoms have typically improved in a median of 22 days after interrupting ABRAXANE therapy. No incidences of grade 4 sensory neuropathies were reported in the clinical trials. Reports of autonomic neuropathy resulting in paralytic ileus have been received as part of the continuing surveillance of paclitaxel injection safety.

Ocular/visual disturbances: Thirteen percent (13%) of all patients (n = 366) treated with ABRAXANE in single-arm and randomized trials reported ocular/visual disturbances, 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/m^2). 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 (44%) of patients treated with ABRAXANE 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. There was no consistent relationship between dose of ABRAXANE and the frequency of arthralgia/myalgia.

Hepatic: Among patients with normal baseline liver function treated with ABRAXANE in the randomized trial, 7%, 36%, 39%, 36%, and 50% had elevations in bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT) and GGT 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. Prolonged exposure to ABRAXANE was not associated with cumulative hepatic toxicity.

Renal: Eleven percent (11%) of patients treated with ABRAXANE in the randomized trial 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 30%, 18%, 27%, and 7% of patients treated with ABRAXANE in the randomized trial. These manifestations were usually mild to moderate. The frequency and severity of GI adverse events were not obviously dose-related. Infrequent reports of esophagitis were reported in the clinical trials. Dehydration was reported commonly in clinical trials. Constipation and anorexia were considered very common.

Injection Site Reactions: Injection site reactions were reported in 1% of patients treated with ABRAXANE and included reactions secondary to extravasation, which were usually mild and included erythema.

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.

Alopecia: Alopecia was observed in almost all of the patients.

Skin: Nail changes (changes in pigmentation or discolouration of nail bed) occurred in 1% of patients treated with ABRAXANE in the randomized trial. Transient skin changes (rash 9%; flushing 2%; pruritus 6%) were observed in the randomized trial. No other skin adverse events were significantly associated with ABRAXANE administration.

Metastatic Pancreatic Cancer

Adverse reactions were assessed in 421 ABRAXANE plus gemcitabine-treated patients and 402 gemcitabine monotherapy treated patients receiving first-line systemic treatment for metastatic adenocarcinoma of the pancreas in a multicenter, multinational, randomized, controlled, open-label trial.

Table 6 provides the frequency and severity of hematologic laboratory-detected abnormalities for the ABRAXANE/gemcitabine group and the gemcitabine group.

Table 6: Hematologic Laboratory-Detected Abnormalities in Metastatic Pancreatic Cancer Clinical Trial

	ABRAXANE(125 mg/m^2)/ Gemcitabine		**Gemcitabine**	
	Grades 1-4 (%)	**Grade 3-4 (%)**	**Grades 1-4 (%)**	**Grade 3-4 (%)**
Anemia[a,b]	97	13	96	12
Neutropenia [a,b]	73	38	58	27
Thrombocytopenia[b,c]	74	13	70	9

a. 405 patients assessed in ABRAXANE/gemcitabine-treated group

b. 388 patients assessed in gemcitabine-treated group

c. 404 patients assessed in ABRAXANE/gemcitabine-treated group

Table 7 provides the frequency and severity of adverse reactions by system organ class/preferred term that have been reported in ≥ 10% of patients with adenocarcinoma of the pancreas who received ABRAXANE and gemcitabine or gemcitabine monotherapy. Within each system organ class grouping, adverse reactions are presented in order of decreasing frequency.

Table 7: Adverse Reactions Reported in ≥ 10% of Patients in Metastatic Pancreatic Cancer Clinical Trial (by MedDRA System Organ Class and Preferred Term)

System Organ Class/ Preferred Term	ABRAXANE (125 mg/m^2) and gemcitabine (N=421)		Gemcitabine (N=402)	
	All Grade	Grade 3 or Higher	All Grade	Grade 3 or Higher
Blood and Lymphatic System Disorders[a]	**280 (67%)**	**202 (48%)**	**238 (59%)**	**128 (32%)**
Anemia	176 (42%)	49 (12%)	133 (33%)	32 (8%)
Neutropenia	175 (42%)	138 (33%)	122 (30%)	85 (21%)
Thrombocytopenia	128 (30%)	53 (13%)	117 (29%)	33 (8%)
Leukopenia	59 (14%)	39 (9%)	39 (10%)	15 (4%)
Gastrointestinal disorders	**352 (84%)**	**114 (27%)**	**315 (78%)**	**92 (23%)**
Nausea	228 (54%)	27 (6%)	192 (48%)	14 (3%)
Diarrhoea	184 (44%)	26 (6%)	95 (24%)	6 (1%)
Vomiting	151 (36%)	25 (6%)	113 (28%)	15 (4%)
Constipation	126 (30%)	12 (3%)	111 (28%)	7 (2%)
Abdominal pain	98 (23%)	27 (6%)	89 (22%)	32 (8%)
Abdominal pain upper	43 (10%)	10 (2%)	28 (7%)	3 (1%)
General disorders and administration site conditions	**361 (86%)**	**132 (31%)**	**299 (74%)**	**76 (19%)**
Fatigue	248 (59%)	77 (18%)	183 (46%)	37 (9%)
Oedema peripheral	194 (46%)	13 (3%)	122 (30%)	12 (3%)
Pyrexia	171 (41%)	12 (3%)	114 (28%)	4 (1%)
Asthenia	79 (19%)	29 (7%)	54 (13%)	17 (4%)
Chills	49 (12%)	0	35 (9%)	0
Investigations	**186 (44%)**	**66 (16%)**	**172 (43%)**	**61 (15%)**
Weight decreased	57 (14%)	1 (<1%)	48 (12%)	2 (<1%)
Alanine aminotransferase increased	46 (11%)	13 (3%)	36 (9%)	15 (4%)
Metabolism and nutrition disorders	**245 (58%)**	**76 (18%)**	**182 (45%)**	**48 (12%)**
Decreased appetite	152 (36%)	23 (5%)	104 (26%)	8 (2%)
Dehydration	87 (21%)	31 (7%)	45 (11%)	10 (2%)
Hypokalaemia	52 (12%)	18 (4%)	28 (7%)	6 (1%)
Musculoskeletal and connective tissue disorders	**177 (42%)**	**19 (5%)**	**107 (27%)**	**12 (3%)**
Pain in extremity	48 (11%)	3 (1%)	24 (6%)	3 (1%)
Arthralgia	47 (11%)	3 (1%)	13 (3%)	1 (<1%)
Myalgia	44 (10%)	4 (1%)	15 (4%)	0
Nervous system disorders	**277 (66%)**	**82 (19%)**	**149 (37%)**	**19 (5%)**
Peripheral neuropathy SMQ[b]	227 (54%)	70 (17%)	51 (13%)	3 (1%)
Dysgeusia	68 (16%)	0	33 (8%)	0

Headache	60 (14%)	1 (<1%)	38 (9%)	1 (<1%)
Dizziness	48 (11%)	3 (1%)	34 (8%)	0
Psychiatric disorders	151 (36%)	7 (2%)	103 (26%)	16 (4%)
Insomnia	64 (15%)	0	46 (11%)	3 (1%)
Depression	51 (12%)	1 (<1%)	24 (6%)	0
Anxiety	35 (8%)	1 (<1%)	45 (11%)	7 (2%)
Respiratory, thoracic and mediastinal disorders	**212 (50%)**	**41 (10%)**	**149 (37%)**	**45 (11%)**
Cough	72 (17%)	0	30 (7%)	0
Dyspnoea	72 (17%)	12 (3%)	62 (15%)	11 (3%)
Epistaxis	64 (15%)	1 (<1%)	14 (3%)	1 (<1%)
Skin and subcutaneous tissue disorders	**294 (70%)**	**19 (5%)**	**127 (32%)**	**3 (1%)**
Alopecia	212 (50%)	6 (1%)	21 (5%)	0
Rash	117 (28%)	7 (2%)	39 (10%)	2 (<1%)

MedDRA = Medical Dictionary for Regulatory Activities.

a. Events reported in this Table are ADR's. Hematologic laboratory detected abnormalities are reported in Table 2.
b. Peripheral neuropathy evaluated using the MedDRA v 15.0 Standardized MedDRA Query (broad scope).

8.3 Less Common Clinical Trial Adverse Reactions

Metastatic Breast Cancer

Cardiovascular: Bradycardia during the 30-minute infusion occurred in < 1% of patients in the phase III study. Cases of cardiac ischemia/infarction and thrombosis/embolism possibly related to ABRAXANE treatment were uncommon. Cases of cerebrovascular attacks (strokes) and transient ischemic attacks were uncommon.

Gastrointestinal: 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 co-administration of G-CSF, were observed in patients treated with paclitaxel injection alone and in combination with other chemotherapeutic agents.

Hepatic: 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.

Hypersensitivity Reactions: Flushing, hypotension, chest pain, and arrhythmia occurring on the day of dosing were all reported at < 1%.

Infections and Infestations: Sepsis and neutropenic sepsis were uncommon events in patients receiving ABRAXANE in pre-market and post-market clinical trials.

Injection Site Reactions: 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. 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.

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

Neurologic: Uncommon serious neurologic events following ABRAXANE administration have included ischemic stroke, metabolic encephalopathy, confusion, dizziness/light-headedness, and mood alteration/depression.

Respiratory: Reports (< 1%) of pneumothorax were uncommon after treatment with ABRAXANE in the randomized trial. 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.

Metastatic Pancreatic Cancer

Additional clinically relevant adverse reactions that were reported in < 10% of the patients with adenocarcinoma of the pancreas who received ABRAXANE/gemcitabine included:

The frequency estimates for adverse reactions are defined using the following convention:

Common (frequent): ≥1/100 and <1/10 (≥1% and <10%)

Uncommon (infrequent): ≥1/1000 and <1/100 (≥0.1% and <1%)

Blood and lymphatic system disorders:

Common: Pancytopenia

Uncommon: thrombotic thrombocytopenic purpura

Cardiac disorders:

Common: Tachycardia, cardiac failure congestive

Eye disorders:

Common: Lacrimation increased

Uncommon: cystoid macular edema

Gastrointestinal disorders:

Common: Stomatitis, dry mouth, intestinal obstruction, colitis

General disorders and administration site conditions:

Common: Infusion site reaction

Hepatobiliary disorders:

Common: Cholangitis

Infections & infestations:

Common: Oral candidiasis, pneumonia, sepsis with or without neutropenia

Investigations:

Common: Aspartate aminotransferase increased, blood bilirubin increased, blood creatinine increased

Musculoskeletal and connective tissue disorders:

Common: Bone pain, muscular weakness

Nervous system disorders:

Common: Peripheral motor neuropathy

Uncommon: VIIth nerve paralysis

Renal and urinary disorders:

Common: Acute renal failure

Uncommon: Haemolytic uraemic syndrome

Respiratory thoracic and mediastinal disorders:

Common: Nasal congestion, pneumonitis

Uncommon: dry throat, nasal dryness

Skin and subcutaneous tissue disorders:

Common: Pruritus, dry skin, nail disorder, flushing

Vascular disorders:

Common: Hypotension, hypertension

8.5 Post-Market Adverse Reactions

The following adverse drug reactions have been identified during post-approval 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.

Blood and Lymphatic System Disorders: Reports of pancytopenia and lymphopenia have been observed.

Cardiac Disorders: Reports of congestive heart failure, left ventricular dysfunction, and atrioventricular block (including second-degree AV block requiring pacemaker placement) have been observed. Most of the individuals had previous or concurrent exposure to cardiotoxic drugs, such as anthracyclines, or had underlying cardiac history.

Eye Disorders: Rare reports of conjunctivitis, increased lacrimation, loss of vision, macula edema, optic neuropathy, dry eye, and hypoaesthesia of the eye have been observed.

There have been reports of reduced visual acuity due to cystoid macular edema (CME) during treatment with ABRAXANE. Based on a number of well documented reports, including literature cases, an association between CME and ABRAXANE is considered to be reasonably well established. Features specific to this rare clinical entity include an absence of vascular leakage with no other precipitating factors, and positive dechallenge in most cases.

General Disorders and Administration Site Conditions: Reports of extravasation have been observed.

Injury, Poisoning and Procedural Complications: Reports of radiation recall phenomenon have been observed.

Immune System Disorders: Rare occurrences of severe hypersensitivity reactions, including anaphylactic reactions, have been reported. Very rarely, fatalities have occurred in these patients. Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be re-challenged with the drug.

Metabolic Disorders: Very rare occurrences of tumor lysis syndrome, some with a fatal outcome, have been reported.

Nervous System Disorders: Reports of crania nerve palsies, vocal cord paresis and motor neuropathy have been observed.

Respiratory Thoracic and Mediastinal Disorders: Reports of pleural effusion, pulmonary edema, diffuse alveolar damage and diffuse pneumonitis have been observed as well as reports of radiation pneumonitis in patients receiving concurrent radiotherapy.

Skin/Subcutaneous Disorders: Reports of erythema, generalized or maculo-papular rash, pruritus, photosensitivity reaction, and in some patients previously exposed to capecitabine, reports of palmar-plantar erythrodyaesthesiae have been observed. Rare reports of Stevens-Johnson syndrome and toxic epidermal necrolysis have also been observed. During post-market surveillance, scleroderma-like changes preceded by chronic edema have been reported with solvent-based paclitaxel injection.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No drug interaction studies have been conducted with ABRAXANE® for Injectable Suspension (paclitaxel powder for injectable suspension) (nanoparticle, albumin-bound [nab®] paclitaxel).

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 substances known to inhibit (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, nelfinavir, grapefruit, Seville oranges, and starfruit) or induce (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine, St. John's Wort) either CYP2C8 or CYP3A4 (see 10 CLINICAL PHARMACOLOGY).

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

Paclitaxel and gemcitabine do not share a common metabolic pathway. Paclitaxel clearance is primarily determined by cytochrome P450 2C8 and 3A4 mediated metabolism followed by biliary excretion, while gemcitabine is inactivated by cytidine deaminase followed by urinary excretion. Some *in vitro* studies have shown effects of paclitaxel on intracellular levels of the active and inactive metabolites of gemcitabine but clinical significance of those observations is unknown. Pharmacokinetic interactions between ABRAXANE and gemcitabine have not been evaluated in humans.

9.5 Drug-Food Interactions

Interactions with food have not been established. Grapefruit products, Seville oranges, and starfruit may interact with ABRAXANE, as they contain inhibitors of CYP3A.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established. St. John's Wort may interact with ABRAXANE, as this herb is a strong inducer of CYP3A.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Paclitaxel, the active pharmaceutical ingredient in ABRAXANE® for Injectable Suspension (paclitaxel powder for injectable suspension) (nanoparticle, albumin-bound [nab®] paclitaxel), 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.

10.2 Pharmacodynamics

In preclinical models, ABRAXANE resulted in higher intra-tumor concentrations of paclitaxel compared to paclitaxel injection. Albumin is known to mediate endothelial transcytosis of plasma constituents and, based on *in vitro* data, it is hypothesized that albumin-bound paclitaxel facilitates the transport of paclitaxel across the endothelial cell via an albumin-receptor (gp60) mediated pathway.

10.3 Pharmacokinetics

Absorption

The pharmacokinetics of total paclitaxel following 30- and 180-minute infusions of ABRAXANE at dose levels of 80 – 375 mg/m^2 were determined in clinical studies. 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 paclitaxel plasma exposure (AUC) was dose proportional from 2653 to 16736 h•ng/mL following administration of ABRAXANE doses from 80 to 300 mg/m2 and the pharmacokinetics of paclitaxel were independent of the duration of intravenous administration.

Distribution:

Following ABRAXANE administration to patients with solid tumors, paclitaxel is evenly distributed into blood cells and plasma and is highly bound to plasma proteins (94%). In a within-patient comparison study, the fraction of unbound paclitaxel in plasma was significantly higher with ABRAXANE (6.2%) than with solvent-based paclitaxel (2.3%). This contributes to significantly higher exposure to unbound paclitaxel with ABRAXANE compared with solvent-based paclitaxel, when the total exposure is comparable. *In vitro* studies of binding to human serum proteins, using paclitaxel at concentrations ranging from 0.1 to 50 µg/mL, indicate that the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

Based on a population pharmacokinetic analysis, the total volume of distribution is approximately 1741 L; 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 volume of distribution and clearance of paclitaxel powder for injectable suspension were greater (by 53% and 43% respectively) than for paclitaxel injection. 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 (approximately 21 hours for each).

Metabolism:

In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6α-hydroxypaclitaxel by CYP2C8; and to two minor metabolites, 3'-p-hydroxypaclitaxel and 6α, 3'-p-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α-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, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-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 9 DRUG INTERACTIONS).

Elimination

After a 30-minute infusion of 260 mg/m2 doses of paclitaxel powder for injectable suspension, 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 6α-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel. Fecal excretion was approximately 20% of the total dose administered.

At the clinical dose range of 80 to 300 mg/m^2, the mean total clearance of paclitaxel ranges from 13 to 30 L/h/m^2, and the mean terminal half-life ranges from 13 to 27 hours.

Possible interactions of paclitaxel with concomitantly administered medications have not been formally investigated. In a rat study in which a single dose of ABRAXANE was concurrently administered with gemcitabine, the exposure of the inactive metabolite of gemcitabine, dFdU was doubled whereas gemcitabine systemic exposure was not affected. The active metabolites of gemcitabine, dFdCDP and dFdCTP, were not measured. The exposure of paclitaxel was not affected.

Special Populations and Conditions

- **Geriatrics:** Population pharmacokinetic analysis for ABRAXANE included patients with ages ranging from 24 to 85 years old and show that age does not significantly influence the maximum elimination rate of paclitaxel. Pharmacokinetic/pharmacodynamics modeling using data from 125 patients with advanced solid tumors suggested that the risk of neutropenia development in the first treatment cycle is positively correlated with increasing age after adjusting for ABRAXANE exposure.
- **Hepatic Insufficiency:** The effect of hepatic impairment on population pharmacokinetics of ABRAXANE was studied in patients with advanced solid tumors. This analysis included patients with normal hepatic function (n=130), and pre-existing mild (n=8), moderate (n=7), or severe (n=5) hepatic impairment (according to NCI Organ Dysfunction Working Group criteria). The results show that mild hepatic impairment (total bilirubin > 1 to ≤ 1.5 x ULN) has no clinically important effect on pharmacokinetics of paclitaxel. Patients with moderate (total bilirubin > 1.5 to ≤ 3 x ULN) or severe (total bilirubin > 3 to ≤ 5 x ULN) hepatic impairment have a 22% to 26% decrease in the maximum elimination rate of paclitaxel and approximately 20% increase in mean paclitaxel AUC compared with patients with normal hepatic function.

  Hepatic impairment has no effect on mean paclitaxel Cmax. In addition, elimination of paclitaxel shows an inverse correlation with total bilirubin and a positive correlation with serum albumin. Pharmacokinetic/pharmacodynamic modeling indicates that there is no correlation between baseline albumin or total bilirubin level and neutropenia after adjusting for ABRAXANE exposure.

  Pharmacokinetic data are not available for patients with total bilirubin > 5 x ULN or for patients with metastatic pancreatic cancer (see 4.2 Recommended Dose and Dosage Adjustment).
- **Renal Insufficiency** Population pharmacokinetic analysis included patients with normal renal function (n=65), and pre-existing mild (n=61), moderate (n=23), or severe (n=1) renal impairment (according to draft FDA guidance criteria 2010). Mild to moderate renal impairment (creatinine clearance ≥ 30 to < 90 mL/min) has no clinically important effect on the maximum elimination rate and systemic exposure (AUC and Cmax) of paclitaxel. Pharmacokinetic data are insufficient for patients with severe renal impairment and not available for patients with end stage kidney disease (see 4.2 Recommended Dose and Dosage Adjustment).
- **Other Intrinsic Factors:** Population pharmacokinetic analyses for ABRAXANE show that body weight (40 to 143 kg), body surface area (1.3 to 2.4 m^2), gender, race (Asian vs White), and type of solid tumors do not have a clinically important effect on the maximum elimination rate of paclitaxel.

11 STORAGE, STABILITY AND DISPOSAL

Store the vials of ABRAXANE® for Injectable Suspension (paclitaxel powder for injectable suspension) (nanoparticle, albumin-bound [nab®] paclitaxel) in original cartons between 20 and 25°C. Retain in the original package to protect from bright light.

Neither freezing nor refrigeration adversely affects the stability of the product.

ABRAXANE reconstituted in the original vial should be used immediately, but may be refrigerated between 2 and 8°C 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. Some settling of the reconstituted suspension may occur. Ensure complete resuspension by mild agitation before use. Discard the reconstituted suspension if precipitates are observed.

The suspension for infusion prepared as recommended in an infusion bag should be used immediately but may be stored at ambient temperature (approximately 20 to 25°C) and ambient lighting conditions for up to 8 hours.

12 SPECIAL HANDLING INSTRUCTIONS

ABRAXANE® for Injectable Suspension (paclitaxel powder for injectable suspension) (nanoparticle, albumin-bound [nab®] paclitaxel) 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.

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

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. 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.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

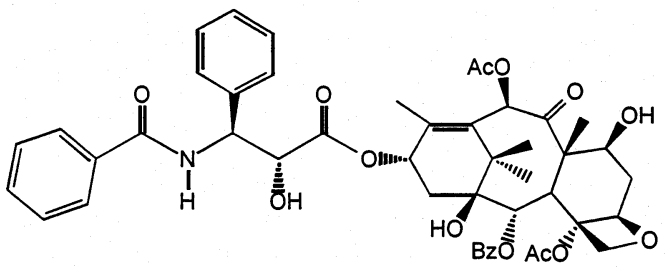
Proper name: Paclitaxel

Chemical name: 5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine

Molecular formula and molecular mass: $C_{47}H_{51}NO_{14}$ 853.91

Structural formula:

Paclitaxel has the following structural formula:



Physicochemical properties: Paclitaxel is a white to off-white crystalline powder. It is highly lipophilic, insoluble in water, and melts at approximately 216 to 217°C.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Metastatic Breast Carcinoma

Data from 460 patients enrolled in a randomized comparative study were available to support the use of ABRAXANE® for Injectable Suspension (paclitaxel powder for injectable suspension) (nanoparticle, albumin-bound [nab®] paclitaxel) in metastatic breast cancer.

Table 8: Summary of Patient Demographics for Clinical Trials in Metastatic Breast Cancer

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n = number)	Mean Age (Range)	Gender and Race
CA012-0	Pivotal: controlled, randomized, multicentre, open label phase III study of ABRAXANE for Injectable Suspension versus Paclitaxel Injection in patients with metastatic breast cancer.	ABRAXANE: 260 mg/m^2 given as a 30-minute infusion vs. Paclitaxel Injection at 175 mg/m^2 given as a 3-hour infusion. Each patient receives drug at 3-week intervals.	460, divided into two arms.	53.2 (26 - 83)	Female (100%) Caucasian: 221 (97%) Black: 1 (< 1%) Asian: 1 (< 1%) Indian-Eastern: 2 (< 1%) Hispanic: 3 (1%) Other: 1 (< 1%)

Randomized Comparative Study - This multicentre 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.

The primary endpoint was Target Lesion Response Rate using RECIST guidelines.

Study results

In the randomized controlled multicentre trial, patients in the ABRAXANE treatment arm had a superior investigator overall target lesion response rate of 33.2% (95% CI: 27.09 to 39.29%), compared to 18.7% (95% CI: 13.58 to 23.76%) for patients in the paclitaxel injection treatment arm. (See **Table 9**).

Table 9: Efficacy in Metastatic Breast Cancer

Endpoint **Overall Investigator Target Lesion Response Rate**	**ABRAXANE®** **260 mg/m^2** **(n = 229)**	**Paclitaxel Injection 175 mg/m^2 (n = 225)**	**P Value**
All Patients %	33.2	18.7	0.001[a*]
95% Confidence interval[b]	(27.09-39.29)	(13.58-23.76)	

a. P value from Cochran-Mantel-Haenszel (CMH) test stratified by 1st line vs > 1st line therapy; * P < 0.05.

b. 95% binomial confidence interval of response rate.

Time to Tumor Progression (TTP) was significantly greater in the ABRAXANE group than in the paclitaxel injection group for all patients [23.0 vs 16.6 weeks (5.3 vs 3.8 months), hazard ratio (HR) = 0.726, (95% CI: 0.589-0.895), P = 0.002]. (See **Table 10**).

Table 10: Time to Tumor Progression

Category	**ABRAXANE 260 mg/m^2 (n = 229)**	**Paclitaxel Injection 175 mg/m^2 (n = 225)**	**P Value[a] (Hazard Ratio) 95% CI**
All Patients			
Median time to disease progression (weeks)	23.0	16.6	0.002* (0.726) 0.589 − 0.895
95% Confidence interval	19.4 − 26.1	15.1 − 20.1	

Median time to disease progression (months)[b]	5.3	3.8	
95% Confidence interval	4.5 − 6.0	3.5 − 4.6	

Note: Time to tumor progression is defined as the number of weeks from the first dose of study drug to the start of disease progression. Patients who did not have disease progression are censored at the last known time the patient was evaluated for response.

CI = Confidence interval

a. P value from log-rank test. * P < 0.050.

b. Conversion to/from weeks to months assumes 30.5 days/month or 4.3571 weeks/month.

Median Progression-Free Survival (PFS) was significantly longer for the ABRAXANE group than for the paclitaxel injection group for all patients [22.7 vs 16.6 weeks (5.2 vs 3.8 months), HR = 0.734, (95% CI: 0.597-0.903), P = 0.003]. (See **Table 11**).

Table 11: Progression-Free Survival

Category	**ABRAXANE 260 mg/m^2 (n = 229)**	**Paclitaxel Injection 175 mg/m^2 (n = 225)**	**P Value[a] (Hazard Ratio) 95% CI**
All Patients			
Median progression-free survival (weeks)	22.7	16.6	0.003* (0.734) 0.597 − 0.903
95% Confidence interval	19.3 − 26.1	15.1 − 19.9	
Median progression-free survival (months)[b]	5.2	3.8	
95% Confidence interval	4.4 − 6.0	3.5 − 4.6	

Note: Progression-free survival is defined as the time from the first dose of study drug to the start of disease progression or patient death (which ever occurred first). Patients who did not have disease progression or have not died are censored at the last known time the patient was alive. If a patient started another oncology therapy during study follow-up prior to disease progression or death, that patient is censored at the last follow-up contact date prior to the start of the new oncology therapy.
ITT = Intent-to-treat; CI = Confidence interval

a. P value from log-rank test. * P < 0.050.

b. Conversion from weeks to months assumes 30.5 days/month or 4.3571 weeks/month.

Median time to death for ABRAXANE and paclitaxel injection groups for all patients was 65.0 vs 55.3 weeks (14.9 vs 12.7 months) respectively, HR = 0.899, (95% CI: 0.728-1.110), P = 0.322. (See **Table 12**).

Table 12: Patient Survival

Category	ABRAXANE 260 mg/m^2 (n = 229)	Paclitaxel Injection 175 mg/m^2 (n = 225)	P Value[a] (Hazard Ratio) 95% CI
All Patients			
Median time to death (weeks)	65.0	55.3	0.322 (0.899) 0.728 − 1.110
95% Confidence interval[b]	53.4 − 76.9	48.0 − 66.4	
Median time to death (months)	14.9	12.7	
95% Confidence interval[b]	12.3 − 17.6	11.0 − 15.2	

Note: Analysis includes patient survival information during study follow-up. Patients who did not die are censored at the last known time the patient was alive.

CI = confidence interval.

a. P value from log-rank test. *P < 0.050.

b. 95% CI for median time to death.

Metastatic Pancreatic Cancer

A multicenter, multinational, randomized, open-label study was conducted in 861 patients to compare ABRAXANE/gemcitabine versus gemcitabine monotherapy as first-line treatment in patients with metastatic adenocarcinoma of the pancreas. Patients who received adjuvant chemotherapy were not eligible for enrollment. ABRAXANE was administered to patients (N=431) as an intravenous infusion over 30-40 minutes at a dose of 125 mg/m^2 followed by gemcitabine as an intravenous infusion over 30-40 minutes at a dose of 1000 mg/m^2 given on Days 1, 8 and 15 of each 28-day cycle. In the comparator treatment group, gemcitabine monotherapy was administered to patients (N=430) as 1000 mg/m^2 given weekly for 7 weeks followed by a 1-week rest period in Cycle 1 and in Cycle 2 and onwards was administered on Days 1, 8 and 15 of a 28-day cycle (consistent with the label recommended dose and regimen). Treatment was administered until disease progression or development of an unacceptable toxicity.

Patient demographics of the intent-to-treat population are shown in **Table 13**. The demographics and disease characteristics were well balanced between the two treatment groups.

Table 13: Summary of Patient Characteristics in Randomized Adenocarcinoma of Pancreas Trial (Intent-to-Treat Population)

Patient Characteristics	ABRAXANE (125 mg/m^2) and gemcitabine (N=431)	Gemcitabine (N=430)
Age (years)		
Median (range)	62 (27, 86)	63 (32, 88)
< 65 years, n (%)	254 (59%)	242 (56%)
≥ 65 years, n (%)	177 (41%)	188 (44%)
Gender (%)		
Male/Female	57%/43%	60%/40%
Karnofsky Performance Status Baseline, n (%)		
100	69 (16%)	69 (16%)
90	179 (42%)	199 (46%)
80	149 (35%)	128 (30%)
70	30 (7%)	33 (8%)
CA 19-9 Baseline, n (%)		
Within normal laboratory limits	60 (14%)	56 (13%)
>ULN but <59 x ULN	122 (28%)	120 (28%)
≥59 x ULN	197 (46%)	195 (45%)
Number of Metastatic Site(s), n (%)		
1	33 (8%)	21 (5%)
2	202 (47%)	206 (48%)
3	136 (32%)	140 (33%)
>3	60 (14%)	63 (15%)
Current Metastatic Site(s), n (%)		
Liver	365 (85%)	360 (84%)
Lung/Thoracic	153 (35%)	184 (43%)
Pancreatic Primary Location, n (%)		

Head	191 (44%)	180 (42%)
Body	132 (31%)	136 (32%)
Tail	105 (24%)	110 (26%)
Biliary Stent, n (%)		
Present at Baseline	80 (19%)	68 (16%)
Whipple Procedure, n (%)		
Performed Prior to Study Entry	32 (7%)	30 (7%)

Patients received a median treatment duration of 3.9 months in the ABRAXANE/gemcitabine group and 2.8 months in the gemcitabine group.

The primary efficacy endpoint was overall survival (OS). The key secondary endpoints were progression-free survival (PFS) and overall response rate (ORR), both assessed by independent, central, blinded radiological review using RECIST guidelines (Version 1.0). Results for overall survival, progression-free survival, and overall response rate are shown in **Table 14**.

Table 14: Efficacy Results from Randomized Study in Patients with Adenocarcinoma of the Pancreas (ITT Population)

	ABRAXANE(125 mg/m^2) and gemcitabine (N = 431)	**Gemcitabine (N = 430)**
Overall Survival		
Number of deaths, n (%)	333 (77)	359 (83)
Median Overall Survival (months)	**8.5**	**6.7**
HR (95% CI) [a], P-value[b]	0.72 (0.62, 0.83), <0.0001	
Progression-free Survival[c]		
Death or progression, n (%)	277 (64)	265 (62)
Median Progression-free Survival (months)	**5.5**	**3.7**
HR (95% CI) [a], P-value[b]	0.69 (0.58, 0.82), <0.0001	
Overall Response Rate[c]		
Confirmed complete or partial overall response, n (%)	**99 (23)**	**31 (7)**
(95% CI) , P-value[d]	3.19 (2.18, 4.66), <0.0001	

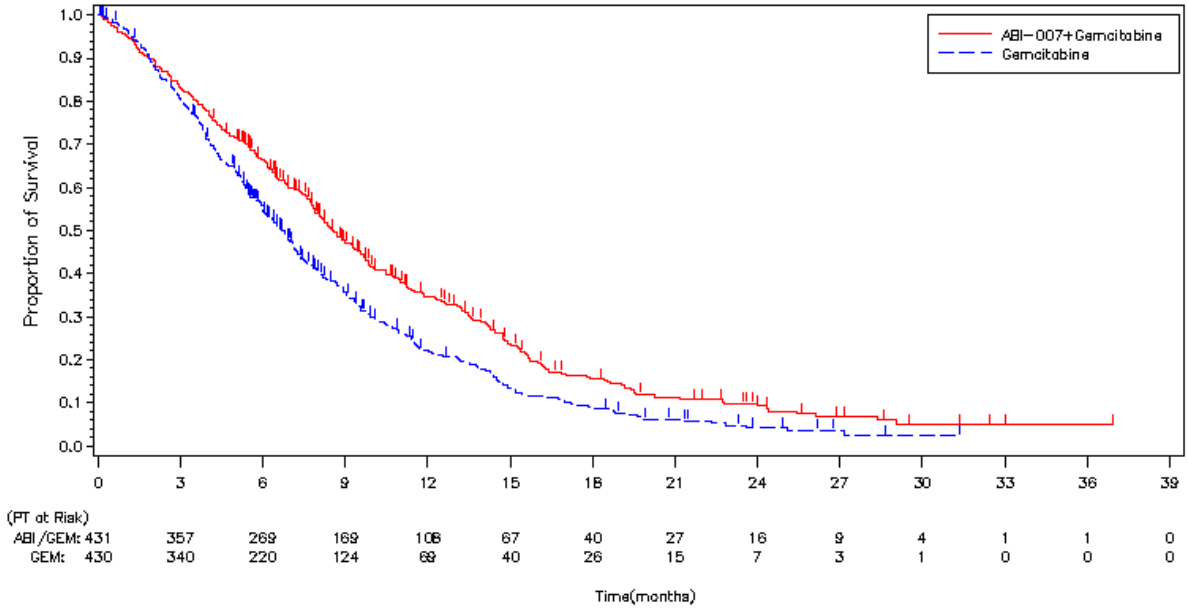
CI = confidence interval, HR = hazard ratio of ABI-007/gemcitabine / gemcitabine, ITT = intent-to-treat population.

a. The associated hazard ratio and 95 % CI is estimated by using stratified Cox proportional hazard model.

b. P-value is based on a stratified log-rank test stratified by geographic region (North America versus Others), Karnofsky performance score (70 to 80 versus 90 to 100), and presence of liver metastasis (yes versus no).
c. Based on Independent Radiological Reviewer Assessment.
d. P-value is for response rate ratio and is based on chi-square test.

There was a statistically significant improvement in OS for patients treated with ABRAXANE/gemcitabine versus gemcitabine alone, with 1.8 months increase in median OS, 28% overall reduction in risk of death and 59% improvement in 1-year survival. The Kaplan-Meier curve for Overall Survival by treatment group is presented in **Figure 1**.

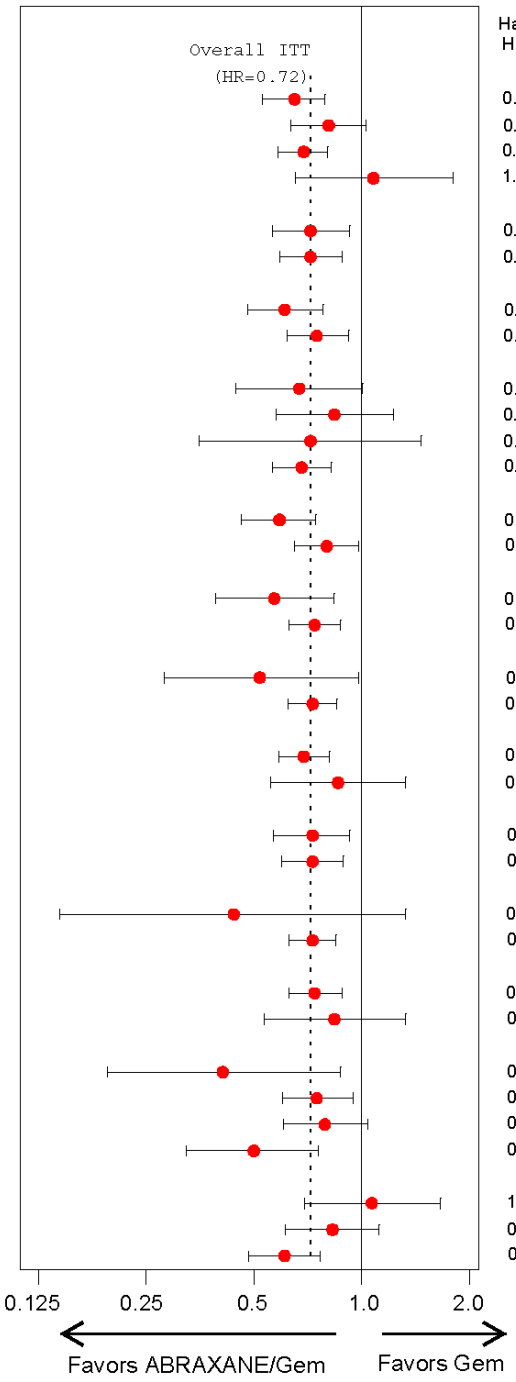
Figure 1: Kaplan-Meier Curve of Overall Survival (Intent-to-treat Population)



An analysis of OS by prespecified subgroups is shown in **Figure 2.**

Figure 2: Forest Plot for Overall Survival

Group	ABRAXANE/Gem Death/n (%)	Gemcitabine Death/n (%)	Hazard Ratio HR (95% CI)
Age (years)			
< 65	188/254 (74)	209/242 (86)	0.65 (0.528, 0.789)
>=65	145/177 (82)	150/188 (80)	0.81 (0.634, 1.027)
< 75	301/390 (77)	323/381 (85)	0.69 (0.584, 0.804)
>=75	32/41 (78)	36/49 (73)	1.08 (0.653, 1.797)
Sex			
Female	138/186 (74)	141/173 (82)	0.72 (0.565, 0.926)
Male	195/245 (80)	218/257 (85)	0.72 (0.592, 0.880)
Karnofsky Performance Status			
70-80	142/179 (79)	146/161 (91)	0.61 (0.481, 0.779)
90-100	187/248 (75)	212/268 (79)	0.75 (0.618, 0.921)
Geographic Region			
Australia	50/61 (82)	53/59 (90)	0.67 (0.445, 1.009)
Eastern Europe	62/64 (97)	59/62 (95)	0.84 (0.579, 1.226)
Western Europe	14/38 (37)	17/38 (45)	0.72 (0.352, 1.467)
North America	207/268 (77)	230/271 (85)	0.68 (0.563, 0.823)
Pancreatic Cancer Primary Location			
Head	142/191 (74)	155/180 (86)	0.59 (0.460, 0.745)
Other	188/237 (79)	201/246 (82)	0.80 (0.651, 0.982)
Presence of Biliary Stent			
Yes	60/80 (75)	59/68 (87)	0.57 (0.391, 0.839)
No	273/351 (78)	300/362 (83)	0.74 (0.628, 0.876)
Previous Whipple Procedure			
Yes	25/32 (78)	23/30 (77)	0.52 (0.280, 0.981)
No	308/399 (77)	336/400 (84)	0.73 (0.623, 0.853)
Presence of Liver Metastases			
Yes	290/365 (79)	309/360 (86)	0.69 (0.588, 0.814)
No	43/66 (65)	50/70 (71)	0.86 (0.556, 1.327)
Presence of Pulmonary Metastases			
Yes	119/153 (78)	157/184 (85)	0.73 (0.568, 0.929)
No	214/278 (77)	202/246 (82)	0.73 (0.597, 0.887)
Peritoneal Carcinomatosis			
Yes	9/19 (47)	8/10 (80)	0.44 (0.143, 1.328)
No	324/412 (79)	351/420 (84)	0.73 (0.625, 0.849)
Stage at Diagnosis			
IV	262/336 (78)	293/354 (83)	0.74 (0.628, 0.882)
Other	52/63 (83)	35/43 (81)	0.84 (0.535, 1.328)
No of Metastatic Sites			
1	21/33 (64)	16/21 (76)	0.41 (0.195, 0.876)
2	159/202 (79)	163/206 (79)	0.75 (0.601, 0.947)
3	104/136 (76)	121/140 (86)	0.79 (0.607, 1.039)
Above 3	49/60 (82)	59/63 (94)	0.50 (0.325, 0.755)
Level of CA19-9			
Within Normal	47/60 (78)	43/56 (77)	1.07 (0.692, 1.661)
ULN to < 59 x ULN	96/122 (79)	95/120 (79)	0.83 (0.613, 1.120)
>=59 x ULN	151/197 (77)	171/195 (88)	0.61 (0.483, 0.766)



15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Single-dose studies: Testicular atrophy/degeneration was observed in single-dose toxicology studies in animals administered paclitaxel formulated as albumin-bound particles at doses lower than the recommended human dose; doses were 54 mg/m^2 in rodents and 175 mg/m^2 in dogs.

ABRAXANE caused temporary, delayed gastrointestinal symptoms, edema, vasculitis and elevated white blood cell counts in dogs at 175 mg/m^2.

Repeat-dose studies: In a repeat-dose toxicity study in rats (0, 60, 120, 180 mg/m^2; i.v; 6 times at 5 day intervals over 30 days), irreversible degenerative changes in the nervous system and eyes and atrophic changes in male reproductive organs were observed at dose ≥120 mg/m^2. The systemic exposure at 120 mg/m^2 in rats was similar to those in humans at the clinically recommended dose regimen. A NOAEL was not established as toxicity was observed in all dose groups in a dose-dependent fashion.

Testicular degeneration was seen in monkeys administered three weekly doses of 108 mg/m^2 paclitaxel formulated as albumin bound particles, which is approximately one-third of the exposure in humans at the clinically recommended dose regimen.

Carcinogenicity:

The carcinogenic potential of ABRAXANE has not been studied.

Genotoxicity:

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

Reproductive and Developmental Toxicology:

Administration of paclitaxel powder for injectable suspension to rats on gestation days 7 to 17 at doses of 6 mg/m^2 (approximately 2% of the daily maximum recommended human dose on a mg/m^2 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 was also exhibited at 3 mg/m^2 (approximately 1% of the daily maximum recommended human dose on a mg/m^2 basis). NOAEL was 3 mg/m^2. Maternal toxicity was observed at ≥ 6 mg/m^2. Teratogenic was observed at 6 -12 mg/m^2 and fetal deaths was observed at ≥ 4 mg/kg/day.

Administration of paclitaxel powder for injectable suspension 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. Dose levels of mg/m^2 refer to mg of paclitaxel in ABRAXANE. 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). Moribund or dead rats exhibited gastrointestinal lesions and reduction in male reproductive organ sizes observed at scheduled necropsies.

Administration of paclitaxel prior to and during mating produced impairment of fertility in male and female rats.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]ABRAXANE® for Injectable Suspension

Paclitaxel powder for injectable suspension

nanoparticle, albumin-bound (nab®) paclitaxel

Read this carefully before you start taking ABRAXANE. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about ABRAXANE.

Serious Warnings and Precautions

- ABRAXANE should only be prescribed by a healthcare professional who has experience with anti-cancer medicines. ABRAXANE should not be substituted with or for other paclitaxel products.
- ABRAXANE can cause the following side effects when taken with a medicine called gemcitabine:
    - **Sepsis** (blood infection). The risk is higher if you have pancreatic cancer and bile system problems.
    - **Pneumonitis** (infection of lung tissue) which in some cases can cause death. Your healthcare professional will monitor your lung health during treatment.
    - **Blood problems**, like bone marrow suppression (low white and/or red blood cell or platelet count). You should not be given ABRAXANE if you have very low white blood cell levels. Your healthcare professional will monitor your white blood cell levels.

  See the 'Serious side effects and what to do about them' table, below, for more information on these and other serious side effects.

- Patients 65 years and older: There are higher risk of side effects such as nose bleeds, diarrhea, dehydration, tiredness and swelling. For patients 75 years and older, there are higher risks of side effects like loss of appetite, dehydration, blood and nervous system problems. Your healthcare professional will decide if ABRAXANE is right for you.

What is ABRAXANE used for?

ABRAXANE is used to treat the following cancers that have spread to other parts of the body:

- breast cancer, and
- pancreatic cancer, when treated in combination with a medicine called gemcitabine.

How does ABRAXANE work?

ABRAXANE is a type of anti-cancer treatment called chemotherapy. ABRAXANE may stop the cancer cells from dividing and growing, so they eventually die. In addition, normal cells may also be affected by ABRAXANE causing some of the side effects. (See "What are possible side effects from using ABRAXANE?" below.)

What are the ingredients in ABRAXANE?

Medicinal ingredient: Paclitaxel

Non-medicinal ingredient: Human albumin

ABRAXANE comes in the following dosage forms:

Lyophilized powder for suspension: 100 mg

Do not use ABRAXANE if:

- you have very low white blood cell counts
- you are allergic to paclitaxel or any of the other ingredients in this medicine or the container

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ABRAXANE. Talk about any health conditions or problems you may have, including if you:

- are experiencing numbness or tingling in your extremities;
- have a history of interstitial lung disease, multiple allergies, chronic cough or shortness of breath;
- have or have had heart problems, fainting spells (syncope), or an irregular heartbeat;
- have liver or kidney problems.

Other warnings you should know about:

Heart problems: ABRAXANE can cause heart rhythm problems. Your healthcare professional will monitor your heart rhythm using an electrocardiogram (ECG).

Hypersensitivity (allergic) reactions: ABRAXANE can cause sever allergic reactions, including anaphylactic reactions, which can cause death.

Nervous system problems: ABRAXANE can cause numbness, tingling or burning feeling in your face, hands or feet. Tell your healthcare professional if you have these symptoms.

Eye problems: ABRAXANE may cause eye problems. Tell your healthcare professional if you have blurry vision or have trouble seeing. They will check your eye health.

See the 'Serious side effects and what to do about them' table, below, for more information on these and other serious side effects.

Pregnancy, breast-feeding and fertility:

Female patients:

- ABRAXANE can harm your unborn baby.
- Avoid getting pregnant while you are taking ABRAXANE. Women of childbearing age must use highly effective birth control during treatment with ABRAXANE and for at least 6 months after the last dose of ABRAXANE.
- If you are pregnant, able to get pregnant or are planning to have a baby, ask your healthcare professional for advice before taking ABRAXANE.
- Tell your healthcare professional right away if you become pregnant or think you may be pregnant during your treatment with ABRAXANE.
- Do not breast-feed while you are taking ABRAXANE.

- ABRAXANE may affect your ability to have a child.

Male patients:

- Avoid fathering a child during treatment with ABRAXANE and for up to 6 months after stopping treatment.
- Use effective birth control during treatment with ABRAXANE.
- ABRAXANE may affect your ability to father a child. Talk to your healthcare professional about options you may have to father a child.

Driving and using machines: ABRAXANE can cause tiredness, weakness and discomfort. Before you drive or do tasks that require special attention, wait until you know how you respond to ABRAXANE

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ABRAXANE:

- medicines for fungal infections such as ketoconazole
- medicines used to treat bacterial infections (antibiotics) such as erythromycin, rifampicin
- medicines used to treat depression such as fluoxetine, St. John's Wort
- medicines used to lower cholesterol such as gemfibrozil
- medicines used to prevent blood clots such as clopidogrel
- medicines used to treat heartburn such as cimetidine
- medicines for HIV infection such as ritonavir, saquinavir, indinavir, nelfinavir, efavirenz, nevirapine
- medicines used to prevent seizures such as carbamazepine, phenytoin
- grapefruit, Seville oranges, starfruit

How to take ABRAXANE:

- ABRAXANE will be given to you by a healthcare professional.
- The powder is first mixed into a solution. This solution is then given to you through a vein (intravenously).

Usual dose:

- The dose you will receive will depend on your disease and will be measured based on your body size.
    - For breast cancer: ABRAXANE is injected into a vein over 30 minutes every 3 weeks.
    - For pancreatic cancer: ABRAXANE is injected into a vein over 30-40 minutes on days 1, 8, and 15 of each 28-day treatment cycle. You will also receive treatment with another medicine, gemcitabine. Gemcitabine is given through your veins. Your healthcare professional will determine your dose and schedule.
- Your healthcare professional may lower your dose, stop your treatment for a period of time or recommend that you stop treatment completely. This may happen if you experience serious side effects.

Overdose:

There is no known antidote for ABRAXANE overdosage.

If you think you, or a person you are caring for, have taken too much ABRAXANE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- ABRAXANE needs to be given on a fixed schedule. Talk to your healthcare professional if you have missed a treatment.

What are possible side effects from using ABRAXANE?

These are not all the possible side effects you may have when taking ABRAXANE. If you experience any side effects not listed here, tell your healthcare professional.

- Hair loss
- Tiredness, weakness
- Mouth or lip sores
- Dry throat or nose
- Mouth fungus
- Joint, muscle or bone pain
- Constipation
- Dehydration
- Difficulty swallowing
- Nose bleeds
- Nail changes
- Rash, itchy skin
- Confusion
- Mood changes, depression, trouble sleeping
- Light headedness

ABRAXANE can cause abnormal blood test results. Your healthcare professional will do blood tests during your treatment. These will tell your healthcare professional how ABRAXANE is affecting your blood, heart, liver, pancreas and kidneys.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Blood disorders (low white and/or red blood cell or platelet count): feeling tired or weak, pale skin, bruising or bleeding for longer than usual if you hurt yourself, fever, chills		X	
Gastrointestinal problems: diarrhea, stomach pain, nausea, vomiting, bloating, bloody stool	X		
COMMON			

Heart problems: fast heartbeat, palpitations, irregular heartbeat, chest pain, difficulty breathing, fainting, low blood pressure, swelling and pain in one part of the body, pain or tenderness or swelling in your arm or leg, skin that is red or warm, tingling or numbness, pale skin, muscle pain or spasms		X	
Injection Site Reactions: blistering, itching, pain, redness, severe skin damage, tenderness, warmth in the area around the injection		X	
Kidney problems: nausea, vomiting, fever, swelling of extremities, fatigue, thirst, dry skin, irritability, dark urine, increased or decreased urine output, blood in the urine, rash, weight gain (from retaining fluid), loss of appetite, abnormal blood test results, mental status changes		X	
Pneumonitis (inflammation of the lung tissue): shortness of breath, cough, fatigue, loss of appetite, unintentional weight loss		X	
Sepsis (infection of the blood): fever or dizziness, chills, high or very low body temperature, little or no urine, low blood pressure, palpitations, rapid breathing, rapid heartbeat		X	
Nervous system problems: numbness, tingling or burning on your face, hands, feet		X	
UNCOMMON			
Stroke (bleeding or blood clot in the brain)**:** sudden numbness, weakness or tingling of the face, arm, or leg, particularly on one side of the body, sudden headache, blurry vision, difficulty swallowing or speaking, or lethargy, dizziness, fainting, vomiting, trouble understanding,		X	

trouble with walking and loss of balance			
RARE			
Hypersensitivity (allergic reaction): fainting, dizziness, shortness of breath, chest pain			X
VERY RARE			
Tumor lysis syndrome (the sudden, rapid death of cancer cells due to the treatment): lack of urination, severe muscle weakness, heart rhythm disturbances, and seizures			X
UNKNOWN			
Eye disorders: blurred vision, loss of vision in eye, increased sensitivity of the eyes to light, eye pain or redness, swelling and itching of the eyelids, decreased sharpness of vision, eye irritation, blocked eye veins		X	
Severe skin reactions: fever, severe rash, swollen lymph glands, flu-like feeling, blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feeling thirsty, urinating less often, less urine		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Your healthcare professional will store ABRAXANE for you.
- Keep out of reach and sight of children.

If you want more information about ABRAXANE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website https://www.bms.com/ca/en, or by contacting 1-866-463-6267.

This leaflet was prepared by Bristol-Myers Squibb Canada, Montreal, Canada H4S 0A4.

Last Revised: MAR 08, 2024