1.3.1.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ABRAXANE (100 mg, powder for suspension for injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg of albumin-bound paclitaxel.

After reconstitution, each ml of the dispersion contains 5 mg of paclitaxel formulated as albumin bound nanoparticles.

Sugar-free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for suspension for infusion.

The reconstituted suspension has a pH of 6 – 7,5 and an osmolality of 300 - 360 mOsm/kg.

White to yellow, lyophilised cake.

After reconstitution, the reconstituted suspension is milky and homogenous without visible precipitates or particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Metastatic Breast Cancer

ABRAXANE is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

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 therapy.

Adenocarcinoma of the Pancreas

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

4.2 Posology and method of administration

Posology

ABRAXANE should be administered under the supervision of a medical practitioner experienced in the use of cancer chemotherapeutic medicines.

Metastatic Breast Cancer

The recommended dose of 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 < 500 cells/mm^3 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.

Non-Small Cell Lung Cancer

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

ABRAXANE should not be administered on Day 1 of a cycle until absolute neutrophil count (ANC) is ≥ 1 500 cells/mm^3 and platelet count is ≥ 100 000 cells/mm^3. For each subsequent weekly dose of ABRAXANE, patients must have an ANC ≥ 500 cells/mm^3 and platelets > 50 000 cells/mm^3 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.

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

Haematologic Toxicity	Occurrence	Dose of ABRAXANE (mg/m^2)	Dose of carboplatin (AUC mg•min/ml)
Nadir ANC < 500/mm^3 with neutropenic fever > 38 °C OR Delay of next cycle due to persistent neutropenia[1] (Nadir ANC < 1 500/mm^3) OR Nadir ANC < 500/mm^3 for > 1 week	First	75	4,5
	Second	50	3,0
	Third	Discontinue Treatment	
Nadir platelets < 50 000/mm^3	First	75	4,5
	Second	Discontinue Treatment	

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

Non-haematologic toxicities:

Guidelines for implementing dose reductions for non-haematologic 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 to ≤ 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 non-haematologic toxicity, interrupt treatment until the toxicity improves to ≤ Grade 2, then restart treatment according to the guidelines in Table 2.

Table 2: Dose Reductions for Non-haematologic Toxicities in Patients with Non-Small Cell Lung Cancer

Adenocarcinoma of the Pancreas

Non-haematologic 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 non-haematologic toxicity	First	75	4,5
	Second	50	3,0
	Third	Discontinue Treatment	
Grade 4 cutaneous toxicity, diarrhoea, or mucositis	First	Discontinue Treatment	

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

Dose adjustments during treatment for adenocarcinoma of the pancreas

Dose level reductions for patients with adenocarcinoma of the pancreas are provided in Table 3.

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

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

Table 3: Dose Level Reductions for Patients with 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

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

Cycle Day	**ANC count ($cells/mm^3$)**		**Platelet count ($cells/mm^3$)**	**ABRAXANE Dose**	**Gemcitabine Dose**
Day 1	≥ 1500	AND	≥ 100 000	Treat on time at current dose levels	

	< 1500	OR	< 10 000	Delay doses until recovery
Day 8	≥ 1000	AND	≥ 75 000	Treat on time at current dose levels
	≥ 500 but < 1000	OR	≥ 50 000 but < 75 000	Reduce doses 1 dose level
	< 500	OR	< 50 000	Withhold doses
Day 15: IF Day 8 doses were given without modification:				
Day 15	≥ 1000	AND	≥ 75 000	Treat on time at current dose levels
	≥ 500 but < 1000	OR	≥ 50 000 but < 75 000	Treat with Day 8 dose level and follow with WBC Growth Factors OR Reduce doses 1 dose level from Day 8 doses
	< 500	OR	< 50 000	Withhold doses
Day 15: IF Day 8 doses were reduced:				
Day 15	≥ 1000	AND	≥ 75 000	Return to the Day 1 dose level and follow with WBC Growth Factors OR Treat with same doses as Day 8

	≥ 500 but < 1000	OR	≥ 50 000 but < 75 000	Treat with Day 8 dose level and follow with WBC Growth Factors OR Reduce doses 1 dose level from Day 8 doses
	< 500	OR	< 50 000	Withhold doses
Day 15: IF Day 8 doses were withheld:				
Day 15	≥ 1000	AND	≥ 75 000	Return to Day 1 dose level and follow with WBC Growth Factors OR Reduce doses 1 dose level from Day 1 doses
	≥ 500 but < 1000	OR	≥ 50 000 but < 75 000	Reduce 1 dose level and follow with WBC Growth Factors OR Reduce doses 2 dose levels from Day 1 doses
	< 500	OR	< 50 000	Withhold doses

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

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

Adverse Drug Reaction	ABRAXANE Dose	Gemcitabine Dose
Febrile Neutropenia: Grade 3 or 4	Withhold doses until fever resolves and ANC ≥ 1500; resume at reduced dose level[a].	
Peripheral Neuropathy: Grade 3 or 4	Withhold dose until improves to ≤ Grade 1; resume at next lower dose level[a]	Treat with same dose
Cutaneous Toxicity: Grade 2 or 3	Reduce 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 1 for dose level reductions.

Special populations:

Paediatrics:

The safety and efficacy of ABRAXANE in children (under 18 years) has not been established.

Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made. There is no relevant use of ABRAXANE in the paediatric population for the indication of metastatic breast cancer or pancreatic adenocarcinoma or non-small cell lung cancer.

Elderly:

No additional dose recommendations, other than those recommended for all patients, are necessary for patient 65 years or older.

Use in 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).

Use in patients with impaired hepatic function:

- For patients with mild hepatic impairment (total bilirubin > 1 to ≤ 1,5 x ULN and aspartate aminotransferase [AST] ≤ 10 x ULN), no dose adjustments are required, regardless of indication. Treat with same doses as patients with normal hepatic function.
- For patients with moderate to severe hepatic impairment (total bilirubin > 1,5 to ≤ 5 x ULN and 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.

Method of administration

Administer reconstituted Abraxane suspension intravenously using an infusion set incorporating a 15 µm filter. Following administration, it is recommended that the intravenous line be flushed with sodium chloride 9 mg/ml (0,9 %) solution for injection to ensure administration of the complete dose.

For instructions on reconstitution of the medicine before administration, see section 6.6.

4.3 Contraindications

- ABRAXANE should not be used in patients who have baseline neutrophil counts of < 1 500 cells/mm^3.
- ABRAXANE is contraindicated in patients with hypersensitivity to paclitaxel or to human albumin.
- ABRAXANE is contraindicated during pregnancy and lactation (see Section 4.6).

4.4 Special warnings and precautions for use

DO NOT SUBSTITUTE ABRAXANE FOR OR WITH OTHER PACLITAXEL FORMULATIONS. ABRAXANE is a formulation of paclitaxel which may have substantially different functional properties compared to those of solution formulations of paclitaxel.

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

Peripheral neuropathy occurs frequently with ABRAXANE. The occurrence of grade 1 or 2 peripheral neuropathy does not generally require dose modification. For single-agent use of ABRAXANE, if grade 3 peripheral neuropathy develops, treatment should be withheld until resolution to grade 0 or 1 for metastatic melanoma or grade 1 or 2 for metastatic breast cancer, 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.

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.

Patients with hepatic impairment may be at increased risk of toxicity, particularly from myelosuppression; such patients should be closely monitored for development of

profound myelosuppression. ABRAXANE is not recommended in patients that have total bilirubin > 5 x ULN or AST > 10 x ULN. In addition, ABRAXANE is not recommended in patients with metastatic adenocarcinoma of the pancreas that have moderate to severe hepatic impairment (total bilirubin > 1,5 x ULN and AST ≤ 10 x ULN).

Cases of severe hypersensitivity reactions, including 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 product.

Special Warnings and Precautions specific to ABRAXANE in combination with gemcitabine:

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 ≥ 1500, then resume treatment at reduced dose levels.

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

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.

4.5 Interactions with other medicines and other forms of interaction

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. ketoconazole, erythromycin, fluoxetine, imidazole antifungals, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or induce (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) either CYP2C8 or CYP3A4.

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.

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

Contraception in males and females

Women of childbearing potential should use effective contraception during treatment and for at least six months after the last dose of ABRAXANE. Male patients with female partners of reproductive potential are advised to use effective contraception

and to avoid fathering a child during treatment with ABRAXANE and for at least three months after the last dose of ABRAXANE.

Pregnancy

ABRAXANE is contraindicated in pregnancy and lactation.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with ABRAXANE and should have a pregnancy test prior to starting treatment with ABRAXANE. A barrier contraceptive method plus one other reliable method of contraception should be used.

ABRAXANE is suspected to cause serious birth defects when administered during pregnancy. Administration of ABRAXANE to rats at doses (approximately 2 % of the daily maximum recommended human dose on a mg/m^2 basis) caused embryo- and fetotoxicity.

Paclitaxel is a potentially carcinogenic and genotoxic agent at clinical doses and has been shown to be clastogenic.

Breastfeeding

Paclitaxel and/or its metabolites were excreted into the milk of lactating rats. It is not known if paclitaxel is excreted in human milk. Because of potential serious adverse reactions in breastfeeding infants, ABRAXANE is contraindicated during lactation. Breastfeeding must be discontinued for the duration of therapy.

Fertility

ABRAXANE induced infertility in male rats. Based on findings in animals, female fertility may be compromised. Male patients should seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with ABRAXANE.

4.7 Effects on ability to drive and use machines

Undesirable effects, such as dizziness, fatigue, somnolence, blurred vision, can affect the ability to operate machines or drive.

4.8 Undesirable effects

a. Summary of the safety profile

The most common clinically significant adverse reactions associated with the use of Abraxane have been neutropenia, peripheral neuropathy, arthralgia/myalgia and gastrointestinal disorders.

b. Tabulated summary of adverse reactions

Table below lists adverse reactions associated with Abraxane monotherapy at any dose in any indication during clinical trials (N = 789), Abraxane in combination with gemcitabine for pancreatic adenocarcinoma from the phase III clinical trial (N = 421), Abraxane in combination with carboplatin for non-small cell lung cancer from the phase III clinical trial (N = 514) and from post-marketing use.

Frequencies 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), not known (cannot be estimated from the available data). Within each

frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 6: Adverse reactions reported with Abraxane

	Monotherapy (N=789)	**Combination therapy with gemcitabine (N =421)**	**Combination therapy with carboplatin (N = 514)**
Infections and infestations			
Common:	Infection, urinary tract infection, folliculitis, upper respiratory tract infection, candidiasis, sinusitis	Sepsis, pneumonia, oral candidiasis	Pneumonia, bronchitis, upper respiratory tract infection, urinary tract infection
Uncommon:	Sepsis[1], neutropenic sepsis[1], pneumonia, oral candidiasis, nasopharyngitis, cellulitis, herpes simplex, viral infection, herpes zoster, fungal infection, catheter-related infection, injection site infection		Sepsis, oral candidiasis

	Monotherapy (N=789)	Combination therapy with gemcitabine (N =421)	Combination therapy with carboplatin (N = 514)
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Uncommon:	Tumour necrosis, metastatic pain		
Blood and lymphatic system disorders			
Very common:	Bone marrow suppression, neutropenia, thrombocytopenia, anaemia, leukopenia, lymphopenia	Neutropenia, thrombocytopenia, anaemia	Neutropenia[3], thrombocytopenia[3], anaemia[3], leukopenia[3]
Common:	Febrile neutropenia	Pancytopenia	Febrile neutropenia, lymphopenia
Uncommon:		Thrombotic thrombocytopenic purpura	Pancytopenia
Rare:	Pancytopenia		
Immune system disorders			
Uncommon:	Hypersensitivity		Medicine hypersensitivity, hypersensitivity
Rare:	Severe hypersensitivity[1]		

	Monotherapy (N=789)	Combination therapy with gemcitabine (N =421)	Combination therapy with carboplatin (N = 514)
Metabolism and nutrition disorders			
Very common:	Anorexia	Dehydration, decreased appetite, hypokalaemia	Decreased appetite
Common:	Dehydration, decreased appetite, hypokalaemia		Dehydration
Uncommon:	Hypophosphataemia, fluid retention, hypoalbuminaemia, polydipsia, hyperglycaemia, hypocalcaemia, hypoglycaemia, hyponatraemia		
Not known:	Tumour lysis syndrome[1]		
Psychiatric disorders			
Very common:		Depression, insomnia	
Common:	Depression, insomnia, anxiety	Anxiety	Insomnia
Uncommon:	Restlessness		

	Monotherapy (N=789)	Combination therapy with gemcitabine (N =421)	Combination therapy with carboplatin (N = 514)
Nervous system disorders			
Very common:	Peripheral neuropathy, neuropathy, hypoaesthesia, paraesthesia	Peripheral neuropathy, dizziness, headache, dysgeusia	Peripheral neuropathy
Common:	Peripheral sensory neuropathy, dizziness, peripheral motor neuropathy, ataxia, headache, sensory disturbance, somnolence, dysgeusia		Dizziness, headache, dysgeusia
Uncommon:	Polyneuropathy, areflexia, syncope, postural dizziness, dyskinesia, hyporeflexia, neuralgia, neuropathic pain, tremor, sensory loss	VIIth nerve paralysis	
Not known:	Cranial nerve palsies multiple [1]		
Eye disorders			

	Monotherapy (N=789)	Combination therapy with gemcitabine (N =421)	Combination therapy with carboplatin (N = 514)
Common:	Vision blurred, lacrimation increased, dry eye, keratoconjunctivitis sicca, madarosis	Lacrimation increased	Vision blurred
Uncommon:	Reduced visual acuity, abnormal vision, eye irritation, eye pain, conjunctivitis, visual disturbance, eye pruritus, keratitis	Cystoid macular oedema	
Rare:	Cystoid macular oedema[1]		
Ear and labyrinth disorders			
Common:	Vertigo		
Uncommon:	Tinnitus, ear pain		
Cardiac disorders			
Common:	Arrhythmia, tachycardia, supraventricular tachycardia	Cardiac failure congestive, tachycardia	

	Monotherapy (N=789)	Combination therapy with gemcitabine (N =421)	Combination therapy with carboplatin (N = 514)
Rare:	Cardiac arrest, cardiac failure congestive, left ventricular dysfunction, atrioventricular block[1], bradycardia		
Vascular disorders			
Common:	Hypertension, lymphoedema, flushing, hot flushes	Hypotension, hypertension	Hypotension, hypertension
Uncommon:	Hypotension, orthostatic hypotension, peripheral coldness	Flushing	Flushing
Rare:	Thrombosis		
Respiratory, thoracic and mediastinal disorders			
Very common:		Dyspnoea, epistaxis, cough	Dyspnoea
Common:	Interstitial pneumonitis[2], dyspnoea, epistaxis, pharyngolaryngeal pain, cough, rhinitis, rhinorrhoea	Pneumonitis, nasal congestion	Haemoptysis, epistaxis, cough

	Monotherapy (N=789)	Combination therapy with gemcitabine (N =421)	Combination therapy with carboplatin (N = 514)
Uncommon:	Pulmonary emboli, pulmonary thromboembolism, pleural effusion, exertional dyspnoea, sinus congestion, decreased breath sounds, productive cough, allergic rhinitis, hoarseness, nasal congestion, nasal dryness, wheezing	Dry throat, nasal dryness	Pneumonitis
Not known:	Vocal cord paresis[1]		
Gastrointestinal disorders			
Very common:	Diarrhoea, vomiting, nausea, constipation, stomatitis	Diarrhoea, vomiting, nausea, constipation, abdominal pain, abdominal pain upper	Diarrhoea, vomiting, nausea, constipation

	Monotherapy (N=789)	Combination therapy with gemcitabine (N =421)	Combination therapy with carboplatin (N = 514)
Common:	Gastrooesophageal reflux disease, dyspepsia, abdominal pain, abdominal distension, abdominal pain upper, oral hypoaesthesia	Intestinal obstruction, colitis, stomatitis, dry mouth	Stomatitis, dyspepsia, dysphagia, abdominal pain
Uncommon:	Rectal haemorrhage, dysphagia, flatulence, glossodynia, dry mouth, gingival pain, loose stools, oesophagitis, abdominal pain lower, mouth ulceration, oral pain		
Hepatobiliary disorders			
Common:		Cholangitis	Hyperbilirubinaemia
Uncommon:	Hepatomegaly		
Skin and subcutaneous tissue disorders			
Very common:	Alopecia, rash	Alopecia, rash	Alopecia, rash

	Monotherapy (N=789)	Combination therapy with gemcitabine (N =421)	Combination therapy with carboplatin (N = 514)
Common:	Pruritus, dry skin, nail disorder, erythema, nail pigmentation/discolouration, skin hyperpigmentation, onycholysis, nail changes	Pruritus, dry skin, nail disorder	Pruritus, nail disorder
Uncommon:	Photosensitivity reaction, urticaria, skin pain, generalised pruritus, pruritic rash, skin disorder, pigmentation disorder, hyperhidrosis, onychomadesis, erythematous rash, generalised rash, dermatitis, night sweats, maculo-papular rash, vitiligo, hypotrichosis, nail bed tenderness, nail discomfort, macular rash, papular rash, skin lesion, swollen face		Skin exfoliation, dermatitis allergic, urticaria

	Monotherapy (N=789)	Combination therapy with gemcitabine (N =421)	Combination therapy with carboplatin (N = 514)
Very rare:	Stevens-Johnson syndrome[1], toxic epidermal necrolysis[1]		
Not known:	Palmar-plantar erythrodysaesthesiae syndrome[1, 4], scleroderma[1]		
Musculoskeletal and connective tissue disorders			
Very common:	Arthralgia, myalgia	Arthralgia, myalgia, pain in extremity	Arthralgia, myalgia
Common:	Back pain, pain in extremity, bone pain, muscle cramps, limb pain	Muscular weakness, bone pain	Back pain, pain in extremity, musculoskeletal 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			

	Monotherapy (N=789)	Combination therapy with gemcitabine (N =421)	Combination therapy with carboplatin (N = 514)
Common:		Acute renal failure	
Uncommon:	Haematuria, dysuria, pollakiuria, nocturia, polyuria, urinary incontinence	Haemolytic uraemic syndrome	
Reproductive system and breast disorders			
Uncommon:	Breast pain		
General disorders and administration site conditions			
Very common:	Fatigue, asthenia, pyrexia	Fatigue, asthenia, pyrexia, oedema peripheral, chills	Fatigue, asthenia, oedema peripheral
Common:	Malaise, lethargy, weakness, peripheral oedema, mucosal inflammation, pain, rigors, oedema, decreased performance status, chest pain, influenza-like illness, hyperpyrexia	Infusion site reaction	Pyrexia, chest pain

	Monotherapy (N=789)	Combination therapy with gemcitabine (N =421)	Combination therapy with carboplatin (N = 514)
Uncommon:	Chest discomfort, abnormal gait, swelling, injection site reaction		Mucosal inflammation, infusion site extravasation, infusion site inflammation, infusion site rash
Rare:	Extravasation		
Investigations			
Very common:		Weight decreased, alanine aminotransferase increased	

	Monotherapy (N=789)	Combination therapy with gemcitabine (N =421)	Combination therapy with carboplatin (N = 514)
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	Aspartate aminotransferase increased, blood bilirubin increased, blood creatinine increased	Weight decreased, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased
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			

	Monotherapy (N=789)	Combination therapy with gemcitabine (N =421)	Combination therapy with carboplatin (N = 514)
Uncommon:	Contusion		
Rare:	Radiation recall phenomenon, radiation pneumonitis		

[1] As reported in the post-marketing surveillance of Abraxane.

[2] The frequency of pneumonitis is calculated based on pooled data in 1310 patients in clinical trials receiving Abraxane monotherapy for breast cancer and for other indications.

[3] Based on laboratory assessments: maximal degree of myelosuppression (treated population).

[4] In some patients previously exposed to capecitabine.

c) Description of selected adverse reactions

This section contains the most common and clinically relevant adverse reactions related to Abraxane.

Adverse reactions were assessed in 229 patients with metastatic breast cancer who were treated with 260 mg/m^2 Abraxane once every three weeks in the pivotal phase III clinical study (Abraxane monotherapy).

Adverse reactions were assessed in 421 patients with metastatic pancreatic cancer who were treated with Abraxane in combination with gemcitabine (125 mg/m^2 Abraxane in combination with gemcitabine at a dose of 1000 mg/m^2 given on Days 1,

8 and 15 of each 28-day cycle) and 402 gemcitabine monotherapy-treated patients receiving first-line systemic treatment for metastatic adenocarcinoma of the pancreas (Abraxane/gemcitabine).

Adverse reactions were assessed in 514 patients with non-small cell lung cancer who were treated with Abraxane in combination with carboplatin (100mg/m^2 Abraxane given on Days 1, 8 and 15 of each 21-day cycle in combination with carboplatin given on Day 1 of each cycle) in the phase III randomized, controlled clinical trial (Abraxane/carboplatin). 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.

Infections and infestations

Abraxane/gemcitabine

Sepsis was reported at a rate of 5 % in patients with or without neutropenia who received Abraxane in combination with gemcitabine during the conduct of a trial in pancreatic adenocarcinoma. Of the 22 cases of sepsis reported in patients treated with Abraxane in combination with gemcitabine, 5 had a fatal outcome. Complications due to the underlying pancreatic cancer, especially biliary obstruction or presence of biliary stent, were identified as significant contributing factors. If a patient becomes febrile (regardless of neutrophil count), initiate treatment with broad spectrum antibiotics. For febrile neutropenia, withhold Abraxane and gemcitabine until fever resolves and ANC ≥ 1500 cells/mm^3, then resume treatment at reduced

dose levels (see section 4.2).

Blood and lymphatic system disorders

Abraxane monotherapy-metastatic breast cancer

In patients with metastatic breast cancer, neutropenia was the most notable important haematological toxicity (reported in 79 % of patients) and was rapidly reversible and dose-dependent; leukopenia was reported in 71 % of patients. Grade 4 neutropenia (< 500 cells/mm^3) occurred in 9 % of patients treated with Abraxane. Febrile neutropenia occurred in four patients on Abraxane. Anaemia (Hb < 10 g/dl) was observed in 46 % of patients on Abraxane and was severe (Hb < 8 g/dl) in three cases. Lymphopenia was observed in 45 % of the patients.

Abraxane/gemcitabine

Table 7 below provides the frequency and severity of haematologic laboratory-detected abnormalities for patients treated with Abraxane in combination with gemcitabine or with gemcitabine.

Table 7: Haematologic laboratory-detected abnormalities in pancreatic adenocarcinoma trial

	Abraxane (125 mg/m^2)/ Gemcitabine		**Gemcitabine**	
	Grades 1-4 (%)	**Grade 3-4 (%)**	**Grades 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

Abraxane/carboplatin

Anaemia and thrombocytopenia were more commonly reported in the Abraxane and carboplatin arm than in the Taxol and carboplatin arm (54 % versus 28 % and 45 % versus 27 % respectively).

Nervous system disorders

Abraxane monotherapy-metastatic breast cancer

In general, the frequency and severity of neurotoxicity was dose-dependent in patients receiving Abraxane. Peripheral neuropathy (mostly Grade 1 or 2 sensory neuropathy) was observed in 68 % of patients on Abraxane with 10 % being Grade 3, and no cases of Grade 4.

Abraxane/gemcitabine

For patients treated with Abraxane in combination with gemcitabine, the median time to first occurrence of Grade 3 peripheral neuropathy was 140 days. The median time to improvement by at least 1 grade was 21 days, and the median time to improvement from Grade 3 peripheral neuropathy to Grade 0 or 1 was 29 days. Of the patients with treatment interrupted due to peripheral neuropathy, 44 % (31/70 patients) were able to resume Abraxane at a reduced dose. No patients treated with Abraxane in combination with gemcitabine had Grade 4 peripheral neuropathy.

Abraxane/carboplatin

For non-small cell lung cancer patients treated with Abraxane and carboplatin, the median time to first occurrence of Grade 3 treatment-related peripheral neuropathy was 121 days, and the median time to improvement from Grade 3 treatment related peripheral neuropathy to Grade 1 was 38 days. No patients treated with Abraxane and carboplatin experienced Grade 4 peripheral neuropathy.

Eye disorders

There have been rare reports during post-marketing surveillance of reduced visual acuity due to cystoid macular oedema during treatment with Abraxane (see section 4.4).

Respiratory, thoracic and mediastinal disorders

Abraxane/gemcitabine

Pneumonitis has been reported at a rate of 4 % with the use of Abraxane in combination with gemcitabine. Of the 17 cases of pneumonitis reported in patients treated with Abraxane in combination with gemcitabine, 2 had a fatal outcome. Monitor patients closely for signs and symptoms of pneumonitis. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with Abraxane and gemcitabine and promptly initiate appropriate treatment and supportive measures (see section 4.2).

Gastrointestinal disorders

Abraxane monotherapy-metastatic breast cancer

Nausea occurred in 29 % of the patients and diarrhoea in 25 % of the patients.

Skin and subcutaneous tissue disorders

Abraxane monotherapy-metastatic breast cancer

Alopecia was observed in > 80 % of the patients treated with Abraxane. The majority of alopecia events occurred less than one month after initiation of Abraxane. Pronounced hair loss ≥ 50 % is expected for the majority of patients who experience alopecia.

Musculoskeletal and connective tissue disorders

Abraxane monotherapy-metastatic breast cancer

Arthralgia occurred in 32 % of patients on Abraxane and was severe in 6 % of cases. Myalgia occurred in 24 % of patients on Abraxane and was severe in 7 % of cases. The symptoms were usually transient, typically occurred three days after Abraxane administration and resolved within a week.

General disorders and administration site conditions

Abraxane monotherapy-metastatic breast cancer

Asthenia/Fatigue was reported in 40 % of the patients.

Paediatric population

The study consisted of 106 patients, 104 of whom were paediatric patients aged from 6 months to less than 18 years (see section 5.1). Every patient experienced at least 1 adverse reaction. The most frequently reported adverse reactions were neutropenia, anaemia, leukopenia and pyrexia. Serious adverse reactions reported in more than 2 patients were pyrexia, back pain, peripheral oedema and vomiting. No new safety

signals were identified in the limited number of paediatric patients treated with Abraxane and the safety profile was similar to that of the adult population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class 26. Cytostatic agents

Pharmacotherapeutic group: Antineoplastic agents, plant alkaloids and other natural products, taxanes, ATC Code: L01CD01

Mechanism of action

In albumin-bound paclitaxel, paclitaxel 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.

Albumin-bound paclitaxel contains human serum albumin-paclitaxel nanoparticles, where the paclitaxel is present in a non-crystalline, amorphous state. Albumin is known to mediate endothelial transcytosis of plasma constituents and in vitro studies demonstrated that albumin-bound paclitaxel increased transport of paclitaxel across endothelial cells.

5.2 Pharmacokinetic properties

Absorption:

Following intravenous administration of albumin-bound paclitaxel, 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 AUC was dose proportional over 80 to 300 mg/m^2 and the pharmacokinetics of paclitaxel for albumin-bound paclitaxel were independent of the duration of intravenous administration.

Distribution:

Following albumin-bound paclitaxel administration to patients with solid tumours, paclitaxel is evenly distributed into blood cells and plasma and is highly bound to plasma proteins (94 %).

In vitro studies of binding to human serum proteins, using paclitaxel at concentrations ranging from 0,1 to 50 µg/ml, indicate that the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

Based on 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:

In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolised primarily to 6α-hydroxypaclitaxel by CYP2C8; and to two minor metabolites, 3'-*p*-hydroxypaclitaxel and 6α, 3'-*p*-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of medicines (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, ciclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel *in vitro*. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4.

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

Excretion:

After a 30-minute infusion of 260 mg/m^2 doses of albumin-bound paclitaxel, the mean values for cumulative urinary recovery of unchanged substance (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.

Pharmacokinetics in children:

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 tumours. 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-normalized 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 medicine exposures were higher than in adult patients. The overall safety profile was manageable without frequent dose reductions or discontinuations.

Pharmacokinetics in elderly:

Population pharmacokinetic analysis for albumin-bound paclitaxel 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 patients with 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=l) 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 patients with hepatic impairment:

The effect of hepatic impairment on population pharmacokinetics of albumin-bound paclitaxel 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 (based on serum bilirubin) (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}.

Elimination of paclitaxel shows an inverse correlation with total bilirubin and a positive correlation with serum albumin.

Pharmacokinetic/pharmacodynamic modeling indicates that there is no correlation between hepatic function (as indicated by the baseline albumin or total bilirubin level) and neutropenia after adjusting for albumin-bound paclitaxel exposure.

Pharmacokinetic data are not available for patients with total bilirubin > 5 x ULN or for patients with metastatic adenocarcinoma of the pancreas.

Other intrinsic factors:

Population pharmacokinetic analyses for albumin-bound paclitaxel 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Approximately 900 mg of human albumin.

6.2 Incompatibilities

In the absence of compatibility studies, ABRAXANE must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vials: 36 months

As the product does not contain any bacteriostatic agent, from a microbiological point of view, the reconstituted or diluted product should be used immediately.

Stability of reconstituted suspension in the vial

The reconstituted ABRAXANE should be used immediately but may be refrigerated at 2 ºC to 8 ºC 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 but may be stored at ambient temperature (approximately 25 º C) and lighting conditions for up to 8 hours.

6.4 Special precautions for storage

Store at or below 25 ºC. Retain in the original package to protect from light.

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

6.5 Nature and contents of container

50 ml clear Type I glass single use vial with a grey rubber stopper.

The stopper is protected with a silver aluminium overseal.

Vials are packed in individual cartons.

6.6 Special precautions for disposal and other handling

Preparation and administration precautions:

ABRAXANE is a cytotoxic anticancer agent and, as with other potentially toxic paclitaxel compounds, caution should be exercised in handling ABRAXANE. The use of gloves, goggles and protective clothing 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 ABRAXANE, events may include tingling, burning and redness. If ABRAXANE contacts mucous membranes, the membranes should be flushed thoroughly with water. Pregnant staff should not handle ABRAXANE.

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.

Reconstitution of the product and administration

ABRAXANE is supplied as a sterile lyophilised powder for reconstitution before use. Each ml of the reconstituted formulation will contain 5 mg/ml paclitaxel.

Using a sterile syringe, slowly inject 20 ml of sodium chloride 9 mg/ml solution for injection to a vial of ABRAXANE. Direct the solution flow onto the inside wall of the vial and take at least 1 minute for the introduction. Do not inject the solution directly onto the lyophilisate as this will result in foaming.

Once the addition is complete, allow the vial to stand for a minimum of 5 minutes to ensure proper wetting of the solid. Then, gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any lyophilisate occurs. Avoid the generation of foam.

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.

Calculate the exact total dosing volume of 5 mg/ml suspension required for the patient and 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, PVC or non-PVC type intravenous bag]. The use of specialized DEHP-free solution containers or administration sets is not necessary to

prepare or administer ABRAXANE infusions. The use of medical devices containing silicone oil as a lubricant (i.e., syringes and I.V. bags) to reconstitute and administer ABRAXANE may result in the formation of proteinaceous strands.

Administer Abraxane using an infusion set incorporating a 15 µm filter to avoid administration of these strands. Use of a 15 µm filter removes strands and does not change the physical or chemical properties of the reconstituted product.

Use of filters with a pore size less than 15 µm may result in blockage of the filter.

The use of specialized di(2-ethylhexyl) phthalate (DEHP)-free solution containers or administration sets is not necessary to prepare or administer ABRAXANE infusions.

Following administration, it is recommended that the intravenous line be flushed with sodium chloride 9 mg/ml (0,9 %) solution for injection to ensure administration of the complete dose.

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

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Key Oncologics (Pty) Ltd

39 Eleventh Avenue

Houghton Estate, 2198

Johannesburg

South Africa

8. REGISTRATION NUMBER

50/26/0182

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

29 September 2017

10. DATE OF REVISION OF THE TEXT

4 September 2025