Product Information
ABRAXANE (nanoparticle albumin-bound paclitaxel)

1 NAME OF THE MEDICINE
nanoparticle albumin-bound paclitaxel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
ABRAXANE (nanoparticle albumin-bound paclitaxel) powder for injection (suspension) is an albumin nanoparticle form of paclitaxel with a mean particle size of approximately 130 nanometres. Paclitaxel exists in the nanoparticles in a non-crystalline, amorphous state. Each vial of ABRAXANE contains paclitaxel and human albumin in the ratio of 1:9. The paclitaxel is contained within nanoparticles that consist of a majority of paclitaxel bound to human albumin.

Each single-use vial contains the following: Paclitaxel 100 mg
ABRAXANE is free of solvents.

The reconstituted medicinal product contains approximately 85 mg sodium per vial when reconstituted with 0.9% sodium chloride.

The active agent in ABRAXANE is paclitaxel, a natural product with antitumour activity. Paclitaxel is obtained from *Taxus media*.

Excipient(s) with known effect
Not applicable. For the full list of excipients, see ***Section 6.1 List of Excipients***.

3 PHARMACEUTICAL FORM
ABRAXANE is supplied as a white to yellow, sterile, lyophilised powder in a 50 mL glass vial.

Paclitaxel is a white to off-white crystalline powder with a molecular weight of 853.91. It is highly lipophilic, insoluble in water.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Metastatic Breast Cancer
ABRAXANE is indicated for the treatment of metastatic carcinoma of the breast after failure of anthracycline therapy.

Non-small Cell Lung Cancer
ABRAXANE, in combination with carboplatin, is indicated for the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation.

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

4.2 DOSE AND METHOD OF ADMINISTRATION
The reconstituted suspension is milky and homogenous without visible particles.

ABRAXANE should be administered under the supervision of a physician experienced in the use of chemotherapeutic agents.

ABRAXANE is for single use in one patient only. Discard any residue.

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

Patients with Hepatic Impairment
For patients with mild hepatic impairment (total bilirubin > 1 to ≤ 1.5 x ULN and aspartate aminotransferase [AST] ≤ 10 x ULN, no dosage 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 AST ≤ 10 x ULN), a 20% reduction in dose is recommended for indications of metastatic breast cancer and non-small cell lung cancer.

- 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 adenocarcinoma of the pancreas 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.

Patients with Impaired Renal Function
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). See ***Section 5.2 Pharmacokinetic properties***.

<u>Metastatic Breast Cancer</u>

The recommended dose for ABRAXANE is 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks.

Dose Adjustments During Treatment for Metastatic Breast Cancer
Patients who experience severe neutropenia (neutrophil <0.5 x 10^9/L for a week or longer) or severe peripheral 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 peripheral neuropathy, additional dose reduction should be made to 180 mg/m^2. ABRAXANE should not be administered until neutrophil counts recover to >1.5 x 10^9/L. For grade 3 peripheral neuropathy hold treatment until resolution to grade 1 or 2, followed by a dose reduction for all subsequent courses of ABRAXANE.

Missed Dose in Metastatic Breast Cancer
ABRAXANE is administered every three weeks. In the event that the next scheduled dose is missed, dosing should occur as soon as possible, consistent with good medical practice, after the missed dose.

<u>Non-Small Cell Lung Cancer</u>

The recommended dose of ABRAXANE is 100 mg/m^2 administered as an intravenous infusion over 30 minutes on Days 1, 8, and 15 of each 21-day cycle. The recommended dose of carboplatin is AUC

= 6 mg•min/mL on Day 1 only of each 21-day cycle, beginning immediately after the end of ABRAXANE administration. Day 1 is the only day of each 21-day cycle when carboplatin is used in combination with ABRAXANE.

Dose Adjustments During Treatment for Non-Small Cell Lung Cancer

Haematologic toxicities in non-small cell lung cancer

ABRAXANE should not be administered on Day 1 of a cycle until absolute neutrophil count (ANC) is ≥1.5 x 10^9/L and platelet count is ≥100 x 10^9/L. For each subsequent weekly dose of ABRAXANE, patients must have an ANC ≥0.5 x 10^9/L and platelets >50 x 10^9/L or the dose is to be withheld until counts recover. When counts recover, resume dosing the following week according to the criteria in Table 1. Reduce subsequent dose only if criteria in Table 1 are met. Weekly pre-dose full blood counts should be performed (see ***Section 4.4 Special warnings and precautions for use***, Haematology).

Table 1: Dose Reductions for Haematologic Toxicities in Non-Small Cell Lung Cancer

Haematologic Toxicity	**Occurrence**	**Dose of ABRAXANE (mg/m^2)**	**Dose of carboplatin (AUC mg•min/mL)**
Nadir ANC <0.5 x 10^9/L with neutropenic fever > 38°C OR Delay of next cycle due to persistent neutropenia[1] (Nadir ANC <1.5 x 10^9/L) OR Nadir ANC <0.5 x 10^9/L for > 1 week	First	75	4.5
	Second	50	3.0
	Third	Discontinue Treatment	
Nadir platelets <50 x 10^9/L	First	75	4.5
	Second	Discontinue Treatment	

[1] Maximum of 7 days post scheduled Day 1 dose of next cycle.

Nonhaematologic toxicities in non-small cell lung cancer

Guidelines for implementing dose reductions for nonhaematologic toxicities are provided in Table 2. For Grade 2 or 3 cutaneous toxicity, Grade 3 mucositis, or Grade 3 diarrhoea, interrupt treatment until the toxicity improves to ≤ Grade 1, then restart treatment according to the guidelines in Table 2. For ≥ Grade 3 peripheral neuropathy, withhold treatment until resolution ≤ Grade 1. Treatment may be resumed at the next lower dose level in subsequent cycles according to the guidelines in Table 2. For any other Grade 3 or 4 nonhaematologic toxicity excluding alopecia, interrupt treatment until the toxicity improves to ≤ Grade 2, then restart treatment according to the guidelines in Table 2.

Table 2: Dose Reductions for Nonhaematologic Toxicities in Non-Small Cell Lung Cancer

Nonhaematologic Toxicity	**Occurrence**	**Dose of ABRAXANE (mg/m^2)**	**Dose of carboplatin (AUC mg•min/mL)**
Grade 2 or 3 cutaneous toxicity Grade 3 diarrhoea Grade 3 mucositis ≥ Grade 3 Peripheral neuropathy Any other Grade 3 or 4 nonhaematologic toxicity excluding alopecia	First	75	4.5
	Second	50	3.0
	Third	Discontinue Treatment	
Grade 4 cutaneous toxicity, diarrhoea, or mucositis	First	Discontinue Treatment	

Metastatic Adenocarcinoma of the Pancreas

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

Dose adjustment

Dose level reductions for patients with metastatic adenocarcinoma of the pancreas are provided in Table 3. Table 3 should be used in combination with the recommended dose modifications for neutropenia and/or thrombocytopenia that are given in Table 4 and the dose modifications for other toxicities (including neuropathy) that are given in Table 5.

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

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

Dose recommendation and modifications for neutropenia and thrombocytopenia at the start of a cycle or within a cycle for patients with metastatic adenocarcinoma of the pancreas are provided in Table 4.

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

Cycle Day	ANC count (10^9/L)		Platelet count (10^9/L)	ABRAXANE Dose	Gemcitabine Dose
Day 1	≥1.5	AND	≥100	Treat on time at current dose levels	
	<1.5	OR	<100	Delay doses until recovery	
Day 8	≥1.0	AND	≥75	Treat on time at current dose levels	
	≥0.5 but <1.0	OR	≥50 but <75	Reduce doses 1 dose level	
	<0.5	OR	<50	Withhold doses	
Day 15: IF Day 8 doses were given without modification					
Day 15	≥1.0	AND	≥75	Treat on time at current dose levels	
	≥0.5 but <1.0	OR	≥50 but <75	Treat at current dose level and follow with WBC Growth Factors OR Reduce doses 1 dose level from Day 8 doses	
	<0.5	OR	<50	Withhold doses	
Day 15: IF Day 8 doses were reduced:					
Day 15	≥1.0	AND	≥75	Return to the Day 1 dose level and follow with WBC Growth Factor OR Treat with same doses as Day 8	
	≥0.5 but <1.0	OR	≥50 but <75	Treat with Day 8 dose level and follow with WBC Growth Factors OR Reduce doses 1 dose level from Day 8 doses	
	<0.5	OR	<50	Withhold doses	
Day 15: IF Day 8 doses were withheld:					
Day 15	≥1.0	AND	≥75	Return to Day 1 dose level and follow with WBC Growth Factor OR Reduce doses 1 dose level from Day 1 dose	
	≥0.5 but <1.0	OR	≥50 but <75	Reduce 1 dose level and follow with WBC Growth Factor OR Reduce doses 2 levels from Day 1 dose	
	<0.5	OR	<50	Withhold doses	

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

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

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

Adverse Drug Reaction	ABRAXANE Dose	Gemcitabine Dose
Febrile Neutropenia: Grade 3 or 4	Withhold doses until fever resolves and ANC $\geq 1.5 \times 10^9$/L; resume at next lower dose level[a]	
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 dose to next lower dose level[a]; discontinue treatment if ADR persists	
Gastrointestinal Toxicity: Grade 3 mucositis or diarrhoea	Withhold doses until improves to ≤ Grade 1; resume at next lower dose level[a]	

Abbreviations: ADR = Adverse Drug Reaction [a] See Table 3 for dose level reductions

Preparation and Administration Precautions

ABRAXANE is a cytotoxic anticancer medicine and, as with other potentially toxic paclitaxel compounds, caution should be exercised in handling ABRAXANE. The use of gloves is recommended. If ABRAXANE (lyophilised cake or reconstituted suspension) contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure to paclitaxel, events may include tingling, burning and redness. If ABRAXANE contacts mucous membranes, the membranes should be flushed thoroughly with water.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during medicine administration. Limiting the infusion of ABRAXANE to 30 minutes, as directed, reduces the likelihood of infusion-related 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)

Do not mix any other medicines with the ABRAXANE infusion.

Preparation for Intravenous Administration
ABRAXANE is supplied as a sterile lyophilised 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	20 mL	5 mg/mL

1. Aseptically, reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection.

2. Slowly inject the 20 mL of 0.9% Sodium Chloride Injection 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 directly onto the lyophilised cake as this will result in foaming.

4. Once the injection is complete, allow the vial to stand for a minimum of 5 minutes to ensure proper wetting of the lyophilised 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 sample 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.

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 bag [plasticised polyvinyl chloride (PVC) containers or non-PVC type intravenous bag]. The use of specialised DEHP-free solution containers or administration sets is not necessary, but may be used if desired to prepare or administer ABRAXANE infusions. The use of medical devices containing silicone oil as a lubricant (i.e. 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. **Do not use a filter with a pore size less than 15 µm**.

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

4.3 CONTRAINDICATIONS

ABRAXANE should not be used in patients who have baseline neutrophil counts of < 1.5 x 10^9/L.

Patients who have exhibited hypersensitivity reactions to ABRAXANE or human albumin should not be treated with ABRAXANE.

ABRAXANE is contraindicated during pregnancy and lactation.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Interchangeability

An albumin form of paclitaxel may substantially affect a medicine's functional properties relative to those of medicine in solution. ABRAXANE is not clinically interchangeable with other paclitaxel formulations. If a decision is made to discontinue ABRAXANE and to begin treatment with other paclitaxel formulations (or vice versa), there should be careful consideration of the differences between these products in indication, pharmacokinetics, dosing, administration, safety profile, and monitoring requirements.

Haematology

Bone marrow suppression is dose dependent and a dose limiting toxicity. ABRAXANE therapy should not be administered to patients with baseline neutrophil counts of less than 1.5 x 10^9/L. 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 >1.5 x 10^9/L and platelets recover to a level >100 x 10^9/L. In the case of severe neutropenia (<0.5 x 10^9/L for seven days or more) during a course of ABRAXANE therapy, a dose reduction for subsequent courses of therapy is recommended (see *Section 4.2* ***Dose and method of administration***).

Peripheral Neuropathy

Peripheral neuropathy is a dose-dependent, dose-limiting toxicity. Peripheral neuropathy occurs frequently with ABRAXANE. The occurrence of grade 1 or 2 peripheral neuropathy does not generally require dose modification. When ABRAXANE is used as monotherapy, if grade 3 peripheral neuropathy develops, treatment should be withheld until resolution to grade 1 or 2 followed by a dose reduction for all subsequent courses of ABRAXANE. For combination use of ABRAXANE and carboplatin, if grade 3 or higher peripheral neuropathy develops, treatment should be withheld until improvement to grade 0 or 1 followed by a dose reduction for all subsequent courses of ABRAXANE and carboplatin (see ***Section 4.2 Dose and method of administration***). For combination use of ABRAXANE and gemcitabine, if Grade 3 or higher peripheral neuropathy develops, withhold ABRAXANE; continue treatment with gemcitabine at the same dose. Resume ABRAXANE at reduced dose when peripheral neuropathy improves to Grade 0 or 1 (see ***Section 4.2 Dose and method of administration***).

Sepsis in Metastatic Adenocarcinoma of the Pancreas

Sepsis was reported at a rate of 5% in 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. Sepsis was more common in the older age group (median age of those with sepsis was 61 years). Two deaths occurred as a result of infection in the ≥75 year-old age group. 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 $\geq$1.5 x10^9/L, then resume treatment at reduced dose levels (see ***Section 4.2 Dose and method of administration***).

Pneumonitis
Pneumonitis has been reported at a rate of 4% when ABRAXANE was used in combination with gemcitabine and has been reported at a rate of 1% when ABRAXANE was used as monotherapy. Monitor patients closely for signs and symptoms of pneumonitis. After ruling out infectious aetiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with ABRAXANE and gemcitabine and promptly initiate appropriate treatment and supportive measures.

Hypersensitivity
Rare occurrences of severe hypersensitivity reactions, including very rare events of anaphylactic reactions with fatal outcome, have been reported. Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be re-challenged with the medicine.

Cross-hypersensitivity between ABRAXANE and other taxane products has been reported and may include severe reactions such as anaphylaxis. Patients with a previous history of hypersensitivity to other taxanes should be closely monitored during initiation of ABRAXANE therapy.

Cardiotoxicity
Uncommon events of congestive heart failure and left ventricular dysfunction have been observed among individuals receiving ABRAXANE. Most of the individuals were previously exposed to cardiotoxic medicines, such as anthracyclines, or had underlying cardiac history. Thus patients receiving ABRAXANE should be vigilantly monitored by physicians for the occurrence of cardiac events.

CNS metastases
The effectiveness and safety of ABRAXANE in patients with CNS metastases has not been established.

Gastrointestinal symptoms
If patients experience nausea, vomiting and diarrhoea following administration of ABRAXANE, they may be treated with commonly used anti-emetics and antidiarrhoeals.

Use in 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 a total bilirubin > 5 x ULN or AST > 10 x ULN. In addition, ABRAXANE is not recommended in patients with metastatic adenocarcinoma of the pancreas that have moderate to severe hepatic impairment (total bilirubin > 1.5 x ULN and AST $\leq$ 10 x ULN). See ***Section 4.2 Dose and method of administration***.

Use in the elderly
Metastatic Breast Cancer
Of the 229 patients in the randomised study who received ABRAXANE, 13% were at least 65 years of age and < 2% were 75 years or older. No toxicities occurred notably more frequently among elderly patients at least 65 years of age who received ABRAXANE.

A subsequent analysis was conducted in 981 patients receiving ABRAXANE monotherapy for metastatic breast cancer; 15% were $\geq$ 65 years old and 2% were $\geq$ 75 years old. A higher incidence of epistaxis, diarrhoea, dehydration, fatigue and peripheral oedema was found in patients $\geq$ 65 years.

Non-Small Cell Lung Cancer

Of the 514 patients in the randomised study who received ABRAXANE and carboplatin, 31% were 65 years or older and 3.5% were 75 years or older. Myelosuppression events, peripheral neuropathy events, and arthralgia were more frequent in patients 65 years or older compared to patients younger than 65 years old. No additional dose reductions, other than those recommended for all patients, are necessary for patients 65 years or older (see ***Section 4.2 Dose and method of administration***).

Metastatic Adenocarcinoma of the Pancreas

Patients 65 years and older

In the randomised study, of the 431 patients with metastatic adenocarcinoma of the pancreas who received ABRAXANE in combination with gemcitabine, 41% were 65 years and older. Diarrhoea, decreased appetite, dehydration and epistaxis were more frequent in patients 65 years or older compared with patients younger than 65 years old.

Patients 75 years and older

Of the 431 patients with metastatic adenocarcinoma of the pancreas who received ABRAXANE in combination with gemcitabine, 10% were 75 years and older. In patients 75 years and older, there was a higher incidence of serious adverse reactions and adverse reactions that led to treatment discontinuation. 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.

Paediatric use

The safety and effectiveness of ABRAXANE in paediatric patients have not been established.

Pharmacokinetics and antitumor activity assessed by the overall response rate (ORR) of nab-paclitaxel were evaluated in a Phase 1/2 study of 107 patients ($\geq$ 6 months to $\leq$ 24 years) with recurrent or refractory paediatric solid tumors. In the Phase 1 portion of the study, the maximum tolerated dose (MTD) was determined to be 240 mg/m^2 administered as an intravenous infusion over 30 minutes on Days 1, 8 and 15 of each 28-day cycle. The MTD was administered in paediatric patients with recurrent or refractory Ewing's sarcoma, neuroblastoma, and rhabdomyosarcoma in the Phase 2 portion of the study.

In general, the weekly drug exposures were higher in paediatric patients than in adult patients. One patient in the rhabdomyosarcoma group (N=14) had a confirmed partial response (PR) resulting in an ORR of 7.1% (95% CI: 0.2, 33.9). No confirmed complete response (CR) or PR was observed in either the Ewing's sarcoma group (N=13) or the neuroblastoma group (N=14). The overall safety profile of nab-paclitaxel in paediatric patients was consistent with the known safety profile in adults.

Effects on laboratory tests

Interactions with laboratory tests have not been established.

Other

Although limited data is available, no clear benefit in terms of prolonged overall survival has been demonstrated in patients with metastatic adenocarcinoma of the pancreas who have normal CA 19-9 levels prior to start of treatment with ABRAXANE and gemcitabine.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

A pharmacokinetic study was conducted with ABRAXANE and carboplatin in non-small cell lung cancer patients. There were no clinically relevant pharmacokinetic interactions for ABRAXANE on the pharmacokinetics of carboplatin and for carboplatin on the pharmacokinetics of paclitaxel when administered as ABRAXANE.

Medicine interaction studies between ABRAXANE and other medicines have not been conducted.

Medicines Metabolised in the Liver

The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Clinical interaction studies between ABRAXANE and inhibitors and inducers of either CYP2C8 or CYP3A4 have not been formally investigated. Therefore, caution should be exercised when administering ABRAXANE concomitantly with medicines known to inhibit (e.g. erythromycin, ketoconazole, fluoxetine, imidazole antifungals, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or induce (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) either CYP2C8 or CYP3A4 (see ***Section 5.2 Pharmacokinetics properties***).

In vitro studies using rat and human liver slices and liver microsomes have shown that the metabolism of paclitaxel is inhibited by a large number of medicines, including CYP2C8 and CYP3A4 substrates, and quinidine, PEG-35 castor oil, quercetin, clozapine, morin, and resveratrol.

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. Pharmacokinetic interactions between ABRAXANE and gemcitabine have not been evaluated in humans.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Administration of paclitaxel prior to and during mating produced impairment of fertility in male and female rats at doses equal to or greater than 1 mg/kg/day (about 0.04 the daily maximum recommended human dose on a mg/m^2 basis).

Administration of ABRAXANE to male rats on a weekly basis for 11 weeks prior to mating with untreated female rats was associated with testicular atrophy/degeneration and reduced fertility accompanied by decreased pregnancy rates and increased loss of embryos in mated females. Testicular atrophy/degeneration has also been observed in single dose toxicology studies in rodents administered ABRAXANE at 6 mg/kg (54 mg/m^2) and dogs administered 8.75 mg/kg (175 mg/m^2).

Infertility

Females and Males

Based on findings in animals, ABRAXANE may impair fertility in females and males of reproductive potential.

Use in pregnancy - Category D

ABRAXANE is a cytotoxic agent. Cytotoxic agents can produce spontaneous abortion, foetal loss and birth defects, including serious birth defects when administered to a pregnant woman. Administration of ABRAXANE to female rats on gestation days 7 to 17 daily 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 foetotoxicity, as indicated by intrauterine mortality, increased resorptions, reduced numbers of live foetuses, reduction in foetal body weight and increase in foetal abnormalities. Foetal abnormalities included skeletal and soft tissue malformations, such as eye bulge, folded retina, and dilation of brain ventricles.

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 medicine is used during pregnancy, or if the patient becomes pregnant while receiving this medicine, the patient should be apprised of the potential hazard to the foetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with ABRAXANE.

Advise females of reproductive potential to use effective contraception during treatment with ABRAXANE and for at least 6 months after the last dose.

Like other genotoxic cytostatics, ABRAXANE can have genotoxic effects. Male patients treated with ABRAXANE are advised to use effective contraception and to avoid fathering a child during and up to six months after treatment.

Use in lactation
Paclitaxel and/or its metabolites were excreted into the milk of lactating rats. Following intravenous administration of radiolabeled paclitaxel to rats on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations. Because many medicines are excreted in human milk and because of the potential for serious adverse reactions in breastfeeding infants, breastfeeding must be discontinued when receiving ABRAXANE therapy.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

ABRAXANE has minor or moderate influence on the ability to drive and use machines. ABRAXANE may cause adverse reactions such as tiredness (very common) and dizziness (common) that may affect the ability to drive and use machinery. Patients should be advised not to drive and use machines if they feel tired or dizzy.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems and drugsafety-STA@stbiopharma.com.

Metastatic Breast Cancer

Table 6: Frequency[a] of Important Treatment Emergent Adverse Effects in Metastatic Breast Cancer in the Randomised Study on an Every-3-Weeks Schedule

	Percent of Patients	
	ABRAXANE 260/30min[b] (n=229)	**Solvent-based paclitaxel 175/3h[c,d] (n=225)**
Bone Marrow		
Neutropenia		
$< 2.0 \times 10^9$/L	80	82
$< 0.5 \times 10^9$/L	9	22
Thrombocytopenia		
$< 100 \times 10^9$/L	2	3
$< 50 \times 10^9$/L	<1	<1
Anaemia		
< 110 g/L	33	25
< 80 g/L	1	<1
Infections	24	20
Neutropenic sepsis	<1	<1
Febrile Neutropenia	2	1
Bleeding	2	2
Hypersensitivity Reaction[e]		
All	4	12
Severe[f]	0	2
Cardiovascular		
Vital Sign Changes[g]		
Bradycardia	<1	<1
Hypotension	5	5
Severe Cardiovascular Events[f]	3	4
Abnormal ECG		
All patients	60	52
Patients with Normal Baseline	35	30
Respiratory		
Cough	7	6
Dyspnea	12	9
Peripheral Neuropathy		
Any Symptoms	71	56
Severe Symptoms[f]	10	2
Myalgia / Arthralgia		
Any Symptoms	44	49
Severe Symptoms[f]	8	4
Asthenia		
Any Symptoms	47	39
Severe Symptoms[f]	8	3

	Percent of Patients	
	ABRAXANE 260/30min[b] (n=229)	**Solvent-based paclitaxel 175/3h[c,d] (n=225)**
Fluid Retention / Oedema		
Any Symptoms	10	8
Severe Symptoms[f]	0	<1
Gastrointestinal		
Nausea		
Any Symptoms	30	22
Severe Symptoms[f]	3	<1
Vomiting		
Any Symptoms	18	10
Severe Symptoms[f]	4	1
Diarrhoea		
Any Symptoms	27	15
Severe Symptoms[f]	<1	1
Mucositis		
Any Symptoms	7	6
Severe Symptoms[f]	<1	0
Alopecia	90	94
Hepatic (Patients with Normal Baseline)		
Bilirubin Elevations	7	7
Alkaline Phosphatase Elevations	36	31
AST (SGOT) Elevations	39	32
Injection Site Reaction	<1	1

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

Adverse Events in Any Trial with Single Agent ABRAXANE

Table 7 lists adverse effects associated with the administration of ABRAXANE to patients from studies in which ABRAXANE has been administered as a single agent at any dose in any indication (N = 789). The frequency of adverse effects listed in Table 7 is defined using the following convention: Very common (≥1/10); common (≥ 1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (< 1/10,000).

Table 7: Adverse Effects Reported With ABRAXANE at Any Dose in Single Agent Clinical Trials

Infections and infestations	*Common*: Infection, urinary tract infection, folliculitis, upper respiratory tract infection, candidiasis, sinusitis *Uncommon*: Oral candidiasis, nasopharyngitis, cellulitis, herpes simplex, viral infection, pneumonia, catheter-related infection, fungal infection, herpes zoster, injection site infection, respiratory tract infections, neutropenic sepsis
Neoplasms benign, malignant and unspecified	*Uncommon:* Metastatic pain, tumour necrosis
Blood and lymphatic system disorders	*Very Common*: Neutropenia, anaemia, leukopenia, thrombocytopenia, lymphopenia, bone marrow suppression *Common*: Febrile neutropenia
Immune system disorders	*Uncommon:* Hypersensitivity *Rare:* Severe hypersensitivity
Metabolism and nutrition disorders	*Very common:* Anorexia *Common:* Dehydration, decreased appetite, hypokalaemia *Uncommon:* Hypophosphataemia, fluid retention, hypoalbuminaemia, polydipsia, hyperglycaemia, hypocalcaemia, hypoglycaemia, hyponatraemia
Psychiatric disorders	*Common*: Insomnia, depression, anxiety *Uncommon*: Restlessness
Nervous system disorders	*Very Common*: Peripheral neuropathy, neuropathy, hypoaesthesia, paraesthesia. *Common*: Sensory neuropathy, peripheral sensory neuropathy, headache, dysgeusia, dizziness, peripheral motor neuropathy, ataxia, sensory disturbance, somnolence. *Uncommon*: Polyneuropathy, areflexia, dyskinesia, hyporeflexia, neuralgia, sensory loss, syncope, postural dizziness , neuropathic pain, tremor
Eye disorders	*Common:* Increased lacrimation, blurred vision, dry eye, keratoconjunctivitis sicca, madarosis *Uncommon*: Eye irritation, eye pain, abnormal vision, reduced visual acuity, conjunctivitis, visual disturbance, eye pruritus, keratitis
Ear and labyrinth disorders	*Common*: Vertigo *Uncommon*: Ear pain, tinnitus
Cardiac disorders	*Common*: Arrhythmia, chest pain, dyspnea, oedema, flushing, hypotension, hypertension, pulmonary emboli, pulmonary thromboembolism, supraventricular tachycardia, Tachycardia *Uncommon*: Congestive heart failure, left ventricular dysfunction *Rare:* Bradycardia, cardiac arrest, atrioventricular block
Vascular disorders	*Common*: Flushing, hot flushes, hypertension, lymphoedema *Uncommon*: Hypotension, peripheral coldness, orthostatic hypotension *Rare:* Thrombosis

Respiratory, thoracic and mediastinal disorders	*Common*: Dyspnoea, epistaxis, pharyngolaryngeal pain, cough, rhinitis, rhinorrhoea *Uncommon*: Productive cough, exertional dyspnoea, sinus congestion, decreased breath sounds, pleural effusion, allergic rhinitis, hoarseness, nasal congestion, nasal dryness, wheezing, pulmonary emboli, pulmonary thromboembolism, radiation pneumonitis *Rare:* Interstitial pneumonitis
Gastrointestinal disorders	*Very Common*: Nausea, diarrhoea, vomiting, constipation, stomatitis, mucositis *Common*: Abdominal pain, abdominal distension, upper abdominal pain, dyspepsia, gastrooesophageal reflux disease, oral hypoaesthesia *Uncommon*: Dysphagia, flatulence, glossodynia, dry mouth, gingival pain, loose stools, oesophagitis, lower abdominal pain, mouth ulceration, oral pain, rectal haemorrhage
Hepatobiliary disorders	*Uncommon*: Hyperbilirubinaemia, hepatomegaly
Skin and subcutaneous tissue disorders	*Very Common*: Alopecia, rash *Common*: Nail disorder, pruritus, dry skin, erythema, nail pigmentation/discolouration, skin hyperpigmentation, onycholysis, nail changes *Uncommon*: Nail bed tenderness, urticaria, skin pain, photosensitivity reaction, pigmentation disorder, pruritic rash, skin disorder, hyperhidrosis, onychomadesis, erythematous rash, generalised rash, dermatitis, night sweats, maculo-papular rash, vitiligo, hypotrichosis, nail discomfort, generalised pruritus, macular rash, papular rash, skin lesion, swollen face
Musculoskeletal and connective tissue disorders	*Very Common*: Arthralgia, myalgia *Common*: Pain in extremity, bone pain, back pain, muscle cramps, limb pain *Uncommon*: Chest wall pain, muscular weakness, neck pain, groin pain, muscle spasms, musculoskeletal pain, flank pain, limb discomfort, muscle weakness
Renal and urinary disorders	*Uncommon*: Dysuria, pollakiuria, haematuria, nocturia, polyuria, urinary incontinence
Reproductive system and breast disorders	*Uncommon*: Breast pain
General disorders and administration site conditions	*Very Common*: Fatigue, asthenia, pyrexia *Common*: Peripheral oedema, mucosal inflammation, pain, rigors, oedema, weakness, decreased performance status, chest pain, influenza-like illness, malaise, lethargy, hyperpyrexia *Uncommon*: Chest discomfort, abnormal gait, swelling, injection site reaction
Investigations	*Common*: Decreased weight, increased alanine aminotransferase, increased aspartate aminotransferase, decreased haematocrit, decreased red blood cell count, increased body temperature, increased gamma-glutamyltransferase, increased blood alkaline phosphatase *Uncommon*: Increased blood pressure, increased weight, increased blood lactate dehydrogenase, increased blood creatinine, increased blood glucose, increased blood phosphorus, decreased blood potassium, increased bilirubin
Injury, poisoning and procedural complications	*Uncommon: Contusion* *Rare: radiation recall phenomenon, radiation pneumonitis*

Non-Small Cell Lung Cancer

Table 8 provides the frequency and severity of adverse reactions by system organ class/preferred term that have been reported in ≥5% of 514 patients with advanced non-small cell lung cancer who received ABRAXANE and carboplatin and 524 patients with advanced non-small cell lung cancer who received solvent-based paclitaxel and carboplatin. Within each system organ class grouping, adverse reactions are presented in order of decreasing frequency.
The frequency estimates for adverse reactions are defined as: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000); and Not known (cannot be estimated from available data – spontaneous reports).

Table 8: Adverse Reactions Reported in ≥5% of Patients in Non-Small Cell Lung Cancer Clinical Trial (by MedDRA System Organ Class and Preferred Term)

System Organ Class	Frequency	Preferred Term	ABRAXANE (100 mg/m^2/week) and carboplatin (N=514)		Solvent-based paclitaxel (200 mg/m^2 every 3 weeks) and carboplatin (N=524)	
			All Grades Toxicity[2] (%)	Grade 3 or Higher Toxicity[3] (%)	All Grades Toxicity[2] (%)	Grade 3 or Higher Toxicity[3] (%)
Blood and lymphatic system disorders[1]	Very Common	Anaemia[1]	97	27	91	7
		Leukopenia[1]	89	24	83	23
		Neutropenia[1]	84	47	83	58
		Thrombocytopenia[1]	67	18	55	9
Skin and subcutaneous tissue disorders	Very Common	Alopecia	56	<1	60	0
		Rash	10	0	8	<1
Nervous system disorders	Very Common	Peripheral neuropathy[4]	48	3	64	12
	Common	Dysgeusia	7	0	6	0
		Headache	7	<1	4	<1
		Dizziness	6	0	4	<1
General disorders and administration site conditions	Very Common	Fatigue	25	4	23	4
		Asthenia	16	3	15	4
		Oedema peripheral	10	0	4	<1
	Common	Pyrexia	9	0	8	0
		Chest pain	5	<1	4	<1
Gastro-intestinal disorders	Very Common	Nausea	27	<1	25	<1
		Constipation	16	<1	13	<1
		Diarrhoea	15	<1	11	0
		Vomiting	12	<1	12	<1
	Common	Stomatitis	6	0	4	0
Respiratory thoracic and mediastinal disorders	Very Common	Dyspnoea	12	3	12	3
	Common	Cough	9	<1	7	0
		Epistaxis	7	0	2	0
		Haemoptysis	4	<1	5	0

Table 8: Adverse Reactions Reported in ≥5% of Patients in Non-Small Cell Lung Cancer Clinical Trial (by MedDRA System Organ Class and Preferred Term) (Continued)

System Organ Class	Frequency	Preferred Term	ABRAXANE (100 mg/m^2/week) and carboplatin (N=514)		Solvent-based paclitaxel (200 mg/m^2 every 3 weeks) and carboplatin (N=524)	
			All Grades Toxicity[2] (%)	Grade 3 or Higher Toxicity[3] (%)	All Grades Toxicity[2] (%)	Grade 3 or Higher Toxicity[3] (%)
Investigations	Common	Alanine aminotransferase increased	9	2	9	<1
		Weight decreased	8	1	6	<1
		Aspartate aminotransferase increased	8	<1	6	<1
Musculo-skeletal and connective tissue disorders	Very Common	Arthralgia	13	<1	25	2
		Myalgia	10	<1	19	2
Metabolic and nutrition disorders	Very Common	Decreased appetite	17	2	18	<1
Infections and infestations	Common	Pneumonia	5	2	3	2
Psychiatric disorders	Common	Insomnia	5	0	8	<1

MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardized MedDRA Query.

[1] The incidence rates in both arms for "All Grades Toxicity" and "Grade 3 or Higher Toxicity" are based on laboratory assessments. Source: CA031 Table 22.0.0. Maximal Degree of Myelosuppression (Treated Population); Neutropenia and Thrombocytopenia: N=508 for the ABRAXANE and carboplatin arm and N=513 for the solvent-based paclitaxel and carboplatin arm; Anaemia and Leukopenia: N=508 for the ABRAXANE and carboplatin arm and N=514 for the solvent-based paclitaxel and carboplatin arm.

[2] Incidences in ≥5% of patients in either arm are included. Source: CA031 Table 21.17.0. Incidence of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Treated Population); CA031 Table 21.17.0 includes Grades 1-5.

[3] Source: CA031 Table 21.18.1. Incidence of Treatment-Emergent Grade 3 or Higher Adverse Events by MedDRA System Organ Class and Preferred Term (Treated Population).

[4] Peripheral neuropathy is defined by the MedDRA v14.0 SMQ neuropathy (broad scope). Sources: CA031 Table 21.17.6 and CA031 Table 21.20.7.

Additional clinically relevant adverse reactions that were reported in ≥1% and <5% of the non-small cell lung cancer patients who received ABRAXANE and carboplatin included:

Blood and lymphatic system disorders: lymphopenia, febrile neutropenia
Skin and subcutaneous tissue disorders: nail disorder, pruritus
Gastrointestinal disorders: dyspepsia, abdominal pain, dysphagia
Investigations: blood alkaline phosphatase increased
Musculoskeletal and connective tissue disorders: back pain, pain in extremity, musculoskeletal pain
Metabolic and nutrition disorders: dehydration
Infections and infestations: bronchitis, upper respiratory tract infection, urinary tract infection
Vascular disorders: hypotension, hypertension
Eye disorders: vision blurred
Hepatobiliary disorders: hyperbilirubinaemia

Additional clinically relevant adverse reactions that were reported in <1% of the non-small cell lung cancer patients who received ABRAXANE and carboplatin included:

Blood and lymphatic system disorders: pancytopenia
Skin and subcutaneous tissue disorders: dermatitis allergic, urticaria, skin exfoliation
General disorders and administration site conditions: mucosal inflammation, infusion site extravasation, infusion site inflammation, infusion site rash
Respiratory thoracic and mediastinal disorders: pneumonitis[1,a]
Infections and infestations: oral candidiasis, sepsis
Vascular disorders: flushing
Immune system disorders: drug hypersensitivity, hypersensitivity

[1] Pneumonitis evaluated using the MedDRA v14.0 Standardised MedDRA Query (SMQ) interstitial lung disease. SMQ is a grouping of several MedDRA preferred terms to capture a medical concept.[a]

Summary of the Safety Profile in Combination with Carboplatin in Non-Small Cell Lung Cancer trials

In the non-small cell lung cancer study, significantly less ≥ grade 3 neuropathy, neutropenia, arthralgia, and myalgia occurred in the ABRAXANE arm, while less thrombocytopenia and anaemia occurred in the paclitaxel arm.

Peripheral Neuropathy in Combination with Carboplatin in Non-Small Cell Lung Cancer trials

In the non-small cell lung cancer study, peripheral neuropathy was graded by the investigator according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0. For ABRAXANE and carboplatin, the median time to first occurrence of grade 3 peripheral neuropathy was 121 days, and the median time to improvement from grade 3 peripheral neuropathy to grade 1 was 38 days. No patients treated with ABRAXANE and carboplatin had grade 4 peripheral neuropathy.

Patient-reported taxane toxicity was assessed using the 4 subscales of the Functional Assessment of Cancer Therapy (FACT)-Taxane questionnaire. Using repeated measure analysis, 3 of the 4 subscales (peripheral neuropathy, pain hands/feet, and hearing) favoured ABRAXANE and carboplatin ($p \leq 0.002$). For the other subscale (oedema), there was no difference in the treatment arms.

Metastatic Adenocarcinoma of the Pancreas

Adverse reactions resulting in death within 30 days of the last dose of study medicine were reported for 4% of patients in the ABRAXANE and gemcitabine group and for 4% of patients in the gemcitabine group.

Clinical Trial Experience in Metastatic Adenocarcinoma of the Pancreas

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 multicentre, multinational, randomised, controlled, open-label trial.

Table 9 provides the frequency and severity of haematologic laboratory-detected abnormalities for the ABRAXANE/gemcitabine group and the gemcitabine group.

Table 9: Haematologic Laboratory-Detected Abnormalities in Metastatic Adenocarcinoma of Pancreas Clinical Trial

	ABRAXANE (125 mg/m^2)/ Gemcitabine		**Gemcitabine**	
	Grade 1-4 (%)	**Grade 3-4 (%)**	**Grade 1-4 (%)**	**Grade 3-4 (%)**
Anaemia[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 10 provides the frequency and severity of adverse reactions by system organ class/preferred term that have been reported in ≥ 10% of patients with metastatic 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 10: Adverse Reactions Reported in ≥ 10% of Patients in Metastatic Adenocarcinoma of Pancreas 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
General disorders and administration site conditions	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
Gastro-intestinal disorders	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%)
Skin and subcutaneous tissue disorders	Alopecia	212 (50%)	6 (1%)	21 (5%)	0
	Rash	117 (28%)	7 (2%)	39 (10%)	2 (<1%)
Nervous system disorders	Peripheral neuropathy SMQ[i)]	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
Metabolism and nutrition disorders	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%)
Respiratory, thoracic and mediastinal disorders	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%)
Investigations	Weight decreased	57 (14%)	1 (<1%)	48 (12%)	2 (<1%)
	Alanine amino-transferase increased	46 (11%)	13 (3%)	36 (9%)	15 (4%)
Musculo-skeletal and connective tissue disorders	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
Psychiatric disorders	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%)

MedDRA = Medical Dictionary for Regulatory Activities.

[i)] Peripheral neuropathy evaluated using the MedDRA v 15.0 Standardized MedDRA Query (broad scope).

Adverse Effects Reported With ABRAXANE/gemcitabine in Clinical Trials

Additional clinically relevant adverse reactions that were reported in at least one patient but in < 10% of the patients with metastatic adenocarcinoma of the pancreas who received ABRAXANE/gemcitabine are listed in Table 11.

The frequency of adverse effects listed in Table 11 is defined using the following convention: Very common (≥1/10); common (≥ 1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (< 1/10,000).

Table 11: Clinically Relevant Adverse Effects Reported With ABRAXANE/gemcitabine in Clinical Trials

General disorders and administration site conditions	*Common*: Infusion site reaction
Gastrointestinal disorders	*Common*: Stomatitis, dry mouth, intestinal obstruction, colitis
Skin and subcutaneous tissue disorders	*Common*: Pruritus, dry skin, nail disorder, flushing
Blood and lymphatic system disorders	*Common:* Pancytopenia *Uncommon*: Thrombotic thrombocytopenic purpura
Nervous system disorders	*Common*: Peripheral neuropathy *Uncommon*: VIIth nerve paralysis
Respiratory thoracic and mediastinal disorders	*Common*: Nasal congestion, pneumonitis *Uncommon*: Dry throat, nasal dryness
Infections & infestations	*Common*: Oral candidiasis, pneumonia, sepsis
Investigations	*Common*: Aspartate aminotransferase increased, blood bilirubin increased, blood creatinine increased
Musculoskeletal and connective tissue disorders	*Common*: Bone pain, muscular weakness
Vascular disorders	*Common*: Hypotension, hypertension
Cardiac disorders	*Common*: Tachycardia, cardiac failure congestive
Eye disorders	*Common*: Lacrimation increased *Uncommon*: Cystoid macular oedema
Hepatobiliary disorders	*Common*: Cholangitis
Renal and urinary disorders	*Common*: Acute renal failure *Uncommon*: Haemolytic uraemic syndrome

Peripheral Neuropathy with ABRAXANE/gemcitabine in Clinical Trials
For ABRAXANE and gemcitabine, the median time to first occurrence of Grade 3 peripheral neuropathy was 140 days. Of the patients who experienced Grade 3 peripheral neuropathy, 63% improved by ≥ 1 grade and 43% had a resolution from Grade 3 to Grade 0 or 1 and the median time to improvement 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.

Sepsis with ABRAXANE/gemcitabine in Clinical Trials
Sepsis was reported at a rate of 5% in 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 $\geq 1.5 \times 10^9$/L, then resume treatment at reduced dose levels (see ***Section 4.2 Dose and method of administration***).

Pneumonitis with ABRAXANE/gemcitabine in Clinical Trials
Pneumonitis has been reported at a rate of 4% with the use of ABRAXANE in combination with gemcitabine. Of the 17 pneumonitis ADRs in the ABRAXANE/gemcitabine arm, 2 had a fatal outcome. Monitor patients closely for signs and symptoms of pneumonitis. After ruling out infectious aetiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with ABRAXANE and gemcitabine and promptly initiate appropriate treatment and supportive measures.

Use in Paediatric Patients
Frequency, type and severity of adverse reactions in paediatric and young adult patients (18 to 24 years) are expected to be the same as in adults.

Use in Patients ≥ 65 Years Old
Of the 421 patients in the randomised study who received ABRAXANE and gemcitabine, 41% were 65 years or older and 10% were 75 years or older. Diarrhoea, 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. 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.

Post-marketing experience

Table 12: Adverse Reactions Reported during Post-Marketing (by MedDRA System Organ Class and Preferred Term in Alphabetical Order)

System Organ Class	Preferred Term
Blood and Lymphatic System Disorders	Pancytopenia
Cardiac Disorders	Atrioventricular block
Eye Disorders	Cystoid macular oedema
Metabolic Disorders	Tumour lysis syndrome
Nervous System Disorders	Cranial nerve palsies, vocal cord paresis
Respiratory, Thoracic and Mediastinal Disorders	Pneumonitis, radiation pneumonitis
Skin/Subcutaneous Disorders	Erythema, maculo-papular rash, palmar-plantar erythrodysaesthesiae in patients previously exposed to capecitabine, photosensitivity reaction, Stevens-Johnson syndrome, toxic epidermal necrolysis
Injury, Poisoning and Procedural Complications	Radiation recall phenomenon
General Disorders and Administration Site Conditions	Extravasation
Immune System Disorders	Severe hypersensitivity, cross-sensitivity between ABRAXANE and other taxanes has been reported

Cystoid Macular Oedema

There have been rare reports (<1/1000 patients) of reduced visual acuity due to cystoid macular oedema (CME) during treatment with ABRAXANE as well as with other taxanes. CME can be expected to resolve after cessation of treatment.

4.9 OVERDOSE

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Paclitaxel, the active pharmaceutical ingredient in ABRAXANE, is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerisation. This stability results in the inhibition of the normal dynamic reorganisation 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.

Clinical trials

Metastatic Breast Carcinoma

In a multi-centre trial, patients with metastatic breast cancer were randomised to receive paclitaxel every 3 weeks, either in a solvent-based form at 175 mg/m^2 in a 3-hour intravenous infusion (n=227) or as ABRAXANE 260 mg/m^2 in a 30-minute intravenous infusion (n=233). Premedication was given with solvent-based paclitaxel to prevent hypersensitivity. The treatments were not blinded. Two patients randomised to solvent-based paclitaxel and four to ABRAXANE did not receive any treatment.

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 only, 40% in the metastatic setting only, and 19% in both metastatic and adjuvant settings. Fifty-nine percent received study medicine as second or greater than second-line therapy. Seventy-seven percent of the patients had been previously exposed to anthracyclines.

Table 13 shows the results of the intent-to-treat analysis.

Table 13: Results for overall response rate, median time to disease progression, and progression-free survival as assessed by the investigator in Randomised Metastatic Breast Cancer Trial (Intent-to-Treat Population)

Efficacy variable	**ABRAXANE (260 mg/m^2) (n=233)**	**Solvent-based paclitaxel (175 mg/m^2) (n=227)**	**p-value Ratio [95% CI]**
Response rate[a] (%)			
	32.6	18.5	≤0.001[b] 1.76 [1.27, 2.45]
**Time to disease progression (months)*			
	Median 5.3	Median 3.8	0.003[c] 0.73 [0.59, 0.90]
**Progression Free Survival (months)*			
	Median 5.2	Median 3.8	0.003[c] 0.73 [0.60, 0.90]
**Survival (months)*			
	Median 15.0	Median 12.7	0.35[c] 0.90 [0.73, 1.12]

*This data is based on Clinical Study Report: CA012-0 Addendum dated Final (23 March-2005)

[a] Response rate is the sum of the complete and partial response rates assessed according to RECIST criteria

[b] Cochran-Mantel-Haenszel test

[c] Log-rank test

Non-Small Cell Lung Cancer

Randomised comparative study

A multicentre, randomised, open-label study was conducted in 1052 chemonaive patients with Stage IIIb/IV non-small cell lung cancer to compare ABRAXANE in combination with carboplatin versus solvent-based paclitaxel in combination with carboplatin as first-line treatment in patients with advanced non-small cell lung cancer. Patients with evidence of active brain metastases, including leptomeningeal involvement, were excluded from the study. ABRAXANE was administered to patients (N=521) as an intravenous infusion over 30 minutes at a dose of 100 mg/m^2 on Days 1, 8, and 15 of each 21-day cycle without any steroid premedication and without granulocyte colony stimulating factor prophylaxis. Beginning immediately after the end of ABRAXANE administration, carboplatin at a dose of AUC = 6 mg•min/mL was administered intravenously on Day 1 only of each 21-day cycle. Solvent-based paclitaxel was administered to patients (N=531) at a dose of 200 mg/m^2 as an intravenous infusion over 3 hours with standard premedication, immediately followed by carboplatin administered intravenously at AUC = 6 mg•min/mL, each medicine was administered on Day 1 of each 21-day cycle. The differences in paclitaxel dose and schedule between the two arms may independently influence the study results and limit direct comparison of dose- and schedule-dependent clinical outcomes and adverse reactions. Treatment was administered until disease progression or development of an unacceptable toxicity.

Patient demographics of the intent-to-treat population are shown in Table 14. The demographics and disease characteristics were well balanced.

Table 14: Summary of Patient Characteristics in Randomised Non-Small Cell Lung Cancer Trial (Intent-to-Treat Population)

Patient Characteristics	ABRAXANE (100 mg/m^2/week) and carboplatin (N=521)	Solvent-based paclitaxel (200 mg/m^2 every 3 weeks) and carboplatin (N=531)
Age (years)		
Median (range)	60.0 (28, 81)	60.0 (24, 84)
< 65 years, n (%)	360 (69%)	348 (66%)
≥ 65 years, n (%)	161 (31%)	183 (34%)
Gender (%)		
Male/Female	75%/25%	75%/25%
Origin, n (%)		
White, Non-Hispanic & Non-Latino	416 (80%)	433 (82%)
Asian	79 (15%)	80 (15%)
Black, of African heritage	12 (2%)	8 (2%)
White, Hispanic or Latino	11 (2%)	5 (< 1%)
Other	2 (< 1%)	5 (< 1%)
North American Indian or Alaska native	1 (< 1%)	0 (0%)
Stage at Randomisation (%)		
IIIb/IV	21%/79%	21%/79%
Histology of Primary Diagnosis		
Carcinoma/Adenocarcinoma	254 (49%)	264 (50%)
Squamous Cell Carcinoma	229 (44%)	221 (42%)
Large Cell Carcinoma	9 (2%)	13 (2%)
Other	29 (6%)	33 (6%)
ECOG PS (%)		
0/1	26%/74%	21%/78%
Smoking Status, N	519	526
Ever/Never Smoked (%)	74%/26%	73%/27%

ECOG PS = Eastern Cooperative Oncology Group Performance Status

Patients received a median of 6 cycles of treatment in both study arms. For the treated population, the median cumulative paclitaxel dose and the median average paclitaxel dose intensity were higher with ABRAXANE administered weekly (1325.0 mg/m^2 and 81.9 mg/m^2/week, respectively) relative to solvent-based paclitaxel administered every 3 weeks (1125.0 mg/m^2 and 65.1 mg/m^2/week, respectively). The median cumulative carboplatin dose and the median average carboplatin dose intensity were lower for the ABRAXANE and carboplatin regimen (3140.5 mg and 166.1 mg/week, respectively) relative to the solvent-based paclitaxel and carboplatin regimen (3315.0 mg and 203.6 mg/week, respectively).

The primary efficacy endpoint was overall response rate defined as the percentage of patients who achieved an objective confirmed complete response or partial response based on an independent, central, blinded radiological review using RECIST guidelines (Version 1.0). Results for overall response rate, progression-free survival, and overall survival are shown in Table 15.

Table 15: Efficacy Results from Randomised Non-Small Cell Lung Cancer Trial (Intent-to-Treat Population)

Efficacy Parameter	ABRAXANE (100 mg/m^2/week) and carboplatin (N=521)	Solvent-based paclitaxel (200 mg/m^2 every 3 weeks) and carboplatin (N=531)
Overall Response Rate		
Confirmed complete or partial overall response, n (%)	170 (33%)	132 (25%)
95% CI	28.6, 36.7	21.2, 28.5
p_A/p_T (95.1% CI)	1.313 (1.082, 1.593)	
P-value[a]	0.005	
Overall Response Rate in the Elderly Subgroup		
Confirmed complete or partial overall response, n/N (%)		
< 65 years	116/360 (32%)	86/348 (25%)
p_A/p_T (95% CI)	1.304 (1.029, 1.652)	
P-value[a]	0.027	
≥ 65 years	54/161 (34%)	46/183 (25%)
p_A/p_T (95% CI)	1.334 (0.958, 1.859)	
P-value[a]	0.087	
Progression-free Survival		
Death or progression, n (%)	297 (57%)	312 (59%)
Median Progression-free Survival (months)	6.3	5.8
95% CI	5.6, 7.0	5.6, 6.7
$HR_{A/T}$ (95.1% CI)	0.902 (0.767, 1.060)	
P-value[b]	0.214	
Non-inferiority Progression-free Survival[c]		
Death or progression, n (%)	429 (82%)	442 (83%)
Median Progression-free Survival (months)	6.8	6.5
95% CI	5.7, 7.7	5.7, 6.9
$HR_{A/T}$ (95% CI)	0.949 (0.830, 1.086)	
Overall Survival[d]		
Number of deaths, n (%)	360 (69%)	384 (72%)
Median Overall Survival (months)	12.1	11.2
95% CI	10.8, 12.9	10.3, 12.6
$HR_{A/T}$ (95.1% CI)	0.922 (0.797, 1.066)	
P-value[b]	0.271	

CI = confidence interval; $HR_{A/T}$ = hazard ratio of ABRAXANE/carboplatin to solvent-based paclitaxel/carboplatin; p_A/p_T = response rate ratio of ABRAXANE/carboplatin to solvent-based paclitaxel/carboplatin.

[a] P-value is based on a chi-square test.

[b] P-value is based on a stratified log-rank test stratified by geographic region and histology of primary diagnosis.

[c] Missing observations or initiation of subsequent new therapy were not used to censor progression-free survival event for this analysis (based on the EMA methodological considerations for PFS). The non-inferiority margin was 15%, or an upper boundary of the 95% CI of the HR < 1.176. This non-inferiority margin was determined after the interim results of the study were known.

[d] Superiority and non-inferiority analyses of overall survival.

The effect of prognostic factors on the primary efficacy endpoint of overall response rate was pre-specified. Two prognostic factors showed a significant interaction (defined as $p \leq 0.10$) with treatment effect on overall response rate: (1) time interval from primary diagnosis to randomisation and (2) histology (see Table 16). There was no interaction between the variable and the treatment effect as measured by overall response rate for the following baseline factors: region, gender, race, age, smoking status, baseline ECOG status, stage at primary diagnosis, time from date of first documented metastasis/relapse to date of study entry, stage at current diagnosis, and number of lesions.

Table 16: Effect of Prognostic Factors on Primary Endpoint of Overall Response Rate in Randomised Non-Small Cell Lung Cancer Trial (Intent-to-Treat Subgroups)

Prognostic Factor Category/Statistic	ABRAXANE (100 mg/m^2/week) and carboplatin (N=521)	Solvent-based paclitaxel (200 mg/m^2 every 3 weeks) and carboplatin (N=531)	Interaction P-value
Time from Date of Primary Diagnosis to Date of Study Entry			0.092
< 1 month	109/347 (31%)	93/345 (27%)	
1-3 months	36/116 (31%)	26/118 (22%)	
≥ 3 months	25/58 (43%)	13/68 (19%)	
Histology at Primary Diagnosis			0.036
Carcinoma/Adenocarcinoma	66/254 (26%)	71/264 (27%)	
Squamous Cell Carcinoma	94/229 (41%)	54/221 (24%)	
Large Cell Carcinoma	3/9 (33%)	2/13 (15%)	
Other	7/29 (24%)	5/33 (15%)	

P-value is based on a logistic regression model with effects for treatment regimen, prognostic factor, and treatment regimen by prognostic factor interaction. A nonsignificant interaction p-value (ie, p-value ≥ 0.100) indicates the treatment regimen effect was consistent within a prognostic factor.

Metastatic Adenocarcinoma of the Pancreas

Randomised comparative study

A multicentre, multinational, randomised, 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. ABRAXANE was administered to patients (N=431) as an intravenous infusion over 30 minutes at a dose of 125 mg/m^2 followed by gemcitabine as an intravenous infusion over 30 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 and disease characteristics of the intent-to-treat population were well balanced between the two treatment groups.

In the intent-to-treat (all-randomised) population, the median age was 63 years, 58% were men, 93% were White, 44% were Karnofsky Performance Status (KPS) 90 and 32% were KPS 80, 46% had baseline CA 19-9 value ≥ 59 x ULN, 43% had primary tumour located in pancreas head, 84% had liver metastases and 39% had lung metastases.

Patients received a median treatment duration of 3.9 months in the ABRAXANE/gemcitabine group and 2.8 months in the gemcitabine group. Nearly one-third (32%) of patients in the ABRAXANE/gemcitabine group compared with 15% of patients in the gemcitabine group received 6 or more months of treatment.

For the treated population, the median relative protocol dose intensity for gemcitabine was 75% in the

ABRAXANE/gemcitabine group and 85% in the gemcitabine group. The median relative dose intensity of ABRAXANE was 81%. A higher median cumulative dose of gemcitabine was delivered in the ABRAXANE/gemcitabine group (11400 mg/m^2) when compared with the gemcitabine group (9000 mg/m^2).

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, radiological review, blinded to the treatment allocation, using RECIST guidelines (Version 1.0).

Results for overall survival, progression-free survival, and overall response rate are shown in Table 17.

Table 17: Efficacy Results from Randomised Study in Patients with Metastatic 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**
95% CI	7.89, 9.53	6.01, 7.23
$HR_{A+G/G}$ (95.1% CI) [a]	0.72 (0.617, 0.835)	
P-value[b]	<0.0001	
Survival Rate % (95% CI) at		
1 Year	35% (29.7, 39.5)	22% (18.1, 26.7)
2 Year	9% (6.2, 13.1)	4% (2.3, 7.2)
75th Percentile Overall Survival (months)	14.8	11.4
Progression-free Survival[c]		
Death or progression, n (%)	277 (64)	265 (62)
Median Progression-free Survival (months)	**5.5**	**3.7**
95% CI	4.47, 5.95	3.61, 4.04
$HR_{A+G/G}$ (95.1% CI) [a]	0.69 (0.581, 0.821)	
P-value[b]	<0.0001	
Overall Response Rate[c]		
Confirmed complete or partial overall response, n (%)	**99 (23)**	**31 (7)**
95% CI	19.1, 27.2	5.0, 10.1
p_{A+G}/p_G (95.1% CI)	3.19 (2.178, 4.662)	
P-value [d]	<0.0001	

CI = confidence interval, $HR_{A+G/G}$ = 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.

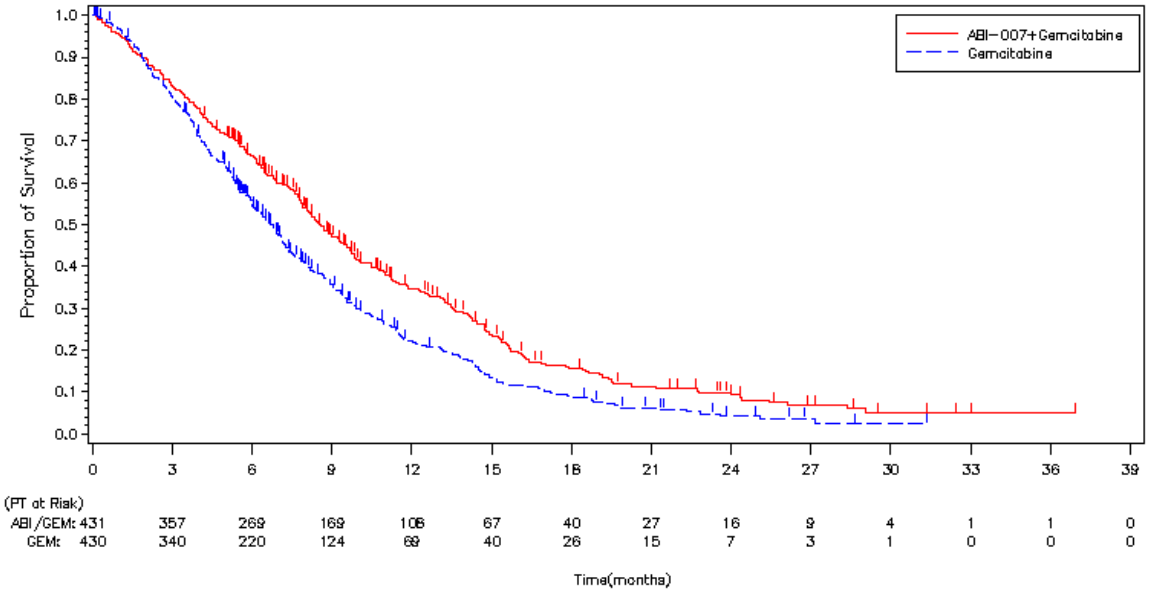
[d] P-value is based on chi-square test.

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, 59% improvement in 1-year survival, and 125% improvement in 2-year survival rates.

OS, PFS and ORR results were also consistent across the prespecified subgroups.

Of the 431 patients in the randomised study who received ABRAXANE and gemcitabine, 41% were 65 years or older and 10% were 75 years or older. 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)



There was a statistically significant improvement in PFS for patients treated with ABRAXANE/gemcitabine versus gemcitabine alone, with 1.8 months increase in median PFS, 31% overall reduction in risk of progression or death, 76% improvement in 6-month risk of progression or death, and 78% improvement in 12-month risk of progression or death.

The Kaplan-Meier curve for Progression-free Survival by Independent Radiological Review is presented in Figure 2.

Figure 2: Kaplan-Meier Curve of Progression-free Survival by Independent Radiological Review (Intent-to-treat Population)

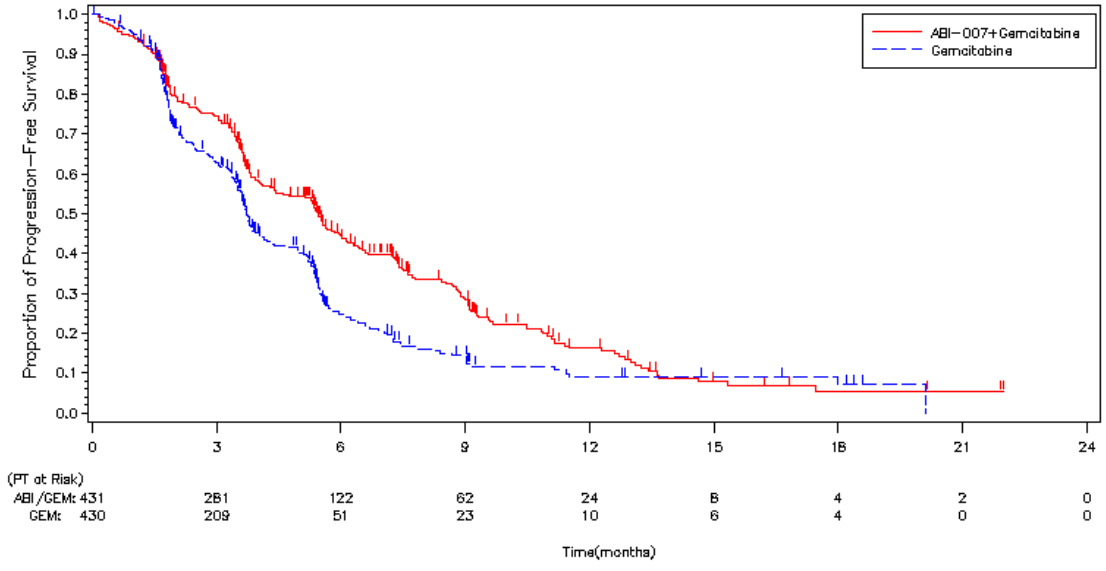


Table 18: Overall Survival of Subgroups Defined by Stratification Factors (Intent-to-treat Population)

Subgroup[1]	ABRAXANE/Gemcitabine (N = 431)		Gemcitabine (N = 430)		Hazard Ratio $HR_{A+G/G}$ and 95% CI
	n (%)	Median OS and 95% CI (Months)	n (%)	Median OS and 95% CI (Months)	
Presence of Liver Metastases					
Yes	365 (85)	8.3(7.72, 9.26)	360 (84)	5.9(5.32, 6.67)	0.69 (0.588, 0.814)
No	66(15)	11.0(8.15, 14.46)	70(16)	10.7(8.28, 13.54)	0.86 (0.556, 1.327)
Geographic Region					
Australia	61 14)	9.2(6.90, 11.01)	59(14)	6.7(5.29, 8.90)	0.67 (0.445, 1.009)
Eastern Europe	64 15)	7.7(6.01, 9.26)	62(14)	5.9(4.67, 7.46)	0.84 (0.579, 1.226)
Western Europe	38(9)	NE	38 9)	6.9(5.09, NE)	0.72 (0.352, 1.467)
North America	268 (62)	8.7(7.89, 9.86)	271 (63)	6.8(6.01, 7.52)	0.68 (0.563, 0.823)
Karnofsky Performance Status					
100	69 (16)		69 (16)		
90	179 (42)	9.7(8.71, 10.91)	199 (46)	7.9(6.97, 9.03)	0.75 (0.618, 0.921)
80	149 (35)		128 (30)		
70	30 (7)	7.6(6.44, 8.38)	33(8)	4.3(3.81, 5.72)	0.61 (0.481, 0.779)

CI = confidence interval; $HR_{A+G/G}$ = hazard ratio of ABRAXANE followed by gemcitabine / gemcitabine alone; NE = not estimable; OS = overall survival.

[1]Based on clinical data.

Note: Subgroup analyses only included patients with corresponding baseline data.

Note: The hazard ratio and two-sided 95% confidence interval, and p-value were estimated using a stratified Cox proportional hazard model.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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 medicine elimination. The medicine exposure (AUC) was dose proportional over 80 to 300 mg/m^2 and the pharmacokinetics of paclitaxel for ABRAXANE were independent of the duration of intravenous administration.

Distribution

Following ABRAXANE administration to patients with solid tumours, 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 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 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.

Metabolism and Excretion
At the clinical dose range of 80 to 300 mg/m^2, the mean total clearance of paclitaxel ranged from 13 to 30 L/h/m^2 and the mean terminal half-life ranged from 13 to 27 hours in patients with metastatic breast cancer, advanced non-small cell lung cancer or other solid tumours.

After a 30-minute infusion of 260 mg/m^2 doses of ABRAXANE, the mean values for cumulative urinary recovery of unchanged medicine (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. Faecal excretion was approximately 20% of the total dose administered. Hepatic metabolism has been demonstrated in animals. 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 ***Section 4.5 Interactions with other medicines and other forms of interations***). The effect of renal or hepatic dysfunction on the disposition of ABRAXANE has not been investigated.
Pharmacokinetics in Paediatrics

The pharmacokinetics of ABRAXANE following 30 minutes of intravenous administration at dose levels of 120 mg/m^2 to 270 mg/m^2 were determined in 64 patients with ages from ≥ 2 to 18 years in a Phase 1/2 study in recurrent or refractory paediatric solid tumors. Following dosing increase from 120 to 270 mg/m^2, the ABRAXANE mean AUC_∞ and C_{max} ranged from 8867 to 14361 ng*hr/mL and from 3488 to 8078 ng/mL, respectively. Dose normalised peak drug exposure values were comparable across the dose range studied; however, dose-normalised total drug exposure values were only comparable across 120 mg/m^2 to 240 mg/m^2 with lower dose-normalised AUC_∞ at the 270 mg/m^2 dose level. At the MTD of 240 mg/m^2, the mean CL was 19.1 L/h and the mean terminal half-life was 13.5 hours.

In children and adolescent patients, exposure to ABRAXANE increased with increasing dose and weekly drug exposures were higher than in adult patients. The overall safety profile was manageable without frequent dose reductions or discontinuations.

Pharmacokinetics in the Elderly
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 and systemic exposure (AUC and C_{max}) of paclitaxel.

Pharmacokinetics in Renal Impairment
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 C_{max}) of paclitaxel.

Pharmacokinetic data are insufficient for patients with severe renal impairment and not available for patients with end stage kidney disease.

Pharmacokinetics in Hepatic Impairment

The effect of hepatic impairment on population pharmacokinetics of ABRAXANE was studied in patients with advanced solid tumours. 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 C_{max}.

In addition, elimination of paclitaxel shows an inverse correlation with total bilirubin and a positive correlation with serum albumin.

Pharmacokinetic/pharmacodynamic modelling indicates that there is no correlation between hepatic function (as indicated by the 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 adenocarcinoma of the pancreas.

See ***Section 4.2 Dose and method of administration*** for dose recommendations.

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 tumours do not have a clinically important effect on the maximum elimination rate and systemic exposure (AUC and C_{max}) of paclitaxel.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

The carcinogenic potential of ABRAXANE has not been studied.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Human albumin solution (containing sodium, sodium octanoate and N-acetyl tryptophan).

6.2 INCOMPATIBILITIES

This medicine must not be mixed with other medicines except those mentioned in ***Section 4.2 Dose and method of administration.***

6.3 SHELF LIFE

Unopened vial

Unopened vials of ABRAXANE are stable until the date indicated on the package when stored between 20ºC to 25ºC, in the original package. Neither freezing nor refrigeration adversely affects the stability of the product.

Storage conditions after reconstitution

Stability of Reconstituted Suspension in the Vial

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

Stability of the Reconstituted Suspension in the Infusion Bag

The suspension for infusion prepared as recommended in an infusion bag should be used immediately. To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2 - 8°C for not more than 8 hours.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store the vials in original cartons below 25ºC. Protect from light.

For storage conditions after reconstitution of the medicine, please refer to ***Section 6.3 Shelf Life***.

6.5 NATURE AND CONTENTS OF CONTAINER

ABRAXANE is supplied as a white to yellow, sterile, lyophilised cake for reconstitution in a 50 mL clear Type I glass vial with either a latex free, bromobutyl or chlorobutyl rubber stopper, individually packaged in a carton. Each single use vial contains 100 mg of paclitaxel and 900 mg of human albumin. After reconstitution with 20 mL of 0.9% Sodium Chloride Injection each millilitre (mL) of reconstituted suspension contains 5 mg of paclitaxel.

ABRAXANE is free of solvents.

Pack Size: 1 single vial in a carton.

AUST R 133500

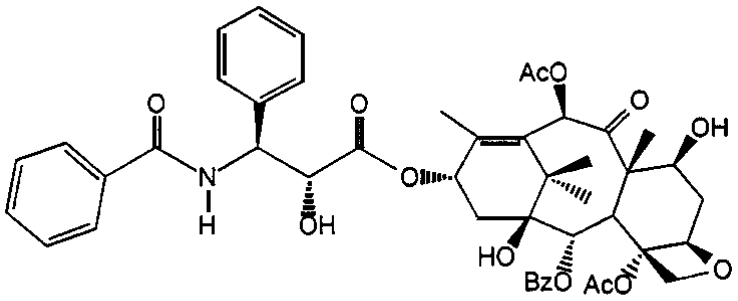
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Procedures for proper handling and disposal of anticancer medicines 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.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The empirical formula for Paclitaxel is $C_{47}H_{51}NO_{14}$. The chemical name for paclitaxel is 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. Paclitaxel has the following chemical structure:



CAS number
The CAS Number for paclitaxel is 33069-62-4.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 / PRESCRIPTION MEDICINE

8 SPONSOR

In Australia:
Abraxis BioScience Australia Pty Ltd
Level 2, 17 Cotham Road
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9 DATE OF FIRST APPROVAL

17 October 2008 (ARTG entry)
15 July 2010 (Date of publication in the New Zealand Gazette of Consent to Distribute Medicine)

10 DATE OF REVISION

To be confirmed (TGA)
07 May 2019 (Medsafe)

SUMMARY TABLE OF CHANGES

Section Changed	Date Changed	Summary of new information
4.4	04Apr19	Additional warning re cross hypersensitivity Additional information for Paediatric Use
4.5	04Apr19	Correction of error - deletion of clopidogrel
4.6	04Apr19	Additional information re effects on fertility
4.6	04Apr19	Additional information re cytotoxic effects during pregnancy
4.8	04Apr19	Additional PM experience with cross-sensitivity Additional information for Use in Paediatrics
5.2	04Apr19	Information on PK in paediatrics