

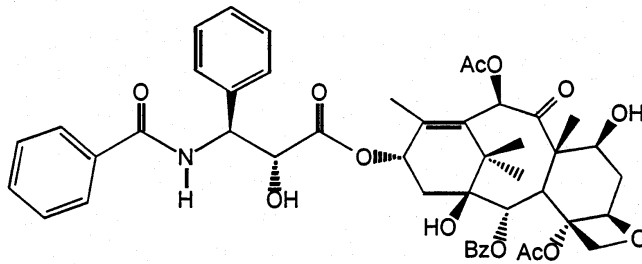
# ABRAXANE<sup>®</sup>

## Product Information

### NAME OF THE MEDICINE

ABRAXANE (nanoparticle albumin-bound paclitaxel) 100 mg powder for injection (suspension).

The empirical formula for Paclitaxel is C<sub>47</sub>H<sub>51</sub>NO<sub>14</sub>. The CAS Number for paclitaxel is 33069-62-4. 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 (2R,3S)-N-benzoyl-3-phenylisoserine. Paclitaxel has the following chemical structure:



### DESCRIPTION

ABRAXANE (nanoparticle albumin-bound paclitaxel) 100 mg 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 an average of 76% paclitaxel bound to 24% human albumin. Following administration, the nanoparticle rapidly dissociates to form albumin-bound paclitaxel and free paclitaxel with a ratio of 94:6.

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

Each single-use vial contains the following:

Paclitaxel 100 mg

*Excipients:*

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

The reconstituted medicinal product contains approximately 85 mg sodium per vial. ABRAXANE is free of solvents.

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

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

## PHARMACOLOGY

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.

### Pharmacokinetics

**Absorption and Distribution:** The pharmacokinetics of total paclitaxel following 30- and 180-minute infusions of ABRAXANE at dose levels of 80 to 375 mg/m<sup>2</sup> 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 terminal half-life was about 27 hours.

AUCs were dose proportional in the range 80 to 300 mg/m<sup>2</sup> and the pharmacokinetics of paclitaxel for ABRAXANE were independent of the duration of administration. The pharmacokinetic parameters in patients with metastatic breast cancer are summarised in Table 1. The large volume of distribution indicates extensive extravascular distribution and/or tissue binding of paclitaxel.

**Table 1: Summary of Pharmacokinetic Parameters in Patients with Metastatic Breast Cancer**

(n = 12; ABRAXANE Dose and Regimen: 260 mg/m<sup>2</sup> q3w\* over 30 min)

	<b>C<sub>max</sub></b> (ng/mL)	<b>T<sub>1/2</sub></b> (h)	<b>AUC<sub>0-∞</sub></b> (h*ng/mL)	<b>Clearance</b> (L/h/m <sup>2</sup> )	<b>Volume of Distribution</b> (L/m <sup>2</sup> )
<b>Single dose mean</b>	18,700	27.4	17,900	15.2	632

\* Once every 3 weeks

*In vitro* studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 µg/mL, indicate that between 89% to 98% of drug is bound, although studies specifically investigating protein binding with this formulation of paclitaxel were not conducted. The presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

**Metabolism and Excretion:** After a 30-minute infusion of 260 mg/m<sup>2</sup> doses of ABRAXANE, the mean values for cumulative urinary recovery of unchanged drug (4%) indicated extensive non-renal clearance. Less than 1% of the total administered dose was excreted in urine as the metabolites 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 **PRECAUTIONS: Interactions with other medicines**). The effect of renal or hepatic dysfunction on the disposition of ABRAXANE has not been investigated.

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

## CLINICAL 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<sup>2</sup> in a 3-hour intravenous infusion (n=227) or as ABRAXANE 260 mg/m<sup>2</sup> 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 drug as second or greater than second-line therapy. Seventy-seven percent of the patients had been previously exposed to anthracyclines.

Table 2 shows the results of the intent-to-treat analysis.

**Table 2: Results for overall response rate, median time to disease progression, and progression-free survival as assessed by the investigator**

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

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

<sup>a</sup> Response rate is the sum of the complete and partial response rates assessed according to RECIST criteria

<sup>b</sup> Cochran-Mantel-Haenszel test

<sup>c</sup> Log-rank test

## INDICATIONS

ABRAXANE is indicated for the treatment of metastatic carcinoma of the breast after failure of anthracycline therapy.

## CONTRAINDICATIONS

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

In patients who have exhibited hypersensitivity reactions to paclitaxel or albumin, patients should not be treated with ABRAXANE.

ABRAXANE is contraindicated during pregnancy and lactation.

## PRECAUTIONS

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.

**Note: An albumin form of paclitaxel may substantially affect a drug's functional properties relative to those of drug in solution. DO NOT SUBSTITUTE ABRAXANE WITH OTHER PACLITAXEL FORMULATIONS.**

### Haematology

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

### Neuropathy

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

### Hepatic Impairment

Patients with hepatic impairment may be at increased risk of toxicity, particularly from myelosuppression, and such patients should be closely monitored for development of profound myelosuppression. The use of ABRAXANE has not been formally studied in patients specifically with hepatic impairment. Patients with severe hepatic impairment should not be treated with ABRAXANE. The appropriate dose regime in patients with mild to moderate hepatic impairment is unknown.

### Effects on Fertility

Administration of albumin-bound paclitaxel 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 albumin-bound paclitaxel particles at 6 mg/kg ( $54 \text{ mg/m}^2$ ) and dogs administered 8.75 mg/kg ( $175 \text{ mg/m}^2$ ).

## **Use in Pregnancy**

### **Category D**

ABRAXANE may cause foetal harm when administered to a pregnant woman.

Administration of albumin-bound paclitaxel to female rats on gestation days 7 to 17 daily at doses of 1 mg/kg (6 mg/m<sup>2</sup>: less than the daily maximum recommended human dose on an AUC 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. 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 foetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with ABRAXANE.

Like other genotoxic cytostatics, ABRAXANE can have genotoxic effects. Male patients treated with ABRAXANE are advised not to father a child during and up to six months after treatment.

### **Use in Lactation**

It is not known whether paclitaxel is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in breastfeeding infants, it is recommended that breastfeeding be discontinued when receiving ABRAXANE therapy.

### **Paediatric Use**

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

### **Use in Elderly**

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.

### **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 was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay.

### **Interactions with Other Medicines**

No drug interaction studies have been conducted with ABRAXANE.

### **Drugs Metabolised in the Liver**

The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Therefore, caution should be exercised when administering ABRAXANE concomitantly with medicines known to inhibit (e.g. erythromycin, ketoconazole, fluoxetine, imidazole antifungals, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or induce (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) either CYP2C8 or CYP3A4.

Possible interactions of albumin-bound paclitaxel with concomitantly administered medications have not been formally investigated in patients. *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 drugs, including CYP2C8 and CYP3A4 substrates, and quinidine, PEG-35 castor oil, quercetin, clozapine, morin, and resveratrol.

### Effects on Laboratory Tests

Interactions with laboratory tests have not been established.

## ADVERSE EFFECTS

**Table 3: Frequency<sup>a</sup> of Important Treatment Emergent Adverse Effects in the Randomised Study on an Every-3-Weeks Schedule**

	Percent of Patients	
	ABRAXANE 260/30min <sup>b</sup> (n=229)	Paclitaxel Injection 175/3h <sup>c,d</sup> (n=225)
<b>Bone Marrow</b>		
Neutropenia		
< 2.0 x 10 <sup>9</sup> /L	80	82
< 0.5 x 10 <sup>9</sup> /L	9	22
Thrombocytopenia		
< 100 x 10 <sup>9</sup> /L	2	3
< 50 x 10 <sup>9</sup> /L	<1	<1
Anaemia		
< 110 g/L	33	25
< 80 g/L	1	<1
Infections	24	20
Febrile Neutropenia	2	1
Bleeding	2	2
<b>Hypersensitivity Reaction<sup>e</sup></b>		
All	4	12
Severe <sup>f</sup>	0	2
<b>Cardiovascular</b>		
Vital Sign Changes <sup>g</sup>		
Bradycardia	<1	<1
Hypotension	5	5
Severe Cardiovascular Events <sup>f</sup>	3	4
<b>Abnormal ECG</b>		
All patients	60	52
Patients with Normal Baseline	35	30

**Table 3: Frequency<sup>a</sup> of Important Treatment Emergent Adverse Effects in the Randomised Study on an Every-3-Weeks Schedule, Continued**

	Percent of Patients	
	ABRAXANE 260/30min <sup>b</sup> (n=229)	Paclitaxel Injection 175/3h <sup>c,d</sup> (n=225)
<b>Respiratory</b>		
Cough	7	6
Dyspnea	12	9
<b>Sensory Neuropathy</b>		
Any Symptoms	71	56
Severe Symptoms <sup>f</sup>	10	2
<b>Myalgia / Arthralgia</b>		
Any Symptoms	44	49
Severe Symptoms <sup>f</sup>	8	4
<b>Asthenia</b>		
Any Symptoms	47	39
Severe Symptoms <sup>f</sup>	8	3
<b>Fluid Retention / Edema</b>		
Any Symptoms	10	8
Severe Symptoms <sup>f</sup>	0	<1
<b>Gastrointestinal</b>		
Nausea		
Any Symptoms	30	22
Severe Symptoms <sup>f</sup>	3	<1
Vomiting		
Any Symptoms	18	10
Severe Symptoms <sup>f</sup>	4	1
Diarrhoea		
Any Symptoms	27	15
Severe Symptoms <sup>f</sup>	<1	1
Mucositis		
Any Symptoms	7	6
Severe Symptoms <sup>f</sup>	<1	0
<b>Alopecia</b>	90	94
<b>Hepatic (Patients with Normal Baseline)</b>		
Bilirubin Elevations	7	7
Alkaline Phosphatase Elevations	36	31
AST (SGOT) Elevations	39	32
<b>Injection Site Reaction</b>	<1	1

a Based on worst grade.

b ABRAXANE dose in mg/m<sup>2</sup>/duration in minutes.

c paclitaxel injection dose in mg/m<sup>2</sup>/duration in hours.

d paclitaxel injection 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 drug dosing.

Table 4 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 undesirable effects listed in Table 4 is defined using the following convention:

Very common ( $\geq 1/10$ ); common ( $\geq 1/100, < 1/10$ ); uncommon ( $\geq 1/1,000, < 1/100$ ); rare ( $\geq 1/10,000, < 1/1,000$ ); very rare ( $< 1/10,000$ ).

**Table 4: Adverse Effects Reported With ABRAXANE at Any Dose in Clinical Trials**

Infections and infestations	<i>Common:</i> Infection, urinary tract infection, folliculitis, upper respiratory tract infection, candidiasis, sinusitis <i>Uncommon:</i> Oral candidiasis, nasopharyngitis, cellulitis, herpes simplex, viral infection, pneumonia, catheter-related infection, fungal infection, herpes zoster, injection site infection, respiratory tract infections
Neoplasms benign, malignant and unspecified	<i>Uncommon:</i> Metastatic pain, tumour necrosis
Blood and lymphatic system disorders	<i>Very Common:</i> Neutropenia, anaemia, leukopenia, thrombocytopenia, lymphopenia, bone marrow suppression <i>Common:</i> Febrile neutropenia
Immune system disorders	<i>Uncommon:</i> Hypersensitivity <i>Rare:</i> Severe hypersensitivity
Metabolism and nutrition disorders	<i>Very common:</i> Anorexia <i>Common:</i> Dehydration, decreased appetite, hypokalaemia <i>Uncommon:</i> Hypophosphataemia, fluid retention, hypoalbuminaemia, polydipsia, hyperglycaemia, hypocalcaemia, hypoglycaemia, hyponatraemia
Psychiatric disorders	<i>Common:</i> Insomnia, depression, anxiety <i>Uncommon:</i> Restlessness
Nervous system disorders	<i>Very Common:</i> Peripheral neuropathy, neuropathy, hypoesthesia, paraesthesia. <i>Common:</i> Sensory neuropathy, peripheral sensory neuropathy, headache, dysgeusia, dizziness, peripheral motor neuropathy, ataxia, sensory disturbance, somnolence. <i>Uncommon:</i> Polyneuropathy, areflexia, dyskinesia, hyporeflexia, neuralgia, sensory loss, syncope, postural dizziness, neuropathic pain, tremor
Eye disorders	<i>Common:</i> Increased lacrimation, blurred vision, dry eye, keratoconjunctivitis sicca, madarosis <i>Uncommon:</i> Eye irritation, eye pain, abnormal vision, reduced visual acuity, conjunctivitis, visual disturbance, eye pruritus, keratitis
Ear and labyrinth disorders	<i>Common:</i> Vertigo <i>Uncommon:</i> Ear pain, tinnitus

Cardiac disorders	<p><i>Common:</i> Arrhythmia, chest pain, dyspnea, edema, flushing, hypotension, hypertension, pulmonary emboli, pulmonary thromboembolism, supraventricular tachycardia, Tachycardia</p> <p><i>Rare:</i> bradycardia, cardiac arrest, congestive heart failure, left ventricular dysfunction</p>
Vascular disorders	<p><i>Common:</i> Flushing, hot flushes, hypertension, lymphoedema</p> <p><i>Uncommon:</i> Hypotension, peripheral coldness, orthostatic hypotension</p> <p><i>Rare:</i> Thrombosis</p>
Respiratory, thoracic and mediastinal disorders	<p><i>Common:</i> Dyspnoea, epistaxis, pharyngolaryngeal pain, cough, rhinitis, rhinorrhoea</p> <p><i>Uncommon:</i> 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</p> <p><i>Rare:</i> Interstitial pneumonitis</p>
Gastrointestinal disorders	<p><i>Very Common:</i> Nausea, diarrhoea, vomiting, constipation, stomatitis, mucositis</p> <p><i>Common:</i> Abdominal pain, abdominal distension, upper abdominal pain, dyspepsia, gastrooesophageal reflux disease, oral hypoaesthesia</p> <p><i>Uncommon:</i> Dysphagia, flatulence, glossodynia, dry mouth, gingival pain, loose stools, oesophagitis, lower abdominal pain, mouth ulceration, oral pain, rectal haemorrhage</p>
Hepatobiliary disorders	<p><i>Uncommon:</i> Hyperbilirubinaemia, hepatomegaly</p>
Skin and subcutaneous tissue disorders	<p><i>Very Common:</i> Alopecia, rash</p> <p><i>Common:</i> Nail disorder, pruritus, dry skin, erythema, nail pigmentation/dicolouration, skin hyperpigmentation, onycholysis, nail changes</p> <p><i>Uncommon:</i> 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</p>
Musculoskeletal and connective tissue disorders	<p><i>Very Common:</i> Arthralgia, myalgia</p> <p><i>Common:</i> Pain in extremity, bone pain, back pain, muscle cramps, limb pain</p> <p><i>Uncommon:</i> Chest wall pain, muscular weakness, neck pain, groin pain, muscle spasms, musculoskeletal pain, flank pain, limb discomfort, muscle weakness</p>
Renal and urinary disorders	<p><i>Uncommon:</i> Dysuria, pollakiuria, haematuria, nocturia, polyuria, urinary incontinence</p>
Reproductive system and breast disorders	<p><i>Uncommon:</i> Breast pain</p>

General disorders and administration site conditions	<p><i>Very Common:</i> Fatigue, asthenia, pyrexia</p> <p><i>Common:</i> Peripheral oedema, mucosal inflammation, pain, rigors, oedema, weakness, decreased performance status, chest pain, influenza-like illness, malaise, lethargy, hyperpyrexia</p> <p><i>Uncommon:</i> Chest discomfort, abnormal gait, swelling, injection site reaction</p>
Investigations	<p><i>Common:</i> 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</p> <p><i>Uncommon:</i> Increased blood pressure, increased weight, increased blood lactate dehydrogenase, increased blood creatinine, increased blood glucose, increased blood phosphorus, decreased blood potassium, increased bilirubin</p>
Injury, poisoning and procedural complications	<p><i>Uncommon:</i> Contusion</p> <p><i>Rare:</i> radiation recall phenomenon, radiation pneumonitis</p>

### Post-marketing experience

**Table 5: 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
Nervous System Disorders	Cranial nerve palsies, vocal cord paresis
Skin/Subcutaneous Disorders	Erythema, maculo-papular rash, palmar-plantar erythrodysesthesiae 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

## **DOSAGE AND 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.

The recommended regimen for ABRAXANE is 260 mg/m<sup>2</sup> administered intravenously over 30 minutes every 3 weeks.

### **Dose Adjustment**

Patients who experience severe neutropenia (neutrophil <500 cells/mm<sup>3</sup> for a week or longer) or severe sensory neuropathy during ABRAXANE therapy should have dosage reduced to 220 mg/m<sup>2</sup> for subsequent courses of ABRAXANE. For recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m<sup>2</sup>. ABRAXANE should not be administered until neutrophil counts recover to >1.5 x 10<sup>9</sup>/L. 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.

### **Missed Dose**

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.

### **Hepatic Insufficiency**

No data are currently available to recommend dosage alterations in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment should not be treated with albumin-bound paclitaxel.

### **Patients with Impaired Renal Function**

Studies in patients with impaired renal function have not been performed and there is insufficient data to permit dosage recommendations in this patient population.

### **Preparation and Administration Precautions**

ABRAXANE is a cytotoxic anticancer drug and, as with other potentially toxic paclitaxel compounds, caution should be exercised in handling ABRAXANE. The use of gloves is recommended. If ABRAXANE (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 drug 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 drugs with the ABRAXANE infusion.

### Preparation for Intravenous Administration

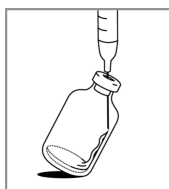
ABRAXANE is supplied as a sterile lyophilised powder for reconstitution before use.

**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 sit 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.

Inject the appropriate amount of reconstituted ABRAXANE into an empty, sterile, polyvinyl chloride (PVC) or non-PVC type IV 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 an in-line filter is not recommended.

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

Retain in the original package to protect from bright light.

Unopened vials of ABRAXANE are stable until the date indicated on the package when stored between 20°C to 25°C, in the original package.

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

#### **Stability of Reconstituted Suspension in the Vial**

Reconstituted ABRAXANE should be used immediately, but may be refrigerated at 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.

#### **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.

#### **OVERDOSAGE**

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

#### **PRESENTATION AND STORAGE CONDITIONS**

##### **Pack**

ABRAXANE is supplied as a white to yellow, sterile, lyophilised cake for reconstitution in a 50 mL clear glass vial with a latex free stopper, individually packaged in a carton. Each single use vial contains 100 mg of paclitaxel and 900 mg of human albumin. ABRAXANE is free of solvents.

After reconstitution with 20 mL of 0.9% Sodium Chloride Injection each millilitre (mL) of reconstituted suspension contains 5 mg of paclitaxel.

Pack Size: 1 single vial in a carton.

##### **Storage**

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

#### **NAME AND ADDRESS OF SPONSOR**

##### In Australia:

Abraxis BioScience Australia Pty Ltd  
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East Kew, Victoria 3102

Distributed by Specialised Therapeutics Australia Pty Ltd

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PO Box 62027  
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**POISON SCHEDULE**

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**DATE OF APPROVAL**

Approved by the Therapeutic Goods Administration on 29 September 2008

Safety Related Notification made: 06 August 2009

Safety Related Notification made: 09 September 2011

Approved by Medsafe on 15 July 2010

Abraxis BioScience Australia Pty Ltd is an indirect subsidiary of Celgene Corporation