PRODUCT MONOGRAPH

Pr PACLitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel

100 mg paclitaxel/vial

Lyophilized Powder

Antineoplastic Agent

Manufacturer:
Panacea Biotec Pharma Limited
B-1, Extension/A-27, Mohan Co-operative Industrial Estate,
Mathura Road
New Delhi, Delhi, India, 110044

Date of Preparation:
November 16, 2021

Importer / Distributor:
Apotex Inc.
Toronto, Ontario, M9L 1T9

Control No.: 253192

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous infusion	Lyophilized powder, 100 mg paclitaxel per single-use vial	Human albumin

INDICATIONS AND CLINICAL USE

Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel is indicated for:

- the treatment of metastatic breast cancer.
- the first-line treatment of metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

Note: An albumin form of paclitaxel may substantially affect a drug's functional properties relative to those of drug in solution. **Do not substitute with or for other paclitaxel formulations.**

Geriatrics:
Evidence from clinical studies in metastatic breast cancer suggests that use of paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in patients over the age of 65 is associated with a higher incidence of epistaxis, diarrhea, dehydration, fatigue and peripheral edema. Evidence from the pivotal clinical study in metastatic pancreatic cancer suggest that patients 75 years or older who received paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in combination with gemcitabine had a higher risk of serious adverse reactions and adverse reactions that led to treatment discontinuation. No survival benefit for the combination treatment of paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel and gemcitabine has been demonstrated for patients 75 years and older, however, clinical studies did not include sufficient number of patients with metastatic pancreatic cancer in this age group to determine whether they respond differently from younger patients (see **WARNINGS AND PRECAUTIONS** section).

Pediatrics (≤16 years of age):
The safety and effectiveness of paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in pediatric patients have not been evaluated.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing of ingredients, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.
- Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel should not be used in patients who have baseline neutrophil counts of < 1,500 cells/mm^3 on day 1 of each treatment cycle.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents (see **INDICATIONS** and **CLINICAL USE** section).
- **Note:** An albumin form of paclitaxel may substantially affect a drug's functional properties relative to those of drug in solution. **Do not substitute with or for other paclitaxel formulations.** In the treatment of metastatic breast cancer, Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel has been evaluated as a single agent only.
- Bone marrow suppression (primarily neutropenia) is dose-dependent and a dose-limiting toxicity of Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel (see **CONTRAINDICATIONS** and **Hematologic** section below).
- Sepsis with or without neutropenia occurred in patients who received paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in combination with gemcitabine (see **Infection** section below).
- Pneumonitis, including some cases that were fatal, occurred in patients receiving paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in combination with gemcitabine (see **Respiratory** section below).
- Patients ≥ 75 years of age treated with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in combination with gemcitabine experienced more toxicity and no demonstrated survival benefit (see **Special Population, Geriatrics** section).

General

Albumin (Human): Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel contains albumin (human), a derivative of human blood and is a nanoparticle albumin-bound (nab) form of paclitaxel. Based on effective donor screening and product manufacturing

processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob Disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

Ability to Drive and Use Machines: Adverse events such as fatigue, weakness and malaise may affect the ability to drive and use machines.

Infection
Sepsis was reported in 5% of patients with or without neutropenia who received paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in combination with gemcitabine. Complications due to the underlying pancreatic cancer, especially biliary obstruction or presence of biliary stent, were identified as significant contributing factors. If a patient becomes febrile (regardless of neutrophil count), initiate treatment with broad spectrum antibiotics. For febrile neutropenia, withhold Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel and gemcitabine until fever resolves and ANC $\geq$ 1500, then resume treatment at reduced dose levels (see **DOSAGE AND ADMINISTRATION**).

Cardiovascular
AV block has been reported during treatment with paclitaxel as well as with the nanoparticle, albumin-bound paclitaxel paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel. Clinical trial information estimates the incidence of atrioventricular block (AV block) in patients treated with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel is 1/1310 (0.08%). In the post-market setting, one patient having no confounding risk factors required pacemaker placement (see **POSTMARKET ADVERSE DRUG REACTIONS**). ECG abnormalities were noted in 60% of patients treated with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in the metastatic breast cancer randomized trial. Among patients with a normal ECG prior to study entry, 35% of patients treated with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel developed an abnormal tracing while on study (see **ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions, Cardiovascular**). ECG monitoring, particularly patients who are predisposed to cardiac risks from underlying malignancy, co-morbidities or concomitant use of chemotherapeutic drugs that may be cardiotoxic, should be considered during treatment with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel. Patients exhibiting signs and symptoms of AV block should be further monitored and appropriate medical therapy administered.

Carcinogenesis and Mutagenesis
The carcinogenic potential of paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel has not been studied.

Paclitaxel has been shown to be clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). Paclitaxel injection was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay (see **TOXICOLOGY**).

Hematologic
Bone marrow suppression (primarily neutropenia) is dose-dependent and a dose-limiting toxicity

of paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel. In clinical studies, Grade 3/4 neutropenia occurred in 34% of patients with metastatic breast cancer and in 38% of patients with pancreatic cancer. Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel therapy should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm^3 and baseline platelet counts of less than 100,000 cells/mm^3 on day 1 of each treatment cycle. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel. Patients should not be retreated with subsequent cycles of Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel until neutrophils recover to a level > 1,500 cells/mm^3 and platelets recover to a level > 100,000 cells/mm^3 (see **ADVERSE EVENTS** and **DOSAGE AND ADMINISTRATION**).

Immune

Very rare occurrences of severe hypersensitivity reactions, including anaphylactic reactions with fatal outcome have been reported. Patients who experience a severe hypersensitivity reaction to Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel should not be re-challenged with the drug. The use of paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in patients exhibiting hypersensitivity to paclitaxel or human albumin has not been studied.

Neurologic

Sensory neuropathy occurs frequently with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel. The occurrence of grade 1 or 2 sensory neuropathy does not generally require dose modification. When Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound 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 Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel (see **DOSAGE AND ADMINISTRATION**). For combination use of Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel and gemcitabine, if grade 3 or higher peripheral neuropathy develops, withhold Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel treatment until resolution to ≤ Grade 1 and resume at a reduced dose for all subsequent courses of Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel. The median time to first occurrence of Grade 3 peripheral neuropathy was 140 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 powder for injectable suspension nanoparticle, albumin-bound paclitaxel at a reduced dose. No patients treated with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel /gemcitabine had Grade 4 peripheral neuropathy (see **DOSAGE AND ADMINISTRATION**).

Ophthalmologic

There have been reports of reduced visual acuity due to cystoid macular edema (CME) during treatment with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel as well as with other taxanes. Most reports of CME have resolved after cessation of the taxane

treatment (see **POSTMARKET ADVERSE DRUG REACTIONS**). Patients with visual impairment during Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel treatment should seek a prompt and complete ophthalmologic examination. Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel should be discontinued if a CME diagnosis is confirmed.

Respiratory

Pneumonitis, including some cases that were fatal, has been reported in 4% of patients treated with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in combination with gemcitabine. Of the 17 pneumonitis ADRs in the paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel/gemcitabine arm, 2 had a fatal outcome. Due to cases of pneumonitis seen in the clinical trial, patients with a history of interstitial lung disease, multiple allergies or progressive dyspnea and unproductive cough were excluded from further enrollment, and it is recommended that such patients not be treated with Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel. Monitor patients closely for signs and symptoms of pneumonitis and interrupt treatment during evaluation of suspected pneumonitis. If a diagnosis of pneumonitis is made, permanently discontinue treatment of Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel and gemcitabine (see **ADVERSE REACTIONS** section and gemcitabine product monograph).

Sexual Function/Reproduction

Men should be advised to use effective contraception and to avoid fathering a child while receiving treatment with Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel and up to six months after treatment.

Administration of paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel to male rats at 42 mg/m^2 on a weekly basis (approximately 16% of the daily maximum recommended human exposure on a mg/m^2 basis) for 11 weeks prior to mating with untreated female rats resulted in significantly reduced fertility accompanied by decreased pregnancy rates and increased loss of embryos in mated females. Dose levels of mg/m^2 refer to mg of paclitaxel in paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel. A low incidence of skeletal and soft tissue fetal anomalies was also observed at doses of 3 and 12 mg/m^2/week in this study (approximately 1 to 5% of the daily maximum recommended human exposure on a mg/m^2 basis). Animal studies with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel showed irreversible, toxic effects on the male reproductive organs including testicular atrophy/degeneration and decreased germinal epithelial cells at clinically relevant exposure levels. Paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel induced infertility in male rats (see **TOXICOLOGY**).

Injection Site Reactions

Injection site reactions can occur with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Special Populations

Pregnant Women/Teratogenic Effects: Paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel to rats on gestation days 7 to 17 at doses of 6 mg/m^2 (approximately 2% of the daily maximum recommended human dose on a mg/m^2 basis) caused embryo- and fetotoxicity, as indicated by intrauterine mortality, increased resorptions (up to 5-fold), reduced numbers of litters and live fetuses, reduction in fetal body weight, and increase in fetal anomalies. Fetal anomalies included soft tissue and skeletal malformations, such as eye bulge, folded retina, microphthalmia, and dilation of brain ventricles. A lower incidence of soft tissue and skeletal malformations was also exhibited at 3 mg/m^2 (approximately 1% of the daily maximum recommended human dose on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women using paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel. Females of reproductive potential should have a pregnancy test prior to starting treatment with Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel.

If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel.

Advise females of reproductive potential to use effective contraception during treatment with Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel and for at least 1 month after the last dose.

There was no exposure in pregnancy in the clinical trials.

Nursing Women: It is not known whether paclitaxel is excreted in human milk. In rats, following intravenous administration of carbon-14 labeled paclitaxel on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, nursing must be discontinued when receiving Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel therapy.

Pediatrics (≤ 16 years of age): The safety and effectiveness of paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in pediatric patients have not been evaluated.

Geriatrics: A pooled analysis conducted in 981 patients receiving paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel monotherapy for metastatic breast cancer, of which 15% were ≥ 65 years old and 2% were ≥ 75 years old, indicated a higher incidence of epistaxis, diarrhea, dehydration, fatigue and peripheral edema in patients ≥ 65 years.

Of the 421 patients with metastatic pancreatic adenocarcinoma in the randomized study who received paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel and

gemcitabine, 41% were 65 years or older and 10% were 75 years or older. Diarrhea, decreased appetite, dehydration and epistaxis were more frequent in patients 65 years or older compared with patients younger than 65 years old. In patients 75 years and older who received paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel and gemcitabine, there was a higher incidence of serious adverse reactions and adverse reactions that led to treatment discontinuation including hematologic toxicities, peripheral neuropathy, decreased appetite and dehydration, and no demonstrated survival benefit. Carefully assess patients 75 years and older for their ability to tolerate Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel in combination with gemcitabine. Give special consideration to performance status, co-morbidities and increased risk of infections.

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

Hepatic Impairment
In the randomized controlled trials, patients were excluded for elevated baseline serum bilirubin. Exposure and toxicity of paclitaxel can increase with hepatic impairment. 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. Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel is not recommended in patients that have total bilirubin > 5 x ULN or AST > 10 x ULN. In addition, Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel is not recommended in patients with metastatic pancreatic cancer that have moderate to severe hepatic impairment (total bilirubin > 1.5 x ULN and AST < 10 x ULN). The starting dose should be reduced for patients with moderate or severe hepatic impairment (see **DOSAGE AND ADMINISTRATION**).

Renal Impairment
The use of paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel has not been adequately studied in patients with severe renal impairment or end stage renal disease (estimated creatinine clearance <30 mL/min). In the randomized controlled trials, patients were excluded for elevated baseline serum creatinine.

Monitoring and Laboratory Tests
In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel. Patients should not be retreated with subsequent cycles of Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel until neutrophils recover to a level > 1,500 cells/mm^3 and platelets recover to a level > 100,000 cells/mm^3 (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In the phase III study of metastatic breast cancer, the adverse events which were very common were those expected for paclitaxel and included alopecia (90%), neutropenia (80%), leukopenia (72%), sensory neuropathy (71%), asthenia (47%), arthralgia/myalgia (44%), AST (SGPT) elevations (39%), alkaline phosphatase elevations (36%), abnormal ECG [all patients (60%) and patients with normal baseline (35%)], anemia in patients with normal baseline (20%), nausea (30%), vomiting (18%), infections (24%), diarrhea (27%), dyspnea (12%), and fluid retention/edema (10%). Approximately 27% of patients receiving paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel on a 3 weekly regimen experienced serious adverse events (SAEs). The events occurring in greater than 10 patients were grade 4 neutropenia (9%), infection (3%), and increased GGT (3%).

In the phase III study of metastatic pancreatic cancer, the most common treatment emergent adverse events (≥ 20%) in patients receiving paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in combination with gemcitabine were: fatigue (59%), nausea (54%), peripheral neuropathy SMQ (54%), alopecia (50%), peripheral edema (46%), diarrhea (44%), anemia (42%), neutropenia (42%), pyrexia (41%), vomiting (36%), decreased appetite (36%), constipation (30%), thrombocytopenia (30%), rash (28%), abdominal pain (23%), and dehydration (21%). Approximately 50% of patients receiving paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel and gemcitabine experienced serious adverse events, including pyrexia, vomiting, dehydration and pneumonia. Adverse reactions resulting in death within 30 days of the last dose of study drug were reported for 4% of patients in the paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel and gemcitabine group and for 4% of patients in the gemcitabine group.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

Metastatic Breast Cancer

The following table shows the frequency of common important adverse events for the patients who received single-agent paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel or paclitaxel injection for the treatment of metastatic breast cancer in the randomized comparative phase III trial.

Table 1: Frequency[a] of Common Important Treatment Emergent Adverse Events in the Randomized Study

	Paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel[b] 260 mg/m^2/30 minutes n = 229 (%)	**Paclitaxel Injection[b] 175 mg/m^2/3 hours n = 225 (%)**
Bone Marrow		
Neutropenia		
< 2.0 x 10^9/L	80	82
< 0.5 x 10^9/L	9	22
Leukopenia		
< 4.0 x 10^9/L	72	79
< 1.0 x 10^9/L	0	1
Thrombocytopenia		
< 100 x 10^9/L	2	3
< 50 x 10^9/L	< 1	< 1
Anemia (normal at baseline)		
<110g/L	33	25
< 80g/L	1	< 1
Infections	24	20
Febrile Neutropenia	2	1
Bleeding	2	2
Hypersensitivity Reaction[c]		
All	4	12
Severe[d]	0	2
Cardiovascular		
Vital Sign Changes[e]		
Bradycardia	< 1	< 1
Hypotension	5	5
Severe Cardiovascular Events[d]	3	4
Abnormal ECG		
All patients	60	52
Patients with Normal Baseline	35	30
Respiratory		
Cough	7	6
Dyspnea	12	9
Sensory Neuropathy		
Any Symptoms	71	56
Severe Symptoms[d]	10	2
Myalgia/Arthralgia		
Any Symptoms	44	49
Severe Symptoms[d]	8	4
Fluid Retention/Edema		
Any Symptoms	10	8
Severe Symptoms[d]	0	< 1

	Paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel[b] 260 mg/m^2/30 minutes n = 229 (%)	Paclitaxel Injection[b] 175 mg/m^2/3 hours n = 225 (%)
Gastrointestinal		
Nausea – Any Symptoms	30	22
Vomiting – Any Symptoms	18	10
Diarrhea – Any Symptoms	27	15
Mucositis – Any Symptoms	7	6
Alopecia	90	94
Asthenia		
Any Symptoms	47	39
Severe Symptoms [d]	8	3
Hepatic (Patients with Normal Baseline)		
Bilirubin Elevations	7	7
Alkaline Phosphatase Elevations	36	31
AST Elevations	39	32
Injection Site Reaction	< 1	1
Skin/Dermatology		
Nail changes	1	0

[a]Based on worst grade.

[b]Paclitaxel injection patients received premedication.

[c]Includes treatment-related events related to hypersensitivity (e.g., flushing, dyspnea, chest pain, hypotension) that began on a day of dosing.

[d]Severe events are defined as at least grade 3 toxicity.

[e]During study drug dosing. Bradycardia defined as pulse < 50 bpm and hypotension defined as diastolic blood pressure < 40 mmHg or decrease in systolic blood pressure of ≥ 30 mmHg.

Adverse Event Experiences by Body System: Unless otherwise noted, the following discussion refers to the primary safety database of 229 patients with metastatic breast cancer treated with single-agent paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in the randomized controlled trial. The frequency and severity of important clinically relevant adverse events for the study are presented above in tabular form. In some instances, rare severe events observed with paclitaxel injection may be expected to occur with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel. Refer to the following section, **Less Common Clinical Trial Adverse Drug Reactions** for the adverse events that occurred at a rate of less than 1%.

Hematologic: Neutropenia, the most important hematologic toxicity, was dose-dependent and generally rapidly reversible. Among patients with metastatic breast cancer in the randomized trial, neutrophil counts declined below 500 cells/mm^3 (grade 4) in 9% of the patients treated with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel at a dose of 260 mg/m^2 compared to 22% in patients receiving Cremophor® based paclitaxel injection at a

dose of 175 mg/m^2.

In the randomized metastatic breast cancer study, infectious episodes were reported in 24% of the patients treated with a dose of 260 mg/m^2 given as a 30-minute infusion. Oral candidiasis, respiratory tract infections and pneumonia were the most frequently reported infectious complications. Febrile neutropenia was reported in 2% of patients in the paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel arm and 1% of patients in the paclitaxel injection arm. Fever occurring at any time during the treatment course was reported in 14% of patients in the paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel arm.

Thrombocytopenia was almost never severe (< 50 x 10^9/L). Two percent of patients treated with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in the randomized trial experienced a decrease in their platelet count below 100 x 10^9/L at least once while on treatment. In the randomized metastatic breast cancer study, bleeding episodes were reported in 2% of the patients in each treatment arm.

Anemia (Hb <110g/L) in patients with normal baseline was observed in 20% of patients treated with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in the randomized trial and was severe (Hb < 80g/L) in 1% of the patients with normal baseline hemoglobin. Red cell transfusions were required in 2% of patients in the phase III study, and in 1% of those with normal baseline hemoglobin levels.

Hypersensitivity Reactions (HSRs): Hypersensitivity reactions to paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel were observed in 4% of all patients. No Grade 3 or 4 treatment-related hypersensitivity reactions occurred in the paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel treatment group. In the phase III study, the hypersensitivity reactions (i.e., those related to hypersensitivity and occurring on the day of dosing) consisted of dyspnea (1%) and flushing, hypotension, chest pain, and arrhythmia (all < 1%).

Cardiovascular: Hypotension, during the 30-minute infusion, occurred in 5% of patients treated with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in the randomized metastatic breast cancer trial. This vital sign change most often caused no symptoms and required neither specific therapy nor treatment discontinuation.

Severe cardiovascular events possibly related to single-agent paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel occurred in approximately 3% of patients in the randomized trial. These events included chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension.

Electrocardiogram (ECG) abnormalities were common among patients at baseline. ECG abnormalities on study did not usually result in symptoms, were not dose-limiting, and required no intervention. ECG abnormalities were noted in 60% of patients treated with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in the metastatic breast cancer

randomized trial. Among patients with a normal ECG prior to study entry, 35% of patients treated with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel developed an abnormal tracing while on study. The most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, and sinus tachycardia.

Respiratory: Dyspnea (12%) and cough (7%) were reported after treatment with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in the randomized trial.

Neurologic: The frequency and severity of neurologic manifestations were influenced by prior and/or concomitant therapy with neurotoxic agents.

In general, the frequency and severity of neurologic manifestations were dose-dependent in patients receiving single-agent paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel. In the randomized trial, sensory neuropathy was observed in 71% of patients (10% severe) in the paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel arm and in 56% of patients (2% severe) in the paclitaxel injection arm. The frequency of sensory neuropathy increased with cumulative dose. Sensory neuropathy was the cause of discontinuation in 7/229 (3%) patients receiving paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in the randomized trial. Severe sensory symptoms have typically improved in a median of 22 days after interrupting paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel therapy. No incidences of grade 4 sensory neuropathies were reported in the clinical trials. Reports of autonomic neuropathy resulting in paralytic ileus have been received as part of the continuing surveillance of paclitaxel injection safety.

Ocular/visual disturbances: Thirteen percent (13%) of all patients (n = 366) treated with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in single-arm and randomized trials reported ocular/visual disturbances, and 1% were severe. The severe cases (keratitis and blurred vision) were reported in patients in a single- arm study who received higher doses than those recommended (300 or 375 mg/m^2). These effects generally have been reversible. However, rare reports in the literature of abnormal visual evoked potentials in patients treated with paclitaxel injection have suggested persistent optic nerve damage.

Arthralgia/Myalgia: Forty-four percent (44%) of patients treated with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in the randomized trial experienced arthralgia/myalgia; 8% experienced severe symptoms. The symptoms were usually transient, occurred two or three days after paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel administration, and resolved within a few days. There was no consistent relationship between dose of paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel and the frequency of arthralgia/myalgia.

Hepatic: Among patients with normal baseline liver function treated with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in the randomized trial, 7%, 36%, 39%, 36%, and 50% had elevations in bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT) and GGT respectively. Grade 3 or 4 elevations in GGT were reported for 14% of patients treated with paclitaxel powder for injectable suspension nanoparticle, albumin-bound

paclitaxel and 10% of patients treated with paclitaxel injection in the randomized trial. Prolonged exposure to paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel was not associated with cumulative hepatic toxicity.

Renal: Eleven percent (11%) of patients treated with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in the randomized trial experienced creatinine elevation, < 1% severe. No discontinuations, dose reductions, or dose delays were caused by renal toxicities.

Gastrointestinal (GI): Nausea, vomiting, diarrhea, and mucositis were reported by 30%, 18%, 27%, and 7% of patients treated with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in the randomized trial. These manifestations were usually mild to moderate. The frequency and severity of GI adverse events were not obviously dose-related. Infrequent reports of esophagitis were reported in the clinical trials. Dehydration was reported commonly in clinical trials. Constipation and anorexia were considered very common.

Injection Site Reactions: Injection site reactions were reported in 1% of patients treated with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel and included reactions secondary to extravasation, which were usually mild and included erythema.

Asthenia: Asthenia was reported in 47% of patients (8% severe) treated with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in the randomized trial. Asthenia included reports of asthenia, fatigue, weakness, lethargy and malaise.

Alopecia: Alopecia was observed in almost all of the patients.

Skin: Nail changes (changes in pigmentation or discolouration of nail bed) occurred in 1% of patients treated with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in the randomized trial. Transient skin changes (rash 9%; flushing 2%; pruritus 6%) were observed in the randomized trial. No other skin adverse events were significantly associated with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel administration.

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

Cardiovascular: Bradycardia during the 30-minute infusion occurred in < 1% of patients in the phase III study. Cases of cardiac ischemia/infarction and thrombosis/embolism possibly related to paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel treatment were uncommon. Cases of cerebrovascular attacks (strokes) and transient ischemic attacks were uncommon.

Gastrointestinal: Rare reports of intestinal obstruction, intestinal perforation, pancreatitis, and ischemic colitis have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel treatment. Rare reports of neutropenic enterocolitis (typhlitis), despite the co-administration of G-CSF, were observed in patients treated with paclitaxel injection alone and in combination with other chemotherapeutic agents.

Hepatic: Rare reports of hepatic necrosis and hepatic encephalopathy leading to death have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel treatment.

Hypersensitivity Reactions: Flushing, hypotension, chest pain, and arrhythmia occurring on the day of dosing were all reported at < 1%.

Infections and Infestations: Sepsis and neutropenic sepsis were uncommon events in patients receiving paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in pre-market and post-market clinical trials.

Injection Site Reactions: Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been received as part of the continuing surveillance of paclitaxel injection safety. In some cases, the onset of the injection site reaction in paclitaxel injection patients either occurred during a prolonged infusion or was delayed by a week to ten days. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel injection at a different site, i.e., "recall", has been reported rarely.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Neurologic: Uncommon serious neurologic events following paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel administration have included ischemic stroke, metabolic encephalopathy, confusion, dizziness/light-headedness, and mood alteration/depression.

Respiratory: Reports (< 1%) of pneumothorax were uncommon after treatment with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in the randomized trial. Rare reports of interstitial pneumonia, lung fibrosis, and pulmonary embolism have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel treatment.

Metastatic Pancreatic Cancer

Adverse reactions were assessed in 421 paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel plus gemcitabine-treated patients and 402 gemcitabine monotherapy treated patients receiving first-line systemic treatment for metastatic adenocarcinoma of the pancreas in a multicenter, multinational, randomized, controlled, open- label trial.

Table 2 provides the frequency and severity of hematologic laboratory-detected abnormalities for the paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel /gemcitabine group and the gemcitabine group.

Table 2: Hematologic Laboratory-Detected Abnormalities in Metastatic Pancreatic Cancer Clinical Trial

	Paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel (125 mg/m^2)/ Gemcitabine		Gemcitabine	
	Grades 1-4 (%)	Grade 3-4 (%)	Grades 1-4 (%)	Grade 3-4 (%)
Anemia[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 powder for injectable suspension nanoparticle, albumin-bound paclitaxel /gemcitabine-treated group

[b] 388 patients assessed in gemcitabine-treated group

[c] 404 patients assessed in paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel /gemcitabine-treated group

Table 3 provides the frequency and severity of adverse reactions by system organ class/preferred term that have been reported in ≥ 10% of patients with adenocarcinoma of the pancreas who received paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel and gemcitabine or gemcitabine monotherapy. Within each system organ class grouping, adverse reactions are presented in order of decreasing frequency.

Table 3: Adverse Reactions Reported in ≥ 10% of Patients in Metastatic Pancreatic Cancer Clinical Trial (by MedDRA System Organ Class and Preferred Term)

System Organ Class/ Preferred Term	Paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel (125 mg/m^2) and gemcitabine (N=421)		Gemcitabine (N=402)	
	All Grade	Grade 3 or Higher	All Grade	Grade 3 or Higher
General disorders and administration site conditions	**361 (86%)**	**132 (31%)**	**299 (74%)**	**76 (19%)**
Fatigue	248 (59%)	77 (18%)	183 (46%)	37 (9%)
Oedema peripheral	194 (46%)	13 (3%)	122 (30%)	12 (3%)
Pyrexia	171 (41%)	12 (3%)	114 (28%)	4 (1%)
Asthenia	79 (19%)	29 (7%)	54 (13%)	17 (4%)
Chills	49 (12%)	0	35 (9%)	0
Gastrointestinal disorders	**352 (84%)**	**114 (27%)**	**315 (78%)**	**92 (23%)**
Nausea	228 (54%)	27 (6%)	192 (48%)	14 (3%)
Diarrhoea	184 (44%)	26 (6%)	95 (24%)	6 (1%)
Vomiting	151 (36%)	25 (6%)	113 (28%)	15 (4%)
Constipation	126 (30%)	12 (3%)	111 (28%)	7 (2%)
Abdominal pain	98 (23%)	27 (6%)	89 (22%)	32 (8%)
Abdominal pain upper	43 (10%)	10 (2%)	28 (7%)	3 (1%)
Skin and subcutaneous tissue disorders	**294 (70%)**	**19 (5%)**	**127 (32%)**	**3 (1%)**

Alopecia	212 (50%)	6 (1%)	21 (5%)	0
Rash	117 (28%)	7 (2%)	39 (10%)	2 (<1%)
Blood and Lymphatic System Disorders[a]	**280 (67%)**	**202 (48%)**	**238 (59%)**	**128 (32%)**
Anemia	176 (42%)	49 (12%)	133 (33%)	32 (8%)
Neutropenia	175 (42%)	138 (33%)	122 (30%)	85 (21%)
Thrombocytopenia	128 (30%)	53 (13%)	117 (29%)	33 (8%)
Leukopenia	59 (14%)	39 (9%)	39 (10%)	15 (4%)
Nervous system disorders	**277 (66%)**	**82 (19%)**	**149 (37%)**	**19 (5%)**
Peripheral neuropathy SMQ[b]	227 (54%)	70 (17%)	51 (13%)	3 (1%)
Dysgeusia	68 (16%)	0	33 (8%)	0
Headache	60 (14%)	1 (<1%)	38 (9%)	1 (<1%)
Dizziness	48 (11%)	3 (1%)	34 (8%)	0
Metabolism and nutrition disorders	**245 (58%)**	**76 (18%)**	**182 (45%)**	**48 (12%)**
Decreased appetite	152 (36%)	23 (5%)	104 (26%)	8 (2%)
Dehydration	87 (21%)	31 (7%)	45 (11%)	10 (2%)
Hypokalaemia	52 (12%)	18 (4%)	28 (7%)	6 (1%)
Respiratory, thoracic and mediastinal disorders	**212 (50%)**	**41 (10%)**	**149 (37%)**	**45 (11%)**
Cough	72 (17%)	0	30 (7%)	0
Dyspnoea	72 (17%)	12 (3%)	62 (15%)	11 (3%)
Epistaxis	64 (15%)	1 (<1%)	14 (3%)	1 (<1%)
Investigations	**186 (44%)**	**66 (16%)**	**172 (43%)**	**61 (15%)**
Weight decreased	57 (14%)	1 (<1%)	48 (12%)	2 (<1%)
Alanine aminotransferase increased	46 (11%)	13 (3%)	36 (9%)	15 (4%)
Musculoskeletal and connective tissue disorders	**177 (42%)**	**19 (5%)**	**107 (27%)**	**12 (3%)**
Pain in extremity	48 (11%)	3 (1%)	24 (6%)	3 (1%)
Arthralgia	47 (11%)	3 (1%)	13 (3%)	1 (<1%)
Myalgia	44 (10%)	4 (1%)	15 (4%)	0
Psychiatric disorders	**151 (36%)**	**7 (2%)**	**103 (26%)**	**16 (4%)**
Insomnia	64 915%)	0	46 (11%)	3 (1%)
Depression	51 (12%)	1 (<1%)	24 (6%)	0
Anxiety	35 (8%)	1 (<1%)	45 (11%)	7 (2%)

MedDRA = Medical Dictionary for Regulatory Activities.

[a] Events reported in this Table are ADR's. Hematologic laboratory detected abnormalities are reported in Table 2.

[b] Peripheral neuropathy evaluated using the MedDRA v 15.0 Standardized MedDRA Query (broad scope).

Less Common Clinical Trial Adverse Drug Reactions

Additional clinically relevant adverse reactions that were reported in < 10% of the patients with adenocarcinoma of the pancreas who received paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel/gemcitabine included:

The frequency estimates for adverse reactions are defined using the following convention:

Common (frequent):	**≥1/100 and <1/10 (≥1% and <10%)**
Uncommon (infrequent):	**≥1/1000 and <1/100 (≥0.1% and <1%)**

General disorders and administration site conditions:
Common: Infusion site reaction

Gastrointestinal disorders:
Common: Stomatitis, dry mouth, intestinal obstruction, colitis

Skin and subcutaneous tissue disorders:
Common: Pruritus, dry skin, nail disorder, flushing

Blood and lymphatic system disorders:
Common: Pancytopenia
Uncommon: thrombotic thrombocytopenic purpura

Nervous system disorders:
Common: Peripheral motor neuropathy
Uncommon: VIIth nerve paralysis

Respiratory thoracic and mediastinal disorders:

Common: Nasal congestion, pneumonitis

Uncommon: dry throat, nasal dryness

Infections & infestations:
Common: Oral candidiasis, pneumonia, sepsis with or without neutropenia

Investigations:
Common: Aspartate aminotransferase increased, blood bilirubin increased, blood creatinine increased

Musculoskeletal and connective tissue disorders:
Common: Bone pain, muscular weakness

Vascular disorders:
Common: Hypotension, hypertension

Cardiac disorders:
Common: Tachycardia, cardiac failure congestive

Eye disorders:
Common: Lacrimation increased
Uncommon: cystoid macular edema

Hepatobiliary disorders:
Common: Cholangitis

Renal and urinary disorders:
Common: Acute renal failure

Uncommon: Haemolytic uraemic syndrome

Postmarket Adverse Drug Reactions

The following adverse drug reactions have been identified during post-approval of paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: Reports of pancytopenia and lymphopenia have been observed.

Cardiac Disorders: Reports of congestive heart failure, left ventricular dysfunction, and atrioventricular block (including second-degree AV block requiring pacemaker placement) have been observed. Most of the individuals had previous or concurrent exposure to cardiotoxic drugs, such as anthracyclines, or had underlying cardiac history.

Eye Disorders: Rare reports of conjunctivitis, increased lacrimation, loss of vision, macula edema, optic neuropathy, dry eye, and hypoaesthesia of the eye have been observed.

There have been reports of reduced visual acuity due to cystoid macular edema (CME) during treatment with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel. Based on a number of well documented reports, including literature cases, an association between CME and paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel is considered to be reasonably well established. Features specific to this rare clinical entity include an absence of vascular leakage with no other precipitating factors, and positive dechallenge in most cases.

General Disorders and Administration Site Conditions: Reports of extravasation have been observed.

Injury, Poisoning and Procedural Complications: Reports of radiation recall phenomenon have been observed.

Immune System Disorders: Rare occurrences of severe hypersensitivity reactions, including anaphylactic reactions, have been reported. Very rarely, fatalities have occurred in these patients. Patients who experience a severe hypersensitivity reaction to Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel should not be re-challenged with the drug.

Metabolic Disorders: Very rare occurrences of tumor lysis syndrome, some with a fatal outcome, have been reported.

Nervous System Disorders: Reports of crania nerve palsies, vocal cord paresis and motor neuropathy have been observed.

Respiratory Thoracic and Mediastinal Disorders: Reports of pleural effusion, pulmonary edema, diffuse alveolar damage and diffuse pneumonitis have been observed as well as reports of

radiation pneumonitis in patients receiving concurrent radiotherapy.

Skin/Subcutaneous Disorders: Reports of erythema, generalized or maculo-papular rash, pruritus, photosensitivity reaction, and in some patients previously exposed to capecitabine, reports of palmar-plantar erythrodyaesthesiae have been observed. Rare reports of Stevens-Johnson syndrome and toxic epidermal necrolysis have also been observed. During post-market surveillance, scleroderma-like changes preceded by chronic edema have been reported with solvent-based paclitaxel injection.

DRUG INTERACTIONS

Overview

No drug interaction studies have been conducted with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel.

The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel concomitantly with substances known to inhibit (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, nelfinavir, grapefruit) or induce (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine, St. John's Wort) either CYP2C8 or CYP3A4 (see **ACTIONS AND CLINICAL PHARMACOLOGY**).

Drug-Drug Interactions

Interactions with other drugs have not been established.
Paclitaxel and gemcitabine do not share a common metabolic pathway. Paclitaxel clearance is primarily determined by cytochrome P450 2C8 and 3A4 mediated metabolism followed by biliary excretion, while gemcitabine is inactivated by cytidine deaminase followed by urinary excretion. Some *in vitro* studies have shown effects of paclitaxel on intracellular levels of the active and inactive metabolites of gemcitabine but clinical significance of those observations is unknown. Pharmacokinetic interactions between paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel and gemcitabine have not been evaluated in humans.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

No premedication to prevent hypersensitivity reactions is required prior to administration of Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel.

The primary elimination pathway for Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel is hepatic metabolism followed by biliary excretion. The exposure to paclitaxel may be higher in patients with hepatic impairment than in patients with normal hepatic function. The starting dose of Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel should be reduced in patients with moderate to severe hepatic impairment (see **Recommended Dose and Dosage Adjustment, Hepatic Impairment**). As renal excretion is a minor elimination pathway for Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel, increased exposure to paclitaxel is not expected in patients with mild to moderate renal impairment. Adjustment of the starting Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel dose is not required for patients with mild to moderate renal impairment (see **Recommended Dose and Dosage Adjustment, Renal Impairment**).

Do not substitute for or with other paclitaxel formulations.

Recommended Dose and Dosage Adjustment

Metastatic Breast Cancer

The recommended regimen for Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel is 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks. Dose levels of mg/m^2 refer to mg of paclitaxel in Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel.

Dose Adjustment for Treatment of Breast Cancer: Patients who experience severe neutropenia (neutrophil < 500 cells/mm^3 for a week or longer) or severe sensory neuropathy during Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel therapy should have dosage reduced to 220 mg/m^2 for subsequent courses of Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel. For recurrence of severe neutropenia or severe sensory neuropathy, an additional dose reduction should be made to 180 mg/m^2. For grade 3 sensory neuropathy, hold treatment until resolution to grade 1 or 2, followed by a dose reduction for all subsequent courses of Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel.

Metastatic Pancreatic Cancer

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

Dose Adjustment for Treatment of Metastatic Pancreatic Cancer:

The recommended dose reductions for paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel and gemcitabine from the clinical trial are outlined in Tables 4 to 6 below. When a dose reduction was required, no dose re-escalation was permitted during the trial (with the exception of Day 15, see Table 5 below).

Due to dose-dependent and dose-limiting myelosuppression (primarily neutropenia) with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in combination with gemcitabine, more conservative dose modifications may be necessary based on clinical judgment and experience with chemotherapeutic drugs. Note that the gemcitabine dose modifications used in the clinical trial differ from the recommendations in the gemcitabine product monograph.

Table 4: Dose Level Reductions for Patients with Metastatic Pancreatic Cancer

Dose Level	**Paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel ® Dose (mg/m^2)**	**Gemcitabine Dose (mg/m^2)**
Full dose	125	1000[a]
1st dose level reduction	100	800 [a]
2nd dose level reduction	75	600 [a]
If additional dose reduction required	Discontinue treatment	Discontinue treatment [a]

[a] dose modifications differ from the recommendations in the gemcitabine product monograph

Table 5: Dose Recommendation and Modifications for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or Within a Cycle for Patients with Metastatic Pancreatic Cancer

Cycle Day	**ANC count ($cells/mm^3$)**		**Platelet count ($cells/mm^3$)**	**Paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel Dose**	**Gemcitabine Dose**
Day 1	≥ 1500	AND	≥ 100,000	Treat on time at current dose levels	
	< 1500	OR	< 100,000	Delay doses until recovery	
Day 8	≥ 1000	AND	≥ 75,000	Treat on time at current dose levels	
	≥ 500 but < 1000	OR	≥ 50,000 but < 75,000	Reduce doses 1 dose level	
	< 500	OR	< 50,000	Withhold doses	

Cycle Day	ANC count (cells/mm^3)		Platelet count (cells/mm^3)	Paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel Dose	Gemcitabine Dose
Day 15: IF Day 8 doses were given without modification:					
Day 15	≥ 1000	AND	≥ 75,000	Treat on time at current dose levels	
	≥ 500 but < 1000	OR	≥ 50,000 but < 75,000	Treat at current dose level and follow with WBC Growth Factors[a, b]	
	< 500	OR	< 50,000	Withhold doses	
Day 15: IF Day 8 doses were reduced:					
Day 15	≥ 1000	AND	≥ 75,000	Return to the Day 1 dose level and follow with WBC Growth Factors[a, b]	
	≥ 500 but < 1000	OR	≥ 50,000 but < 75,000	Treat with Day 8 dose level and follow with WBC Growth Factors[a, b]	
	< 500	OR	< 50,000	Withhold doses	
Day 15: IF Day 8 doses were withheld:					
Day 15	≥ 1000	AND	≥ 75,000	Return to Day 1 dose level and follow with WBC Growth Factors[a, b]	
	≥ 500 but < 1000	OR	≥ 50,000 but < 75,000	Reduce 1 dose level and follow with WBC Growth Factors[a, b]	
	< 500	OR	< 50,000	Withhold doses	

Abbreviations: ANC = Absolute Neutrophil Count; WBC GF = white blood cell growth factor.
[a] In the clinical trials, G-CSF was optional if descent only affected platelets.
[b] If WBC Growth Factors are not available, a reduction in dose levels is recommended. Although this option was not included in the clinical trial protocol this approach is consistent with clinical practice.

Table 6: Dose Modifications for Other Adverse Drug Reactions in Patients with Metastatic Pancreatic Cancer

Adverse Drug Reaction	Paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel Dose	Gemcitabine Dose
Febrile Neutropenia: Grade 3 or 4	Withhold doses until fever resolves and ANC ≥ 1500; resume at reduced dose levels.	

Peripheral Neuropathy: Grade 3 or 4	Withhold dose until improves to ≤ Grade 1; resume at reduced dose level	Treat with same dose
Cutaneous Toxicity: Grade 2 or 3	Reduce doses 1 level; discontinue treatment if ADR persists	
Gastrointestinal Toxicity: Grade 3 mucositis or diarrhea	Withhold doses until improves to ≤ Grade 1; resume at reduced dose levels	

Abbreviations: ADR = Adverse Drug Reaction

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 patients with moderate to severe hepatic impairment (total bilirubin > 1.5 to ≤ 5 x ULN and aspartate aminotransferase [AST] ≤ 10 x ULN), a 20% reduction in dose is recommended for metastatic breast cancer patients. The reduced dose may be escalated to the dose for patients with normal hepatic function if the patient is tolerating the treatment for at least two cycles. There are insufficient data to permit dosage recommendations for patients with metastatic pancreatic cancer that have moderate to severe hepatic impairment.

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

Renal Impairment

Adjustment of the starting Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound 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 to permit dosage recommendations in patients with severe renal impairment or end stage renal disease (estimated creatinine clearance < 30 mL/min).

Administration

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. Limiting the infusion of Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel to 30 minutes, as directed, reduces the likelihood of infusion-related reactions (see **WARNINGS AND PRECAUTIONS, Injection Site Reactions**).

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).

Slowly withdraw the dosing volume of the reconstituted Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel from the vial(s) into a syringe. Inject the appropriate amount of reconstituted Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel into an empty, sterile, intravenous infusion bag (plasticized polyvinyl chloride (PVC) containers, PVC or non-PVC type i.v. bag). No further dilution is required. The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel infusions.

The use of medical devices containing silicone oil as a lubricant (ie, syringes and IV bags) to reconstitute and administer Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel may result in the formation of proteinaceous strands. Visually inspect the reconstituted Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel suspension in the IV bag prior to administration. If strands are observed, administer reconstituted Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel through a 15 mcm filter. If strands are present and a 15 mcm filter is not available, discard the product. Do not use a filter with a pore size less than 15 mcm.

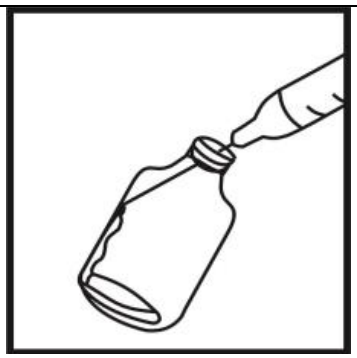
Do not mix any other drugs with the Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel infusion.

Reconstitution

Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel is supplied as a sterile lyophilized powder for reconstitution before use. **Avoid errors, read entire preparation instructions prior to reconstitution**.

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
50 mL	20 mL 0.9% Sodium Chloride Injection, USP	20 mL	5 mg/mL

1. **Aseptically, reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP.**
2. **Slowly inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of 1 minute, using the sterile syringe to direct the solution flow onto the INSIDE WALL OF THE VIAL.**



3. **DO NOT INJECT the 0.9% Sodium Chloride Injection, USP, directly onto the lyophilized cake as this will result in foaming.**
4. **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.**
5. **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.**
6. **If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides**.

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.

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

Stability of Reconstituted Suspension in the Vial

Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel reconstituted in the vial should be used immediately, but may be refrigerated between 2°C and 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. Some settling of the reconstituted suspension may occur. 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.

Inject the appropriate amount of reconstituted Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel into an empty, sterile, i.v. bag (plasticized polyvinyl chloride (PVC) containers, PVC or non-PVC type i.v. bag). No further dilution is required. The use of specialized DEHP-free solution containers or administration sets may also be used but are not required to prepare or administer Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel infusions.

The use of medical devices containing silicone oil as a lubricant (ie, syringes and IV bags) to reconstitute and administer Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel may result in the formation of proteinaceous strands. Visually inspect the reconstituted Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel in the IV bag prior to administration. If strands are observed, administer reconstituted

Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel through a 15 mcm filter. If strands are present and a 15 mcm filter is not available, discard the product. Do not use a filter with a pore size less than 15 mcm.

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 20 to 25°C) and ambient lighting conditions for up to 8 hours.

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

Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel is a cytotoxic anticancer drug and, as with other potentially toxic paclitaxel compounds, caution should be exercised in handling Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel. The use of gloves is recommended. If Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel (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 Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel contacts mucous membranes, the membranes should be flushed thoroughly with water.

OVERDOSAGE

There is no known antidote for Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, sensory neurotoxicity, and mucositis.

For management of a suspected drug overdose, contact your regional poison control centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Paclitaxel, the active pharmaceutical ingredient in Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. Paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Pharmacodynamics

In preclinical models, paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel resulted in higher intra-tumor concentrations of paclitaxel compared to paclitaxel injection. Albumin is known to mediate endothelial transcytosis of plasma constituents and, based on *in vitro* data, it is hypothesized that albumin-bound paclitaxel facilitates the transport of paclitaxel across the endothelial cell via an albumin-receptor (gp60) mediated pathway.

Pharmacokinetics

Absorption: The pharmacokinetics of total paclitaxel following 30- and 180-minute infusions of paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel at dose levels of 80 to 375 mg/m^2 were determined in clinical studies. Following intravenous administration of paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel, paclitaxel plasma concentrations declined in a biphasic manner, the initial rapid decline representing distribution to the peripheral compartment and the slower second phase representing drug elimination.

The paclitaxel plasma exposure (AUC) was dose proportional from 2653 to 16736 h•ng/mL following administration of paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel doses from 80 to 300 mg/m^2 and the pharmacokinetics of paclitaxel were independent of the duration of intravenous administration.

Distribution: Following paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel administration to patients with solid tumors, paclitaxel is evenly distributed into blood cells and plasma and is highly bound to plasma proteins (94%). In a within-patient comparison study, the fraction of unbound paclitaxel in plasma was significantly higher with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel (6.2%) than with solvent-based paclitaxel (2.3%). This contributes to significantly higher exposure to unbound paclitaxel with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel compared with solvent- based paclitaxel, when the total exposure is comparable. *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 a 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.

The pharmacokinetic data of 260 mg/m^2 paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel administered over 30 minutes was compared to the pharmacokinetics of 175 mg/m^2 paclitaxel injection over 3 hours. The volume of distribution and clearance of paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel were greater (by 53% and 43% respectively) than for paclitaxel injection. Differences in C_{max} and C_{max} corrected for dose, reflected differences in total dose and rate of infusion. There were no differences in terminal half-lives (approximately 21 hours for each).

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

Excretion and Elimination: After a 30-minute infusion of 260 mg/m^2 doses of paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel, the mean values for cumulative urinary recovery of unchanged drug (4%) indicated extensive non-renal clearance. Less than 1% of the total administered dose was excreted in urine as the metabolites 6α-hydroxypaclitaxel and 3'-*p*-hydroxypaclitaxel. Fecal excretion was approximately 20% of the total dose administered.

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

Possible interactions of paclitaxel with concomitantly administered medications have not been formally investigated. In a rat study in which a single dose of paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel was concurrently administered with gemcitabine, the exposure of the inactive metabolite of gemcitabine, dFdU was doubled whereas gemcitabine systemic exposure was not affected. The active metabolites of gemcitabine, dFdCDP and dFdCTP, were not measured. The exposure of paclitaxel was not affected.

Special Patient Populations

Geriatrics: Population pharmacokinetic analysis for paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel included patients with ages ranging from 24 to 85 years old and show that age does not significantly influence the maximum elimination rate of paclitaxel.

Pharmacokinetic/pharmacodynamics modeling using data from 125 patients with advanced solid tumors suggested that the risk of neutropenia development in the first treatment cycle is positively correlated with increasing age after adjusting for paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel exposure.

Hepatic Insufficiency: The effect of hepatic impairment on population pharmacokinetics of paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel was studied in patients with advanced solid tumors. This analysis included patients with normal hepatic function (n=130), and pre-existing mild (n=8), moderate (n=7), or severe (n=5) hepatic impairment

(according to NCI Organ Dysfunction Working Group criteria). The results show that mild hepatic impairment (total bilirubin > 1 to ≤ 1.5 x ULN) has no clinically important effect on pharmacokinetics of paclitaxel. Patients with moderate (total bilirubin > 1.5 to ≤ 3 x ULN) or severe (total bilirubin > 3 to ≤ 5 x ULN) hepatic impairment have a 22% to 26% decrease in the maximum elimination rate of paclitaxel and approximately 20% increase in mean paclitaxel AUC compared with patients with normal hepatic function.

Hepatic impairment has no effect on mean paclitaxel C_{max}. In addition, elimination of paclitaxel shows an inverse correlation with total bilirubin and a positive correlation with serum albumin. Pharmacokinetic/pharmacodynamic modeling indicates that there is no correlation between baseline albumin or total bilirubin level and neutropenia after adjusting for paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel exposure. Pharmacokinetic data are not available for patients with total bilirubin > 5 x ULN or for patients with metastatic pancreatic cancer (see **DOSAGE AND ADMINISTRATION, Hepatic Impairment**).

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=1) 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 (see **DOSAGE AND ADMINISTRATION, Renal Impairment**).

Other Intrinsic Factors: Population pharmacokinetic analyses for paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel show that body weight (40 to 143 kg), body surface area (1.3 to 2.4 m^2), gender, race (Asian vs White), and type of solid tumors do not have a clinically important effect on the maximum elimination rate of paclitaxel.

STORAGE AND STABILITY

Store the vials of Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel in original cartons between 20°C and 25°C. Retain in the original package to protect from bright light.

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

Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel reconstituted in the original vial should be used immediately, but may be refrigerated between 2°C and 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. Some settling of the reconstituted suspension may occur. Ensure complete resuspension by mild agitation before use. Discard the reconstituted suspension if precipitates are observed.

The suspension for infusion prepared as recommended in an infusion bag should be used

immediately, but may be stored at ambient temperature (approximately 20°C to 25°C) and ambient lighting conditions for up to 8 hours.

SPECIAL HANDLING INSTRUCTIONS

Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel is a cytotoxic anticancer drug and, as with other potentially toxic paclitaxel compounds, caution should be exercised in handling Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel. The use of gloves is recommended.

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate (see **REFERENCES**).

Accidental Exposure: No reports of accidental exposure to Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel have been received. However, upon inhalation of paclitaxel, dyspnea, chest pain, burning eyes, sore throat, and nausea have been reported. Following topical exposure, events have included tingling, burning, and redness. If Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel (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 Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel contacts mucous membranes, the membranes should be flushed thoroughly with water.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel is supplied as a white to off white powder/cake for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Paclitaxel exists in the particle in a non-crystalline, amorphous state. Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel is free of solvents.

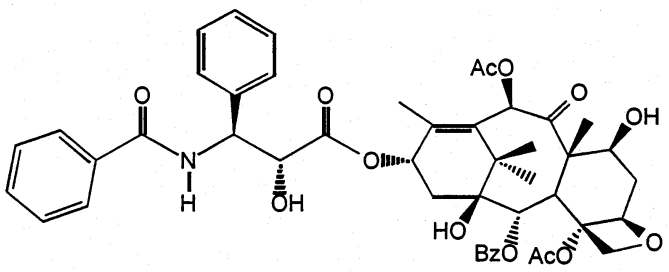
Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel is available in a single-use glass vial with a vial stopper not made with natural rubber latex, individually packaged in a carton.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name	:	Paclitaxel
Chemical name	:	5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine
Molecular formula and molecular mass	:	$C_{47}H_{51}NO_{14}$ 853.91
Structural formula	:	Paclitaxel has the following structural formula



Physicochemical properties	:	Paclitaxel is a white to off-white crystalline powder. It is highly lipophilic, insoluble in water, and melts at approximately 216 to 217°C.

CLINICAL TRIALS

Study demographics and trial design

Metastatic Breast Carcinoma

Data from 460 patients enrolled in a randomized comparative study were available to support the use of paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in metastatic breast cancer.

Table 7: Summary of Patient Demographics for Clinical Trials in Metastatic Breast Cancer

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n = number)	Mean Age (Range)	Gender and Race
CA012-0	Pivotal: controlled, randomized, multicentre, open label phase III study of paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel versus Paclitaxel Injection in patients with metastatic breast cancer.	Paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel: 260 mg/m^2 given as a 30-minute infusion vs. Paclitaxel Injection at 175 mg/m^2 given as a 3-hour infusion. Each patient receives drug at 3-week intervals.	460, divided into two arms.	53.2 (26 - 83)	Female (100%) Caucasian: 221 (97%) Black: 1 (< 1%) Asian: 1 (< 1%) Indian-Eastern: 2 (< 1%) Hispanic: 3 (1%) Other: 1 (< 1%)

Randomized Comparative Study - This multicentre trial was conducted in 460 patients with metastatic breast cancer. Patients were randomized to receive paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel at a dose of 260 mg/m^2 given as a 30-minute infusion, or paclitaxel injection at 175 mg/m^2 given as a 3-hour infusion. 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, 40% in the metastatic setting, and 19% in both metastatic and adjuvant settings. Fifty- nine percent received study drug as second or greater than second-line therapy. Seventy-seven percent of the patients had been previously exposed to anthracyclines.

The primary endpoint was Target Lesion Response Rate using RECIST guidelines.

Study results

In the randomized controlled multicentre trial, patients in the paclitaxel powder for injectable suspension

nanoparticle, albumin-bound paclitaxel treatment arm had a superior investigator overall target lesion response rate of 33.2% (95% CI: 27.09 to 39.29%), compared to 18.7% (95% CI: 13.58 to 23.76%) for patients in the paclitaxel injection treatment arm. (See Table 8).

Table 8: Efficacy in Metastatic Breast Cancer

Endpoint **Overall Investigator Target Lesion Response Rate**	**Paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel** **260 mg/m^2** **(n = 229)**	**Paclitaxel Injection** **175 mg/m^2** **(n = 225)**	**P Value**
All Patients %	33.2	18.7	0.001[a*]
95% Confidence interval [b]	(27.09-39.29)	(13.58-23.76)	

[a] P value from Cochran-Mantel-Haenszel (CMH) test stratified by 1st line vs > 1st line therapy; * P < 0.05.

[b] 95% binomial confidence interval of response rate.

Time to Tumor Progression (TTP) was significantly greater in the paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel group than in the paclitaxel injection group for all patients [23.0 vs 16.6 weeks (5.3 vs 3.8 months), hazard ratio (HR) = 0.726, (95% CI: 0.589-0.895), P = 0.002]. (See Table 9).

Table 9: Time to Tumor Progression

Category	**Paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel** **260 mg/m^2** **(n = 229)**	**Paclitaxel Injection** **175 mg/m^2** **(n = 225)**	**P Value** [a] **(Hazard Ratio)** **95% CI**
All Patients			
Median time to disease progression (weeks)	23.0	16.6	0.002* (0.726) 0.589 − 0.895
95% Confidence interval	19.4 − 26.1	15.1 − 20.1	
Median time to disease progression (months)[b]	5.3	3.8	
95% Confidence interval	4.5 − 6.0	3.5 − 4.6	

Note: Time to tumor progression is defined as the number of weeks from the first dose of study drug to the start of disease progression. Patients who did not have disease progression are censored at the last known time the patient was evaluated for response.

CI = Confidence interval

[a] P value from log-rank test. * P < 0.050.

[b] Conversion to/from weeks to months assumes 30.5 days/month or 4.3571 weeks/month.

Median Progression-Free Survival (PFS) was significantly longer for the paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel group than for the paclitaxel injection group for all patients

[22.7 vs 16.6 weeks (5.2 vs 3.8 months), HR = 0.734, (95% CI: 0.597-0.903), P = 0.003]. (See Table 10).

Table 10: Progression-Free Survival

Category	Paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel 260 mg/m^2 (n = 229)	Paclitaxel Injection 175 mg/m^2 (n = 225)	P Value [a] (Hazard Ratio) 95% CI
All Patients			
Median progression-free survival (weeks)	22.7	16.6	0.003* (0.734) 0.597 − 0.903
95% Confidence interval	19.3 − 26.1	15.1 − 19.9	
Median progression-free survival (months)[b]	5.2	3.8	
95% Confidence interval	4.4 − 6.0	3.5 − 4.6	

Note: Progression-free survival is defined as the time from the first dose of study drug to the start of disease progression or patient death (which ever occurred first). Patients who did not have disease progression or have not died are censored at the last known time the patient was alive. If a patient started another oncology therapy during study follow-up prior to disease progression or death, that patient is censored at the last follow-up contact date prior to the start of the new oncology therapy.
ITT = Intent-to-treat; CI = Confidence interval

[a] P value from log-rank test. * P < 0.050.

[b] Conversion from weeks to months assumes 30.5 days/month or 4.3571 weeks/month.

Median time to death for paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel and paclitaxel injection groups for all patients was 65.0 vs 55.3 weeks (14.9 vs 12.7 months) respectively, HR = 0.899, (95% CI: 0.728-1.110), P = 0.322. (See Table 11).

Table 11: Patient Survival

Category	Paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel 260 mg/m^2 (n = 229)	Paclitaxel Injection 175 mg/m^2 (n = 225)	P Value [a] (Hazard Ratio) 95% CI
All Patients			
Median time to death (weeks)	65.0	55.3	0.322 (0.899) 0.728 − 1.110
95% Confidence interval [b]	53.4 − 76.9	48.0 − 66.4	
Median time to death (months)	14.9	12.7	
95% Confidence interval [b]	12.3 − 17.6	11.0 − 15.2	

Note: Analysis includes patient survival information during study follow-up. Patients who did not die are censored at the last known time the patient was alive.
CI = confidence interval.

[a] P value from log-rank test. *P < 0.050.

[b] 95% CI for median time to death.

Metastatic Pancreatic Cancer

A multicenter, multinational, randomized, open-label study was conducted in 861 patients to compare paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel /gemcitabine versus gemcitabine monotherapy as first-line treatment in patients with metastatic adenocarcinoma of the pancreas. Patients who received adjuvant chemotherapy were not eligible for enrollment. Paclitaxel powder for injectable suspension nanoparticle, albumin-bound 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 group, gemcitabine monotherapy was administered to patients (N=430) as 1000 mg/m^2 given weekly for 7 weeks followed by a 1-week rest period in Cycle 1 and in Cycle 2 and onwards was administered on Days 1, 8 and 15 of a 28-day cycle (consistent with the label recommended dose and regimen). Treatment was administered until disease progression or development of an unacceptable toxicity.

Patient demographics of the intent-to-treat population are shown in Table 12. The demographics and disease characteristics were well balanced between the two treatment groups.

Table 12: Summary of Patient Characteristics in Randomized Adenocarcinoma of Pancreas Trial (Intent-to-Treat Population)

Patient Characteristics	**Paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel (125 mg/m^2) and gemcitabine (N=431)**	**Gemcitabine (N=430)**
Age (years)		
Median (range)	62 (27, 86)	63 (32, 88)
< 65 years, n (%)	254 (59%)	242 (56%)
≥ 65 years, n (%)	177 (41%)	188 (44%)
Gender (%)		
Male/Female	57%/43%	60%/40%
Karnofsky Performance Status Baseline, n (%)		
100	69 (16%)	69 (16%)
90	179 (42%)	199 (46%)
80	149 (35%)	128 (30%)
70	30 (7%)	33 (8%)
CA 19-9 Baseline, n (%)		
Within normal laboratory limits	60 (14%)	56 (13%)
>ULN but <59 x ULN	122 (28%)	120 (28%)
≥59 x ULN	197 (46%)	195 (45%)
Number of Metastatic Site(s), n (%)		
1	33 (8%)	21 (5%)
2	202 (47%)	206 (48%)
3	136 (32%)	140 (33%)
>3	60 (14%)	63 (15%)

Patient Characteristics	Paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel (125 mg/m^2) and gemcitabine (N=431)	Gemcitabine (N=430)
Current Metastatic Site(s), n (%)		
Liver	365 (85%)	360 (84%)
Lung/Thoracic	153 (35%)	184 (43%)
Pancreatic Primary Location, n (%)		
Head	191 (44%)	180 (42%)
Body	132 (31%)	136 (32%)
Tail	105 (24%)	110 (26%)
Biliary Stent, n (%)		
Present at Baseline	80 (19%)	68 (16%)
Whipple Procedure, n (%)		
Performed Prior to Study Entry	32 (7%)	30 (7%)

Patients received a median treatment duration of 3.9 months in the paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel /gemcitabine group and 2.8 months in the gemcitabine group.

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). Results for overall survival, progression-free survival, and overall response rate are shown in Table 13.

Table 13: Efficacy Results from Randomized Study in Patients with Adenocarcinoma of the Pancreas (ITT Population)

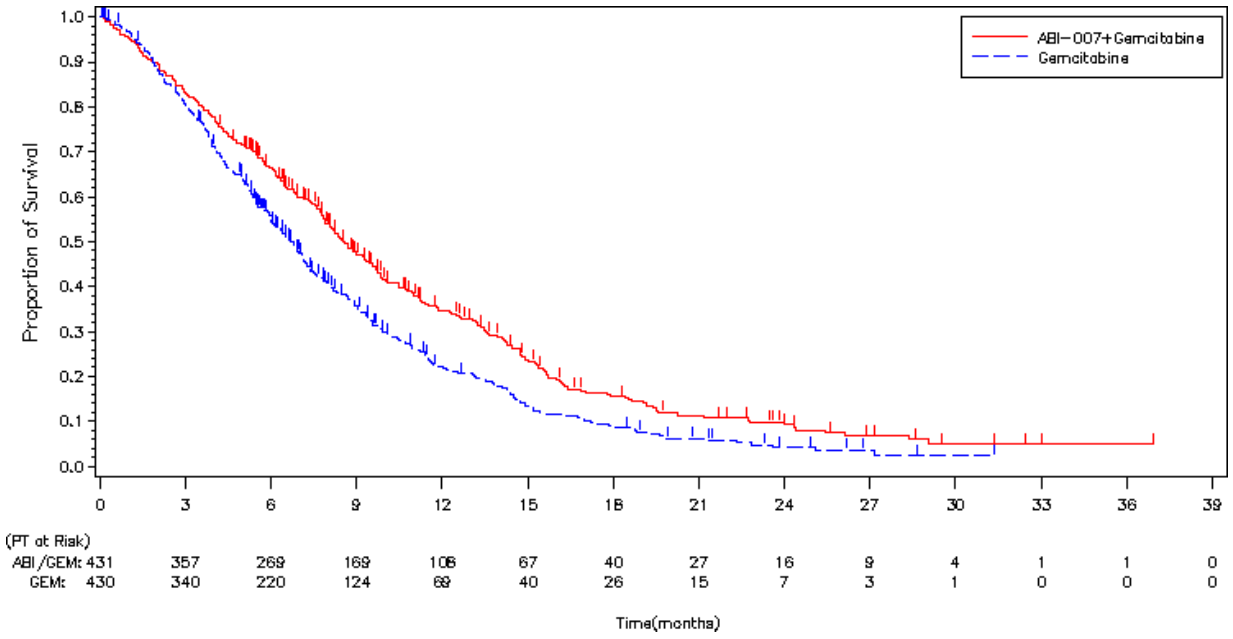
	Paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel (125 mg/m^2) and gemcitabine (N = 431)	Gemcitabine (N = 430)
Overall Survival		
Number of deaths, n (%)	333 (77)	359 (83)
Median Overall Survival (months)	**8.5**	**6.7**
HR (95% CI) [a], P-value[b]	0.72 (0.62, 0.83), <0.0001	
Progression-free Survival[c]		
Death or progression, n (%)	277 (64)	265 (62)
Median Progression-free Survival (months)	**5.5**	**3.7**
HR (95% CI) [a], P-value[b]	0.69 (0.58, 0.82), <0.0001	
Overall Response Rate[c]		
Confirmed complete or partial overall response, n (%)	**99 (23)**	**31 (7)**

(95% CI) , P-value[d]	3.19 (2.18, 4.66), <0.0001

CI = confidence interval, HR = hazard ratio of ABI-007/gemcitabine / gemcitabine, ITT = intent-to-treat population.
[a] The associated hazard ratio and 95 % CI is estimated by using stratified Cox proportional hazard model.
[b] P-value is based on a stratified log-rank test stratified by geographic region (North America versus Others), Karnofsky performance score (70 to 80 versus 90 to 100), and presence of liver metastasis (yes versus no).
[c] Based on Independent Radiological Reviewer Assessment.
[d] P-value is for response rate ratio and is based on chi-square test.

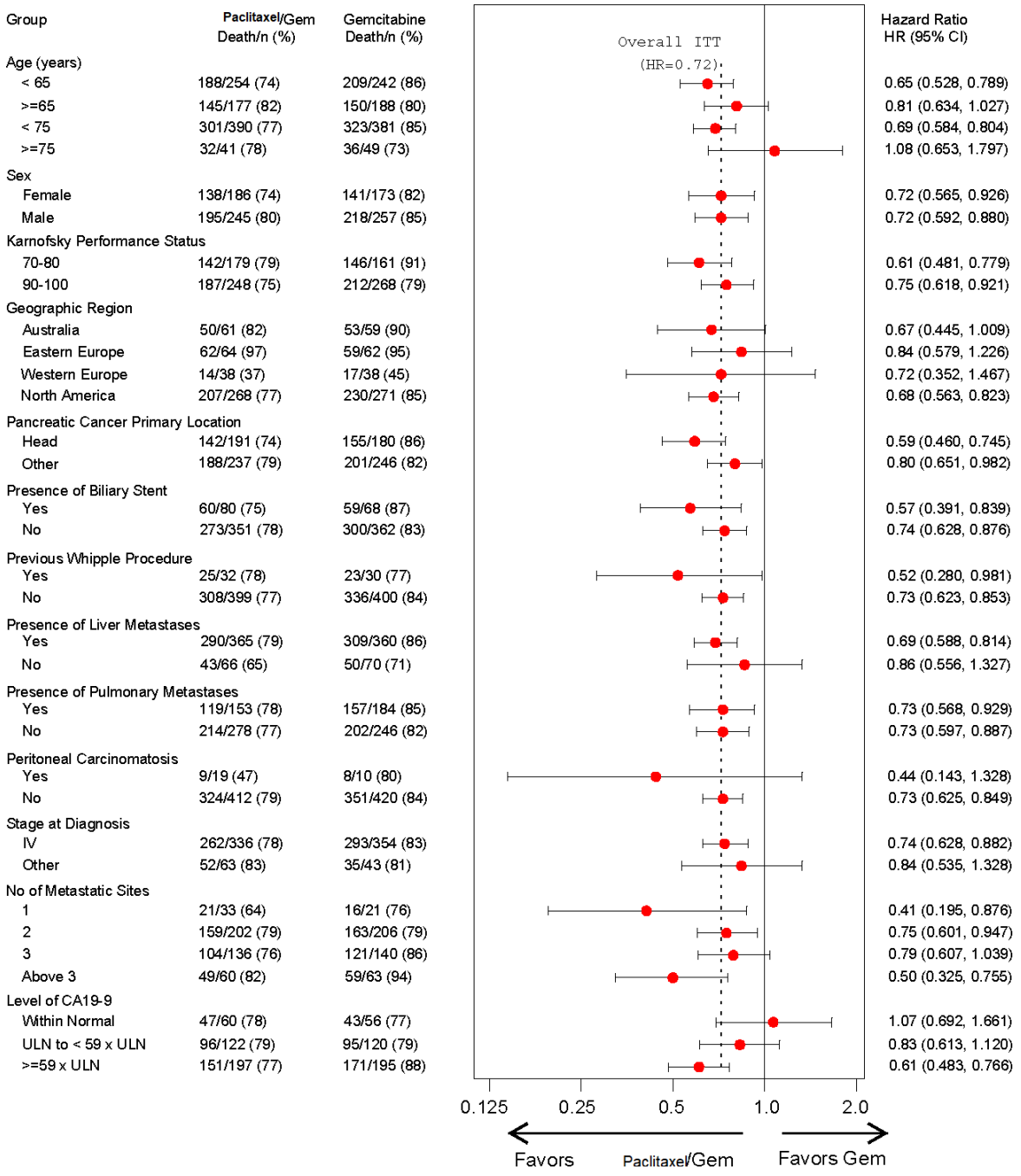
There was a statistically significant improvement in OS for patients treated with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel /gemcitabine versus gemcitabine alone, with 1.8 months increase in median OS, 28% overall reduction in risk of death and 59% improvement in 1-year survival. The Kaplan- Meier curve for Overall Survival by treatment group is presented in Figure 1.

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



An analysis of OS by prespecified subgroups is shown in Figure 2.

Figure 2: Forest Plot for Overall Survival



DETAILED PHARMACOLOGY

See **ACTION AND CLINICAL PHARMACOLOGY**.

TOXICOLOGY

Table 14: Summary of Single Dose Toxicity Studies

Study No. Objective	Species/ Sex, n	Dose/Route of Administration	Results
P0397006 Single dose acute toxicity	Sprague Dawley Rat/ 6 females, 6 males per group, 10 groups, n = 120	Paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel doses of 5, 9, 30, 90 and 120 mg/kg, Intravenous Paclitaxel Injection doses of 5, 9 and 30 mg/kg	• 1 paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel treated animal (90 mg/kg) had unexplained death; no other mortality; all 12 animals treated with 30 mg/kg paclitaxel injection died by Day 4 of study. • Significant diffuse degeneration and necrosis of testes/epididymis in male rats given paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel at 9 mg/kg dose and higher. No notable changes in 31-day necropsy compared to 8-day necropsy; no changes were seen in the testes of animals treated with 5 and 9 mg/kg paclitaxel injection. • In paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel treated animals, organ abnormalities found in 2 female rats at 9 mg/kg, 1 female rat at 90 mg/kg; no other notable female toxicity. • Cerebral cortical necrosis in rats given 9 mg/kg paclitaxel injection; no cortical changes in rats given up to 120 mg/kg paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel.
P0897001 Single dose acute toxicity	Beagle Dog/ 2 females and 2 males, n = 4	175 mg/m^2 paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel Intravenous No comparator	• Paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel caused temporary, delayed gastrointestinal symptoms, edema, vasculitis and elevated white blood cell counts. Probable acute serum sickness (type I immune reaction) due to canine reaction to human albumin. • No mortality.
P0997006 Single, i.v. dose acute toxicity	Beagle Dog/ 2 females and 2 males per group/ n = 12	175 mg/m^2 paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel, albumin, or vehicle control solution/ Intravenous	• All groups [paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel, vehicle control (formulated human albumin) and Albumin Human, USP] had symptoms of acute serum sickness reaction due to canine reaction to human albumin. Testicular atrophy was seen in paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel treated males.

Study No. Objective	Species/ Sex, n	Dose/Route of Administration	Results
LyChron-001 Single dose acute toxicity	Male domestic swine, n = 12	Paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel: 1 mg/kg, 3 mg/kg or 6 mg/kg, or vehicle (human albumin in saline), Intravenous	• Paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel was not observed at 1 mg/kg or 3 mg/kg; gastrointestinal symptoms and high temperature were noticed at 6 mg/kg; 1 of 3 animals at 6 mg/kg died from pneumonitis. Neutrophilia was observed in the high dose group. The pneumonitis and neutrophilia are suggestive of hypersensitivity pneumonitis related to the human albumin, which is exacerbated by the paclitaxel. No toxicity was observed for vehicle (human albumin).

Table 15: Summary of Repeated Dose Toxicity Studies

Study No. Objective	Species/ n	Dose/Route of Administration	Results
SRI-LIF-97-171-9024.2 Multiple, i.v. dose efficacy and toxicity of paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel	NCr-nu female mice with MX-1 human mammary tumors, n = 175	1. Paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel or paclitaxel injection 30, 20, 13.4 mg/kg/day, qd x 5, i.v. administration	1. No signs of frank toxicity after 5 daily i.v. doses of paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel and Taxol up to 30 mg/kg/day. There were no non-specific deaths in paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel treated animals at doses of 13.4-45 mg/kg/day.
		2. Paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel, bulk paclitaxel or paclitaxel 100, 67, 45 mg/kg/day, qd x 5, i.v. administration	2. Daily i.v. doses of paclitaxel injection for up to 5 days caused deaths in all animals at doses of 45, 67, and 100 mg/kg/day.
		3. Paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel, 45, 30, 20, 13.4 mg/kg/day, qd x 5, i.v. administration; HA, 600 mg/kg/day qd x 5, i.v., paclitaxel injection, 30, 20, 13.4 mg/kg/day, qd x 5, i.v. administration	3. Paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel gave CR of tumors in all animals at highest 3 doses, and 4/5 and 3/5 at 13.4 mg/kg/day.

Study No. Objective	Species/ n	Dose/Route of Administration	Results
08CA21 One-month intravenous intermittent dose toxicity study of ABI-007 in rats with a 4-week recovery period	Rat, Crl:CD(SD) strain Main study: n = 16/sex/dose group; Reversibility portion of study: n = 6/group	Repeated dosing with ABI-007 (0, 10, 20, and 30 mg/kg) IV a total of 6 times at 5-day intervals over 30 days	Toxicity consisted mainly of clinical signs (alopecia, scab formation, edema, gait disturbance, weight loss, and decreased food consumption), atrophic changes in lymphatic/hematopoietic tissues, male reproductive organs, and skin, and degenerative changes in the nervous system and eyes. Most changes were irreversible at the 20 and 30 mg/kg doses by the time of recovery sacrifice including changes in the nervous system, eyes, and male reproductive organs. The systemic exposure at 20 mg/kg in rats was similar to those in humans at the clinically recommended dose regimen. Mortality: 1/32 (Day 24) at 10 mg/kg; 4/32 (Day 29) in 20 mg/kg; 23/32 (Day 17 through Day 30) at 30 mg/kg. A NOAEL was not established as toxicity was observed in all dose groups in a dose- dependent fashion.
SNBL.119.11 A Weekly Three Dose Intravenous Toxicology Study of paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel in Cynomolgus Monkeys	Cynomolgus monkey n = 3/sex	9 mg/kg once weekly for three weeks via slow bolus intravenous infusion	Changes included adverse clinical observations (hunched posture, emesis, diarrhea), decreased food consumption (in females) and body weights (in females), and changes in urinalysis, hematology, and serum chemistry parameters. Post-mortem changes included decreased thymic size, organ weight changes, and histopathologic lesions (hepatic leukocytosis and centrilobular vacuolation myocardial karyomegaly, testicular seminiferous tubule degeneration). In monkeys, the systemic exposure at 9 mg/kg dose was approximately one-third of the exposure in humans at the clinically recommended dose regimen.

HA= human albumin

Table 16: Summary of Reproductive Toxicity Studies

Study No. Objective	Species/ n	Dose/Route of Administration	Results
4701-001 Developmental toxicity study of paclitaxel in rats	Crl:CD® (SD)IGS BR VAF/Plus® female rat, n = 25 or 28 per group (193)	Dose: 0.5, 1.0, 2.0, 4.0, 8.0 mg paclitaxel/kg, qd gestation days 7-17 Vehicle (HA), qd gestation days 7-17 Control (saline), qd gestation days 7-17, Intravenous slow bolus injection.	NOAEL paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel 0.5 mg/kg/day; maternal and developmental toxicity at ≥ 1 mg/kg/day; teratogenic at 1-2 mg/kg/day; fetal deaths at ≥ 4 mg/kg/day.
4701-002 Fertility and general reproduction toxicity study of paclitaxel in male rats	Crl:CD® (SD)IGS BR VAF/Plus® male rat, n = 30 rats per group (210)	Dose: 0.5, 2, 7, 16 and 32 mg paclitaxel/kg/week, qwk x 12 Vehicle (HA) qwk x 12 Control (saline) qwk x 12	NOAEL male fertility of 2 mg/kg/week. Significant reduction in fertility at 7 mg/kg/week and infertile at 16 mg/kg/week. NOAEL for offspring of male rats 7 mg/kg/wk. Mortality: 1, 1, 3, 9, 30 rats in 0.5, 2, 7, 16, 32 mg/kg dose groups moribund sacrificed or found dead. Moribund or dead rats exhibited GI lesions; reduction in male reproductive organ sizes observed at scheduled necropsies. Dose-dependent reductions in body weight gains seen for 2 and 7 mg/kg/wk; dose-dependent weight loss seen for 16 and 32 mg/kg/wk. Mating performance/fertility of 7 mg/kg/wk group returned by 3rd cohabitation, mating performance of 16 mg/kg/wk group by 3rd cohabitation/fertility by 4th.

NOAEL = no observed adverse effect level; HA= human albumin

Administration of paclitaxel prior to and during mating produced impairment of fertility in male and female rats.

Paclitaxel has been shown to be clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). Paclitaxel injection was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay.

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PART III: CONSUMER INFORMATION

Pr PACLitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel

This leaflet is part III of a three-part "Product Monograph" published when Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel is a prescription cancer medicine. It is injected into a vein and it is used to treat advanced breast cancer and metastatic pancreatic cancer.

WHAT IS CANCER?
Under normal conditions, the cells in your body divide and grow in an orderly, controlled way. Cell division and growth are necessary for the human body to perform its functions and to repair itself, when necessary. Cancer cells are different from normal cells because they are not able to control their own growth. The reasons for this abnormal growth are not yet fully understood. A tumor is a mass of unhealthy cells that are dividing and growing fast and in an uncontrolled way. When a tumor invades surrounding healthy body tissue, it is known as a malignant tumor. A malignant tumor can spread (metastasize) from its original site to other parts of the body if not found and treated early.

What it does:
Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel is a type of medical treatment called chemotherapy. The purpose of chemotherapy is to kill cancer cells or prevent their growth.

All cells, whether they are healthy cells or cancer cells, go through several stages of growth. During one of the stages, the cell starts to divide. Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel may stop the cells from dividing and growing, so they eventually die. In addition, normal cells may also be affected by Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel causing some of the side effects. (See SIDE EFFECTS AND WHAT TO DO ABOUT THEM below.)

When it should not be used:
Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel should not be given to patients with dangerously low white blood cell counts or to patients who are allergic to the drug or any of the components of it.

What the medicinal ingredient is:
Paclitaxel

What the important nonmedicinal ingredients are:
Human albumin

What dosage form it comes in:
Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel is supplied in vials of 100 mg paclitaxel each of which contains the product in a powder form. It can be used after the health professional adds a solution to it. At that point, Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel is injected into a vein [intravenous (i.v.) infusion] over 30 minutes.

IMPORTANT: PLEASE READ

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel should be administered under the supervision of a doctor who works with cancer medicines.
- Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel should not be given to patients with dangerously low white blood cell counts. To make sure that your blood counts are in the proper range, you will be asked to have frequent tests.
- Your doctor has prescribed this particular paclitaxel product which contains no solvents, unlike other paclitaxel products. This may reduce some of the adverse effects that may be caused by these other ingredients, such as allergic reactions. Your doctor may not wish any other paclitaxel products to be substituted for Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel, so you may wish to check to ensure you have received the correct medication.

BEFORE you use Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel, talk to your doctor or pharmacist if:

- you are experiencing numbness or tingling in your extremities;
- you suspect that you are pregnant, plan to become pregnant or are nursing. Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel can cause harm to the fetus. Avoid becoming pregnant while taking Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel and if you become pregnant during treatment, contact your doctor immediately. Men should be advised to use effective contraception and to avoid fathering a child while receiving treatment with Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel and up to six months after treatment;
- you are breast-feeding or plan to breast-feed. Breast-feeding must be discontinued while taking Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel;
- you have any allergies to this drug or its ingredients or components of the container.
- you have a history of interstitial lung disease, multiple allergies, chronic cough or shortness of breath.
- you have or have had heart problems, fainting spells (syncope), or an irregular heartbeat.
- you have liver or kidney problems

INTERACTIONS WITH THIS MEDICATION

No studies have been done on how this drug interacts with other drugs**.**

PROPER USE OF THIS MEDICATION

Usual Adult Dose:

For the treatment of advanced breast cancer Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel is injected into a vein [intravenous (i.v.) infusion] over 30 minutes at a dose of 260 mg/m^2 every 3 weeks. The usual dose for metastatic pancreatic cancer is 125 mg/m^2 over 30 to 40 minutes on days 1, 8, and 15 of each 28-day treatment cycle with gemcitabine given immediately after Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel.

Overdose:

There is no known antidote for Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel overdosage.

If you think you, or a person you are caring for, have taken too much Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

Talk to your doctor if you have missed a treatment.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Most patients taking Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel will experience side effects, although it is not always possible to tell whether such effects are caused by Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel, another medicine they may be taking, or the cancer itself. Important side effects are described below; however, some patients may experience other side effects that are less common. Report any unusual symptoms to your doctor.

Important side effects observed in studies of patients taking Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel were as follows:

Hair Loss: Complete hair loss, or alopecia, almost always occurs with Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel. This usually involves the loss of eyebrows, eyelashes, and pubic hair, as well as scalp hair. It can occur suddenly after treatment has begun, but usually happens 14 to 21 days after treatment. Hair generally grows back after you've finished your Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel treatment.

Infections Due to Low White Blood Cell Count: Among the body's defenses against bacterial infections are white blood cells. Between your Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel treatment cycles, you will often have blood tests to check your white blood cell counts. Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel usually causes a brief drop in white blood cells. If you have a fever (temperature above 100.4°F/38°C) or other sign of infection, tell your doctor right away. Sometimes serious infections develop that require treatment in the hospital with antibiotics. Serious illness or death could result if such infections are not treated when white blood cell counts are low.

Numbness, Tingling, or Burning (Neuropathy): These symptoms in the hands and/or feet occur often Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel and usually get better or go away without medication within three weeks of interrupting treatment. Weakness or paralysis of the muscles of the face have also been reported with the use of Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel. Be sure to tell your doctor about any numbness, tingling or burning that you have in your face, hands or feet so that he/she can decide the best approach for relief of your symptoms. Sometimes it is necessary to interrupt treatment with Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel until these symptoms improve. After improvement, treatment can be restarted at a lower dose.

Fatigue and Weakness: Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel may cause fatigue, weakness, lethargy and malaise. These side effects are usually self-limited and do not require dose modification or interruption.

Low Red Blood Cell Count: Red blood cells deliver oxygen to tissues throughout all parts of the body and take carbon dioxide from the tissues by using a protein called hemoglobin. A lowering of the volume of red blood cells may occur following Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel treatment causing anemia. Some patients may need a blood transfusion to treat the anemia. Patients can feel tired, tire easily, appear pale, and become short of breath. Contact your doctor if you experience any of these symptoms following Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel treatment.

Mouth or Lip Sores (Mucositis): Some patients develop redness and/or sores in the mouth or on the lips. These symptoms might occur a few days after the Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel treatment and usually decrease or disappear within one week. Talk with your doctor about proper mouth care and

other ways to prevent or reduce your chances of developing mucositis.

Joint and Muscle Pain: You may get joint and muscle pain a few days after your Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel treatment. These symptoms usually disappear in a few days. Although pain medicine may not be necessary, tell your doctor if you are uncomfortable.

Stomach Upset and Diarrhea: Some patients experience nausea, vomiting, and/or diarrhea following Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel use. If you experience nausea or stomach upset, tell your doctor because medicines can be given that almost always reduce or eliminate these symptoms. Diarrhea will usually disappear without treatment; however, if you experience severe abdominal or stomach area pain and/or severe diarrhea, tell your doctor right away.

Heart and Blood Vessel (Cardiovascular) Effects: Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel may cause a drop in heart rate (bradycardia), low blood pressure (hypotension), irregular heartbeat, and chest pain. The patient usually does not notice these changes. You should notify your doctor if you feel dizziness, chest pain, shortness of breath, or faint during treatment with. Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel

Irritation at the Injection Site: Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel may cause irritation at the site where it enters the vein. Reactions may include discomfort, redness, swelling, inflammation (of the surrounding skin or of the vein itself), and ulceration (open sores). These reactions are usually caused by the i.v. (intravenous) fluid leaking into the surrounding area. *If you notice anything unusual at the site of the injection (needle), either during or after treatment, tell your doctor right away*.

Respiratory: Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel may cause shortness of breath and cough. Sometimes these symptoms are a sign of serious lung inflammation due to Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel. You should notify your doctor right away if you develop a cough and/or shortness of breath while taking Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel treatment.

Ability to Drive and Use Machines: Adverse events such as fatigue, weakness and malaise may affect your ability to drive and use machines.

Other Side Effects: Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel may cause mild allergic reactions during the infusion such as flushing. Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel may also cause vision disturbances, changes in your nails and rash. Tell your doctor if you experience blurry or decreased central vision. Rare occurrences of severe allergic reactions have been reported with paclitaxel powder for injectable suspension nanoparticle, albumin-bound paclitaxel. In very rare cases these reactions have been fatal. Patients who experience a severe allergic reaction to Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel should not receive Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel again.

Talk with your doctor or other healthcare professional to discuss ways to prevent or reduce some of these side effects. Because this leaflet does not include all possible side effects that can occur with Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel, it is important to talk with your doctor about other possible side effects.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Common	**fever**		**X**	
	numbness, tingling or burning in the extremities		**X**	
Uncommon	**redness, swelling, irritation or discomfort at the injection site**		**X**	
	cough, shortness of breath		**X**	
Rare	**fainting, dizziness, shortness of breath, chest pain**		**X**	
Very Rare	**Symptoms of tumor lysis syndrome: lack of urination, severe muscle weakness, heart rhythm disturbances, and seizures**			**X**

This is not a complete list of side effects. For any unexpected effects while taking Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel, contact your doctor or pharmacist.

HOW TO STORE IT

Your doctor or pharmacist will store Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel for you.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about Paclitaxel Powder for Injectable Suspension Nanoparticle, Albumin-bound Paclitaxel:

- Talk to your healthcare professional
  - Find the full Product Monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html). Find the Consumer Information on the manufacturer's website (http://www.apotex.ca/products) or by calling 1-800-667-4708.

This leaflet can also be found at: http://www.apotex.ca/products.

This leaflet was prepared by:

Importer / Distributor: Apotex Inc., Toronto,
Ontario, M9L 1T9

Manufactured by:
Panacea Biotec Pharma Limited
B-1, Extension/A-27, Mohan Co-operative
Industrial Estate, Mathura Road
New Delhi, Delhi, India, 110044

Last Prepared: November 16, 2021