Summary of Product Characteristics for Pharmaceutical Products

1. Name of the Drug Product

Nab-Xelpac Injection

2. Qualitative and Quantitative Composition

Each Vial contains Nanoparticle albumin-bound paclitaxel 100mg

For a full list of excipients, see section 6.1.

3. Pharmaceutical Form

Lyophilized Powder for Injection

4. Clinical particulars

4.1 Therapeutic indications

Paclitaxel 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.

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

Paclitaxel 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

Paclitaxel 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 Paclitaxel 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 Paclitaxel 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. Paclitaxel should not be administered until neutrophil counts recover to >1500 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 Paclitaxel 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 1000 mg/m^2 administered

intravenously over 30 minutes immediately after the completion of Paclitaxel 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	**Paclitaxel Dose (mg/m^2)**	**Gemcitabine Dose (mg/m^2)**
Full dose	125	1000
1st dose level reduction	100	800
2nd dose level reduction	75	600
If additional dose reduction required	Discontinue treatment	Discontinue treatment

Table 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 ($cells/mm^3$)**	**Paclitaxel 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	≥ 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	≥ 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)	**Paclitaxel 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 ≤ Grade 1; resume at next lower dose level[a]	Treat with same dose

Cutaneous Toxicity:	Reduce to next lower dose level[a];
Grade 2 or 3	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 Paclitaxel 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 Paclitaxel administration.

Dose adjustments during treatment of non-small cell lung cancer:

Paclitaxel should not be administered on Day 1 of a cycle until absolute neutrophil count (ANC) is ≥1500 cells/mm^3 and platelet count is ≥100,000 cells/mm^3. For each subsequent weekly dose of Paclitaxel, 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 Paclitaxel (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 <1500/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 Paclitaxel and carboplatin simultaneously. On Days 8 or 15 of the 21-day cycle reduce the dose of Paclitaxel; 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 Paclitaxel (mg/m^2)[1]**	**Dose of carboplatin (AUC mg•min/mL)[1]**
Grade 2 or 3 cutaneous toxicity Grade 3 diarrhoea Grade 3 mucositis ≥ Grade 3 peripheral neuropathy Any other Grade 3 or 4 non-haematologic toxicity	First	75	4.5
	Second	50	3.0
	Third	Discontinue Treatment	
Grade 4 cutaneous toxicity, diarrhoea, or mucositis	First	Discontinue Treatment	

[1]On Day 1 of the 21-day cycle reduce the dose of Paclitaxel and carboplatin simultaneously. On Days 8 or 15 of the 21-day cycle reduce the dose of Paclitaxel; 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.

For patients with metastatic adenocarcinoma of the pancreas that have moderate to severe hepatic impairment, there are insufficient data to permit dosage recommendations.
For patients with total bilirubin > 5 x ULN or AST > 10 x ULN, there are insufficient data to permit dosage recommendations regardless of indication.

Renal impairment

Adjustment of the starting Paclitaxel 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 Paclitaxel in patients with severe renal impairment or end stage renal disease (estimated creatinine clearance <30 ml/min).

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 randomized study who received Paclitaxel 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. However, a subsequent analysis in 981 patients receiving Paclitaxel 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.
treatment discontinuation. Patients with pancreatic adenocarcinoma aged 75 years and older should be carefully assessed before treatment is considered.
Of the 514 patients with non-small cell lung cancer in the randomized study who received Paclitaxel 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/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 in children and adolescents aged 0 to less than 18 years has not been established. Currently available data are described in section s 4.8, 5.1 and 5.2 but no recommendation on a posology can be made. There is no relevant use of Paclitaxel 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 Paclitaxelsuspension 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Patients who have baseline neutrophil counts <1500 cells/mm3.

4.4 Special warnings and precautions for use

Paclitaxel is an albumin-bound nanoparticle formulation of Paclitaxel, which may have substantially different pharmacological properties compared to other formulations of Paclitaxel. 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. Neutropenia is dose-dependent and a dose-limiting toxicity. Frequent monitoring of blood cell counts should be performed during Paclitaxel therapy. Patients should not be retreated with subsequent cycles of Paclitaxel until neutrophils recover to >1500 cells/mm^3 and platelets recover to >100,000 cells/mm^3.

Neuropathy

Sensory neuropathy occurs frequently with Paclitaxel, although development of severe symptoms is less common. The occurrence of Grade 1 or 2 sensory neuropathy does not generally require dose reduction. When Paclitaxel 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 Paclitaxelis recommended. For combination use of Paclitaxel and gemcitabine, if Grade 3 or higher peripheral neuropathy develops, withhold Paclitaxel; continue treatment with gemcitabine at the same dose. Resume Paclitaxelat reduced dose when peripheral neuropathy improves to Grade 0 or 1. For combination use of Paclitaxel 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 Paclitaxel and carboplatin.

Sepsis

treatment with broad spectrum antibiotics. For febrile neutropenia, withhold Paclitaxel and gemcitabine until fever resolves and ANC ≥ 1500 cells/mm^3, then resume treatment at reduced dose levels.

Pneumonitis

Pneumonitis occurred in 1% of patients when Paclitaxel was used as monotherapy and in 4% of patients when Paclitaxel 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 Paclitaxel and gemcitabine and promptly initiate appropriate treatment and supportive measures.

Hepatic impairment

Because the toxicity of Paclitaxel can be increased with hepatic impairment, administration of Paclitaxel 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.

Paclitaxelis not recommended in patients that have total bilirubin > 5 x ULN or AST > 10 x ULN. In addition, Paclitaxel is not recommended in patients with metastatic adenocarcinoma ofthe pancreas that have moderate to severe hepatic impairment (total bilirubin > 1.5 x ULN and AST ≤ 10 x ULN).

Cardiotoxicity

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

CNS metastases

The effectiveness and safety of Paclitaxel 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 Paclitaxel, 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 Paclitaxel and gemcitabine in comparison to gemcitabine monotherapy has been demonstrated. In the very elderly (≥75 years) who received Paclitaxel 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 Paclitaxe lin combination with gemcitabine with special consideration to performance status, co-morbidities and increased risk of infections.

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 Paclitaxeland gemcitabine.

Erlotinib should not be co-administered with Paclitaxel plus gemcitabine.

Excipients

When reconstituted, each ml of Paclitaxel 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 Interaction with other medicinal products and other forms of interaction

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 and gemcitabine have not been evaluated in humans.

A pharmacokinetic study was conducted with Paclitaxel and carboplatin in non-small cell lung cancer patients. There were no clinically relevant pharmacokinetic interactions between Paclitaxel and carboplatin.

Paclitaxel 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. Paclitaxel 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. 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. 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 induced infertility in male rats. 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 have been neutropenia, peripheral neuropathy, arthralgia/myalgia and gastrointestinal disorders.

The frequencies of adverse reactions associated with the administration of Paclitaxel are listed in Table 6 (Paclitaxel asmonotherapy) and Table 7 (Paclitaxel in combination with gemcitabine), and Table 9 (Paclitaxel in combination with carboplatin).

Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥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 (Paclitaxel administered as monotherapy)

Tabulated list of adverse reactions

Table 6 lists adverse reactions associated with the administration of Paclitaxel to patients from studies in which Paclitaxel has been administered as monotherapy at any dose in any indication (N = 789).

Table 6: Adverse reactions reported with Paclitaxel monotherapy at any dose in clinical studies

Infections and infestations	*Common*: Infection, urinary tract infection, folliculitis, upper respiratory tract infection, candidiasis, sinusitis *Uncommon*: Oral candidiasis, nasopharyngitis, cellulitis, herpes simplex, viral infection, pneumonia, catheter-related infection, fungal infection, herpes zoster, injection site infection, sepsis[2], neutropenic sepsis[2]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	*Uncommon:* Metastatic pain, tumour necrosis
Blood and lymphatic system disorders	*Very common*: Neutropenia, anaemia, leukopenia, thrombocytopenia, lymphopenia, bone marrow suppression *Common*: Febrile neutropenia *Rare*: Pancytopenia
Immune system disorders	*Uncommon[1]:* Hypersensitivity *Rare:* Severe hypersensitivity

Metabolism and nutrition disorders	*Very common:* Anorexia *Common:* Dehydration, decreased appetite, hypokalaemia *Uncommon:* Hypophosphataemia, fluid retention, hypoalbuminaemia, polydipsia, hyperglycaemia, hypocalcaemia, hypoglycaemia, hyponatraemia
Psychiatric disorders	*Common*: Insomnia, depression, anxiety *Uncommon*: Restlessness
Nervous system disorders	*Very common*: Peripheral neuropathy, neuropathy, hypoaesthesia, paraesthesia *Common*: Peripheral sensory neuropathy, headache, dysgeusia, dizziness, peripheral motor neuropathy, ataxia, sensory disturbance, somnolence *Uncommon*: Polyneuropathy, areflexia, dyskinesia, hyporeflexia, neuralgia, sensory loss, syncope, postural dizziness, neuropathic pain, tremor
Eye disorders	*Common:* Increased lacrimation, blurred vision, dry eye, keratoconjunctivitissicca, madarosis *Uncommon*: Eye irritation, eye pain, abnormal vision, reduced visual
	acuity, conjunctivitis, visual disturbance, eye pruritus, keratitis *Rare*: Cystoid macular oedema[2]
Ear and labyrinth disorders	*Common*: Vertigo *Uncommon*: Ear pain, tinnitus
Cardiac disorders	*Common*: Tachycardia, arrhythmia, supraventricular tachycardia *Rare:* bradycardia, cardiac arrest, left ventricular dysfunction, congestive heart failure, atrioventricular block[2]
Vascular disorders	*Common*: Flushing, hot flushes, hypertension, lymphoedema *Uncommon*: Hypotension, peripheral coldness, orthostatic hypotension *Rare:* Thrombosis
Respiratory, thoracic and mediastinal disorders	*Common*: Interstitial pneumonitis[3], dyspnoea, epistaxis, pharyngolaryngeal pain, cough, rhinitis, rhinorrhoea *Uncommon*: Productive cough, exertionaldyspnoea, sinus congestion, decreased breath sounds, pleural effusion, allergic rhinitis, hoarseness, nasal congestion, nasal dryness, wheezing, pulmonary emboli, pulmonary thromboembolism
Gastrointestinal disorders	*Very common*: Nausea, diarrhoea, vomiting, constipation, stomatitis *Common*: Abdominal pain, abdominal distension, upper abdominal pain, dyspepsia, gastrooesophageal reflux disease, oral hypoaesthesia *Uncommon*: Dysphagia, flatulence, glossodynia, dry mouth, gingival pain, loose stools, oesophagitis, lower abdominal pain, mouth ulceration, oral pain, rectal haemorrhage
Hepatobiliary disorders	*Uncommon*: Hepatomegaly

Skin and subcutaneous tissue disorders	*Very common*: Alopecia, rash *Common*: Nail disorder, pruritus, dry skin, erythema, nail pigmentation/discolouration, skin hyperpigmentation, onycholysis, nail changes *Uncommon*: Nail bed tenderness, urticaria, skin pain, photosensitivity reaction, pigmentation disorder, pruritic rash, skin disorder, hyperhidrosis, onychomadesis, erythematous rash, generalised rash, dermatitis, night sweats, maculo-papular rash, vitiligo, hypotrichosis, nail discomfort, generalized pruritus, macular rash, papular rash, skin lesion, swollen face *Very rare:* Stevens-Johnson syndrome[2], toxic epidermal necrolysis[2]
Musculoskeletal and connective tissue disorders	*Very common*: Arthralgia, myalgia. *Common*: Pain in extremity, bone pain, back pain, muscle cramps, limb pain *Uncommon*: Chest wall pain, muscular weakness, neck pain, groin pain, muscle spasms, musculoskeletal pain, flank pain, limb discomfort, muscle weakness
Renal and urinary disorders	*Uncommon*: Dysuria, pollakiuria, haematuria, nocturia, polyuria, urinary incontinence
Reproductive system and breast disorders	*Uncommon: Breast pain*
General disorders and administration site conditions	*Very common: Fatigue, asthenia, pyrexia* *Common: Peripheral oedema, mucosal inflammation, pain, rigors, oedema, weakness, decreased performance status, chest pain, influenza- like illness, malaise, lethargy, hyperpyrexia* *Uncommon: Chest discomfort, abnormal gait, swelling, injection site reaction* *Rare: Extravasation*
Investigations	*Common: Decreased weight, increased alanine aminotransferase, increased aspartate aminotransferase, decreased haematocrit, decreased red blood cell count, increased body temperature, increased gamma- glutamyltransferase, increased blood alkaline phosphatase* *Uncommon: Increased blood pressure, increased weight, increased blood lactate dehydrogenase, increased blood creatinine, increased blood glucose, increased blood phosphorus, decreased blood potassium, increased bilirubin*
Injury, poisoning and procedural complications	*Uncommon: Contusion* *Rare: Radiation recall phenomenon, radiation pneumonitis*

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 Paclitaxel.
[3] The frequency of pneumonitis is calculated based on pooled data in 1310 patients in clinical trials receiving Paclitaxel monotherapy for breast cancer and for other indications using MedDRA SMQ Interstitial lung disease.

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/m^2 Paclitaxel 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/mm^3) occurred in 9% of patients treated with Paclitaxel. Febrile neutropenia occurred in four patients on Paclitaxel. Anaemia (Hb< 10 g/dl) was observed in 46% of patients on Paclitaxel 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 Paclitaxel. Peripheral neuropathy (mostly Grade 1 or 2 sensory neuropathy) was observed in 68% of patients on Paclitaxel 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 >80% of the patients treated with Paclitaxel. The majority of alopecia events occurred less than one month after initiation of Paclitaxel. Pronounced hair loss
≥50% is expected for the majority of patients who experience alopecia.
Musculoskeletal and connective tissue disorders
Arthralgia occurred in 32% of patients on Paclitaxel and was severe in 6% of cases. Myalgia occurred in 24% of patients on Paclitaxel and was severe in 7% of cases. The symptoms were usually transient, typically occurred three days after Paclitaxel administration and resolved within a week.
General disorders and administration site conditions
Asthenia/Fatigue was reported in 40% of the patients.
Pancreatic adenocarcinoma (Paclitaxel administered in combination with gemcitabine)
Tabulated list of adverse reactions
Adverse reactions were assessed in 421 patients treated with Paclitaxel 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 7 lists adverse reactions assessed in patients with pancreatic adenocarcinoma treated with Paclitaxel in combination with gemcitabine.

Table 7: Adverse reactions reported with Paclitaxel in combination with gemcitabine (N

=421)

Infections and infestations	*Common*: Sepsis, pneumonia, oral candidiasis
Blood and lymphatic system disorders	*Very common*: Neutropenia, anaemia, thrombocytopenia *Common*: Pancytopenia *Uncommon*: Thrombotic thrombocytopenic purpura
Metabolism and nutrition disorders	*Very common*: Dehydration, decreased appetite, hypokalaemia
Psychiatric disorders	*Very common*: Insomnia, depression *Common*: Anxiety
Nervous system disorders	*Very common*: Peripheral neuropathy[1], dysgeusia, headache, dizziness *Uncommon*: VIIth nerve paralysis
Eye disorders	*Common*: Lacrimation increased *Uncommon*: Cystoid macular oedema
Cardiac disorders	*Common*: Cardiac failure congestive, tachycardia
Vascular disorders	*Common*: Hypotension, hypertension
Respiratory, thoracic and mediastinal disorders	*Very common*: Dyspnoea, epistaxis, cough *Common*: Pneumonitis[2], nasal congestion *Uncommon*: Dry throat, nasal dryness
Gastrointestinal disorders	*Very common*: Nausea, diarrhoea, vomiting, constipation, abdominal pain, abdominal pain upper *Common*: Stomatitis, intestinal obstruction, colitis, dry mouth
Hepatobiliary disorders	*Common*: Cholangitis
Skin and subcutaneous tissue disorders	*Very common*: Alopecia, rash *Common*: Pruritus, dry skin, nail disorder, flushing
Musculoskeletal and connective tissue disorders	*Very common*: Pain in extremity, arthralgia, myalgia *Common*: Muscular weakness, bone pain
Renal and urinary disorders	*Common*: Acute renal failure *Uncommon*: Haemolyticuraemic syndrome
General disorders	*Very common*: Fatigue, oedema peripheral, pyrexia, asthenia, chills
and administration site conditions	*Common: Infusion site reaction*

Investigations	*Very common: Weight decreased, alanine aminotransferase increased Common: 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).

[1] Peripheral neuropathy evaluated using the SMQ (broad scope).

[2] Pneumonitis is evaluated using the SMQ interstitial lung disease (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 Paclitaxel 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/m^2 Paclitaxel in combination with gemcitabine at a dose of 1000 mg/m^2 given on Days 1, 8 and 15 of each 28-day cycle in the phase III clinical study.

Blood and lymphatic system disorders

Table 8 provides the frequency and severity of haematologic laboratory-detected abnormalities for patients treated with Paclitaxel in combination with gemcitabine or with gemcitabine.

Table 8: Haematologic laboratory-detected abnormalities in pancreatic adenocarcinoma trial

	Paclitaxel (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
Thrombocytopeniab, c	74	13	70	9

[a] 405 patients assessed in Paclitaxel/gemcitabine-treated group

[b] 388 patients assessed in gemcitabine-treated group

[c] 404 patients assessed in Paclitaxel/gemcitabine-treated group

Peripheral neuropathy

For patients treated with Paclitaxel 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 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 Paclitaxel 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 Paclitaxel and gemcitabine until fever resolves and ANC ≥ 1500 cells/mm^3, then resume treatment at reduced dose levels.

Pneumonitis

Pneumonitis has been reported at a rate of 4% with the use of Paclitaxel in combination with gemcitabine. Of the 17 cases of pneumonitis reported in patients treated with Paclitaxel 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 Paclitaxel and gemcitabine and promptly initiate appropriate treatment and supportive measures.

Non-small cell lung cancer (Paclitaxel administered in combination with carboplatin)

Tabulated list of adverse reactions

Table 9 lists adverse reactions associated with the administration of Paclitaxel in combination with carboplatin.

Table 9: Adverse reactions reported with Paclitaxel in combination with carboplatin (N = 514)

Infections and infestations	*Common:* Pneumonia, bronchitis, upper respiratory tract infection, urinary tract infection *Uncommon:* Sepsis, oral candidiasis
Blood and lymphatic system disorders[1]	*Very common:* Neutropenia[1], thrombocytopenia[1], anaemia[1], leukopenia[1] *Common:* Febrile neutropenia, lymphopenia *Uncommon:* Pancytopenia
Immune system disorders	*Uncommon:* Drug hypersensitivity, hypersensitivity
Metabolism and nutrition disorders	*Very common:* Decreased appetite *Common:* Dehydration
Psychiatric	*Common:* Insomnia

disorders	
Nervous system disorders	*Very common:* Peripheral neuropathy[2] *Common:* Dysgeusia, headache, dizziness
Eye disorders	*Common:* Vision blurred
Vascular disorders	*Common:* Hypotension, hypertension *Uncommon:* Flushing
Respiratory thoracic and mediastinal disorders	*Very common:* Dyspnoea *Common:* Haemoptysis, epistaxis, cough *Uncommon:* Pneumonitis[3]
Gastrointestinal disorders	*Very common:* Diarrhoea, vomiting, nausea, constipation *Common:* Stomatitis, dyspepsia, abdominal pain, dysphagia
Hepatobiliary disorders	*Common:* Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	*Very common:* Rash, alopecia *Common:* Pruritus, nail disorder *Uncommon:* Skin exfoliation, dermatitis allergic, urticaria
Musculoskeletal and connective tissue disorders	*Very common:* Arthralgia, myalgia *Common:* Back pain, pain in extremity, musculoskeletal pain
General disorders and administration site conditions	*Very common:* Fatigue, asthenia, oedema peripheral *Common*: Pyrexia, chest pain *Uncommon:* Mucosal inflammation, infusion site extravasation, infusion site inflammation, infusion site rash
Investigations	*Common:* Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, weight decreased

MedDRA = Medical Dictionary for Regulatory Activities: SMQ = Standardized MedDRA Query

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

[2] Peripheral neuropathy is evaluated using the SMQ neuropathy (broad scope)

[3] Pneumonitis is evaluated using the SMQ interstitial lung disease (broad scope)

For non-small cell lung cancer patients treated with Paclitaxel 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 and carboplatin experienced Grade 4 peripheral neuropathy.

Anemia and thrombocytopenia were more commonly reported in the

Paclitaxel arm than in the Taxol arm (54% versus 28% and 45% versus 27% respectively).
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) favored Paclitaxel and carboplatin ($p \leq 0.002$). For the other subscale (oedema), there was no difference in the treatment arms.

Post-marketing experience

Cranial nerve palsies, vocal cord paresis, and rare reports of severe hypersensitivity reactions have been reported during post-marketing surveillance of Paclitaxel.
There have been rare reports of reduced visual acuity due to cystoid macular oedema during treatment with Paclitaxel. Upon diagnosis of cystoid macular oedema, treatment with Paclitaxel should be discontinued.
There have been reports of tumourlysis syndrome during treatment with Paclitaxel. Scleroderma of the skin has been reported. In some patients previously exposed to capecitabine, reports of palmar-plantar erythrodysaesthesiae have been reported as part of the continuing surveillance of Paclitaxel. 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.

Paediatric population

The study consisted of 106 patients, 104 of whom were paediatric patients aged from 6 months to less than 18 years. 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 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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

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.

Paclitaxel 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 caveolartranscytosis of plasma constituents, and *in vitro* studies demonstrated that the presence of albumin in Paclitaxel enhances transport of Paclitaxel across endothelial cells. It is hypothesised that this enhanced transendothelialcaveolar 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 in metastatic breast cancer. This information is presented below.

Single-arm open-label studies

In one study, Paclitaxel 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 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 10: Results for overall response rate, median time to disease progression, and progression-free survival as assessed by the investigator

Efficacy variable	Paclitaxel (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]
**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 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 Paclitaxel 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 Paclitaxel/gemcitabine versus gemcitabine monotherapy as first-line treatment in patients with metastatic adenocarcinoma of the pancreas. Paclitaxel 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 1000 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 randomized to receive Paclitaxel 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 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/gemcitabine arm and 2.8 months in the gemcitabine arm. 32% of patients in the Paclitaxel/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/gemcitabine arm and 85% in the gemcitabine arm. The median relative dose intensity of Paclitaxel was 81%. A higher median cumulative dose of gemcitabine was delivered in the Paclitaxel/gemcitabine arm (11400 mg/m^2) when compared with the gemcitabine arm (9000 mg/m^2).

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

Table 11: Efficacy results from randomized study in patients with pancreatic adenocarcinoma (Intent-to-treat population)

	Paclitaxel(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)

HRA+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)
HRA+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
pA+G/pG (95% CI)	3.19 (2.178, 4.662)	
P-value (chi-square test)	<0.0001	

CI = confidence interval, HRA+G/G = hazard ratio of Paclitaxel+gemcitabine/gemcitabine, pA+G/pG=response rate ratio of Paclitaxel+gemcitabine/gemcitabine

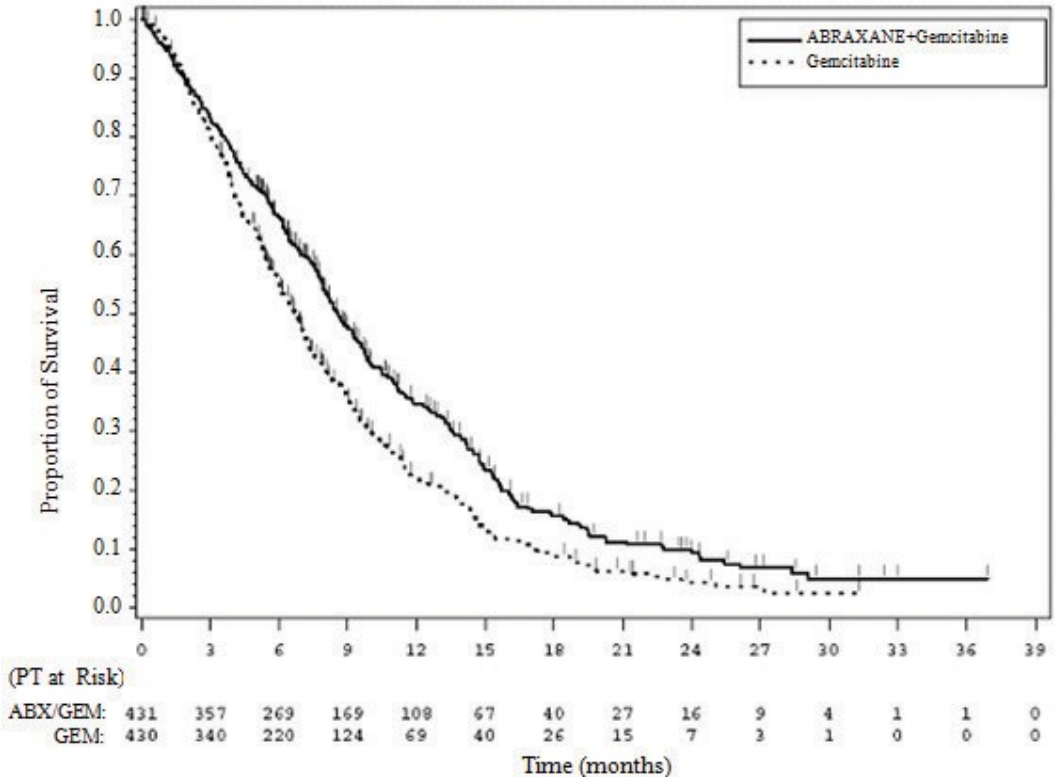
[a] stratified Cox proportional hazard model

[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/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/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/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/gemcitabine versus gemcitabine alone, with 1.8 months increase in median PFS.

Non-small cell lung cancer

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 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 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 of200 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/carboplatin arm had a significantly higher overall response rate compared with patients in the control arm: 33% versus 25%, p = 0.005 (Table 12). There was a significant difference in overall response rate in the Paclitaxel/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 12: Overall response rate in randomized non-small cell lung cancer trial (intent-to-treat population)

Efficacy Parameter	**Paclitaxel (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
pA/pT (95.1% CI)	1.313 (1.082, 1.593)	
P-value[a]	0.005	

CI = confidence interval; HRA/T = hazard ratio of Paclitaxel/carboplatin to solvent-based Paclitaxel/carboplatin; pA/pT = response rate ratio of Paclitaxel/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 13).

Table 13: Non-inferiority analyses on progression-free survival and overall survival in randomized non-small cell lung cancer trial (intent-to-treat population)

Efficacy Parameter	**Paclitaxel (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)
HRA/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)
HRA/T (95.1% CI)	0.922 (0.797, 1.066)	

CI = confidence interval; HRA/T = hazard ratio of Paclitaxel/carboplatin to solvent-based Paclitaxel/carboplatin; pA/pT = response rate ratio of Paclitaxel/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. Study ABI-007-PST-001, a Phase 1/2, multicenter, open-label, dose-finding study to assess the safety, tolerability and preliminary efficacy of weekly Paclitaxel inpaediatric 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/m2, 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 inpaediatric patients was consistent with the known safety profile of Paclitaxel in adults (see section 4.8). Based on these results, it was concluded that Paclitaxel 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 at dose levels of 80 to 375 mg/m^2 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/m^2.

In a study in patients with advanced solid tumours, the pharmacokinetic characteristics of Paclitaxel following Paclitaxel 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 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 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 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 was evaluated by ultrafiltration in a

Paclitaxel (6.2%) than with solvent-based Paclitaxel (2.3%). This resulted in significantly higher exposure to unbound Paclitaxel with Paclitaxel 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 1741 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 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

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

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

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 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-inf) and Cmax ranged from 8867 to 14361 ng*hr/ml and from 3488 to 8078 ng/ml, respectively.

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

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

Other intrinsic factors

Population pharmacokinetic analyses for Paclitaxel 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 phosphoribosyltransferase (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 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
Albumin Human
Water for Injection

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store in a cool and dry place, away from light. Keep out of the reach of Children.

6.5 Nature and contents of container
Primary Packaging: Clear glass vial USP Type-1
Secondary Packaging: Paper board carton
Pack size: 1 × 1's vial in Box

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder and manufacturing site addreesses

Marketing authorization holder:

Company Name:	Beacon Business Center
Address:	9/B/2, Toyenbee Circular Road, Motijheel, Dhaka-1223,
Country:	Bangladesh

Manufacturing site address:

Company Name:	Beacon Business Center
Address:	9/B/2, Toyenbee Circular Road, Motijheel, Dhaka-1223,
Country:	Bangladesh

8. Marketing authorization Number:

CTD9745

9. Date of first authorization/renewal of the authorization

20/06/2023

10. Date of revision of the text

14/09/2023

11. Dosimetry

Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:

Not Applicable