

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Abraxane 5 mg/ml powder for suspension for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg of paclitaxel formulated as albumin bound nanoparticles.
Each vial contains 250 mg of paclitaxel formulated as albumin bound nanoparticles.

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

Excipients with known effect

Each ml of concentrate contains 0.183 mmol sodium, which is 4.2 mg of sodium.

For the 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.

The powder is white to yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Abraxane monotherapy is indicated for the treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated (see section 4.4).

Abraxane in combination with gemcitabine is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas.

4.2 Posology and method of administration

Abraxane should only be administered under the supervision of a qualified oncologist in units specialised in the administration of cytotoxic agents. It should not be substituted for or with other paclitaxel formulations.

Posology

Breast cancer

The recommended dose of Abraxane is 260 mg/m² administered intravenously over 30 minutes every 3 weeks.

Dose adjustments during treatment of breast cancer

Patients who experience severe neutropenia (neutrophil count < 500 cells/mm³ for a week or longer) or severe sensory neuropathy during Abraxane therapy should have the dose reduced to 220 mg/m² for subsequent courses. Following recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m². Abraxane should not be administered until neutrophil counts recover to >1500 cells/mm³. For grade 3 sensory neuropathy withhold treatment until resolution to grade 1 or 2, followed by a dose reduction for all subsequent courses.

Pancreatic adenocarcinoma

The recommended dose of Abraxane in combination with gemcitabine is 125 mg/m² administered intravenously over 30 minutes on Days 1, 8 and 15 of each 28-day cycle. The concurrent recommended dose of gemcitabine is 1000 mg/m² administered intravenously over 30 minutes immediately after the completion of Abraxane administration on Days 1, 8 and 15 of each 28-day cycle.

Dose adjustments during treatment of pancreatic adenocarcinoma

Table 1: Dose level reductions for patients with pancreatic adenocarcinoma

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

Table 2: Dose modifications for neutropenia and/or thrombocytopenia at the start of a cycle or within a cycle for patients with pancreatic adenocarcinoma

Cycle Day	ANC count (cells/mm ³)		Platelet count (cells/mm ³)	Abraxane Dose	Gemcitabine Dose
Day 1	< 1500	OR	< 100,000	Delay doses until recovery	
Day 8	≥ 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	≥ 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 levels 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 levels 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	$\geq 75,000$	Return to Day 1 dose levels and follow with WBC Growth Factors OR Reduce doses 1 dose level from Day 1 doses
	≥ 500 but < 1000	OR	$\geq 50,000$ 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 3: Dose modifications for other adverse drug reactions in patients with pancreatic adenocarcinoma

Adverse Drug Reaction (ADR)	Abraxane Dose	Gemcitabine Dose
Febrile Neutropenia: Grade 3 or 4	Withhold doses until fever resolves and ANC ≥ 1500 ; resume at next lower dose level ^a	
Peripheral Neuropathy: Grade 3 or 4	Withhold dose until improves to \leq 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 \leq Grade 1; resume at next lower dose level ^a	

^aSee Table 1 for dose level reductions

Special populations

Patients with hepatic impairment

Insufficient data are currently available to recommend dose modifications in patients with mild to moderate hepatic impairment that ensure acceptable toxicity while maintaining efficacy of Abraxane. Patients with severe hepatic impairment should not be treated with paclitaxel (see sections 4.4. and 5.2).

Patients with renal impairment

Studies in patients with impaired renal function have not been performed and insufficient data are currently available to recommend dose modifications of Abraxane in patients with renal impairment (see section 5.2).

Older people

No additional dosage reductions, other than those for all patients, are recommended for patients 65 years and older.

Of the 229 patients in the randomized study who received Abraxane monotherapy for breast cancer, 13% were at least 65 years of age and < 2% were 75 years and older. No toxicities occurred notably more frequently among patients at least 65 years of age who received Abraxane.

Of the 421 patients with pancreatic adenocarcinoma in the randomized study who received Abraxane in combination with gemcitabine, 41% were 65 years and older and 10% were 75 years and older. In patients aged 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 (see section 4.4). Patients with pancreatic adenocarcinoma aged 75 years and older should be carefully assessed before treatment is considered (see section 4.4).

Paediatric population

The safety and efficacy of Abraxane in children and adolescents aged 0-17 years has not been established. There is no relevant use of Abraxane in the paediatric population in the indication of metastatic breast cancer or pancreatic adenocarcinoma.

Method of administration

Abraxane is administered intravenously.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Lactation (see section 4.6).

Patients who have baseline neutrophil counts <1500 cells/mm³.

4.4 Special warnings and precautions for use

Abraxane is an albumin-bound nanoparticle formulation of paclitaxel, which may have substantially different pharmacological properties compared to other formulations of paclitaxel (see sections 5.1 and 5.2). It should not be substituted for or with other paclitaxel formulations.

Hypersensitivity

Rare occurrences of severe hypersensitivity reactions, including very rare events of anaphylactic reactions with fatal outcome, have been reported. If a hypersensitivity reaction occurs, the medicinal product should be discontinued immediately, symptomatic treatment should be initiated, and the patient should not be rechallenged with paclitaxel.

Haematology

Bone marrow suppression (primarily neutropenia) occurs frequently with Abraxane. Neutropenia is dose-dependent and a dose-limiting toxicity. Frequent monitoring of blood cell counts should be

performed during Abraxane therapy. Patients should not be retreated with subsequent cycles of Abraxane until neutrophils recover to >1500 cells/mm³ and platelets recover to $>100,000$ cells/mm³ (see section 4.2).

Neuropathy

Sensory neuropathy occurs frequently with Abraxane, although development of severe symptoms is less common. The occurrence of grade 1 or 2 sensory neuropathy does not generally require dose reduction. When Abraxane is used as monotherapy, if grade 3 sensory neuropathy develops, treatment should be withheld until resolution to grade 1 or 2 followed by a dose reduction for all subsequent courses of Abraxane is recommended (see section 4.2). 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).

Sepsis

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 cells/mm³, then resume treatment at reduced dose levels (see section 4.2).

Pneumonitis

Pneumonitis occurred in 1% of patients when Abraxane was used as monotherapy and in 4% of patients when Abraxane was used in combination with gemcitabine. Closely monitor all patients 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).

Hepatic impairment

Because the toxicity of paclitaxel can be increased with hepatic impairment, administration of Abraxane in patients with hepatic impairment should be performed with caution. 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.

Patients with severe hepatic impairment (bilirubin > 5 x ULN or AST/ALT > 10 x ULN) have not been studied and should not be treated with Abraxane. The appropriate dose regimen in patients with less severe hepatic impairment is unknown. A dose reduction in patients with bilirubin >2 ULN must be considered since paclitaxel clearance is decreased in patients with high bilirubin levels (see section 5.2).

Cardiotoxicity

Rare reports of congestive heart failure and left ventricular dysfunction have been observed among individuals receiving Abraxane. Most of the individuals were previously exposed to cardiotoxic medicinal products 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 central nervous system (CNS) metastases has not been established. CNS metastases are generally not well controlled by systemic chemotherapy.

Gastrointestinal symptoms

If patients experience nausea, vomiting and diarrhoea following the administration of Abraxane, they may be treated with commonly used anti-emetics and constipating agents.

Patients 75 years and older

For patients of 75 years and older, no benefit for the combination treatment of Abraxane and gemcitabine in comparison to gemcitabine monotherapy has been demonstrated. In the very elderly (≥ 75 years) who received Abraxane and gemcitabine, there was a higher incidence of serious adverse reactions and adverse reactions that led to treatment discontinuation including haematologic toxicities, peripheral neuropathy, decreased appetite and dehydration. Patients with pancreatic adenocarcinoma aged 75 years and older should be carefully assessed for their ability to tolerate Abraxane in combination with gemcitabine with special consideration to performance status, co-morbidities and increased risk of infections (see section 4.2 and 4.8)

Other

Although limited data is available, no clear benefit in terms of prolonged overall survival has been demonstrated in pancreatic adenocarcinoma patients with normal CA 19-9 levels prior to start of treatment with Abraxane and gemcitabine (see section 5.1).

Erlotinib should not be coadministered to Abraxane plus gemcitabine (see section 4.5).

Excipients

When reconstituted, each ml of Abraxane concentrate contains 0.183 mmol sodium, which is 4.2 mg of sodium. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interactions with other medicinal products and other forms of interaction

No interaction studies have been performed.

The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4 (see section 5.2). Therefore, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or induce (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) either CYP2C8 or CYP3A4.

Paclitaxel and gemcitabine do not share a common metabolic pathway. Paclitaxel clearance is primarily determined by CYP2C8 and CYP3A4 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.

Abraxane is indicated as monotherapy for breast cancer, or in combination with gemcitabine for pancreatic adenocarcinoma (see section 4.1). Abraxane should not be used in combination with other anticancer agents.

4.6 Fertility, pregnancy and lactation

Contraception in males and females

Women of childbearing potential should use effective contraception during treatment and up to 1 month after receiving treatment with Abraxane. Male patients treated with Abraxane are advised not to father a child during and up to six months after treatment.

Pregnancy

There are very limited data on the use of paclitaxel in human pregnancy. Paclitaxel is suspected to cause serious birth defects when administered during pregnancy. Studies in animals have shown reproductive toxicity (see section 5.3). Abraxane should not be used in pregnancy, and in women of childbearing potential not using effective contraception, unless the clinical condition of the mother requires treatment with paclitaxel.

Breast-feeding

It is not known if paclitaxel is excreted in human milk. Because of potential serious adverse reactions in breast-feeding infants, Abraxane is contraindicated during lactation. Breast-feeding must be discontinued for the duration of therapy.

Fertility

Abraxane induced infertility in male rats (see section 5.3). 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

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 Undesirable effects

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.

The frequencies of adverse reactions associated with the administration of Abraxane are listed in Table 4 (Abraxane as monotherapy) and Table 5 (Abraxane in combination with gemcitabine).

Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1000$), very rare ($< 1/10,000$). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Breast cancer (Abraxane administered as monotherapy)

Tabulated list of adverse reactions

Table 4 lists adverse reactions associated with the administration of Abraxane to patients from studies in which Abraxane has been administered as monotherapy at any dose in any indication (N = 789).

Table 4: Adverse reactions reported with Abraxane monotherapy at any dose in clinical studies

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, sepsis ² , neutropenic sepsis ²
Neoplasms benign, malignant and unspecified (including cysts and polyps)	<i>Uncommon:</i> Metastatic pain, tumour necrosis

Blood and lymphatic system disorders	<p><i>Very common:</i> Neutropenia, anaemia, leukopenia, thrombocytopenia, lymphopenia, bone marrow suppression</p> <p><i>Common:</i> Febrile neutropenia</p> <p><i>Rare:</i> Pancytopenia</p>
Immune system disorders	<p><i>Uncommon</i>¹: Hypersensitivity</p> <p><i>Rare:</i> Severe hypersensitivity</p>
Metabolism and nutrition disorders	<p><i>Very common:</i> Anorexia</p> <p><i>Common:</i> Dehydration, decreased appetite, hypokalaemia</p> <p><i>Uncommon:</i> Hypophosphataemia, fluid retention, hypoalbuminaemia, polydipsia, hyperglycaemia, hypocalcaemia, hypoglycaemia, hyponatraemia</p>
Psychiatric disorders	<p><i>Common:</i> Insomnia, depression, anxiety</p> <p><i>Uncommon:</i> Restlessness</p>
Nervous system disorders	<p><i>Very common:</i> Peripheral neuropathy, neuropathy, hypoaesthesia, paraesthesia</p> <p><i>Common:</i> Peripheral sensory neuropathy, headache, dysgeusia, dizziness, peripheral motor neuropathy, ataxia, sensory disturbance, somnolence</p> <p><i>Uncommon:</i> Polyneuropathy, areflexia, dyskinesia, hyporeflexia, neuralgia, sensory loss, syncope, postural dizziness, neuropathic pain, tremor</p>
Eye disorders	<p><i>Common:</i> Increased lacrimation, blurred vision, dry eye, keratoconjunctivitis sicca, madarosis</p> <p><i>Uncommon:</i> Eye irritation, eye pain, abnormal vision, reduced visual acuity, conjunctivitis, visual disturbance, eye pruritus, keratitis</p> <p><i>Rare:</i> Cystoid macular oedema²</p>
Ear and labyrinth disorders	<p><i>Common:</i> Vertigo</p> <p><i>Uncommon:</i> Ear pain, tinnitus</p>
Cardiac disorders	<p><i>Common:</i> Tachycardia, arrhythmia, supraventricular tachycardia</p> <p><i>Rare:</i> bradycardia, cardiac arrest, left ventricular dysfunction, congestive heart failure, atrioventricular block²</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> Interstitial pneumonitis³, 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</p>
Gastrointestinal disorders	<p><i>Very common:</i> Nausea, diarrhoea, vomiting, constipation, stomatitis</p> <p><i>Common:</i> Abdominal pain, abdominal distension, upper abdominal pain, dyspepsia, gastrooesophageal reflux disease, oral hypoesthesia</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> 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, generalized pruritus, macular rash, papular rash, skin lesion, swollen face</p> <p><i>Very rare:</i> Stevens-Johnson syndrome², toxic epidermal necrolysis²</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> <p><i>Rare:</i> Extravasation</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>

MedDRA = Medical Dictionary for Regulatory Activities.

SMQ = Standardized MedDRA Query; SMQ is a grouping of several MedDRA preferred terms to capture a medical concept.

¹ The frequency of hypersensitivity reactions is calculated based on one definitely related case in a population of 789 patients.

² As reported in the post-marketing surveillance of Abraxane.

³ 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 using MedDRA SMQ Interstitial lung disease. See section 4.4.

Description of selected adverse reactions

The following are the most common and clinically relevant adverse reactions related to 229 patients with metastatic breast cancer who were treated with 260 mg/m² Abraxane once every three weeks in the pivotal phase III clinical study.

Blood and lymphatic system disorders

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/mm³) 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.

Nervous system disorders

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.

Gastrointestinal disorders

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

Skin and subcutaneous tissue disorders

Alopecia was observed in 90% of the patients treated with Abraxane.

Musculoskeletal and connective tissue disorders

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

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

Pancreatic adenocarcinoma (Abraxane administered in combination with gemcitabine)

Tabulated list of adverse reactions

Adverse reactions were assessed in 421 patients treated with Abraxane in combination with gemcitabine and 402 gemcitabine monotherapy-treated patients receiving first-line systemic treatment for metastatic adenocarcinoma of the pancreas in a phase III randomized, controlled, open-label trial. Table 5 lists adverse reactions assessed in patients with pancreatic adenocarcinoma treated with Abraxane in combination with gemcitabine.

Table 5: Adverse reactions reported with Abraxane in combination with gemcitabine (N =421)

Infections and infestations	<i>Common:</i> Sepsis, pneumonia, oral candidiasis
Blood and lymphatic system disorders	<i>Very common:</i> Neutropenia, anaemia, thrombocytopenia <i>Common:</i> Pancytopenia <i>Uncommon:</i> Thrombotic thrombocytopenic purpura
Metabolism and nutrition disorders	<i>Very common:</i> Dehydration, decreased appetite, hypokalaemia
Psychiatric disorders	<i>Very common:</i> Insomnia, depression <i>Common:</i> Anxiety
Nervous system disorders	<i>Very common:</i> Peripheral neuropathy ^a , dysgeusia, headache, dizziness <i>Uncommon:</i> VII th nerve paralysis
Eye disorders	<i>Common:</i> Lacrimation increased <i>Uncommon:</i> Cystoid macular oedema
Cardiac disorders	<i>Common:</i> Cardiac failure congestive, tachycardia
Vascular disorders	<i>Common:</i> Hypotension, hypertension
Respiratory, thoracic and mediastinal disorders	<i>Very Common:</i> Dyspnoea, epistaxis, cough <i>Common:</i> Pneumonitis, nasal congestion <i>Uncommon:</i> Dry throat, nasal dryness
Gastrointestinal disorders	<i>Very Common:</i> Nausea, diarrhoea, vomiting, constipation, abdominal pain, abdominal pain upper <i>Common:</i> Stomatitis, intestinal obstruction, colitis, dry mouth
Hepatobiliary disorders	<i>Common:</i> Cholangitis
Skin and subcutaneous tissue disorders	<i>Very Common:</i> Alopecia, rash <i>Common:</i> Pruritus, dry skin, nail disorder, flushing
Musculoskeletal and connective tissue disorders	<i>Very common:</i> Pain in extremity, arthralgia, myalgia <i>Common:</i> Muscular weakness, bone pain

Renal and urinary disorders	<i>Common:</i> Acute renal failure <i>Uncommon:</i> Haemolytic uraemic syndrome
General disorders and administration site conditions	<i>Very common:</i> Fatigue, oedema peripheral, pyrexia, asthenia, chills <i>Common:</i> Infusion site reaction
Investigations	<i>Very common:</i> Weight decreased, alanine aminotransferase increased <i>Common:</i> Aspartate aminotransferase increased, blood bilirubin increased, blood creatinine increased

MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardized MedDRA Query (a grouping of several MedDRA preferred terms to capture a medical concept).

^a Peripheral neuropathy evaluated using the Standardized MedDRA Query (broad scope).

In this phase III randomized, controlled, open-label trial, adverse reactions resulting in death within 30 days of the last dose of study drug were reported for 4% of patients receiving Abraxane in combination with gemcitabine and for 4% of patients receiving gemcitabine monotherapy.

Description of selected adverse reactions

The following are the most common and important incidences of adverse reactions related to 421 patients with metastatic adenocarcinoma of the pancreas who were treated with 125 mg/m² Abraxane in combination with gemcitabine at a dose of 1000 mg/m² given on Days 1, 8 and 15 of each 28-day cycle in the phase III clinical study.

Blood and lymphatic system disorders

Table 6 provides the frequency and severity of haematologic laboratory-detected abnormalities for patients treated with Abraxane in combination with gemcitabine or with gemcitabine.

Table 6: 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

Peripheral Neuropathy

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.

Sepsis

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. 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 $ANC \geq 1500 \text{ cells/mm}^3$, then resume treatment at reduced dose levels (see section 4.2).

Pneumonitis

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).

Post-marketing experience

Cranial nerve palsies, vocal cord paresis, and rare reports of severe hypersensitivity reactions have been reported during post-marketing surveillance of Abraxane.

There have been rare reports of reduced visual acuity due to cystoid macular oedema during treatment with Abraxane. Upon diagnosis of cystoid macular oedema, treatment with Abraxane should be discontinued.

In some patients previously exposed to capecitabine, reports of palmar-plantar erythrodysesthesiae have been reported as part of the continuing surveillance of Abraxane. Because these events have been reported voluntarily during clinical practice, true estimates of frequency cannot be made and a causal relationship to the events has not been established.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via **the national reporting system listed in Appendix V**.

4.9 Overdose

There is no known antidote for paclitaxel overdose. In the event of an overdose, the patient should be closely monitored. Treatment should be directed at the major anticipated toxicities, which are bone marrow suppression, mucositis and peripheral neuropathy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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. In addition, paclitaxel induces abnormal arrays or “bundles” of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Abraxane contains human serum albumin-paclitaxel nanoparticles of approximately 130 nm in size, where the paclitaxel is present in a non-crystalline, amorphous state. Upon intravenous administration, the nanoparticles dissociate rapidly into soluble, albumin bound paclitaxel complexes of approximately 10 nm in size. Albumin is known to mediate endothelial caveolar transcytosis of plasma constituents, and *in vitro* studies demonstrated that the presence of albumin in Abraxane enhances transport of paclitaxel across endothelial cells. It is hypothesised that this enhanced transendothelial caveolar transport is mediated by the gp-60 albumin receptor, and that there is enhanced accumulation of paclitaxel in the area of tumour due to the albumin-binding protein Secreted Protein Acidic Rich in Cysteine (SPARC).

Clinical efficacy and safety

Breast cancer

Data from 106 patients accrued in two single-arm open-label studies and from 454 patients treated in a randomised Phase III comparative study are available to support the use of Abraxane in metastatic breast cancer. This information is presented below.

Single-arm open-label studies

In one study, Abraxane was administered as a 30-minute infusion at a dose of 175 mg/m² to 43 patients with metastatic breast cancer. The second trial utilised a dose of 300 mg/m² as a 30 minute infusion in 63 patients with metastatic breast cancer. Patients were treated without steroid pre-treatment or planned G-CSF support. Cycles were administered at 3 week intervals. The response rates in all patients were 39.5% (95% CI: 24.9%-54.2%) and 47.6% (95% CI: 35.3%-60.0%), respectively. The median time to disease progression was 5.3 months (175 mg/m²; 95% CI: 4.6-6.2 months) and 6.1 months (300 mg/m²; 95% CI: 4.2-9.8 months).

Randomised comparative study

This multi-centre trial was conducted in patients with metastatic breast cancer, who were treated every 3 weeks with single-agent paclitaxel, either as solvent-based paclitaxel 175 mg/m² given as a 3-hour infusion with premedication to prevent hypersensitivity (N = 225), or as Abraxane 260 mg/m² given as a 30 minute infusion without premedication (N = 229).

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 medicinal product as second or greater than second-line therapy. Seventy-seven percent of the patients had been previously exposed to anthracyclines.

Results for overall response rate and time to disease progression, and progression-free survival and survival for patients receiving > 1st-line therapy, are shown below.

Table 7: 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 ²)	Solvent-based paclitaxel (175 mg/m ²)	p-value
<i>Response rate [95% CI] (%)</i>			
> 1 st -line therapy	26.5 [18.98, 34.05] (n = 132)	13.2 [7.54, 18.93] (n = 136)	0.006 ^a
<i>*Median time to disease progression [95% CI] (weeks)</i>			
> 1 st -line therapy	20.9 [15.7, 25.9] (n = 131)	16.1 [15.0, 19.3] (n = 135)	0.011 ^b
<i>*Median progression free survival [95% CI] (weeks)</i>			
> 1 st -line therapy	20.6 [15.6, 25.9] (n = 131)	16.1 [15.0, 18.3] (n = 135)	0.010 ^b
<i>*Survival [95% CI] (weeks)</i>			
> 1 st -line therapy	56.4 [45.1, 76.9] (n = 131)	46.7 [39.0, 55.3] (n = 136)	0.020 ^b

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

^a Chi-squared test

^b Log-rank test

Two hundred and twenty nine patients treated with Abraxane in the randomized, controlled clinical trial were evaluated for safety. Neurotoxicity to paclitaxel was evaluated through improvement by one grade for patients experiencing grade 3 peripheral neuropathy at any time during therapy. The natural course of peripheral neuropathy to resolution to baseline due to cumulative toxicity of Abraxane after > 6 courses of treatment was not evaluated and remains unknown.

Pancreatic adenocarcinoma

A multicenter, multinational, randomized, open-label study was conducted in 861 patients to compare Abraxane/gemcitabine versus gemcitabine monotherapy as first-line treatment in patients with metastatic adenocarcinoma of the pancreas. Abraxane was administered to patients (N = 431) as an intravenous infusion over 30-40 minutes at a dose of 125 mg/m² followed by gemcitabine as an intravenous infusion over 30-40 minutes at a dose of 1000 mg/m² given on Days 1, 8 and 15 of each 28-day cycle. In the comparator treatment arm, gemcitabine monotherapy was administered to patients (N = 430) in accordance with the recommended dose and regimen. Treatment was administered until disease progression or development of an unacceptable toxicity. Of the 431 patients with pancreatic adenocarcinoma who were randomized to receive Abraxane in combination with gemcitabine, the majority (93%) were white, 4% were black and 2% were Asian. 16% had a Karnofsky Performance Status of 100; 42% had a KPS of 90; 35% had a KPS of 80; 7% had a KPS of 70; and <1% of patients had a KPS

of below 70. Patients with high cardiovascular risk, history of peripheral artery disease and/or of connective tissue disorders and/or interstitial lung disease were excluded from the study.

Patients received a median treatment duration of 3.9 months in the Abraxane/gemcitabine arm and 2.8 months in the gemcitabine arm. 32% of patients in the Abraxane/gemcitabine arm compared with 15% of patients in the gemcitabine arm received 6 or more months of treatment. For the treated population, the median relative dose intensity for gemcitabine was 75% in the Abraxane/gemcitabine arm and 85% in the gemcitabine arm. The median relative dose intensity of Abraxane was 81%. A higher median cumulative dose of gemcitabine was delivered in the Abraxane/gemcitabine arm (11400 mg/m²) when compared with the gemcitabine arm (9000 mg/m²).

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

Table 8: Efficacy results from randomized study in patients with pancreatic adenocarcinoma (Intent-to-treat population)

	Abraxane(125 mg/m²)/gemcitabine (N=431)	Gemcitabine (N=430)
Overall Survival		
Number of deaths (%)	333 (77)	359 (83)
Median Overall Survival, months (95% CI)	8.5 (7.89, 9.53)	6.7 (6.01, 7.23)
HR _{A+G/G} (95% 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)
75 th Percentile Overall Survival (months)	14.8	11.4
Progression-free Survival		
Death or progression, n (%)	277 (64)	265 (62)
Median Progression-free Survival, months (95% CI)	5.5 (4.47, 5.95)	3.7 (3.61, 4.04)
HR _{A+G/G} (95% CI) ^a	0.69 (0.581, 0.821)	
P-value ^b	<0.0001	
Overall Response Rate		
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% CI)	3.19 (2.178, 4.662)	
P-value (chi-square test)	<0.0001	

CI = confidence interval, HR_{A+G/G} = hazard ratio of Abraxane+gemcitabine/gemcitabine,

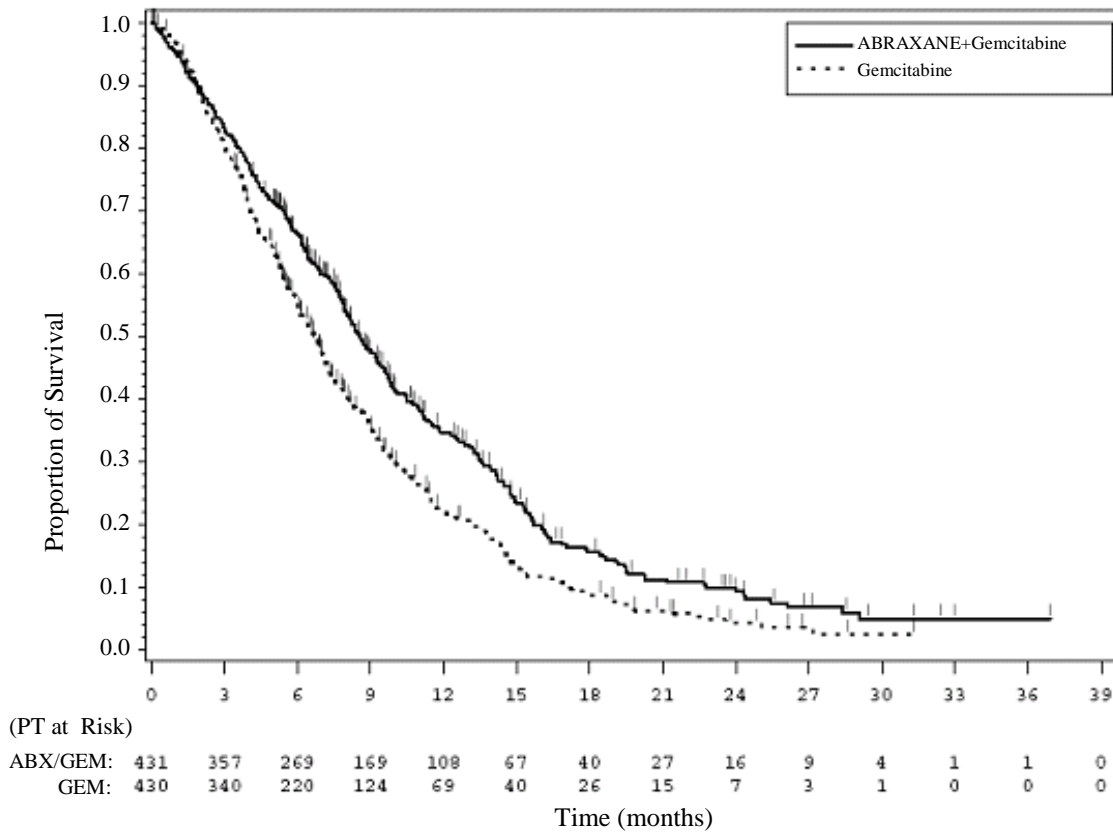
p_{A+G}/p_G=response rate ratio of Abraxane+gemcitabine/gemcitabine

^a stratified Cox proportional hazard model

^b stratified log-rank test, stratified by geographic region (North America versus others), KPS (70 to 80 versus 90 to 100), and presence of liver metastasis (yes versus no).

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.

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



Treatment effects on OS favoured the Abraxane/gemcitabine arm across the majority of pre-specified subgroups (including gender, KPS, geographic region, primary location of pancreatic cancer, stage at diagnosis, presence of liver metastases, presence of peritoneal carcinomatosis, prior Whipple procedure, presence of biliary stent at baseline, presence of pulmonary metastases, and number of metastatic sites). For patients ≥ 75 years of age in the Abraxane/gemcitabine and gemcitabine arms the survival Hazard Ratio (HR) was 1.08 (95% CI 0.653, 1.797). For patients with normal baseline CA 19-9 levels the survival HR was 1.07 (95% CI 0.692, 1.661).

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.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Abraxane in all subsets of the paediatric population in the treatment of metastatic breast cancer and pancreatic adenocarcinoma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of total paclitaxel following 30- and 180-minute infusions of Abraxane at dose levels of 80 to 375 mg/m² were determined in clinical studies. The paclitaxel exposure (AUC) increased linearly from 2653 to 16736 ng.hr/ml following dosing from 80 to 300 mg/m².

Following intravenous administration of Abraxane to patients with metastatic breast cancer at the recommended clinical dose of 260 mg/m², paclitaxel plasma concentrations declined in a multiphasic manner. The mean C_{max} of paclitaxel, which occurred at the end of the infusion, was 18.7 µg/ml. The

mean total clearance was 15 l/hr/m². The terminal half-life was about 27 hours. The mean volume of distribution was 632 l/m²; the large volume of distribution indicates extensive extravascular distribution and/or tissue binding of paclitaxel.

In a study in patients with advanced solid tumours, the pharmacokinetic characteristics of paclitaxel following Abraxane administered intravenously at 260 mg/m² over 30 minutes were compared with those following 175 mg/m² of the solvent-based paclitaxel injection administered over 3 hours. The clearance of paclitaxel with Abraxane was larger (43%) than that following a solvent-based paclitaxel injection and its volume of distribution was also higher (53%). Differences in C_{max} and C_{max} corrected for dose reflected differences in total dose and rate of infusion. There were no differences in terminal half-lives.

In a repeat dose study with 12 patients receiving Abraxane administered intravenously at the approved dose, inpatient variability in systemic paclitaxel exposure (AUC_{inf}) was 19% (range = 3.21%-27.70%). There was no evidence for accumulation of paclitaxel with multiple treatment courses.

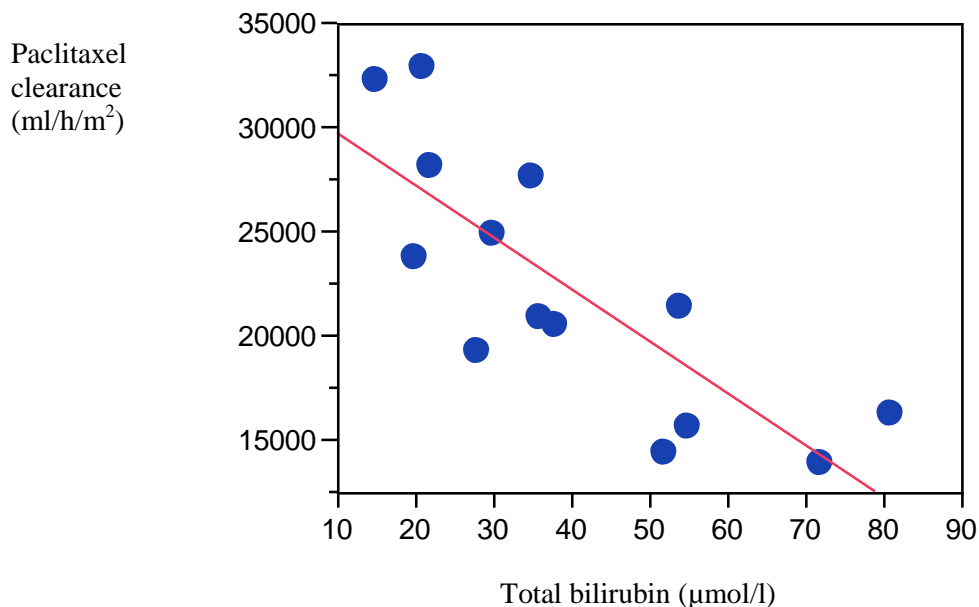
An analysis of patient exposure (AUC_{inf}) against bodyweight indicated a trend toward reduced AUC at 260 mg/m² Abraxane, with decreased body weight. Patients weighing 50 kg had paclitaxel AUC approximately 25% lower than those weighing 75 kg. The clinical relevance of this finding is uncertain.

The protein binding of paclitaxel following Abraxane was evaluated by ultrafiltration. The fraction of free paclitaxel was significantly higher with Abraxane (6.2%) than with solvent-based paclitaxel (2.3%). This resulted in significantly higher exposure to unbound paclitaxel with Abraxane compared with solvent-based paclitaxel, even though the total exposure is comparable. This is possibly due to paclitaxel not being trapped in Cremophor EL micelles as with solvent-based paclitaxel. Based on the published literature, *in vitro* studies of binding to human serum proteins, (using paclitaxel at 6µM) the presence of ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

Based on the published literature, *in vitro* studies with human liver microsomes and tissue slices show that paclitaxel is metabolised primarily to 6α-hydroxypaclitaxel; and to two minor metabolites, 3'-p-hydroxypaclitaxel and 6α-3'-p-dihydroxypaclitaxel. The formation of these hydroxylated metabolites is catalysed by CYP2C8, -3A4, and both -2C8 and -3A4 respectively.

The pharmacokinetic profile of Abraxane administered as a 30 minute infusion was evaluated in 15 out of 30 patients with three levels of hepatic impairment based on serum bilirubin and liver enzyme levels. Figure 2 shows the correlation between paclitaxel clearance and total blood bilirubin as measured just prior to dosing.

Figure 2: Correlation between paclitaxel clearance and total blood bilirubin



The effect of renal dysfunction on the disposition of paclitaxel has not been formally investigated.

In patients with metastatic breast cancer, after a 30 minute infusion of Abraxane at 260 mg/m², the mean value for cumulative urinary excretion of unchanged active substance accounted for 4% of the total administered dose with less than 1% as the metabolites 6 α -hydroxypaclitaxel and 3'-p-hydroxypaclitaxel, indicating extensive non-renal clearance. Paclitaxel is principally eliminated by hepatic metabolism and biliary excretion.

Pharmacokinetics of paclitaxel in patients aged over 65 years seems comparable to that in patients less than 65 years. However, little information in patients over 75 years is available as only 3 patients over 75 years of age were included in the pharmacokinetic analysis.

5.3 Preclinical safety data

The carcinogenic potential of paclitaxel has not been studied. However, based on the published literature, paclitaxel is a potentially carcinogenic and genotoxic agent at clinical doses, based upon its pharmacodynamic mechanism of action. Paclitaxel has been shown to be clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). Paclitaxel has been shown to be genotoxic *in vivo* (micronucleus test in mice), but it did not induce mutagenicity in the Ames test or the Chinese hamster ovary/hypoxanthine-guanine phosphoribosyl transferase (CHO/HGPRT) gene mutation assay.

Paclitaxel at doses below the human therapeutic dose was associated with low fertility and foetal toxicity in rats. Animal studies with Abraxane showed non-reversible, toxic effects on the male reproductive organs at clinically relevant exposure levels.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human albumin solution (containing sodium, sodium caprylate and N-acetyl DL tryptophanate).

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials

3 years

Stability of reconstituted suspension in the vial

After first reconstitution, the suspension should be filled into an infusion bag immediately. However, chemical and physical in use stability has been demonstrated for 8 hours at 2°C-8°C in the original carton, and protected from bright light. Alternative light-protection may be used in the clean room.

Stability of the reconstituted suspension in the infusion bag

After reconstitution, the reconstituted suspension in the infusion bag should be used immediately. However chemical and physical in use stability has been demonstrated for 8 hours not above 25°C.

6.4 Special precautions for storage

Unopened vials

Keep the vial in the outer carton in order to protect from light.

Reconstituted suspension

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

50 ml vial (type 1 glass) with a stopper (butyl rubber), with an overseal (aluminium), containing 100 mg of paclitaxel formulated as albumin bound nanoparticles.

100 ml vial (type 1 glass) with a stopper (butyl rubber), with an overseal (aluminium), containing 250 mg of paclitaxel formulated as albumin bound nanoparticles.

Pack size of one vial.

6.6 Special precautions for disposal and other handling

Preparation and administration precautions

Paclitaxel is a cytotoxic anticancer medicinal product and, as with other potentially toxic compounds, caution should be exercised in handling Abraxane. The use of gloves, goggles and protective clothing is recommended. If the suspension contacts the skin, the skin should be washed immediately and thoroughly with soap and water. If it contacts mucous membranes, the membranes should be flushed thoroughly with water. Abraxane should only be prepared and administered by personnel appropriately trained in the handling of cytotoxic agents. Pregnant staff should not handle Abraxane.

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

Reconstitution and administration of the product

Abraxane is supplied as a sterile lyophilised powder for reconstitution before use. After reconstitution, each ml of suspension contains 5 mg of paclitaxel formulated as albumin bound nanoparticles.

100 mg vial: Using a sterile syringe, 20 ml of sodium chloride 9 mg/ml (0.9%) solution for infusion should slowly be injected into a vial of Abraxane over a minimum of 1 minute.

250 mg vial: Using a sterile syringe, 50 ml of sodium chloride 9 mg/ml (0.9%) solution for infusion should slowly be injected into a vial of Abraxane over a minimum of 1 minute.

The solution should be directed onto the inside wall of the vial. The solution should not be injected directly onto the powder as this will result in foaming.

Once the addition is complete, the vial should be allowed to stand for a minimum of 5 minutes to ensure proper wetting of the solid. Then, the vial should gently and slowly be swirled and/or inverted for at least 2 minutes until complete resuspension of any powder occurs. The generation of foam must be avoided. If foaming or clumping occurs, the solution must stand for at least 15 minutes until foam subsides.

The reconstituted suspension should be milky and homogenous without visible precipitates. If precipitates or settling are visible, the vial should be gently inverted again to ensure complete resuspension prior to use. Some settling of the reconstituted suspension may occur. Complete resuspension should be ensured by mild agitation before use.

Discard the reconstituted suspension if precipitates are observed.

The exact total dosing volume of 5 mg/ml suspension required for the patient should be calculated and the appropriate amount of reconstituted Abraxane should be injected into an empty, sterile, PVC or non-PVC type intravenous bag. The use of specialized di(2-ethylhexyl)phthalate (DEHP)-free solution containers or administration sets is not necessary to prepare or administer Abraxane infusions. In-line filters should not be used.

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

7. MARKETING AUTHORISATION HOLDER

Celgene Europe Limited
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/428/001

EU/1/07/428/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 January 2008

Date of latest renewal: 11 January 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Celgene Europe Limited
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Abraxane 5 mg/ml powder for suspension for infusion

paclitaxel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 100 mg of paclitaxel formulated as albumin bound nanoparticles.

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

3. LIST OF EXCIPIENTS

Excipients: Human albumin solution (containing sodium, sodium caprylate and N-acetyl DL tryptophanate).

Contains sodium, see package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for suspension for infusion.

1 vial

100 mg/20 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Abraxane should not be substituted for or with other paclitaxel formulations.

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Unopened vials: Keep the vial in the outer carton in order to protect from light.

After first reconstitution: 8 hours in a refrigerator in the vial when kept in the outer carton in order to protect from light.

In an infusion bag: up to 8 hours not above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Limited
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/428/001

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Vial

1. NAME OF THE MEDICINAL PRODUCT

Abraxane 5 mg/ml powder for suspension for infusion

paclitaxel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 100 mg of paclitaxel formulated as albumin bound nanoparticles.

After reconstitution, each ml of suspension contains 5 mg of paclitaxel.

3. LIST OF EXCIPIENTS

Excipients: Human albumin solution (containing sodium, sodium caprylate and N-acetyl DL tryptophanate).

Contains sodium, see package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for suspension for infusion.

1 vial

100 mg/20 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

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13. BATCH NUMBER

Batch:

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15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Abraxane 5 mg/ml powder for suspension for infusion

paclitaxel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 250 mg of paclitaxel formulated as albumin bound nanoparticles.

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

3. LIST OF EXCIPIENTS

Excipients: Human albumin solution (containing sodium, sodium caprylate and N-acetyl DL tryptophanate).

Contains sodium, see package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for suspension for infusion.

1 vial

250 mg/50 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Abraxane should not be substituted for or with other paclitaxel formulations.

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Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Vial

1. NAME OF THE MEDICINAL PRODUCT

Abraxane 5 mg/ml powder for suspension for infusion

paclitaxel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 250 mg of paclitaxel formulated as albumin bound nanoparticles.

After reconstitution, each ml of suspension contains 5 mg of paclitaxel.

3. LIST OF EXCIPIENTS

Excipients: Human albumin solution (containing sodium, sodium caprylate and N-acetyl DL tryptophanate).

Contains sodium, see package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for suspension for infusion.

1 vial

250 mg/50 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Unopened vials: Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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EU/1/07/428/002

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Abraxane 5 mg/ml powder for suspension for infusion

paclitaxel

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Abraxane is and what it is used for
2. What you need to know before you are given Abraxane
3. How to use Abraxane
4. Possible side effects
5. How to store Abraxane
6. Contents of the pack and other information

1. What Abraxane is and what it is used for

What Abraxane is

Abraxane contains, as its active substance, paclitaxel attached to the human protein albumin, in the form of tiny particles known as nanoparticles. Paclitaxel belongs to a group of medicines called “taxanes” used in cancer.

- Paclitaxel is the part of the medicine that affects the cancer, it works by stopping cancer cells from dividing – this means that they die.
- Albumin is the part of the medicine that helps paclitaxel dissolve in the blood and get across the walls of the blood vessels into the tumour. This means that other chemicals that can cause side effects that can be life threatening are not needed. Such side effects occur far less with Abraxane.

What Abraxane is used for

Abraxane is used to treat the following types of cancer:

Breast Cancer

- Breast cancer which has spread to other parts of the body (this is called “metastatic” breast cancer).
- Abraxane is used in metastatic breast cancer when at least one other therapy has been tried but has not worked and you are unsuitable for treatments containing a group of medicines called “anthracyclines”.
- People with metastatic breast cancer who received Abraxane where another therapy had failed, were more likely to experience a reduction in tumour size, and lived longer than people who took an alternative therapy.

Pancreatic cancer

- Abraxane is used together with a medicine called gemcitabine if you have metastatic cancer of the pancreas. People with metastatic pancreatic cancer (pancreatic cancer that has spread to other parts

of the body) who received Abraxane with gemcitabine in a clinical trial lived longer than people who had only received gemcitabine.

2. What you need to know before you are given Abraxane

Do not use Abraxane

- if you are allergic (hypersensitive) to paclitaxel or any of the other ingredients of Abraxane (listed in section 6);
- if you are breast-feeding;
- if you have a low white blood cell count (baseline neutrophil counts <1500 cells/mm³ - your doctor will advise you on this).

Warnings and precautions

Talk to your doctor or nurse before using Abraxane

- if you have poor kidney function;
- if you have severe liver problems;
- if you have heart problems.

Talk to your doctor or nurse if you experience any of these conditions whilst being treated with Abraxane, your doctor may wish to stop treatment or reduce the dose:

- if you experience any abnormal bruising, bleeding, or signs of infections such as a sore throat or a fever;
- if you experience numbness, tingling, pricking sensations, sensitivity to touch, or muscle weakness;
- if you experience breathing problems, like shortness of breath or dry cough.

Children and adolescents

This medicine has not been studied in children and adolescents, as breast cancer and pancreatic cancer does not occur in these age groups.

Other medicines and Abraxane

Tell your doctor if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription, including herbal medicines. This is because Abraxane can affect the way some other medicines work. Also, some other medicines can affect the way Abraxane works.

Take care and speak to your doctor when taking Abraxane at the same time as any of the following:

- medicines for treating infections (i.e. antibiotics such erythromycin, rifampicin, etc.; ask your doctor, nurse or pharmacist if you are unsure whether the medicine you are taking is an antibiotic), and including medicines for treating fungal infections (e.g. ketoconazole)
- medicines used to help you stabilize your mood also sometimes referred to as anti-depressants (e.g. fluoxetine)
- medicines used to treat seizures (epilepsy) (e.g. carbamazepine, phenytoin)
- medicines used to help you lower blood lipid levels (e.g. gemfibrozil)
- medicine used for heartburn or stomach ulcers (e.g. cimetidine)
- medicines used to treat HIV and AIDS (e.g. ritonavir, saquinavir, indinavir, nelfinavir, efavirenz, nevirapine)

Pregnancy breast-feeding and fertility

Paclitaxel may cause serious birth defects and should therefore not be used if you are pregnant.

Women of childbearing age should use effective contraception during and up to 1 month after receiving treatment with Abraxane.

Do not breast feed when taking Abraxane as it is not known if the active ingredient paclitaxel passes into the mother's milk.

Male patients are advised to not father a child during and up to six months after treatment and should seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with Abraxane.

Ask your doctor for advice before taking this medicine.

Driving and using machines

Some people may feel tired or dizzy after being given Abraxane. If this happens to you, do not drive or use any tools or machines.

If you are given other medicines as part of your treatment, you should ask your doctor for advice on driving and using machines.

Abraxane contains sodium

Each ml of Abraxane contains approximately 4.2 mg of sodium. This should be taken into consideration by if you are on a controlled sodium diet.

3. How to use Abraxane

Abraxane will be given to you by a doctor or nurse into a vein from an intravenous drip. The dose you receive is based on your body surface area and blood test results. The usual dose is for breast cancer is 260 mg/m² of body surface area given over a 30 minute period. The usual dose for advanced pancreatic cancer is 125 mg/m² of body surface area given over a 30 minute period.

How often will you receive Abraxane?

For treatment of metastatic breast cancer, Abraxane is usually given once every three weeks (on day 1 of a 21-day cycle).

For treatment of advanced pancreatic cancer, Abraxane is given on days 1, 8 and 15 of each 28-day treatment cycle with gemcitabine being given immediately after the Abraxane.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everyone gets them.

The **very common** side effects may affect more than 1 in 10 people:

- Loss of hair, rash
- Abnormal decrease in the number of types of white blood cells (neutrophils, lymphocytes or leukocytes) in the blood
- Deficiency of red blood cells
- Reduction in the number of platelets in the blood
- Effect on peripheral nerves (pain, and numbness)
- Pain in a joint or joints
- Pain in the muscles
- Nausea, diarrhoea, constipation, sore mouth, loss of appetite

- Vomiting
- Weakness and tiredness, fever
- Dehydration, taste disturbance, weight loss
- Low levels of potassium in the blood
- Depression, sleep problems
- Headache
- Chills
- Difficulty in breathing
- Dizziness
- Swelling of mucosal and soft tissues
- Increased liver function tests
- Pain in extremities
- Cough
- Abdominal pain
- Nose bleeds

The **common** side effects may affect up to 1 in 10 people:

- Itching, dry skin, nail disorder
- Infection, fever with decrease in the number of a type of white blood cell (neutrophils) in the blood, flushing, thrush, severe infection in your blood which may be caused by reduced white blood cells
- Reduction in all blood cell counts
- Chest, throat or abdominal pain
- Indigestion, abdominal discomfort
- Stuffy nose
- Pain in back or limbs, bone pain, muscle cramps
- Diminished muscular coordination or difficulty in reading, increased or decreased tears, loss of eyelashes
- Changes in heart rate or rhythm, heart failure
- Decreased blood pressure
- Redness or swelling at the site where the needle entered the body
- Anxiety
- Infection in the lungs
- Obstruction in the gut, inflammation of the large bowel, inflammation of the bile duct
- Acute kidney failure
- Dry mouth
- Muscle weakness

The **uncommon** side effects may affect up to 1 in 100 people:

- Increased blood pressure, increased weight, increased lactate dehydrogenase in the blood, decreased kidney function, increased blood sugar, increased phosphorus in the blood, decreased potassium in the blood
- Nerve disorder, decreased or lack of reflexes, involuntary movements, pain along a nerve, loss of feeling, fainting, dizziness when standing up, painful numbness or tingling, shaking, facial nerve paralysis
- Irritated eyes, painful eyes, red eyes, itchy eyes, blurred or double vision, reduced vision, or seeing flashing lights, blurred vision due to swelling of the retina (cystoid macular oedema)
- Ear pain, ringing in your ears
- Coughing with phlegm, shortness of breath when walking or climbing stairs, runny nose, or dry nose, decreased breath sounds, water on the lung, loss of voice, difficulty in breathing, dry cough, blood clot in the lung, dry throat

- Difficulty swallowing, gas, loose stools, heartburn, stomach cramps, painful or sore mouth and gums, rectal bleeding
- Painful urination, frequent urination, blood in the urine, inability to hold your urine
- Fingernail pain, fingernail discomfort, loss of fingernails, hives, skin pain, red skin from sunlight, skin discolouration, red rash, itchy rash, increased sweating, night sweats, white areas on the skin, less hair, overall itching, sores, swollen face
- Decreased phosphorus in the blood, fluid retention, low albumin in the blood, increased thirst, decreased calcium in the blood, decreased sugar in the blood, decreased sodium in the blood
- Thrush, pain and swelling in the nose and throat, skin infections, infection due to catheter line, infection
- Bruising
- Pain at site of tumour, death of the tumour
- Decreased blood pressure when standing up, coldness in your hands and feet
- Chest pain or heaviness, difficulty walking, swelling
- Allergic reaction
- Decreased liver function, increased size of liver
- Pain in the breast
- Restlessness
- Small bleedings in your skin due to blood clots
- A condition involving destruction of red blood cells and acute kidney failure

The **rare** side effects may affect up to 1 in 1,000 people:

- Skin reaction to another agent or lung inflammation following radiation
- Blood clot
- Very slow pulse, heart attack
- Leaking of drug outside the vein
- A disorder of the electrical conduction system of the heart (atrioventricular block)

The **very rare** side effects may affect up to 1 in 10,000 people:

- Severe inflammation/eruption of the skin and mucous membranes (Stevens-Johnson syndrome, toxic epidermal necrolysis)

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Abraxane

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial after EXP. The expiry date refers to the last day of that month.

Unopened vials: Keep the vial in the outer carton in order to protect from light.

After first reconstitution the suspension should be used immediately. If not used immediately, the suspension may be stored in a refrigerator (2°C-8°C) for up to 8 hours in the vial when kept in the outer carton in order to protect it from light.

The reconstituted suspension in the intravenous drip may be stored for up to 8 hours at a temperature not above 25°C.

Your doctor or pharmacist is responsible for disposing of any unused Abraxane correctly.

6. Contents of the pack and further information

What Abraxane contains

The active substance is paclitaxel.

Each vial contains 100 mg or 250 mg of paclitaxel formulated as albumin bound nanoparticles.

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

The other ingredient is human albumin (containing sodium, sodium caprylate and N-acetyl DL tryptophanate).

What Abraxane looks like and contents of the pack

Abraxane is a white to yellow powder for suspension for infusion. Abraxane is available in glass vials containing 100 mg or 250 mg of paclitaxel formulated as albumin bound nanoparticles.

Each pack contains 1 vial.

Marketing Authorisation Holder and Manufacturer

Celgene Europe Limited
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

For any information about this medicine, please contact the Marketing Authorisation Holder.

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>

Medical or healthcare professionals

The following information is intended for medical or healthcare professionals only:

Instructions for use, handling and disposal

Preparation and administration precautions

Paclitaxel is a cytotoxic anticancer medicinal product and, as with other potentially toxic compounds, caution should be exercised in handling Abraxane. Gloves, goggles and protective clothing should be used. If Abraxane suspension contacts the skin, the skin should be washed immediately and thoroughly with soap and water. If Abraxane contacts mucous membranes, the membranes should be flushed thoroughly with water. Abraxane should only be prepared and administered by personnel appropriately trained in the handling of cytotoxic agents. Pregnant staff should not handle Abraxane.

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

Reconstitution of the product and administration

Abraxane should be administered under the supervision of a qualified oncologist in units specialised in the administration of cytotoxic agents.

Abraxane is supplied as a sterile lyophilised powder for reconstitution before use. After reconstitution, each ml of suspension contains 5 mg of paclitaxel formulated as albumin bound nanoparticles.

Reconstitution of 100 mg:

Using a sterile syringe, 20 ml of sodium chloride 9 mg/ml (0.9%) solution for infusion should slowly be injected into the 100 mg vial of Abraxane over a minimum of 1 minute.

Reconstitution of 250 mg:

Using a sterile syringe, 50 ml of sodium chloride 9 mg/ml (0.9%) solution for infusion should slowly be injected into the 250 mg vial of Abraxane over a minimum of 1 minute.

The solution should be directed onto the inside wall of the vial. The solution should not be injected directly onto the powder as this will result in foaming.

Once the addition is complete, the vial should be allowed to stand for a minimum of 5 minutes to ensure proper wetting of the solid. Then, the vial should gently and slowly be swirled and/or inverted for at least 2 minutes until complete resuspension of any powder occurs. The generation of foam should be avoided. If foaming or clumping occurs, the suspension should stand for at least 15 minutes until foam subsides.

The reconstituted suspension should be milky and homogenous without visible precipitates. If precipitates or settling are visible, the vial should be gently inverted again to ensure complete resuspension prior to use. Some settling of the reconstituted suspension may occur. Complete resuspension should be ensured by mild agitation of the vial before use.

If precipitates are observed, the reconstituted suspension should be discarded.

The exact total dosing volume of 5 mg/ml suspension required for the patient should be calculated and the appropriate amount of reconstituted Abraxane should be injected into an empty, sterile, 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. In-line filters should not be used.

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

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

Stability

Unopened vials of Abraxane are stable until the date indicated on the package when the vial is kept in the outer carton in order to protect from light. Neither freezing nor refrigeration adversely affects the stability of the product. This medicinal product does not require any special temperature storage conditions.

Stability of the reconstituted suspension in the vial

After first reconstitution, the suspension should be filled into an infusion bag immediately. However, chemical and physical in use stability has been demonstrated for 8 hours at 2°C-8°C in the original carton, and protected from bright light.

Stability of the reconstituted suspension in the infusion bag

After reconstitution, the reconstituted suspension in the infusion bag should be used immediately. However chemical and physical in use stability has been demonstrated for 8 hours not above 25°C.

ANNEX IV

**CONCLUSIONS ON MARKETING PROTECTION PRESENTED BY THE EUROPEAN
MEDICINES AGENCY**

Conclusions presented by the European Medicines Agency on:

- **one-year marketing protection**

The CHMP reviewed the data submitted by the Marketing Authorisation Holder, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies as further explained in the European Public Assessment Report.