For the use of an Oncologists or a Hospital or laboratory only

NAB TORTAXEL

(Paclitaxel (Protein-Bound Particles) for Injectable Suspension)

COMPOSITION

Each vial contains:
Paclitaxel I.P…….. 100 mg
Human Albumin I.P. …….. q.s.

DOSAGE FORM

Lyophilized powder for suspension for infusion

INDICATION

Paclitaxel (protein-bound particles) for injectable suspension is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy.

DOSE AND METHOD OF ADMINISTRATION

Paclitaxel (protein-bound particles) for injectable suspensionshould only be administered under the supervision of a qualified oncologist in units specialised in theadministration of cytotoxic agents. It should not be substituted for or with other paclitaxel formulations.

Posology

Breast cancer

The recommended dose of paclitaxel (protein-bound particles) for injectable suspension 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 severesensory neuropathy during paclitaxel (protein-bound particles) for injectable suspension 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 madeto 180 mg/m^2. Paclitaxel (protein-bound particles) for injectable suspension should not be administered until neutrophil counts recover to >1500 $cells/mm^3$. For Grade 3sensory neuropathy, withhold treatment until resolution to Grade 1 or 2, followed by a dose reduction for allsubsequent courses.

Special populations

Patients with 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 normalhepatic function.

For metastatic breast cancer patients with moderate to severe hepatic impairment (total bilirubin > 1.5 to ≤ 5 x ULNand AST ≤ 10 x ULN), a 20% reduction in dose is recommended. The

reduced dose may be escalated to the dose forpatients with normal hepatic function if the patient is tolerating the treatment for at least two cycles.

For patients with total bilirubin > 5 x ULN or AST > 10 x ULN, there are insufficient data to permit dosagerecommendations regardless of indication.

Patients with renal impairment
Adjustment of the starting paclitaxel (protein-bound particles) injectable suspension dose is not required for patients with mild to moderate renal impairment(estimated creatinineclearance ≥30 to <90 ml/min). There are insufficient data available to recommend dosemodifications of paclitaxel (protein-bound particles) injectable suspension in patients with severe renal impairment or end stage renal disease (estimated Creatinineclearance <30 ml/min)

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

Of the 229 patients in the randomized study who received paclitaxel (protein-bound particles) injectable suspension monotherapy for breast cancer, 13% were atleast 65 years of age and < 2% were 75 years and older. No toxicities occurred notably more frequently amongpatients at least 65 years of age who received paclitaxel (protein-bound particles) injectable suspension. However, a subsequent analysis in 981 patients receivingpaclitaxel (protein-bound particles) injectable suspension 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.

Pharmacokinetic/pharmacodynamicmodelling using data from 125 patients with advanced solid tumours indicatesthat patients ≥ 65 years of age may be more susceptible to development of neutropenia within the first treatmentcycle.

Paediatric population
The safety and efficacy of paclitaxel (protein-bound particles) injectable suspension in children and adolescents aged 0-17 years has not been established. There isno relevant use of paclitaxel (protein-bound particles) injectable suspension in the paediatric population in the indication of metastatic breast cancer.

Preparation & administrative precautions

- Paclitaxel (protein-bound particles) for injectable suspension is a cytotoxic anticancer drug and, as with other potentially toxic paclitaxel compounds, caution should be exercised in handling it. The use of gloves is recommended. If lyophilized cake or reconstituted suspension contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure to paclitaxel, events may include tingling, burning and redness. If it contacts mucous membranes, the membranes should be flushed thoroughly with water.

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

- No premedication to prevent hypersensitivity reactions is required prior to administration

Preparation for intravenous administration
Paclitaxel (protein-bound particles) for injectable suspension is supplied as asterile lyophilized powder for reconstitution before use.

AVOID ERRORS, READ ENTIRE PREPARATION INSTRUCTIONSPRIOR TO RECONSTITUTION.

Preparation Instructions prior to reconstitution
- Aseptically, reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection IP.

- Slowly inject the 20 mL of 0.9% Sodium Chloride Injection IP over a minimum of 1 minute, using the sterile syringe to direct the solution flow onto THE INSIDE WALL OF THE VIAL.

- DO NOT INJECT the 0.9% Sodium Chloride Injection IP directly onto the lyophilized cake as this will result in foaming. Once the injection is complete, allow the vial to sit for a minimum of 5 minutes to ensure proper wetting of the lyophilized cake/powder.

- Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs. Avoid generation of foam.

- If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.

Each mL of the reconstituted formulation will contain 5 mg/mL paclitaxel. Calculate the exact total dosing volume of 5 mg/mL suspension required for the patient : Dosing volume (mL) = Total dose (mg)/ 5(mg/mL).

The reconstituted suspension should be milky and homogenous without visible particulates. If particulates or settling are visible, the vial should be gently inverted again to ensure complete resuspension prior to use. Discard the reconstituted suspension if precipitates are observed. Discard any unused portion.

Inject the appropriate amount of reconstituted Paclitaxel (protein-bound particles) for injectable suspension into an empty, sterile IV bag [plasticized polyvinyl chloride (PVC) containers, PVC or non-PVC type IV bag]. The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer infusions. The use of an in-line filter is not recommended.

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

Stability
Unopened vials of Paclitaxel (protein-bound particles) for injectable suspension are stable until the date indicated on the package when stored between 20°C to 25°C in the original package. Neither freezing nor refrigeration adversely affects the stability of the product.

Stability of reconstituted suspension in the Vial
Reconstituted Paclitaxel (protein-bound particles) for injectable suspension should be used immediately, but may be refrigerated at 2°C to 8°C for a maximum of 8 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion.

Stability of reconstituted suspension in the infusion bag
The suspension for infusion prepared as recommended in an infusion bag should be used immediately, but may be stored at ambient temperature (approximately 25°C) and lighting conditions for up to 4 hours. Discard any unused portion.

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 receivingtreatment with Paclitaxel (protein-bound particles) for injectable suspension. Male patients treated with Paclitaxel (protein-bound particles) for injectable suspension are advised not to father a child during and up to sixmonths after treatment.

Pregnancy
There are very limited data on the use of paclitaxel in human pregnancy. Paclitaxel is suspected to cause seriousbirth defects when administered during pregnancy. Studies in animals have shown reproductive toxicity. Paclitaxel (protein-bound particles) for injectable suspension should not be used in pregnancy, and in women of childbearing potential not using effectivecontraception, unless the clinical condition of the mother requires treatment with paclitaxel.

Breast-feeding
It is not known if paclitaxel is excreted in human milk. Because of potential serious adverse reactions in breastfeedinginfants, Paclitaxel (protein-bound particles) for injectable suspension is contraindicated during lactation. Breast-feeding must be discontinued for the duration oftherapy.

Fertility
Paclitaxel (protein-bound particles) for injectable suspension induced infertility in male rats. Male patients should seek advice on conservation of spermprior to treatment because of the possibility of irreversible infertility due to therapy with Paclitaxel (protein-bound particles) for injectable suspension.

CONTRAINDICATIONS
- Hypersensitivity to the active substance or to any of the excipients.
- Lactation.
- Patients who have baseline neutrophil counts <1500 cells/mm^3.

WARNINGS AND PRECAUTIONS

Paclitaxel (protein-bound particles) for injectable suspension is an albumin-bound nanoparticle formulation of paclitaxel, which may have substantially differentpharmacological properties compared to other formulations of paclitaxel. It should not besubstituted for or with other paclitaxel formulations.

Hypersensitivity

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

Haematology

Bone marrow suppression (primarily neutropenia) occurs frequently with paclitaxel (protein-bound particles) for injectable suspension. Neutropenia is dose-dependentand a dose-limiting toxicity. Frequent monitoring of blood cell counts should be performed during Paclitaxel (protein-bound particles) for injectable suspension therapy.

Patients should not be retreated with subsequent cycles of Paclitaxel (protein-bound particles) for injectable suspension until neutrophils recover to >1500 cells/mm^3 andplatelets recover to >100,000 cells/mm^3.

Neuropathy

Sensory neuropathy occurs frequently with Paclitaxel (protein-bound particles) for injectable suspension, 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 (protein-bound particles) for injectable suspension isused as monotherapy, if Grade 3 sensory neuropathy develops, treatment should be withheld until resolution to Grade1 or 2 followed by a dose reduction for all subsequent courses of Paclitaxel (protein-bound particles) for injectable suspension is recommended. Forcombination use of Paclitaxel (protein-bound particles) for injectable suspension and gemcitabine, if Grade 3 or higher peripheral neuropathy develops, withhold Paclitaxel (protein-bound particles) for injectable suspension; continue treatment with gemcitabine at the same dose. Resume Paclitaxel (protein-bound particles) for injectable suspension at reduced dose whenperipheral neuropathy improves to Grade 0 or 1. For combination use of Paclitaxel (protein-bound particles) for injectable suspension and carboplatin,if Grade 3 or higher peripheral neuropathy develops, treatment should be withheld until improvement to Grade 0 or 1followed by a dose reduction for all subsequent courses of Paclitaxel (protein-bound particles) for injectable suspension and carboplatin.

Sepsis

Sepsis was reported at a rate of 5% in patients with or without neutropenia who received Paclitaxel (protein-bound particles) for injectable suspension in combinationwith gemcitabine. Complications due to the underlying pancreatic cancer, especially biliary obstruction or presence ofbiliary stent, were identified as significant contributing factors. If a patient becomesfebrile (regardless of neutrophilcount), initiate treatment with broad spectrum antibiotics. For febrile

neutropenia, withhold Paclitaxel (protein-bound particles) for injectable suspension and gemcitabineuntil fever resolves and ANC ≥ 1500 cells/mm^3, and then resume treatment at reduced dose levels.

Pneumonitis

Pneumonitis occurred in 1% of patients when Paclitaxel (protein-bound particles) for injectable suspension was used as monotherapy and in 4% of patients when Paclitaxel (protein-bound particles) for injectable suspension was used in combination with gemcitabine. Closely monitor all patients for signs and symptoms ofpneumonitis. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinuetreatment with Paclitaxel (protein-bound particles) for injectable suspension 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 (protein-bound particles) for injectable suspension in patientswith hepatic impairment should be performed with caution. Patients with hepatic impairment may be at increased riskof toxicity, particularly from myelosuppression; such patients should be closely monitored for development of profoundmyelosuppression.

Paclitaxel (protein-bound particles) for injectable suspension is not recommended in patients that have total bilirubin > 5 x ULN or AST > 10 x ULN. In addition, Paclitaxel (protein-bound particles) for injectable suspension is not recommended in patients with metastatic adenocarcinoma of the pancreas that have moderate tosevere 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 individualsreceiving Paclitaxel (protein-bound particles) for injectable suspension. Most of the individuals were previously exposed to cardiotoxic medicinal products such asanthracyclines, or had underlying cardiac history. Thus patients receiving Paclitaxel (protein-bound particles) for injectable suspension should be vigilantly monitored byphysicians for the occurrence of cardiac events.

CNS metastases

The effectiveness and safety of Paclitaxel (protein-bound particles) for injectable suspension in patients with central nervous system (CNS) metastases has not beenestablished. CNS metastases are generally not well controlled by systemic chemotherapy.

Gastrointestinal symptoms

If patients experience nausea, vomiting and diarrhoea following the administration of Paclitaxel (protein-bound particles) for injectable suspension, they may be treatedwith 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 (protein-bound particles) for injectable suspension andgemcitabine incomparison to gemcitabine monotherapy has been demonstrated. In the very elderly (≥75 years) who received Paclitaxel (protein-bound particles) for injectable suspension and gemcitabine, there was a higher incidence of serious adverse reactions and adverse reactions that ledto treatment discontinuation including haematologic toxicities, peripheral neuropathy, decreased appetite anddehydration. Patients with pancreatic adenocarcinoma aged 75 years and older should be carefully assessed for theirability to tolerate Paclitaxel (protein-bound particles) for injectable suspension in combination with gemcitabine with special consideration to performance status, comorbiditiesand increased risk of infections.

Other
Although limited data is available, no clear benefit in terms of prolonged overall survival has been demonstrated inpancreatic adenocarcinoma patients with normal CA 19-9 levels prior to start of treatment with Paclitaxel (protein-bound particles) for injectable suspension andgemcitabine.

Erlotinib should not be coadministered with Paclitaxel (protein-bound particles) for injectable suspension plus gemcitabine.

Effects on ability to drive and use machines
Paclitaxel (protein-bound particles) for injectable suspension has minor or moderate influence on the ability to drive and use machines. Paclitaxel (protein-bound particles) for injectable suspension may cause adversereactions such as tiredness (very common) and dizziness (common) that may affect the ability to drive and usemachinery. Patients should be advised not to drive and use machines if they feel tired or dizzy.

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

Paclitaxel and gemcitabine do not share a common metabolic pathway. Paclitaxel clearance is primarily determined by CYP2C8 and CYP3A4 mediated metabolism followed by biliary excretion, while gemcitabine is inactivated by cytidinedeaminase followed by urinary excretion. Pharmacokinetic interactions between Paclitaxel (protein-bound particles) for injectable suspension and gemcitabine have not been evaluated in humans.

UNDESIRABLE EFFECTS
Summary of the safety profile
The most common clinically significant adverse reactions associated with the use of Paclitaxel (protein-bound particles) for injectable suspension have beenneutropenia, peripheral neuropathy, arthralgia/myalgia and gastrointestinal disorders.

The frequencies of adverse reactions associated with the administration of Paclitaxel (protein-bound particles) for injectable suspension are listed in Table 1(Paclitaxel (protein-bound particles) for injectable suspension asmonotherapy) and Table 2 (Paclitaxel (protein-bound particles) for injectable suspension in combination with gemcitabine), and Table 3(Paclitaxel (protein-bound particles) for injectable suspension in combinationwith 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 inorder of decreasing seriousness.

Breast cancer (Paclitaxel (protein-bound particles) for injectable suspension administered as monotherapy)
Tabulated list of adverse reactions

Table 1 lists adverse reactions associated with the administration of Paclitaxel (protein-bound particles) for injectable suspension to patients from studies in which Paclitaxel (protein-bound particles) for injectable suspension has been administered as monotherapy at any dose in any indication (N = 789).

Table 1: Adverse reactions reported with Paclitaxel (protein-bound particles) for injectable suspension 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 medicalconcept.

[1] The frequency of hypersensitivity reactions is calculated based on one definitely related case in a population of 789patients.
[2] As reported in the post-marketing surveillance of Paclitaxel (protein-bound particles) for injectable suspension .
[3] The frequency of pneumonitis is calculated based on pooled data in 1310 patients in clinical trials receiving Paclitaxel (protein-bound particles) for injectable suspension 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 metastaticbreast cancer who were treated with 260 mg/m^{2}Paclitaxel (protein-bound particles) for injectable suspension once every three weeks in the pivotal phase III clinicalstudy.

Blood and lymphatic system disorders
Neutropenia was the most notable important haematological toxicity (reported in 79% of patients), and was rapidlyreversible 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 (protein-bound particles) for injectable suspension. Febrile neutropenia occurred in four patients on Paclitaxel (protein-bound particles) for injectable suspension.Anaemia (Hb< 10 g/dl) was observed in 46% of patients on Paclitaxel (protein-bound particles) for injectable suspension, and was severe (Hb< 8 g/dl) in three cases.Lymphopenia was observed in 45% of the patient.

Nervous system disorders
In general, the frequency and severity of neurotoxicity was dose-dependent in patients receiving Paclitaxel (protein-bound particles) for injectable suspension. Peripheralneuropathy (mostly Grade 1 or 2 sensory neuropathy) was observed in 68% of patients on Paclitaxel (protein-bound particles) for injectable suspension with 10% beingGrade 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 (protein-bound particles) for injectable suspension. The majority of alopecia events occurred lessthan one month after initiation of Paclitaxel (protein-bound particles) for injectable suspension. Pronounced hair loss ≥50% is expected for the majority of patients whoexperience alopecia.

Musculoskeletal and connective tissue disorders
Arthralgia occurred in 32% of patients on Paclitaxel (protein-bound particles) for injectable suspension and was severe in 6% of cases. Myalgia occurred in 24% ofpatients on Paclitaxel (protein-bound particles) for injectable suspension and was severe in 7% of cases. The symptoms were usually transient, typically occurred threedays after Paclitaxel (protein-bound particles) for injectable suspension administration and resolved within a week.

General disorders and administration site conditions
Asthenia/Fatigue was reported in 40% of the patients.

Pancreatic adenocarcinoma (Paclitaxel (protein-bound particles) for injectable suspension administered in combination with gemcitabine)
Tabulated list of adverse reactions
Adverse reactions were assessed in 421 patients treated with Paclitaxel (protein-bound particles) for injectable suspension in combination with gemcitabine and 402gemcitabine monotherapy-treated patients receiving first-line systemic treatment for metastatic adenocarcinoma ofthe pancreas in a phase III randomized, controlled, open-label trial. Table 2 lists adverse reactions

assessed inpatients with pancreatic adenocarcinoma treated with Paclitaxel (protein-bound particles) for injectable suspension in combination with gemcitabine.

Table 2: Adverse reactions reported with Paclitaxel (protein-bound particles) for injectable suspension 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 and administration site conditions	*Very common*: Fatigue, oedema peripheral, pyrexia, asthenia, chills *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 severalMedDRA 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 lastdose of study drug were reported for 4% of patients receiving Paclitaxel (protein-bound particles) for injectable suspension 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 withmetastatic adenocarcinoma of the pancreas who were treated with 125 mg/m^{2}Paclitaxel (protein-bound particles) for injectable suspension in combination withgemcitabine 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 3 provides the frequency and severity of haematologic laboratory-detected abnormalities for patients treatedwith Paclitaxel (protein-bound particles) for injectable suspension in combination with gemcitabine or with gemcitabine.

Table 3: Haematologic laboratory-detected abnormalities in pancreatic adenocarcinoma trial

	Paclitaxel (protein-bound particles) for injectable suspension (125 mg/m^2)/ Gemcitabine		**Gemcitabine**	
	Grades 1-4 (%)	**Grade 3-4 (%)**	**Grades 1-4 (%)**	**Grade 3-4 (%)**
Anaemia[a,b]	97	13	96	12
Neutropenia[a,b]	73	38	58	27
Thrombocytopenia[b,c]	74	13	70	9

[a] 405 patients assessed in Paclitaxel (protein-bound particles) for injectable suspension /gemcitabine-treated group
[b] 388 patients assessed in gemcitabine-treated group
[c] 404 patients assessed in Paclitaxel (protein-bound particles) for injectable suspension /gemcitabine-treated group

Peripheral neuropathy
For patients treated with Paclitaxel (protein-bound particles) for injectable suspension in combination with gemcitabine, the median time to first occurrence of Grade 3peripheral neuropathy was 140 days. The median time to improvement by at least 1 grade was 21 days, and themedian time to improvement from Grade 3 peripheral neuropathy to Grade 0 or 1 was 29 days. Of the patients withtreatment interrupted due to peripheral neuropathy, 44% (31/70 patients) were able to resume Paclitaxel (protein-bound particles) for injectable suspension at a

reduceddose. No patients treated with Paclitaxel (protein-bound particles) for injectable suspension 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 (protein-bound particles) for injectable suspension in combinationwith gemcitabine during the conduct of a trial in pancreatic adenocarcinoma. Complications due to the underlyingpancreatic cancer, especially biliary obstruction or presence of biliary stent, were identified as significant contributingfactors. If a patient becomes febrile (regardless of neutrophil count), initiate treatment with broad spectrum antibiotics.

For febrile neutropenia, withhold Paclitaxel (protein-bound particles) for injectable suspension and gemcitabine until fever resolves and ANC $\geq$ 1500 cells/mm^3, thenresume treatment at reduced dose levels.

Pneumonitis
Pneumonitis has been reported at a rate of 4% with the use of Paclitaxel (protein-bound particles) for injectable suspension in combination with gemcitabine. Of the 17cases of pneumonitis reported in patients treated with Paclitaxel (protein-bound particles) for injectable suspension in combination with gemcitabine, 2 had a fataloutcome. Monitor patients closely for signs and symptoms of pneumonitis. After ruling out infectious etiology andupon making a diagnosis of pneumonitis, permanently discontinue treatment with Paclitaxel (protein-bound particles) for injectable suspension and gemcitabine andpromptly initiate appropriate treatment and supportive measures.

Non-small cell lung cancer (Paclitaxel (protein-bound particles) for injectable suspension administered in combination with carboplatin)
Tabulated list of adverse reactions
Table 4 lists adverse reactions associated with the administration of Paclitaxel (protein-bound particles) for injectable suspension in combination with carboplatin.

Table 4: Adverse reactions reported with Paclitaxel (protein-bound particles) for injectable suspension 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 disorders	*Common:* Insomnia
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
Hepatobiliarydisordesrs	*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 (protein-bound particles) for injectable suspension and carboplatin, the median time to first occurrence ofGrade 3 treatment related peripheral neuropathy was 121 days, and the median time to improvement from Grade 3treatment related peripheral neuropathy to Grade 1 was 38 days. No patients treated with Paclitaxel (protein-bound particles) for injectable suspension and carboplatinexperienced Grade 4 peripheral neuropathy.

Anemia and thrombocytopenia were more commonly reported in the Paclitaxel (protein-bound particles) for injectable suspension 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 CancerTherapy (FACT)-Taxane questionnaire. Using repeated measure analysis, 3 of the 4 subscales (peripheralneuropathy, pain hands/feet, and hearing) favored Paclitaxel (protein-bound particles) for injectable suspension 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 reportedduring post-marketing surveillance of Paclitaxel (protein-bound particles) for injectable suspension.

There have been rare reports of reduced visual acuity due to cystoid macular oedema during treatment with Paclitaxel (protein-bound particles) for injectable suspension. Upon diagnosis of cystoid macular oedema, treatment with Paclitaxel (protein-bound particles) for injectable suspension should bediscontinued.

In some patients previously exposed to capecitabine, reports of palmar-plantar erythrodysaesthesiae have beenreported as part of the continuing surveillance of Paclitaxel (protein-bound particles) for injectable suspension. Because these events have been reported voluntarilyduring clinical practice, true estimates of frequency cannot be made and a causal relationship to the events has notbeen established.

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

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES
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 stabilizes microtubules by preventing depolymerisation. This stability results in the inhibition of the normal dynamicreorganisation of the microtubule network that is essential for vital interphase and mitotic cellular functions. Inaddition, paclitaxel induces abnormal arrays or “bundles” of microtubules throughout the cell cycle and multiple astersof microtubules during mitosis.

Paclitaxel (protein-bound particles) for injectable suspension contains human serum albumin-paclitaxel nanoparticles of approximately 130 nm in size, where thepaclitaxel is present in a non-crystalline, amorphous state. Upon intravenous administration, the nanoparticlesdissociate rapidly into soluble, albumin bound paclitaxel complexes of approximately 10 nm in size. Albumin is knownto mediate endothelial caveolartranscytosis of plasma constituents, and *in vitro* studies demonstrated that thepresence of albumin in Paclitaxel (protein-bound particles) for injectable suspension enhances transport of paclitaxel across endothelial cells. It is hypothesised that thisenhanced transendothelialcaveolar transport is mediated by the gp-60 albumin receptor, and that there is enhancedaccumulation of paclitaxel in the area of tumour due to the albumin-binding protein Secreted Protein Acidic Rich inCysteine (SPARC).

Pharmacokinetic properties
The pharmacokinetics of total paclitaxel following 30- and 180-minute infusions of Paclitaxel (protein-bound particles) for injectable suspension at dose levels of 80 to375 mg/m^2 were determined in clinical studies. The paclitaxel exposure (AUC) increased linearly from 2653 to 16736ng.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 (protein-bound particles) for injectable suspension 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, theplasma clearance of paclitaxel with Paclitaxel (protein-bound particles) for injectable suspension was larger (43%) than that following a solvent-based paclitaxel injectionand 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 (protein-bound particles) for injectable suspension administered intravenously at 260 mg/m^2, intrapatientvariability in AUC was 19% (range = 3.21%-27.70%). There was no evidence for accumulation of paclitaxel withmultiple treatment courses.

Distribution
Following Paclitaxel (protein-bound particles) for injectable suspension administration to patients with solid tumours, paclitaxel is evenly distributed into blood cells andplasma and is highly bound to plasma proteins (94%).

The protein binding of paclitaxel following Paclitaxel (protein-bound particles) for injectable suspension was evaluated by ultrafiltration in a within-patient comparisonstudy. The fraction of free paclitaxel was significantly higher with Paclitaxel (protein-bound particles) for injectable suspension (6.2%) than with solvent-based paclitaxel(2.3%). This resulted in significantly higher exposure to unbound paclitaxel with Paclitaxel (protein-bound particles) for injectable suspension compared with solventbasedpaclitaxel, even though the total exposure is comparable. This is possibly due to paclitaxel not being trapped inCremophor EL micelles as with solvent-based paclitaxel. Based on the published literature, *in vitro* studies of bindingto human serum proteins, (using paclitaxel at concentrations ranging from 0.1 to 50 µg/ml), indicate that the presenceof 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 largevolume 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 paclitaxelis 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 (protein-bound particles) for injectable suspension at 260 mg/m^2, the mean value forcumulative urinary excretion of unchanged active substance accounted for 4% of the total administered dose with lessthan 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 (protein-bound particles) for injectable suspension was studied in patients with advancedsolid 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 onpharmacokinetics 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 andapproximately 20% increase in mean paclitaxel AUC compared with patients with normal hepatic function. Hepaticimpairment has no effect on mean paclitaxel C_{max}. In addition, elimination of paclitaxel shows an inverse correlationwith total bilirubin and a positive correlation with serum albumin.

Pharmacokinetic/pharmacodynamic modeling indicates that there is no correlation between hepatic function (asindicated by the baseline albumin or total bilirubin level) and neutropenia after adjusting for Paclitaxel (protein-bound particles) for injectable suspension 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 moderaterenal impairment (creatinine clearance ≥30 to <90 ml/min) has no clinically important effect on the maximumelimination rate and systemic exposure (AUC and C_{max}) of paclitaxel. Pharmacokinetic data are insufficient forpatients with severe renal impairment and not available for patients with end stage kidney disease.

Older people
Population pharmacokinetic analysis for Paclitaxel (protein-bound particles) for injectable suspension included patients with ages ranging from 24 to 85 years old andshows that age does

not significantly influence the maximum elimination rate and systemic exposure (AUC and C_{max})of paclitaxel.

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

Other intrinsic factors

Population pharmacokinetic analyses for Paclitaxel (protein-bound particles) for injectable suspension indicate that gender, race (Asian vs. White), and type of solidtumours do not have a clinically important effect on systemic exposure (AUC and C_{max}) of paclitaxel. Patientsweighing 50 kg had paclitaxel AUC approximately 25% lower than those weighing 75 kg. The clinical relevance of thisfinding is uncertain.

Preclinical safety data

The carcinogenic potential of paclitaxel has not been studied. However, based on the published literature, paclitaxel isa potentially carcinogenic and genotoxic agent at clinical doses, based upon its pharmacodynamic mechanism ofaction. Paclitaxel has been shown to be clastogenic*in vitro* (chromosome aberrations in human lymphocytes) and *invivo* (micronucleus test in mice). Paclitaxel has been shown to be genotoxic*in vivo* (micronucleus test in mice), but itdid 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 and foetal toxicity in rats.Animal studies with Paclitaxel (protein-bound particles) for injectable suspension showed non-reversible, toxic effects on the male reproductive organs at clinicallyrelevant exposure levels.

EXPIRY DATE

Do not use later than date of expiry.

PACKAGING INFORMATION

Paclitaxel (Protein-Bound Particles) for Injectable Suspension is available in 50 mL vial.

For : 100 mg per vial : 50 mL U.S.P. Type-I clear tubular glass vial

STORAGE AND HANDLING INSTRUCTIONS

Store vial in its original carton at controlled room temperature between 20°C and 25°C. Protect from bright light. Keep out of reach of children.

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