SUMMARY OF PRODUCT CHARACTERISTICS

1.NAME OF THE MEDICINAL PRODUCT

Bugvi 5 mg/ml poeder voor dispersie voor infusie

2.QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

For the full list of excipients, see section 6.1.

3.PHARMACEUTICAL FORM

Powder for dispersion for infusion.
The reconstituted dispersion 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

<Invented name> 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).

<Invented name> in combination with gemcitabine is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas.

<Invented name> in combination with carboplatin is indicated for the first-line treatment of non-small cell lung cancer in adult patients who are not candidates for potentially curative surgery and/or radiation therapy.

4.2 Posology and method of administration

<Invented name> 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 <Invented name> is 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks.

Dose adjustments during treatment of breast cancer
Patients who experience severe neutropenia (neutrophil count < 500 cells/mm^3 for a week or longer) or severe sensory neuropathy during <Invented name> therapy should have the dose reduced to 220 mg/m^2 for subsequent courses. Following recurrence of severe neutropenia or

severe sensory neuropathy, additional dose reduction should be made to 180 mg/m^2. <Invented name> should not be administered until neutrophil counts recover to > 1 500 cells/mm^3. 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 <Invented name> in combination with gemcitabine is 125 mg/m^2 administered intravenously over 30 minutes on Days 1, 8 and 15 of each 28-day cycle. The concurrent recommended dose of gemcitabine is 1 000 mg/m^2 administered intravenously over 30 minutes immediately after the completion of <Invented name> 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	<Invented name> dose (mg/m^2)	Gemcitabine dose (mg/m^2)
Full dose	125	1 000
1st dose level reduction	100	800
2nd 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)	<Invented name> dose	Gemcitabine dose
Day 1	< 1 500	OR	< 100 000	Delay doses until recovery	
Day 8	≥ 500 but < 1 000	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 < 1 000	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	≥ 1 000	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 < 1 000	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	≥ 1 000	AND	≥ 75 000	Return to the Day 1 dose levels and follow with WBC Growth Factors OR Reduce doses 1 dose level from Day 1 doses	
	≥ 500 but < 1 000	OR	≥ 50 000 but < 75 000	Reduce 1 dose level and follow with WBC Growth Factors	

Cycle day	ANC count (cells/mm^3)		Platelet count (cells/mm^3)	<Invented name> dose	Gemcitabine dose
				OR Reduce doses 2 dose level 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)	<Invented name> dose	Gemcitabine dose
Febrile neutropenia: Grade 3 or 4	Withhold doses until fever resolves and ANC ≥ 1 500; resume at next lower 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]	

[a] See Table 1 for dose level reductions

Non-small cell lung cancer

The recommended dose of <Invented name> 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 <Invented name> administration.

Dose adjustments during treatment of non-small cell lung cancer

<Invented name> 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 <Invented name>, 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 4. Reduce subsequent dose only if criteria in Table 4 are met.

Table 4: Dose reductions for haematologic toxicities in patients with non-small cell lung cancer

Haematologic Toxicity	Occurrence	Dose of <Invented name> (mg/m^2) [1]	Dose of carboplatin (AUC mg•min/ml) [1]
Nadir ANC < 500/mm^3 with neutropenic fever > 38 °C OR Delay of next cycle due to persistent neutropenia [2] (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] On Day 1 of the 21-day cycle reduce the dose of <Invented name> and carboplatin simultaneously. On Days 8 or 15 of the 21-day cycle reduce the dose of <Invented name>; reduce the dose of carboplatin in the subsequent cycle.

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

For Grade 2 or 3 cutaneous toxicity, Grade 3 diarrhoea, or Grade 3 mucositis, interrupt treatment until the toxicity improves to ≤ Grade 1, then restart treatment according to the guidelines in Table 5. 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 5. 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 5.

Table 5: Dose reductions for non-haematologic toxicities in patients with non-small cell lung cancer

Non-haematologic Toxicity	Occurrence	Dose of <Invented name> (mg/m^2) [1]	Dose of carboplatin (AUC mg•min/ml) [1]
Grade 2 or 3 cutaneous toxicity	First	75	4.5
Grade 3 diarrhoea	Second	50	3.0
Grade 3 mucositis ≥ Grade 3 peripheral neuropathy Any other Grade 3 or 4 non-haematologic toxicity	Third	Discontinue treatment	
Grade 4 cutaneous toxicity, diarrhoea, or mucositis	First	Discontinue treatment	

[1] On Day 1 of the 21-day cycle reduce the dose of <Invented name> and carboplatin simultaneously. On Days 8 or 15 of the 21-day cycle reduce the dose of <Invented name>; reduce the dose of carboplatin in the subsequent cycle.

Special populations

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

For metastatic breast cancer patients and non-small cell lung cancer 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. 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 (see sections 4.4 and 5.2).

For patients with metastatic adenocarcinoma of the pancreas that have moderate to severe hepatic impairment, there are insufficient data to permit dosage recommendations (see sections 4.4 and 5.2).

For patients with total bilirubin > 5 x ULN or AST > 10 x ULN, there are insufficient data to permit dosage recommendations regardless of indication (see sections 4.4 and 5.2).

Renal impairment
Adjustment of the starting <Invented name> dose is not required for patients with mild to moderate renal impairment (estimated creatinine clearance ≥ 30 to < 90 ml/min). There are insufficient data available to recommend dose modifications of <Invented name> in patients with severe renal impairment or end stage renal disease (estimated creatinine clearance < 30 ml/min) (see section 5.2).

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

Of the 229 patients in the randomised study who received paclitaxel formulated as albumin bound nanoparticles 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 paclitaxel formulated as albumin bound nanoparticles. However, a subsequent analysis in 981 patients receiving paclitaxel formulated as albumin bound nanoparticles monotherapy for metastatic breast cancer, of which 15 % were ≥ 65 years old and 2 % were ≥ 75 years old, showed a higher incidence of epistaxis, diarrhoea,

dehydration, fatigue and peripheral oedema in patients ≥ 65 years.

Of the 421 patients with pancreatic adenocarcinoma in the randomised study who received paclitaxel formulated as albumin bound nanoparticles 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 paclitaxel formulated as albumin bound nanoparticles 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).

Of the 514 patients with non-small cell lung cancer in the randomised study who received paclitaxel formulated as albumin bound nanoparticles in combination with carboplatin, 31 % were 65 years or older and 3.5 % were 75 years or older. Myelosuppression events, peripheral neuropathy events, and arthralgia were more frequent in patients 65 years or older compared to patients younger than 65 years of age. There is limited experience of paclitaxel formulated as albumin bound nanoparticles/carboplatin use in patients 75 years or older.

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

Paediatric population
The safety and efficacy of paclitaxel formulated as albumin bound nanoparticles in children and adolescents aged 0 to less than 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 <Invented name> in the paediatric population for the indication of metastatic breast cancer or pancreatic adenocarcinoma or non-small cell lung cancer.

Method of administration
Administer reconstituted <Invented name> dispersion 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 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 < 1 500 cells/mm^3.

4.4 Special warnings and precautions for use

<Invented name> 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 paclitaxel formulated as albumin bound nanoparticles. Neutropenia is dose-dependent and a dose-limiting toxicity. Frequent monitoring of blood cell counts should be performed during <Invented name> therapy. Patients should not be retreated with subsequent cycles of <Invented name> until neutrophils recover to > 1 500 cells/mm^3 and platelets recover to > 100 000 cells/mm^3 (see section 4.2).

Neuropathy

Sensory neuropathy occurs frequently with paclitaxel formulated as albumin bound nanoparticles, although development of severe symptoms is less common. The occurrence of Grade 1 or 2 sensory neuropathy does not generally require dose reduction. When <Invented name> 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 <Invented name> is recommended (see section 4.2). For combination use of <Invented name> and gemcitabine, if Grade 3 or higher peripheral neuropathy develops, withhold <Invented name>; continue treatment with gemcitabine at the same dose. Resume <Invented name> at reduced dose when peripheral neuropathy improves to Grade 0 or 1 (see section 4.2). For combination use of <Invented name> 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 <Invented name> and carboplatin (see section 4.2).

Sepsis

Sepsis was reported at a rate of 5 % in patients with or without neutropenia who received paclitaxel formulated as albumin bound nanoparticles 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 <Invented name> and gemcitabine until fever resolves and ANC ≥ 1 500 cells/mm^3, then resume treatment at reduced dose levels (see section 4.2).

Pneumonitis

Pneumonitis occurred in 1 % of patients when paclitaxel formulated as albumin bound nanoparticles was used as monotherapy and in 4 % of patients when paclitaxel formulated as albumin bound nanoparticles was used in combination with gemcitabine. Closely monitor all patients for signs and symptoms of pneumonitis. After ruling out infectious aetiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with <Invented name> 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 <Invented name> in patients with hepatic impairment should be performed with caution. 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.

<Invented name> is not recommended in patients that have total bilirubin > 5 x ULN or AST > 10 x ULN. In addition, <Invented name> 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) (see section 5.2).

Cardiotoxicity

Rare reports of congestive heart failure and left ventricular dysfunction have been observed among individuals receiving paclitaxel formulated as albumin bound nanoparticles. Most of the individuals were previously exposed to cardiotoxic medicinal products such as anthracyclines or had underlying cardiac history. Thus, patients receiving <Invented name> should be

vigilantly monitored by physicians for the occurrence of cardiac events.

CNS metastases
The effectiveness and safety of paclitaxel formulated as albumin bound nanoparticles 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 <Invented name>, they may be treated with commonly used anti-emetics and constipating agents.

Eye disorders
Cystoid macular oedema (CMO) has been reported in patients treated with paclitaxel formulated as albumin bound nanoparticles. Patients with impaired vision should undergo a prompt and complete ophthalmologic examination. In case CMO is diagnosed, <Invented name> treatment should be discontinued and appropriate treatment initiated (see section 4.8).

Patients 75 years and older
For patients of 75 years and older, no benefit for the combination treatment of paclitaxel formulated as albumin bound nanoparticles and gemcitabine in comparison to gemcitabine monotherapy has been demonstrated. In the very elderly (≥ 75 years) who received paclitaxel formulated as albumin bound nanoparticles 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 <Invented name> 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 paclitaxel formulated as albumin bound nanoparticles and gemcitabine (see section 5.1).

Erlotinib should not be co-administered with paclitaxel plus gemcitabine (see section 4.5).

Excipients
This medicinal product contains less than 1 mmol sodium (23 mg) per ml reconstituted solution, that is to say essentially ‘sodium-free’.

4.5 Interactions with other medicinal products and other forms of interaction

The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4 (see section 5.2). Therefore, in the absence of a PK drug-drug interaction study, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because toxicity of paclitaxel may be increased due to higher paclitaxel exposure. Administering paclitaxel concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended because efficacy may be compromised because of lower paclitaxel exposures.

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 paclitaxel formulated as albumin bound

nanoparticles and gemcitabine have not been evaluated in humans.

A pharmacokinetic study was conducted with paclitaxel formulated as albumin bound nanoparticles and carboplatin in non-small cell lung cancer patients. There were no clinically relevant pharmacokinetic interactions between paclitaxel formulated as albumin bound nanoparticles and carboplatin.

<Invented name> is indicated as monotherapy for breast cancer, in combination with gemcitabine for pancreatic adenocarcinoma, or in combination with carboplatin for non-small cell lung cancer (see section 4.1). <Invented name> should not be used in combination with other anticancer agents.

Paediatric population
Interaction studies have only been performed in adults.

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 paclitaxel. Male patients treated with paclitaxel are advised to use effective contraception and to avoid fathering 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). Women of childbearing potential should have a pregnancy test prior to starting treatment with paclitaxel. Paclitaxel 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
Paclitaxel and/or its metabolites were excreted into the milk of lactating rats (see section 5.3). It is not known if paclitaxel is excreted in human milk. Because of potential serious adverse reactions in breast-feeding infants, paclitaxel is contraindicated during lactation. Breast-feeding must be discontinued for the duration of therapy.

Fertility
Paclitaxel formulated as albumin bound nanoparticles induced infertility in male rats (see section 5.3). Based on findings in animals, male and 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 paclitaxel.

4.7 Effects on ability to drive and use machines

Paclitaxel has minor or moderate influence on the ability to drive and use machines. Paclitaxel 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 paclitaxel formulated as albumin bound nanoparticles have been neutropenia, peripheral neuropathy, arthralgia/myalgia and gastrointestinal disorders.

Tabulated list of adverse reactions

Table 6 lists adverse reactions associated with paclitaxel formulated as albumin bound nanoparticles monotherapy at any dose in any indication during clinical trials (N = 789), paclitaxel in combination with gemcitabine for pancreatic adenocarcinoma from the phase III clinical trial (N = 421), paclitaxel formulated as albumin bound nanoparticles 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 paclitaxel

	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.
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.		Drug hypersensitivity, hypersensitivity.
Rare	Severe hypersensitivity [1].		
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.	

	Monotherapy (N=789)	Combination therapy with gemcitabine (N =421)	Combination therapy with carboplatin (N = 514)
Common	Depression, insomnia, anxiety.	Anxiety.	Insomnia.
Uncommon	Restlessness.		
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			
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.	
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.
Uncommon	Pulmonary emboli, pulmonary thromboembolism, pleural effusion, exertional dyspnoea, sinus congestion, decreased breath sounds, productive cough, allergic	Dry throat, nasal dryness.	Pneumonitis.

	Monotherapy (N=789)	Combination therapy with gemcitabine (N =421)	Combination therapy with carboplatin (N = 514)
	rhinitis, hoarseness, nasal congestion, nasal dryness, wheezing.		
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.
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.
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.
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.		

	Monotherapy (N=789)	Combination therapy with gemcitabine (N =421)	Combination therapy with carboplatin (N = 514)
Renal and urinary disorders			
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.
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.	
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			
Uncommon	Contusion.		
Rare	Radiation recall phenomenon, radiation pneumonitis.		

[1] As reported in the post-marketing surveillance of paclitaxel formulated as albumin bound nanoparticles.
[2] The frequency of pneumonitis is calculated based on pooled data in 1 310 patients in clinical trials receiving paclitaxel formulated as albumin bound nanoparticles 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.

Description of selected adverse reactions

This section contains the most common and clinically relevant adverse reactions related to paclitaxel formulated as albumin bound nanoparticles.

Adverse reactions were assessed in 229 patients with metastatic breast cancer who were treated with 260 mg/m^2 paclitaxel formulated as albumin bound nanoparticles once every three

weeks in the pivotal phase III clinical study (paclitaxel formulated as albumin bound nanoparticles monotherapy).

Adverse reactions were assessed in 421 patients with metastatic pancreatic cancer who were treated with paclitaxel formulated as albumin bound nanoparticles in combination with gemcitabine (125 mg/m^2 paclitaxel in combination with gemcitabine at a dose of 1 000 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 (paclitaxel/gemcitabine).

Adverse reactions were assessed in 514 patients with non-small cell lung cancer who were treated with paclitaxel formulated as albumin bound nanoparticles in combination with carboplatin (100 mg/m^2 paclitaxel 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 randomised, controlled clinical trial (paclitaxel formulated as albumin bound nanoparticles/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 paclitaxel formulated as albumin bound nanoparticles and carboplatin ($p \leq 0.002$). For the other subscale (oedema), there was no difference in the treatment arms.

Infections and infestations

Paclitaxel formulated as albumin bound nanoparticles/gemcitabine

Sepsis was reported at a rate of 5 % in patients with or without neutropenia who received paclitaxel formulated as albumin bound nanoparticles in combination with gemcitabine during the conduct of a trial in pancreatic adenocarcinoma. Of the 22 cases of sepsis reported in patients treated with paclitaxel formulated as albumin bound nanoparticles 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 <Invented name> and gemcitabine until fever resolves and ANC ≥ 1 500 cells/mm^3, then resume treatment at reduced dose levels (see section 4.2).

Blood and lymphatic system disorders

Paclitaxel formulated as albumin bound nanoparticles 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 paclitaxel formulated as albumin bound nanoparticles. Febrile neutropenia occurred in four patients on paclitaxel formulated as albumin bound nanoparticles. Anaemia (Hb < 10 g/dl) was observed in 46 % of patients on paclitaxel formulated as albumin bound nanoparticles and was severe (Hb < 8 g/dl) in three cases. Lymphopenia was observed in 45 % of the patients.

Paclitaxel formulated as albumin bound nanoparticles/gemcitabine

Table 7 provides the frequency and severity of haematologic laboratory-detected abnormalities for patients treated with paclitaxel formulated as albumin bound nanoparticles in combination with gemcitabine or with gemcitabine.

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

	Paclitaxel formulated as albumin bound nanoparticles (125 mg/m^2)/gemcitabine		**Gemcitabine**	
	Grades 1-4 (%)	**Grades 3-4 (%)**	**Grades 1-4 (%)**	**Grades 3-4 (%)**
Anaemia [a,b]	97	13	96	12
Neutropenia [a,b]	73	38	58	27

	Paclitaxel formulated as albumin bound nanoparticles (125 mg/m^2)/gemcitabine		Gemcitabine	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Thrombocytopenia [a,b]	74	13	70	9

[a] 405 patients assessed in paclitaxel formulated as albumin bound nanoparticles/gemcitabine-treated group
[b] 388 patients assessed in gemcitabine-treated group
[c] 404 patients assessed in paclitaxel formulated as albumin bound nanoparticles/gemcitabine-treated group

Paclitaxel formulated as albumin bound nanoparticles/carboplatin
Anaemia and thrombocytopenia were more commonly reported in the paclitaxel formulated as albumin bound nanoparticles and carboplatin arm than in the paclitaxel and carboplatin arm (54 % versus 28 % and 45 % versus 27 % respectively).

Nervous system disorders
Paclitaxel formulated as albumin bound nanoparticles monotherapy-metastatic breast cancer
In general, the frequency and severity of neurotoxicity was dose-dependent in patients receiving paclitaxel formulated as albumin bound nanoparticles. Peripheral neuropathy (mostly Grade 1 or 2 sensory neuropathy) was observed in 68 % of patients on paclitaxel formulated as albumin bound nanoparticles with 10 % being Grade 3, and no cases of Grade 4.

Paclitaxel formulated as albumin bound nanoparticles/gemcitabine
For patients treated with paclitaxel formulated as albumin bound nanoparticles 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 paclitaxel at a reduced dose. No patients treated with paclitaxel formulated as albumin bound nanoparticles in combination with gemcitabine had Grade 4 peripheral neuropathy.

Paclitaxel formulated as albumin bound nanoparticles/carboplatin
For non-small cell lung cancer patients treated with paclitaxel formulated as albumin bound nanoparticles 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 paclitaxel formulated as albumin bound nanoparticles 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 paclitaxel formulated as albumin bound nanoparticles (see section 4.4).

Respiratory, thoracic and mediastinal disorders
Paclitaxel formulated as albumin bound nanoparticles/gemcitabine
Pneumonitis has been reported at a rate of 4 % with the use of paclitaxel formulated as albumin bound nanoparticles in combination with gemcitabine. Of the 17 cases of pneumonitis reported in patients treated with paclitaxel formulated as albumin bound nanoparticles in combination with gemcitabine, 2 had a fatal outcome. Monitor patients closely for signs and symptoms of pneumonitis. After ruling out infectious aetiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with <Invented name> and gemcitabine and promptly initiate appropriate treatment and supportive measures (see section 4.2).

Gastrointestinal disorders
Paclitaxel formulated as albumin bound nanoparticles monotherapy-metastatic breast cancer
Nausea occurred in 29 % of the patients and diarrhoea in 25 % of the patients.

Skin and subcutaneous tissue disorders
Paclitaxel formulated as albumin bound nanoparticles monotherapy-metastatic breast cancer
Alopecia was observed in > 80 % of the patients treated with paclitaxel formulated as albumin bound nanoparticles. The majority of alopecia events occurred less than one month after initiation of paclitaxel formulated as albumin bound nanoparticles. Pronounced hair loss ≥ 50 % is expected for the majority of patients who experience alopecia.

Musculoskeletal and connective tissue disorders
Paclitaxel formulated as albumin bound nanoparticles monotherapy-metastatic breast cancer
Arthralgia occurred in 32 % of patients on paclitaxel formulated as albumin bound nanoparticles and was severe in 6 % of cases. Myalgia occurred in 24 % of patients on paclitaxel formulated as albumin bound nanoparticles and was severe in 7 % of cases. The symptoms were usually transient, typically occurred three days after paclitaxel formulated as albumin bound nanoparticles administration and resolved within a week.

General disorders and administration site conditions
Paclitaxel formulated as albumin bound nanoparticles 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 paclitaxel formulated as albumin bound nanoparticles 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 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.

<Invented name> 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 paclitaxel formulated as albumin bound nanoparticles 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 paclitaxel formulated as albumin bound nanoparticles in metastatic breast cancer. This information is presented below.

Single-arm open-label studies
In one study, paclitaxel formulated as albumin bound nanoparticles was administered as a 30-minute infusion at a dose of 175 mg/m^2 to 43 patients with metastatic breast cancer. The second trial utilised a dose of 300 mg/m^2 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/m^2; 95 % CI: 4.6-6.2 months) and 6.1 months (300 mg/m^2; 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/m^2 given as a 3-hour infusion with premedication to prevent hypersensitivity (N = 225), or as paclitaxel formulated as albumin bound nanoparticles 260 mg/m^2 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 8: Results for overall response rate, median time to disease progression, and progression-free survival as assessed by the investigator

Efficacy variable	Paclitaxel formulated as albumin bound nanoparticles (260 mg/m^2)	Solvent-based paclitaxel (175 mg/m^2)	p-value
Response rate [95 % CI] (%)			
> 1st-line therapy	26.5 [18.98, 34.05] (n = 132)	13.2 [7.54, 18.93] (n = 136)	0.006 [a]
** Median time to disease progression [95 % CI] (weeks)*			
> 1st-line therapy	20.9 [15.7, 25.9] (n = 131)	16.1 [15.0, 19.3] (n = 135)	0.011 [b]

Efficacy variable	Paclitaxel formulated as albumin bound nanoparticles (260 mg/m^2)	Solvent-based paclitaxel (175 mg/m^2)	p-value
** Median progression free survival [95 % CI] (weeks)*			
> 1st-line therapy	20.6 [15.6, 25.9] (n = 131)	16.1 [15.0, 18.3] (n = 135)	0.010 [b]
** Survival [95 % CI] (weeks)*			
> 1st-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 paclitaxel formulated as albumin bound nanoparticles in the randomised, 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 paclitaxel formulated as albumin bound nanoparticles after > 6 courses of treatment was not evaluated and remains unknown.

Pancreatic adenocarcinoma

A multicentre, multinational, randomised, open-label study was conducted in 861 patients to compare paclitaxel formulated as albumin bound nanoparticles/gemcitabine versus gemcitabine monotherapy as first-line treatment in patients with metastatic adenocarcinoma of the pancreas. Paclitaxel formulated as albumin bound nanoparticles was administered to patients (N = 431) as an intravenous infusion over 30-40 minutes at a dose of 125 mg/m^2 followed by gemcitabine as an intravenous infusion over 30-40 minutes at a dose of 1 000 mg/m^2 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 randomised to receive paclitaxel formulated as albumin bound nanoparticles 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 paclitaxel formulated as albumin bound nanoparticles/gemcitabine arm and 2.8 months in the gemcitabine arm. 32 % of patients in the paclitaxel formulated as albumin bound nanoparticles/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 paclitaxel formulated as albumin bound nanoparticles/gemcitabine arm and 85 % in the gemcitabine arm. The median relative dose intensity of paclitaxel formulated as albumin bound nanoparticles was 81 %. A higher median cumulative dose of gemcitabine was delivered in the paclitaxel formulated as albumin bound nanoparticles/gemcitabine arm (11 400 mg/m^2) when compared with the gemcitabine arm (9 000 mg/m^2).

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

Table 9: Efficacy results from randomised study in patients with pancreatic adenocarcinoma (Intent-to-treat population)

	Paclitaxel formulated as albumin bound nanoparticles (125 mg/m^2)/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)
75th 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	

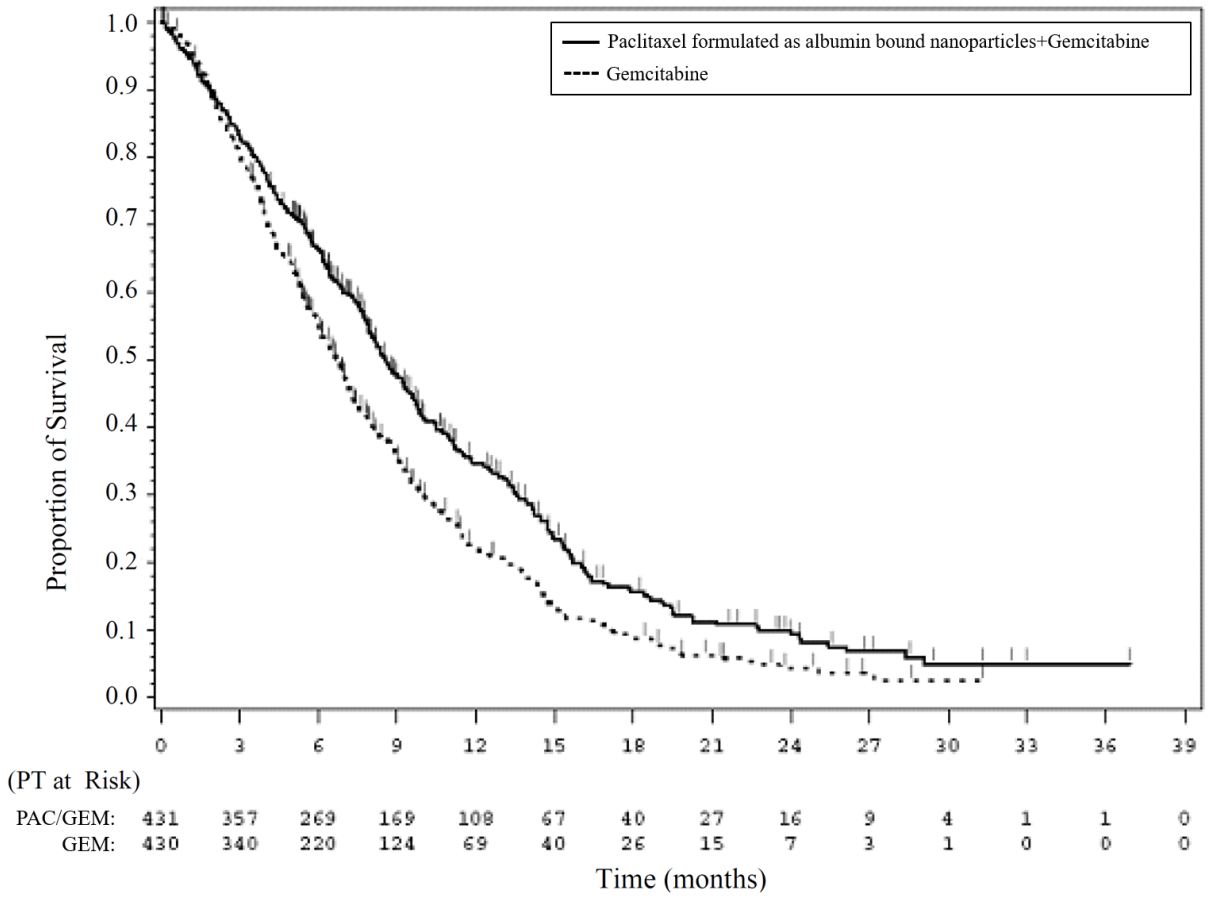
CI = confidence interval, $HR_{A+G/G}$ = hazard ratio of paclitaxel formulated as albumin bound nanoparticles +gemcitabine/gemcitabine, p_{A+G}/p_G = response rate ratio of paclitaxel formulated as albumin bound nanoparticles +gemcitabine/gemcitabine

[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 paclitaxel formulated as albumin bound nanoparticles/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 paclitaxel formulated as albumin bound nanoparticles/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 paclitaxel formulated as albumin bound nanoparticles/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 paclitaxel formulated as albumin bound nanoparticles/gemcitabine versus gemcitabine alone, with 1.8 months increase in median PFS.

Non-small cell lung cancer
A multicentre, randomised, open-label study was conducted in 1 052 chemotherapy-naive patients with Stage IIIb/IV non-small cell lung cancer. The study compared paclitaxel formulated as albumin bound nanoparticles in combination with carboplatin versus solvent-based paclitaxel in combination with carboplatin as first-line treatment in patients with advanced non-small cell lung cancer. Over 99 % of patients had an ECOG (Eastern Cooperative Oncology Group) performance status of 0 or 1. Patients with pre-existing neuropathy of Grade ≥ 2 or serious medical risk factors involving any of the major organ systems were excluded. Paclitaxel formulated as albumin bound nanoparticles was administered to patients (N=521) as an intravenous infusion over 30 minutes at a dose of 100 mg/m^2 on Days 1, 8 and 15 of each 21-day cycle without any steroid premedication and without granulocyte colony stimulating factor prophylaxis. Beginning immediately after the end of paclitaxel formulated as albumin bound nanoparticles administration, carboplatin at a dose of AUC = 6 mg•min/ml was administered intravenously on Day 1 only of each 21-day cycle. Solvent-based paclitaxel was administered to patients (N=531) at a dose of 200 mg/m^2 as an intravenous infusion over 3 hours with standard premedication, immediately followed by carboplatin administered intravenously at AUC = 6 mg•min/ml. Each drug was administered

on Day 1 of each 21-day cycle. In both study arms treatment was administered until disease progression or development of an unacceptable toxicity. Patients received a median of 6 cycles of treatment in both study arms.

The primary efficacy endpoint was overall response rate defined as the percentage of patients who achieved an objective confirmed complete response or partial response based on an independent, central, blinded radiological review using RECIST (Version 1.0). Patients in the paclitaxel formulated as albumin bound nanoparticles/carboplatin arm had a significantly higher overall response rate compared with patients in the control arm: 33 % versus 25 %, p = 0.005 (Table 10). There was a significant difference in overall response rate in the paclitaxel formulated as albumin bound nanoparticles/carboplatin arm compared to the control arm in patients with non-small cell lung cancer of squamous histology (N=450, 41 % vs. 24 %, p<0.001), however this difference did not translate into a difference in PFS or OS. There was no difference in ORR between the treatment arms in patients with non-squamous histology (N=602, 26 % vs 25 %, p=0.808).

Table 10: Overall response rate in randomised non-small cell lung cancer trial (intent-to-treat population)

Efficacy Parameter	Paclitaxel formulated as albumin bound nanoparticles (100 mg/m^2/week) +carboplatin (N=521)	Solvent-based paclitaxel (200 mg/m^2 every 3 weeks) +carboplatin (N=531)
Overall Response Rate (independent review)		
Confirmed complete or partial overall response, n (%)	170 (33 %)	132 (25 %)
95 % CI (%)	28.6, 36.7	21.2, 28.5
p_A/p_T (95.1 % CI)	1.313 (1.082, 1.593)	
P-value [a]	0.005	

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

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

There was no statistically significant difference in progression-free survival (by blinded radiologist assessment) and overall survival between the two treatment arms. A non-inferiority analysis was conducted for PFS and OS, with a pre-specified non-inferiority margin of 15 %. The non-inferiority criterion was met for both PFS and OS with the upper bound of the 95 % confidence interval for the associated hazard ratios being less than 1.176 (Table 11).

Table 11: Non-inferiority analyses on progression-free survival and overall survival in randomised non-small cell lung cancer trial (intent-to-treat population)

Efficacy Parameter	Paclitaxel formulated as albumin bound nanoparticles (100 mg/m^2/week) + carboplatin (N=521)	Solvent-based paclitaxel (200 mg/m^2 every 3 weeks) + carboplatin (N=531)
Progression-free Survival [a] (independent review)		
Death or progression, n (%)	429 (82 %)	442 (83 %)
Median PFS (95 % CI) (months)	6.8 (5.7, 7.7)	6.5 (5.7, 6.9)
$HR_{A/T}$ (95 % CI)	0.949 (0.830, 1.086)	
Overall Survival		
Number of deaths, n (%)	360 (69 %)	384 (72 %)
Median OS (95 % CI) (months)	12.1 (10.8, 12.9)	11.2 (10.3, 12.6)
$HR_{A/T}$ (95.1 % CI)	0.922 (0.797, 1.066)	

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

[a] Per EMA methodological considerations for PFS endpoint, missing observations or initiation of subsequent new therapy were not used for censoring.

Paediatric population
Safety and effectiveness in paediatric patients have not been established (see section 4.2).

Study ABI-007-PST-001, a Phase 1/2, multicentre, open-label, dose-finding study to assess the safety, tolerability and preliminary efficacy of weekly paclitaxel formulated as albumin bound nanoparticles in paediatric patients with recurrent or refractory solid tumours included a total of 106 patients aged ≥ 6 months to ≤ 24 years.

The Phase 1 portion of the study included a total of 64 patients aged from 6 months to less than 18 years old and determined the maximum tolerated dose (MTD) to be 240 mg/m^2, administered as an intravenous infusion over 30 minutes, on Days 1, 8, and 15 of each 28-day cycle.

The Phase 2 portion enrolled a total of 42 patients using a Simon two-stage minimax design, aged from 6 months to 24 years with recurrent or refractory Ewing's sarcoma, neuroblastoma or rhabdomyosarcoma for the evaluation of antitumour activity assessed by the overall response rate (ORR). Of the 42 patients, 1 patient was < 2, 27 were aged ≥ 2 to < 12, 12 were aged ≥ 12 to < 18 and 2 adult patients were aged ≥ 18 to 24 years old.

Patients were treated for a median of 2 cycles at the MTD. From the 41 patients eligible for efficacy evaluation in stage 1, 1 patient in the rhabdomyosarcoma group (N=14) had a confirmed partial response (PR) resulting in an ORR of 7.1 % (95 % CI: 0.2, 33.9). No confirmed complete response (CR) or PR was observed in either the Ewing's sarcoma group (N=13) or the neuroblastoma group (N=14). None of the study arms continued into stage 2 because the protocol-defined requirement of ≥ 2 patients to have a confirmed response was not met.

The median overall survival results, including the 1-year follow-up period were 32.1 weeks (95 % CI: 21.4, 72.9), 32.0 weeks (95 % CI: 12, not established) and 19.6 weeks (95 % CI: 4, 25.7) for the Ewing's sarcoma, neuroblastoma and rhabdomyosarcoma groups, respectively.

The overall safety profile of paclitaxel formulated as albumin bound nanoparticles in paediatric patients was consistent with the known safety profile of paclitaxel formulated as albumin bound nanoparticles in adults (see section 4.8). Based on these results, it was concluded that paclitaxel formulated as albumin bound nanoparticles as monotherapy does not have meaningful clinical activity or survival benefit that warrants further development in the paediatric population.

5.2 Pharmacokinetic properties

The pharmacokinetics of total paclitaxel following 30- and 180-minute infusions of paclitaxel formulated as albumin bound nanoparticles at dose levels of 80 to 375 mg/m^2 were determined in clinical studies. The paclitaxel exposure (AUC) increased linearly from 2 653 to 16 736 ng.hr/ml following dosing from 80 to 300 mg/m^2.

In a study in patients with advanced solid tumours, the pharmacokinetic characteristics of paclitaxel following paclitaxel formulated as albumin bound nanoparticles administered intravenously at 260 mg/m^2 over 30 minutes were compared with those following 175 mg/m^2 of the solvent-based paclitaxel injection administered over 3 hours. Based on non-compartmental PK analysis, the plasma clearance of paclitaxel with paclitaxel formulated as albumin bound nanoparticles was larger (43 %) than that following a solvent-based paclitaxel injection and its volume of distribution was also higher (53 %). There were no differences in terminal half-lives.
In a repeat dose study with 12 patients receiving paclitaxel formulated as albumin bound

nanoparticles administered intravenously at 260 mg/m^2, intra-patient variability in AUC was 19 % (range = 3.21 %-37.70 %). There was no evidence for accumulation of paclitaxel with multiple treatment courses.

Distribution

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

The protein binding of paclitaxel following paclitaxel formulated as albumin bound nanoparticles was evaluated by ultrafiltration in a within-patient comparison study. The fraction of free paclitaxel was significantly higher with paclitaxel formulated as albumin bound nanoparticles (6.2 %) than with solvent-based paclitaxel (2.3 %). This resulted in significantly higher exposure to unbound paclitaxel with paclitaxel formulated as albumin bound nanoparticles 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 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 1 741 l; the large volume of distribution indicates extensive extravascular distribution and/or tissue binding of paclitaxel.

Biotransformation and elimination

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, CYP3A4, and both CYP2C8 and CYP3A4 isoenzymes, respectively.

In patients with metastatic breast cancer, after a 30-minute infusion of paclitaxel formulated as albumin bound nanoparticles at 260 mg/m^2, 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 6α-hydroxypaclitaxel and 3'-*p*-hydroxypaclitaxel, indicating extensive non-renal clearance. Paclitaxel is principally eliminated by hepatic metabolism and biliary excretion.

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

Hepatic impairment

The effect of hepatic impairment on population pharmacokinetics of paclitaxel formulated as albumin bound nanoparticles was studied in patients with advanced solid tumours. This analysis included patients with normal hepatic function (n=130), and pre-existing mild (n=8), moderate (n=7), or severe (n=5) hepatic impairment (according to NCI Organ Dysfunction Working Group criteria). The results show that mild hepatic impairment (total bilirubin > 1 to ≤ 1.5 x ULN) has no clinically important effect on pharmacokinetics of paclitaxel. Patients with moderate (total bilirubin > 1.5 to ≤ 3 x ULN) or severe (total bilirubin > 3 to ≤ 5 x ULN) hepatic impairment have a 22 % to 26 % decrease in the maximum elimination rate of paclitaxel and approximately 20 % increase in mean paclitaxel AUC compared with patients with normal hepatic function. Hepatic impairment has no effect on mean paclitaxel C_{max}. In addition, elimination of paclitaxel shows an inverse correlation with total bilirubin and a positive correlation with serum albumin.

Pharmacokinetic/pharmacodynamic modelling indicates that there is no correlation between

hepatic function (as indicated by the baseline albumin or total bilirubin level) and neutropenia after adjusting for paclitaxel formulated as albumin bound nanoparticles exposure.

Pharmacokinetic data are not available for patients with total bilirubin > 5 x ULN or for patients with metastatic adenocarcinoma of the pancreas (see section 4.2).

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.

Elderly
Population pharmacokinetic analysis for paclitaxel formulated as albumin bound nanoparticles included patients with ages ranging from 24 to 85 years old and shows that age does not significantly influence the maximum elimination rate and systemic exposure (AUC and C_{max}) of paclitaxel.

Pharmacokinetic/pharmacodynamic modelling using data from 125 patients with advanced solid tumours indicates that patients ≥ 65 years of age may be more susceptible to development of neutropenia within the first treatment cycle, although the plasma paclitaxel exposure is not affected by age.

Paediatric population
The pharmacokinetics of paclitaxel following 30 minutes of intravenous administration at dose levels of 120 mg/m^2 to 270 mg/m^2 were determined in 64 patients (2 to ≤ 18 years) in Phase 1 of a Phase 1/2 study in recurrent or refractory paediatric solid tumours. Following dosing increase from 120 to 270 mg/m^2, the paclitaxel mean $AUC_{(0\text{-}inf)}$ and C_{max} ranged from 8 867 to 14 361 ng*hr/ml and from 3 488 to 8 078 ng/ml, respectively.

Dose normalised peak drug exposure values were comparable across the dose range studied; however, dose-normalised total drug exposure values were only comparable across 120 mg/m^2 to 240 mg/m^2; with lower dose-normalised AUC_{∞} at the 270 mg/m^2 dose level. At the MTD of 240 mg/m^2, the mean CL was 19.1 l/h and the mean terminal half-life was 13.5 hours.

In children and adolescent patients, exposure to paclitaxel increased with higher dosing and weekly drug exposures were higher than in adult patients.

Other intrinsic factors
Population pharmacokinetic analyses for paclitaxel formulated as albumin bound nanoparticles indicate that gender, race (Asian vs. White), and type of solid tumours do not have a clinically important effect on systemic exposure (AUC and C_{max}) of paclitaxel. Patients weighing 50 kg had paclitaxel AUC approximately 25 % lower than those weighing 75 kg. The clinical relevance of this finding is uncertain.

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 when administered prior and during mating in male and female rats and foetal toxicity in rats. Animal studies with paclitaxel formulated as albumin bound nanoparticles showed non-reversible, toxic effects on the male reproductive organs at clinically relevant exposure levels.

Paclitaxel and/or its metabolites were excreted into the milk of lactating rats. Following intravenous administration of radiolabelled paclitaxel to rats on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations.

6.PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human albumin (containing sodium caprylate and N-acetyl-L-tryptophan).

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 dispersion in the vial
Chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C-8 °C in the original carton, protected from light.

Stability of the reconstituted dispersion in the infusion bag
Chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C-8 °C followed by 4 hours at 25 °C, protected from light.

However, from a microbiological point of view, unless the method of reconstituting and filling of the infusion bags precludes the risks of microbial contamination, the product should be used immediately after reconstitution and filling of the infusion bags.

If not used immediately, in-use storage times and conditions are the responsibility of the user.

The total combined storage time of reconstituted medicinal product in the vial and in the infusion bag when refrigerated and protected from light is 24 hours. This may be followed by storage in the infusion bag for 4 hours below 25 °C.

6.4 Special precautions for storage

Unopened vials
Keep the vial 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.

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

6.5 Nature and contents of container

50 ml vial with a stopper (bromobutyl rubber), with an aluminium flip-off seal, containing 100 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 paclitaxel. The use of gloves, goggles and protective clothing is recommended. If the dispersion 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. Paclitaxel should only be prepared and administered by personnel appropriately trained in the handling of cytotoxic agents. Pregnant staff should not handle paclitaxel.

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 paclitaxel to 30 minutes, as directed, reduces the likelihood of infusion-related reactions.

Reconstitution and administration of the product
<Invented name> is supplied as a sterile lyophilised powder for reconstitution before use. After reconstitution, each ml of dispersion 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 <Invented name> 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 redispersion of any powder occurs. The generation of foam must be avoided. If foaming or clumping occurs, the dispersion must stand for at least 15 minutes until foam subsides.

The reconstituted dispersion should be milky and homogenous without visible precipitates. Some settling of the reconstituted dispersion may occur. If precipitates or settling are visible, the vial should be gently inverted again to ensure complete redispersion prior to use.

Inspect the dispersion in the vial for particulate matter. Do not administer the reconstituted dispersion if particulate matter is observed in the vial.

The exact total dosing volume of 5 mg/ml dispersion required for the patient should be calculated and the appropriate amount of reconstituted <Invented name> should be injected into an empty, sterile, PVC or non-PVC type intravenous bag.

The use of medical devices containing silicone oil as a lubricant (i.e. syringes and IV bags) to reconstitute and administer <Invented name> may result in the formation of proteinaceous strands. Administer <Invented name> 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 specialised di(2-ethylhexyl)phthalate (DEHP)-free solution containers or administration sets is not necessary to prepare or administer <Invented name> 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.

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

7. MARKETING AUTHORISATION HOLDER

STADA Arzneimittel AG
Stadastrasse 2-18
61118 Bad Vilbel
Duitsland

8. MARKETING AUTHORISATION NUMBER(S)

Bugvi 5 mg/ml poeder voor dispersie voor infusie RVG 129035

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 19 juni 2024

10. DATE OF REVISION OF THE TEXT