

# **PACLITAXEL- paclitaxel injection, powder, lyophilized, for suspension**

## **Sandoz Inc**

### **HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use **PACLITAXEL PROTEIN-BOUND PARTICLES FOR INJECTABLE SUSPENSION (ALBUMIN-BOUND)** safely and effectively. See full prescribing information for **PACLITAXEL PROTEIN-BOUND PARTICLES FOR INJECTABLE SUSPENSION (ALBUMIN-BOUND)**.

**PACLITAXEL** protein-bound particles for injectable suspension (albumin-bound), for intravenous use  
Initial U.S. Approval: 2005

#### **WARNING: SEVERE MYELOSUPPRESSION**

*See full prescribing information for complete boxed warning.*

- **Do not administer paclitaxel protein-bound particles for injectable suspension (albumin-bound) therapy to patients with baseline neutrophil counts of less than 1,500 cells/mm<sup>3</sup>. ( 4)**
- **Monitor for neutropenia, which may be severe and result in infection or sepsis. ( 5.1, 5.3)**
- **Perform frequent complete blood cell counts on all patients receiving paclitaxel protein-bound particles for injectable suspension (albumin-bound). ( 5.1, 5.3)**

#### **INDICATIONS AND USAGE**

Paclitaxel protein-bound particles for injectable suspension (albumin-bound) is a microtubule inhibitor indicated for the treatment of:

- Metastatic breast cancer, after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated. ( 1.1)

#### **DOSAGE AND ADMINISTRATION**

- **Do not substitute paclitaxel protein-bound particles for injectable suspension (albumin-bound) for other paclitaxel products. (2.1)**
- **Extravasation:** Closely monitor the infusion site for extravasation and infiltration. ( 2.1)
- **Metastatic Breast Cancer (MBC):** Recommended dosage of paclitaxel protein-bound particles for injectable suspension (albumin-bound) is 260 mg/m<sup>2</sup> intravenously over 30 minutes every 3 weeks. ( 2.2)
- **Use in Patients with Hepatic Impairment:** Paclitaxel protein-bound particles for injectable suspension (albumin-bound) is not recommended for use in patients with AST > 10 × ULN; or bilirubin > 5 × ULN. For MBC, reduce starting dose in patients with moderate to severe hepatic impairment. ( 2.5)
- **Dose Reductions for Adverse Reactions:** Dose reductions or discontinuation may be needed based on severe hematologic, neurologic, cutaneous, or gastrointestinal toxicities. ( 2.6)

#### **DOSAGE FORMS AND STRENGTHS**

For injectable suspension: white to yellow, sterile, lyophilized powder containing 100 mg of paclitaxel formulated as albumin-bound particles in single-dose vial for reconstitution. ( 3)

#### **CONTRAINDICATIONS**

- Neutrophil counts of < 1,500 cells/mm<sup>3</sup>. ( 4)
- Severe hypersensitivity reactions to paclitaxel protein-bound particles for injectable suspension (albumin-bound). ( 4)

#### **WARNINGS AND PRECAUTIONS**

- Sensory neuropathy occurs frequently and may require dose reduction or treatment interruption. ( 5.2)
- Sepsis occurred in patients with or without neutropenia who received paclitaxel protein-bound particles for injectable suspension (albumin-bound) in combination with gemcitabine; interrupt paclitaxel protein-bound particles for injectable suspension (albumin-bound) and gemcitabine until sepsis resolves, and if neutropenia, until neutrophils are at least 1500 cells/mm<sup>3</sup>, then resume treatment at reduced dose levels. ( 5.3)
- Pneumonitis occurred with the use of paclitaxel protein-bound particles for injectable suspension (albumin-bound) in combination with gemcitabine; permanently discontinue treatment with paclitaxel protein-bound particles for injectable suspension (albumin-bound) and gemcitabine. ( 5.4)
- Severe hypersensitivity reactions with fatal outcome have been reported. Do not rechallenge with this drug. ( 4, 5.5)
- Exposure and toxicity of paclitaxel can be increased in patients with hepatic impairment, consider dose reduction and closely monitor patients with hepatic impairment. ( 2.5, 5.6)
- Paclitaxel protein-bound particles for injectable suspension (albumin-bound) contains albumin derived from human blood, which has a theoretical risk of viral transmission. ( 5.7)
- Paclitaxel protein-bound particles for injectable suspension (albumin-bound) can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception. ( 5.8, 8.1, 8.3)

#### **ADVERSE REACTIONS**

- The most common adverse reactions (≥ 20%) in metastatic breast cancer are alopecia, neutropenia, sensory neuropathy, abnormal ECG, fatigue/asthenia, myalgia/arthritis, AST elevation, alkaline phosphatase elevation, anemia, nausea, infections, and diarrhea. ( 6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

----- **DRUG INTERACTIONS** -----

Use caution when concomitantly administering paclitaxel protein-bound particles for injectable suspension (albumin-bound) with inhibitors or inducers of either CYP2C8 or CYP3A4. ( 7)

----- **USE IN SPECIFIC POPULATIONS** -----

- Lactation: Advise not to breastfeed. ( 8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

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**FULL PRESCRIBING INFORMATION: CONTENTS\***

**WARNING: NEUTROPENIA**

**1 INDICATIONS AND USAGE**

- 1.1 Metastatic Breast Cancer

**2 DOSAGE AND ADMINISTRATION**

- 2.1 Important Administration Instructions
- 2.2 Recommended Dosage for Metastatic Breast Cancer
- 2.5 Dosage Modifications for Hepatic Impairment
- 2.6 Dosage Modifications for Adverse Reactions
- 2.7 Preparation for Intravenous Administration
- 2.8 Stability

**3 DOSAGE FORMS AND STRENGTHS**

**4 CONTRAINDICATIONS**

**5 WARNINGS AND PRECAUTIONS**

- 5.1 Severe Myelosuppression
- 5.2 Severe Neuropathy
- 5.3 Sepsis
- 5.4 Pneumonitis
- 5.5 Severe Hypersensitivity
- 5.6 Use in Patients with Hepatic Impairment
- 5.7 Albumin (Human)
- 5.8 Embryo-Fetal Toxicity

**6 ADVERSE REACTIONS**

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

**7 DRUG INTERACTIONS**

**8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

**10 OVERDOSAGE**

**11 DESCRIPTION**

**12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics

**13 NONCLINICAL TOXICOLOGY**

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

**14 CLINICAL STUDIES**

- 14.1 Metastatic Breast Cancer

**15 REFERENCES**

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**17 PATIENT COUNSELING INFORMATION**

\* Sections or subsections omitted from the full prescribing information are not listed.

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## FULL PRESCRIBING INFORMATION

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

#### WARNING: NEUTROPENIA

- Do not administer paclitaxel protein-bound particles for injectable suspension (albumin-bound) therapy to patients who have baseline neutrophil counts of less than 1,500 cells/mm<sup>3</sup> [see *Contraindications (4)*].
- Monitor for neutropenia, which may be severe and result in infection or sepsis, it is recommended that frequent [see *Warnings and Precautions (5.1, 5.3)*].
- Perform frequent complete blood cell counts on all patients receiving paclitaxel protein-bound particles for injectable suspension (albumin-bound) [see *Contraindications (4), Warnings and Precautions (5.1, 5.3)*].

## 1 INDICATIONS AND USAGE

### 1.1 Metastatic Breast Cancer

Paclitaxel protein-bound particles for injectable suspension (albumin-bound) is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Important Administration Instructions

**DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS. Paclitaxel protein-bound particles for injectable suspension (albumin-bound) has different dosage and administration instructions from other paclitaxel products.**

Closely monitor the infusion site for extravasation or drug infiltration during administration. Limiting the infusion of paclitaxel protein-bound particles for injectable suspension (albumin-bound) to 30 minutes may reduce the risk of infusion-related reactions [see *Adverse Reactions (6.2)*].

Consider premedication in patients who have had prior hypersensitivity reactions to paclitaxel protein-bound particles for injectable suspension (albumin-bound). Do not re-challenge patients who experience a severe hypersensitivity reaction to paclitaxel protein-bound particles for injectable suspension (albumin-bound) [see *Contraindications (4) and Warnings and Precautions (5.5)*].

### 2.2 Recommended Dosage for Metastatic Breast Cancer

After failure of combination chemotherapy for metastatic breast cancer or relapse within 6 months of adjuvant chemotherapy, the recommended regimen for paclitaxel protein-bound particles for injectable suspension (albumin-bound) is 260 mg/m<sup>2</sup> administered intravenously over 30 minutes every 3 weeks.

### 2.5 Dosage Modifications for Hepatic Impairment

For patients with moderate or severe hepatic impairment, reduce the starting dose of paclitaxel protein-bound particles for injectable suspension (albumin-bound) as shown in Table 1.

**Table 1: Recommendations for Starting Dose in Patients with Moderate and Severe Hepatic Impairment**

	AST Levels		Bilirubin Levels	Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) Dose <sup>a</sup>
				MBC
Moderate	< 10 x ULN	AND	> 1.5 to ≤ 3 x ULN	200 mg/m <sup>2</sup> <sup>b</sup>
Severe	< 10 x ULN	AND	> 3 to ≤ 5 x ULN	200 mg/m <sup>2</sup> <sup>b</sup>
	> 10 x ULN	OR	> 5 x ULN	not recommended

AST = Aspartate Aminotransferase; MBC = Metastatic Breast Cancer; ULN = Upper limit of normal.

<sup>a</sup>Dosage recommendations are for the first course of therapy. The need for further dose adjustments in subsequent courses should be based on individual tolerance.

<sup>b</sup>A dose increase to 260 mg/m<sup>2</sup> for patients with metastatic breast cancer in subsequent courses should be considered if the patient tolerates the reduced dose for two cycles.

## 2.6 Dosage Modifications for Adverse Reactions

### Metastatic Breast Cancer

Patients who experience severe neutropenia (neutrophils less than 500 cells/mm<sup>3</sup> for a week or longer) or severe sensory neuropathy during paclitaxel protein-bound particles for injectable suspension (albumin-bound) therapy should have dosage reduced to 220 mg/m<sup>2</sup> for subsequent courses of paclitaxel protein-bound particles for injectable suspension (albumin-bound). For recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m<sup>2</sup>. 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 protein-bound particles for injectable suspension (albumin-bound) [see *Contraindications (4), Warnings and Precautions (5.1, 5.2) and Adverse Reactions (6.1)*].

## 2.7 Preparation for Intravenous Administration

Paclitaxel protein-bound particles for injectable suspension (albumin-bound) is a cytotoxic drug. Follow applicable special handling and disposal procedures. <sup>1</sup>The use of gloves is recommended. If paclitaxel protein-bound particles for injectable suspension (albumin-bound) (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 protein-bound particles for injectable suspension (albumin-bound) contacts mucous membranes, the membranes should be flushed thoroughly with water.

Paclitaxel protein-bound particles for injectable suspension (albumin-bound) is supplied as a sterile lyophilized powder for reconstitution before use.

Read the entire preparation instructions prior to reconstitution.

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.

Each mL of the reconstituted formulation will contain 5 mg/mL paclitaxel.

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.

Calculate the exact total dosing volume of 5 mg/mL suspension required for the patient and slowly withdraw the dosing volume of the reconstituted suspension from the vial(s) into a syringe:  $\text{Dosing volume (mL)} = \text{Total dose (mg)} / 5 \text{ (mg/mL)}$ .

Inject the appropriate amount of reconstituted paclitaxel protein-bound particles for injectable suspension (albumin-bound) into an empty, sterile intravenous bag [plasticized polyvinyl chloride (PVC) containers, PVC or non-PVC type intravenous bag]. The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer paclitaxel protein-bound particles for injectable suspension (albumin-bound) infusions. The use of medical devices containing silicone oil as a lubricant (i.e., syringes and intravenous bags) to reconstitute and administer paclitaxel protein-bound particles for injectable suspension (albumin-bound) may result in the formation of proteinaceous strands.

Visually inspect the reconstituted paclitaxel protein-bound particles for injectable suspension (albumin-bound) suspension in the intravenous bag prior to administration. Discard the reconstituted suspension if proteinaceous strands, particulate matter, or discoloration are observed.

## 2.8 Stability

Unopened vials of paclitaxel protein-bound particles for injectable suspension (albumin-bound) are stable until the date indicated on the package when stored between 20°C to 25°C (68°F to 77°F) in the original package. Neither freezing nor refrigeration adversely affects the stability of the product.

### *Stability of Reconstituted Suspension in the Vial*

Reconstituted paclitaxel protein-bound particles for injectable suspension (albumin-bound) in the vial should be used immediately, but may be refrigerated at 2°C to 8°C (36°F to 46°F) for a maximum of 24 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion.

### *Stability of Reconstituted Suspension in the Infusion Bag*

The suspension for infusion when prepared as recommended in an infusion bag should be used immediately, but may be refrigerated at 2°C to 8°C (36°F to 46°F) and protected from bright light for a maximum of 24 hours.

The total combined refrigerated storage time of reconstituted paclitaxel protein-bound particles for injectable suspension (albumin-bound) in the vial and in the infusion bag is 24 hours. This may be followed by storage in the infusion bag at ambient temperature (approximately 25°C) and lighting conditions for a maximum of 4 hours.

Discard any unused portion.

## 3 DOSAGE FORMS AND STRENGTHS

For injectable suspension, for intravenous use: white to yellow, sterile lyophilized powder containing 100 mg of paclitaxel formulated as albumin-bound particles in single-dose vial for reconstitution.

## 4 CONTRAINDICATIONS

Paclitaxel protein-bound particles for injectable suspension (albumin-bound) is contraindicated in patients with:

- Baseline neutrophil counts of  $< 1,500$  cells/mm<sup>3</sup> [see *Warnings and Precautions (5.1)*]
- A history of severe hypersensitivity reactions to paclitaxel protein-bound particles for injectable suspension (albumin-bound) [see *Warnings and Precautions (5.5)*]

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Severe Myelosuppression

Severe myelosuppression (primarily neutropenia) is dose-dependent and a dose-limiting toxicity of paclitaxel protein-bound particles for injectable suspension (albumin-bound). In clinical studies, Grade 3-4 neutropenia occurred in 34% of patients with metastatic breast cancer (MBC).

Monitor for severe neutropenia and thrombocytopenia by performing complete blood cell counts frequently, including prior to dosing on Day 1 (for MBC). Do not administer paclitaxel protein-bound particles for injectable suspension (albumin-bound) to patients with baseline absolute neutrophil counts (ANC) of less than 1,500 cells/mm<sup>3</sup> [see *Contraindications (4)*].

In the case of severe neutropenia ( $< 500$  cells/mm<sup>3</sup> for seven days or more) during a course of paclitaxel protein-bound particles for injectable suspension (albumin-bound) therapy, reduce the dose of paclitaxel protein-bound particles for injectable suspension (albumin-bound) in subsequent courses in patients with MBC.

In patients with MBC, resume treatment with every-3-week cycles of paclitaxel protein-bound particles for injectable suspension (albumin-bound) after ANC recovers to a level  $> 1,500$  cells/mm<sup>3</sup> and platelets recover to a level  $> 100,000$  cells/mm<sup>3</sup> [see *Dosage and Administration (2.6)*].

### 5.2 Severe Neuropathy

Sensory neuropathy is dose- and schedule-dependent [see *Adverse Reactions (6.1)*]. If  $\geq$  Grade 3 sensory neuropathy develops, withhold paclitaxel protein-bound particles for injectable suspension (albumin-bound) treatment until resolution to Grade 1 or 2 for metastatic breast cancer followed by a dose reduction for all subsequent courses of paclitaxel protein-bound particles for injectable suspension (albumin-bound) [see *Dosage and Administration (2.6)*].

### 5.3 Sepsis

Sepsis occurred in 5% of patients with or without neutropenia who received paclitaxel protein-bound particles for injectable suspension (albumin-bound) in combination with gemcitabine. Biliary obstruction or presence of biliary stent were risk factors for severe or fatal sepsis.

If a patient becomes febrile (regardless of ANC) initiate treatment with broad spectrum antibiotics. For febrile neutropenia, interrupt paclitaxel protein-bound particles for injectable suspension (albumin-bound) and gemcitabine until fever resolves and ANC  $\geq 1,500$ , then resume treatment at reduced dose levels [see *Dosage and Administration (2.6)*].

### 5.4 Pneumonitis

Pneumonitis, including some cases that were fatal, occurred in 4% of patients receiving paclitaxel protein-bound particles for injectable suspension (albumin-bound) in combination with gemcitabine.

Monitor patients for signs and symptoms of pneumonitis and interrupt paclitaxel protein-bound particles for injectable suspension (albumin-bound) and gemcitabine during evaluation of suspected pneumonitis. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with paclitaxel protein-bound particles for injectable suspension (albumin-bound) and gemcitabine.

### 5.5 Severe Hypersensitivity

Severe and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, have been reported. Do not rechallenge patients who experience a severe hypersensitivity reaction to paclitaxel protein-bound particles for injectable suspension (albumin-bound) with this drug [see *Contraindications (4)*].

Cross-hypersensitivity between paclitaxel protein-bound particles for injectable suspension (albumin-bound) and other taxane products has been reported and may include severe reactions such as anaphylaxis. Closely monitor patients with a previous history of hypersensitivity to other taxanes during initiation of paclitaxel protein-bound particles for injectable suspension (albumin-bound) therapy.

### **5.6 Use in Patients with Hepatic Impairment**

The exposure and toxicity of paclitaxel can be increased in patients with hepatic impairment. Closely monitor patients with hepatic impairment for severe myelosuppression.

Paclitaxel protein-bound particles for injectable suspension (albumin-bound) is not recommended in patients who have total bilirubin >5 x ULN or AST >10 x ULN. Reduce the starting dose for patients with moderate or severe hepatic impairment [see *Dosage and Administration (2.5)*, *Use in Specific Populations (8.7)*, *Clinical Pharmacology (12.3)*].

### **5.7 Albumin (Human)**

Paclitaxel protein-bound particles for injectable suspension (albumin-bound) contains albumin (human), a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries a 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.

### **5.8 Embryo-Fetal Toxicity**

Based on mechanism of action and findings in animals, paclitaxel protein-bound particles for injectable suspension (albumin-bound) can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of paclitaxel formulated as albumin-bound particles to rats during pregnancy at doses lower than the maximum recommended human dose, based on body surface area, caused embryo-fetal toxicities, including intrauterine mortality, increased resorptions, reduced numbers of live fetuses, and malformations.

Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception and avoid becoming pregnant during treatment with paclitaxel protein-bound particles for injectable suspension (albumin-bound) and for at least six months after the last dose of paclitaxel protein-bound particles for injectable suspension (albumin-bound) [see *Use in Specific Populations (8.1, 8.3)*, *Clinical Pharmacology (12.1)*].

Based on findings from genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception and avoid fathering a child during treatment with paclitaxel protein-bound particles for injectable suspension (albumin-bound) and for at least three months after the last dose of paclitaxel protein-bound particles for injectable suspension (albumin-bound) [see *Use in Specific Populations (8.1, 8.3)*, *Nonclinical Toxicology (13.1)*].

## **6 ADVERSE REACTIONS**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse reactions ( $\geq 20\%$ ) with single-agent use of paclitaxel protein-bound particles for injectable suspension (albumin-bound) in metastatic breast cancer are alopecia, neutropenia, sensory neuropathy, abnormal ECG, fatigue/asthenia, myalgia/arthritis, AST elevation, alkaline phosphatase elevation, anemia, nausea, infections, and diarrhea [see *Adverse Reactions (6.1)*].

The most common adverse reactions resulting in permanent discontinuation of paclitaxel protein-bound particles for injectable suspension (albumin-bound) are neutropenia (3%), thrombocytopenia (3%), and peripheral neuropathy (1%). The most common adverse reactions resulting in dose reduction of paclitaxel protein-bound particles for injectable suspension (albumin-bound) are neutropenia (24%), thrombocytopenia (13%), and anemia (6%). The most common adverse reactions leading to withholding or delay in paclitaxel protein-bound particles for injectable suspension (albumin-bound) dosing are neutropenia (41%), thrombocytopenia (30%), and anemia (16%).

The most common serious adverse reactions of paclitaxel protein-bound particles for injectable suspension (albumin-bound) (with a  $\geq 1\%$  higher incidence) are pyrexia (6%), dehydration (5%), pneumonia (4%), and vomiting (4%). The most common adverse reactions resulting in permanent discontinuation of paclitaxel protein-bound particles for injectable suspension (albumin-bound) are peripheral neuropathy (8%), fatigue (4%), and thrombocytopenia (2%). The most common adverse reactions resulting in dose reduction of paclitaxel protein-bound particles for injectable suspension (albumin-bound) are neutropenia (10%) and peripheral neuropathy (6%). The most common adverse reactions leading to withholding or delay in paclitaxel protein-bound particles for injectable suspension (albumin-bound) dosing are neutropenia (16%), thrombocytopenia (12%), fatigue (8%), peripheral neuropathy (15%), anemia (5%), and diarrhea (5%).

## 6.1 Clinical Trials Experience

### Metastatic Breast Cancer

Table 6 shows the frequency of important adverse reactions in the randomized comparative trial for the patients who received either single-agent paclitaxel protein-bound particles for injectable suspension (albumin-bound) or paclitaxel injection for the treatment of metastatic breast cancer.

**Table 6: Adverse Reactions in the Randomized Metastatic Breast Cancer Study on an Every-3-Weeks Schedule**

	Percent of Patients	
	Paclitaxel Protein-bound Particles for Injectable Suspension (albumin-bound) 260 mg/m <sup>2</sup> over 30 min (n=229)	Paclitaxel Injection 175 mg/m <sup>2</sup> over 3 h <sup>a</sup> (n=225)
<b>Bone Marrow</b>		
Neutropenia		
< 2 x 10 <sup>9</sup> /L	80	82
< 0.5 x 10 <sup>9</sup> /L	9	22
Thrombocytopenia		
< 100 x 10 <sup>9</sup> /L	2	3
< 50 x 10 <sup>9</sup> /L	<1	<1
Anemia		
< 11 g/dL	33	25
< 8 g/dL	1	<1
Infections	24	20
Febrile Neutropenia	2	1
Neutropenic Sepsis	<1	<1
Bleeding	2	2
<b>Hypersensitivity Reaction<sup>b</sup></b>		
All	4	12
Severe <sup>c</sup>	0	2
<b>Cardiovascular</b>		
Vital Sign Changes During Administration		
Bradycardia	<1	<1
Hypotension	5	5
Severe Cardiovascular		



Severe Cardiovascular Events <sup>c</sup>	3	4
<b>Abnormal ECG</b>		
All Patients	60	52
Patients with Normal Baseline	35	30
<b>Respiratory</b>		
Cough	7	6
Dyspnea	12	9
<b>Sensory Neuropathy</b>		
Any Symptoms	71	56
Severe Symptoms <sup>c</sup>	10	2
<b>Myalgia / Arthralgia</b>		
Any Symptoms	44	49
Severe Symptoms <sup>c</sup>	8	4
<b>Asthenia</b>		
Any Symptoms	47	39
Severe Symptoms <sup>c</sup>	8	3
<b>Fluid Retention/Edema</b>		
Any Symptoms	10	8
Severe Symptoms <sup>c</sup>	0	<1
<b>Gastrointestinal</b>		
Nausea		
Any Symptoms	30	22
Severe Symptoms <sup>c</sup>	3	<1
Vomiting		
Any Symptoms	18	10
Severe Symptoms <sup>c</sup>	4	1
Diarrhea		
Any Symptoms	27	15
Severe Symptoms <sup>c</sup>	<1	1
Mucositis		
Any Symptoms	7	6
Severe Symptoms <sup>c</sup>	<1	0
<b>Alopecia</b>	90	94
<b>Hepatic</b> (Patients with Normal Baseline)		
Bilirubin Elevations	7	7
Alkaline Phosphatase Elevations	36	31
AST (SGOT) Elevations	39	32
<b>Injection Site Reaction</b>	<1	1

<sup>a</sup>Paclitaxel injection patients received premedication.

<sup>b</sup>Includes treatment-related events related to hypersensitivity (e.g., flushing, dyspnea, chest pain, hypotension) that began on a day of dosing.

<sup>c</sup>Severe events are defined as at least Grade 3 toxicity.

### Other Adverse Reactions

#### Hematologic Disorders

Neutropenia was dose dependent and reversible. Among patients with metastatic breast cancer in the randomized trial, neutrophil counts declined below 500 cells/mm<sup>3</sup> (Grade 4) in 9% of the patients treated with a dose of 260 mg/m<sup>2</sup> compared to 22% in patients receiving paclitaxel injection at a dose of 175 mg/m<sup>2</sup>. Pancytopenia has been observed in clinical trials.

#### Infections

Infectious episodes were reported in 24% of the patients treated with paclitaxel protein-bound particles for injectable suspension (albumin-bound). Oral candidiasis, respiratory tract infections and pneumonia were the most frequently reported infectious

complications.

#### *Hypersensitivity Reactions (HSRs)*

Grade 1 or 2 HSRs occurred on the day of paclitaxel protein-bound particles for injectable suspension (albumin-bound) administration and consisted of dyspnea (1%) and flushing, hypotension, chest pain, and arrhythmia (all <1%). The use of paclitaxel protein-bound particles for injectable suspension (albumin-bound) in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied.

#### *Cardiovascular*

Hypotension, during the 30-minute infusion, occurred in 5% of patients. Bradycardia, during the 30-minute infusion, occurred in <1% of patients. These vital sign changes most often caused no symptoms and required neither specific therapy nor treatment discontinuation.

Severe cardiovascular events possibly related to single-agent paclitaxel protein-bound particles for injectable suspension (albumin-bound) occurred in approximately 3% of patients. These events included cardiac ischemia/infarction, chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension. Cases of cerebrovascular attacks (strokes) and transient ischemic attacks have been reported.

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. Among patients with a normal ECG prior to study entry, 35% of all patients 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%), cough (7%), and pneumothorax (<1%) were reported after treatment with paclitaxel protein-bound particles for injectable suspension (albumin-bound).

#### *Neurologic*

The frequency and severity of sensory neuropathy increased with cumulative dose. Sensory neuropathy was the cause of paclitaxel protein-bound particles for injectable suspension (albumin-bound) discontinuation in 7/229 (3%) patients. Twenty-four patients (10%) treated with paclitaxel protein-bound particles for injectable suspension (albumin-bound) developed Grade 3 peripheral neuropathy; of these patients, 14 had documented improvement after a median of 22 days; 10 patients resumed treatment at a reduced dose of paclitaxel protein-bound particles for injectable suspension (albumin-bound) and 2 discontinued due to peripheral neuropathy. Of the 10 patients without documented improvement, 4 discontinued the study due to peripheral neuropathy.

No Grade 4 sensory neuropathies were reported. Only one incident of motor neuropathy (Grade 2) was observed in either arm of the controlled trial.

#### *Vision Disorders*

Ocular/visual disturbances occurred in 13% of all patients (n=366) treated with paclitaxel protein-bound particles for injectable suspension (albumin-bound) and 1% were severe. The severe cases (keratitis and blurred vision) were reported in patients who received higher doses than those recommended (300 or 375 mg/m<sup>2</sup>). These effects generally have been reversible.

#### *Arthralgia/Myalgia*

The symptoms were usually transient, occurred two or three days after paclitaxel protein-bound particles for injectable suspension (albumin-bound) administration, and resolved within a few days.

#### *Hepatic*

Grade 3 or 4 elevations in GGT were reported for 14% of patients treated with paclitaxel protein-bound particles for injectable suspension (albumin-bound) and 10% of patients treated with paclitaxel injection in the randomized trial.

#### *Renal*

Overall 11% of patients experienced creatinine elevation, 1% severe. No discontinuations, dose reductions, or dose delays were caused by renal toxicities.

#### *Other Clinical Events*

Nail changes (changes in pigmentation or discoloration of nail bed) have been reported. Edema occurred in 10% of patients; no patients had severe edema. Dehydration and pyrexia were also reported.

## **6.2 Postmarketing Experience**

The following adverse reactions have been identified during postapproval use of paclitaxel protein-bound particles for injectable suspension (albumin-bound) or with paclitaxel injection and may be expected to occur with paclitaxel protein-bound particles for injectable suspension (albumin-bound). 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.

### *Hypersensitivity Reactions*

Severe and sometimes fatal hypersensitivity reactions. Cross-hypersensitivity between paclitaxel protein-bound particles for injectable suspension (albumin-bound) and other taxanes has been reported.

### *Cardiovascular*

Congestive heart failure, left ventricular dysfunction, and atrioventricular block. Most patients were previously exposed to cardiotoxic drugs, such as anthracyclines, or had underlying cardiac history.

### *Respiratory*

Pneumonitis, interstitial pneumonia, and pulmonary embolism

Radiation pneumonitis in patients receiving concurrent radiotherapy.

Lung fibrosis has been reported with paclitaxel injection.

### *Neurologic*

Cranial nerve palsies and vocal cord paresis, as well as autonomic neuropathy resulting in paralytic ileus.

### *Vision Disorders*

Reduced visual acuity due to cystoid macular edema (CME). After cessation of treatment, CME may improve, and visual acuity may return to baseline. Abnormal visual evoked potentials in patients treated with paclitaxel injection suggest persistent optic nerve damage.

### *Hepatic*

Hepatic necrosis and hepatic encephalopathy leading to death in patients treated with paclitaxel injection.

### *Gastrointestinal (GI)*

Intestinal obstruction, intestinal perforation, pancreatitis, and ischemic colitis. In patients treated with paclitaxel injection, neutropenic enterocolitis (typhlitis) despite the coadministration of G-CSF, alone and in combination with other chemotherapeutic agents.

### *Injection Site Reaction*

Extravasation. Closely monitor the paclitaxel protein-bound particles for injectable suspension (albumin-bound) infusion site for possible infiltration during drug administration [see *Dosage and Administration 2.1*] .

Severe events such as phlebitis, cellulitis, induration, necrosis, and fibrosis have been reported with paclitaxel injection. In some cases, the onset of the injection site reaction occurred during a prolonged infusion or was delayed up to ten days. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel injection at a different site has been reported.

### *Metabolic and Nutritional Disorders*

Tumor lysis syndrome

### *Other Clinical Events*

Skin reactions including generalized or maculopapular rash, erythema, and pruritus  
Photosensitivity reactions, radiation recall phenomenon, scleroderma, and in some patients previously exposed to capecitabine, reports of palmar-plantar erythrodysesthesia. Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

Conjunctivitis, cellulitis, and increased lacrimation have been reported with paclitaxel injection.

#### *Accidental Exposure*

Upon inhalation of paclitaxel, dyspnea, chest pain, burning eyes, sore throat, and nausea have been reported.

Following topical exposure, tingling, burning, and redness have been reported.

## **7 DRUG INTERACTIONS**

The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. Caution should be exercised when administering paclitaxel protein-bound particles for injectable suspension (albumin-bound) concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

Based on its mechanism of action and findings in animals, paclitaxel protein-bound particles for injectable suspension (albumin-bound) can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology (12.1)*]. There are no available human data on paclitaxel protein-bound particles for injectable suspension (albumin-bound) use in pregnant women to inform the drug-associated risk.

In animal reproduction studies, administration of paclitaxel formulated as albumin-bound particles to pregnant rats during the period of organogenesis resulted in embryo-fetal toxicity at doses approximately 2% of the daily maximum recommended human dose on a mg/m<sup>2</sup> basis (see Data). Advise females of reproductive potential of the potential risk to a fetus.

The background rate of major birth defects and miscarriage is unknown for the indicated population. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

#### Data

##### *Animal Data*

In embryo-fetal development studies, intravenous administration of paclitaxel formulated as albumin-bound particles to rats during pregnancy, on gestation days 7 to 17 at doses of 6 mg/m<sup>2</sup> (approximately 2% of the daily maximum recommended human dose on a mg/m<sup>2</sup> basis) caused embryo-fetal toxicities, 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.

### **8.2 Lactation**

#### Risk Summary

There are no data on the presence of paclitaxel in human milk, or its effect on the breastfed child or on milk production. In animal studies, paclitaxel and/or its metabolites were excreted into the milk of lactating rats (see Data). Because of the potential for serious adverse reactions in a breastfed child from paclitaxel protein-bound particles for injectable suspension (albumin-bound), advise lactating women not to breastfeed during

treatment with paclitaxel protein-bound particles for injectable suspension (albumin-bound) and for two weeks after the last dose.

## Data

### *Animal Data*

Following intravenous administration of radiolabeled paclitaxel to rats on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations.

## **8.3 Females and Males of Reproductive Potential**

Based on animal studies and mechanism of action, paclitaxel protein-bound particles for injectable suspension (albumin-bound) can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*].

### Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to starting treatment with paclitaxel protein-bound particles for injectable suspension (albumin-bound).

### Contraception

#### *Females*

Advise females of reproductive potential to use effective contraception and avoid becoming pregnant during treatment with paclitaxel protein-bound particles for injectable suspension (albumin-bound) and for at least six months after the last dose of paclitaxel protein-bound particles for injectable suspension (albumin-bound).

#### *Males*

Based on findings in genetic toxicity and animal reproduction studies, advise males with female partners of reproductive potential to use effective contraception and avoid fathering a child during treatment with paclitaxel protein-bound particles for injectable suspension (albumin-bound) and for at least three months after the last dose of paclitaxel protein-bound particles for injectable suspension (albumin-bound) [see *Use in Specific Populations (8.1)* and *Nonclinical Toxicology (13.1)*].

### Infertility

#### *Females and Males*

Based on findings in animals, paclitaxel protein-bound particles for injectable suspension (albumin-bound) may impair fertility in females and males of reproductive potential [see *Nonclinical Toxicology (13.1)*].

## **8.4 Pediatric Use**

Safety and effectiveness in pediatric patients have not been established. Pharmacokinetics, safety, and antitumor activity of paclitaxel protein-bound particles for injectable suspension (albumin-bound) were assessed in an open-label, dose escalation, dose expansion study ( NCT01962103) in 96 pediatric patients aged 1.4 to < 17 years with recurrent or refractory pediatric solid tumors. The maximum tolerated dose (MTD) normalized for body surface area (BSA) was lower in pediatric patients compared to adults. No new safety signals were observed in pediatric patients across these studies.

Paclitaxel protein-bound exposures normalized by dose were higher in 96 pediatric patients (aged 1.4 to < 17 years) as compared to those in adults.

## **8.5 Geriatric Use**

Of the 229 patients in the randomized study who received paclitaxel protein-bound particles for injectable suspension (albumin-bound) for the treatment of metastatic breast cancer, 13% were at least 65 years of age and < 2% were 75 years or older. This study of paclitaxel protein-bound particles for injectable suspension (albumin-bound) did not include a sufficient number of patients with metastatic breast cancer who were 65 years and older to determine whether they respond differently from younger patients.

A subsequent pooled analysis was conducted in 981 patients receiving paclitaxel protein-

bound particles for injectable suspension (albumin-bound) monotherapy for metastatic breast cancer, of which 15% were 65 years of age or older and 2% were 75 years of age or older. A higher incidence of epistaxis, diarrhea, dehydration, fatigue, and peripheral edema was found in patients 65 years of age or older.

## 8.6 Renal Impairment

No adjustment of the starting paclitaxel protein-bound particles for injectable suspension (albumin-bound) dose is required for patients with mild to moderate renal impairment (estimated creatinine clearance 30 to <90 mL/min) [see *Clinical Pharmacology (12.3)*]. 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).

## 8.7 Hepatic Impairment

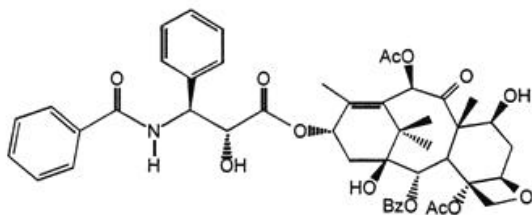
No adjustment of the starting paclitaxel protein-bound particles for injectable suspension (albumin-bound) dose is required for patients with mild hepatic impairment (total bilirubin > ULN and  $\leq 1.5 \times$  ULN and aspartate aminotransferase [AST]  $\leq 10 \times$  ULN). Reduce paclitaxel protein-bound particles for injectable suspension (albumin-bound) starting dose in patients with moderate to severe hepatic impairment [see *Dosage and Administration (2.5)* and *Clinical Pharmacology (12.3)*]. Paclitaxel protein-bound particles for injectable suspension (albumin-bound) is not recommended for use in patients with total bilirubin > 5 x ULN or AST > 10 x ULN [see *Dosage and Administration (2.5)*, *Warnings and Precautions (5.6)*, and *Clinical Pharmacology (12.3)*].

## 10 OVERDOSAGE

There is no known antidote for paclitaxel protein-bound particles for injectable suspension (albumin-bound) overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, sensory neurotoxicity, and mucositis.

## 11 DESCRIPTION

Paclitaxel protein-bound particles for injectable suspension (albumin-bound) is paclitaxel formulated as albumin-bound nanoparticles with a mean particle size of approximately 130 nanometers. Paclitaxel exists in the particles in a non-crystalline, amorphous state. Paclitaxel is a microtubule inhibitor. The chemical name for paclitaxel is 5 $\beta$ ,20-Epoxy-1,2 $\alpha$ ,4,7 $\beta$ ,10 $\beta$ ,13 $\alpha$ -hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine. The empirical formula is C<sub>47</sub>H<sub>51</sub>NO<sub>14</sub> and the molecular weight is 853.92. Paclitaxel has the following structural formula:



Paclitaxel is a white to off-white crystalline powder. It is highly lipophilic, insoluble in water, and melts at approximately 213°C to 216°C.

Paclitaxel protein-bound particles for injectable suspension (albumin-bound) is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Each single-dose vial contains 100 mg of paclitaxel (bound to human albumin) and approximately 900 mg of human albumin (containing sodium caprylate and sodium acetyltryptophanate). Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel formulated as albumin-bound particles. Paclitaxel protein-bound particles for injectable suspension (albumin-bound) is free of solvents.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Paclitaxel protein-bound particles for injectable suspension (albumin-bound) is a microtubule inhibitor 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.

### 12.3 Pharmacokinetics

The pharmacokinetics of total paclitaxel following 30- and 180-minute infusions of paclitaxel protein-bound particles for injectable suspension (albumin-bound) at dose levels of 80 to 375 mg/m<sup>2</sup> (0.31 to 1.15 times the maximum approved recommended dosage) were determined in clinical studies. Dose levels of mg/m<sup>2</sup> refer to mg of paclitaxel in paclitaxel protein-bound particles for injectable suspension (albumin-bound). Following intravenous administration of paclitaxel protein-bound particles for injectable suspension (albumin-bound) to patients with solid tumors, 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.

Following paclitaxel protein-bound particles for injectable suspension (albumin-bound) infusion, paclitaxel exhibited linear drug exposure (AUC) across clinical doses ranging from 80 to 300 mg/m<sup>2</sup> (0.31 to 1.15 times the maximum approved recommended dosage). The pharmacokinetics of paclitaxel in paclitaxel protein-bound particles for injectable suspension (albumin-bound) were independent of the duration of intravenous administration.

The pharmacokinetic data of 260 mg/m<sup>2</sup> paclitaxel protein-bound particles for injectable suspension (albumin-bound) administered over a 30-minute infusion was compared to the pharmacokinetics of 175 mg/m<sup>2</sup> paclitaxel injection over a 3-hour infusion. Clearance was larger (43%) and the volume of distribution was higher (53%) for paclitaxel protein-bound particles for injectable suspension (albumin-bound) than for paclitaxel injection. There were no differences in terminal half-lives.

#### Distribution

Following paclitaxel protein-bound particles for injectable suspension (albumin-bound) administration to patients with solid tumors, paclitaxel is evenly distributed into blood cells and plasma and is highly bound to plasma proteins (94%). The total volume of distribution is approximately 1741 L; the large volume of distribution indicates extensive extravascular distribution and/or tissue binding of paclitaxel.

In a within-patient comparison study, the fraction of unbound paclitaxel in plasma was significantly higher with paclitaxel protein-bound particles for injectable suspension (albumin-bound) (6.2%) than with solvent-based paclitaxel (2.3%). This contributes to significantly higher exposure to unbound paclitaxel with paclitaxel protein-bound particles for injectable suspension (albumin-bound) compared with solvent-based paclitaxel, when the total exposure is comparable. *In vitro* studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 µg/mL, indicated that the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

#### Elimination

At the clinical dose range of 80 to 300 mg/m<sup>2</sup> (0.31 to 1.15 times the maximum approved recommended dosage), the mean total clearance of paclitaxel ranges from 13 to 30 L/h/m<sup>2</sup> and the mean terminal half-life ranges from 13 to 27 hours.

#### Metabolism

*In vitro* studies with human liver microsomes and tissue slices showed that paclitaxel in paclitaxel protein-bound particles for injectable suspension (albumin-bound) 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, 17 $\alpha$ -ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6 $\alpha$ -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 (7)*].

#### *Excretion*

After a 30-minute infusion of 260 mg/m<sup>2</sup> doses of paclitaxel protein-bound particles for injectable suspension (albumin-bound), 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 6 $\alpha$ -hydroxypaclitaxel and 3'-*p*-hydroxypaclitaxel. Fecal excretion was approximately 20% of the total dose administered.

#### Specific Populations

No clinically meaningful differences in the pharmacokinetics of paclitaxel in paclitaxel protein-bound particles for injectable suspension (albumin-bound) were observed based on body weight (40 to 143 kg), body surface area (1.3 to 2.4 m<sup>2</sup>), sex, race (Asian vs. White), age (24 to 85 years), type of solid tumors, mild to moderate renal impairment (creatinine clearance 30 to <90 mL/min), and mild hepatic impairment (total bilirubin >1 to  $\leq 1.5 \times$  ULN and AST  $\leq 10 \times$  ULN).

Patients with moderate (total bilirubin >1.5 to 3  $\times$  ULN and AST  $\leq 10 \times$  ULN) or severe (total bilirubin >3 to 5  $\times$  ULN) hepatic impairment had 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 (total bilirubin  $\leq$  ULN and AST  $\leq$  ULN) [see *Dosage and Administration (2.5)* and *Use in Specific Populations (8.7)*].

The effect of severe renal impairment or end stage renal disease (creatinine clearance < 30 mL/min) on the pharmacokinetics of paclitaxel in paclitaxel protein-bound particles for injectable suspension (albumin-bound) is unknown.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

The carcinogenic potential of paclitaxel protein-bound particles for injectable suspension (albumin-bound) has not been studied.

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

Administration of paclitaxel formulated as albumin-bound particles to male rats at 42 mg/m<sup>2</sup> on a weekly basis (approximately 16% of the daily maximum recommended human exposure on a body surface area 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. A dose of 42 mg/m<sup>2</sup> also reduced male reproductive organ weights, mating performance, and sperm production. Testicular atrophy/degeneration was observed in single-dose toxicology studies in animals administered paclitaxel formulated as albumin-bound particles at doses lower than the recommended human dose; doses were 54 mg/m<sup>2</sup> in rodents and 175 mg/m<sup>2</sup> in dogs. Similar testicular degeneration was seen in monkeys administered three weekly doses of 108 mg/m<sup>2</sup> paclitaxel formulated as albumin bound particles.

Administration of paclitaxel prior to and during mating produced impairment of fertility in male and female rats. Paclitaxel caused reduced fertility and reproductive indices, and increased embryo-fetal toxicity.

## **14 CLINICAL STUDIES**



## 14.1 Metastatic Breast Cancer

Data from 106 patients accrued in two single arm open label studies and from 460 patients enrolled in a randomized comparative study were available to support the use of paclitaxel protein-bound particles for injectable suspension (albumin-bound) in metastatic breast cancer.

### Single Arm Open Label Studies

In one study, paclitaxel protein-bound particles for injectable suspension (albumin-bound) was administered as a 30-minute infusion at a dose of 175 mg/m<sup>2</sup> to 43 patients with metastatic breast cancer. The second trial utilized a dose of 300 mg/m<sup>2</sup> as a 30-minute infusion in 63 patients with metastatic breast cancer. Cycles were administered at 3-week intervals. Objective responses were observed in both studies.

### Randomized Comparative Study

This multicenter trial was conducted in 460 patients with metastatic breast cancer. Patients were randomized to receive paclitaxel protein-bound particles for injectable suspension (albumin-bound) at a dose of 260 mg/m<sup>2</sup> given as a 30-minute infusion, or paclitaxel injection at 175 mg/m<sup>2</sup> 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.

In this trial, patients in the paclitaxel protein-bound particles for injectable suspension (albumin-bound) treatment arm had a statistically significantly higher reconciled target lesion response rate (the trial primary endpoint) of 21.5% (95% CI: 16.2% to 26.7%), compared to 11.1% (95% CI: 6.9% to 15.1%) for patients in the paclitaxel injection treatment arm. See Table 11. There was no statistically significant difference in overall survival between the two study arms.

**Table 11: Efficacy Results from Randomized Metastatic Breast Cancer Trial**

		<b>Paclitaxel Protein-bound Particles for Injectable Suspension (albumin- bound) 260 mg/m<sup>2</sup></b>	<b>Paclitaxel Injection 175 mg/m<sup>2</sup></b>
<b>Reconciled Target Lesion Response Rate (primary endpoint) <sup>a</sup></b>			
All randomized patients	Response Rate [95% CI]	50/233 (21.5%) [16.19% to 26.73%]	25/227 (11.1%) [6.94% to 15.09%]
	p-value <sup>b</sup>	0.003	
Patients who had failed combination chemotherapy or relapsed within 6 months of adjuvant chemotherapy <sup>c</sup>	Response Rate [95% CI]	20/129 (15.5%) [9.26% to 21.75%]	12/143 (8.4%) [3.85% to 12.94%]

<sup>a</sup>Reconciled Target Lesion Response Rate (TLRR) was the prospectively defined protocol specific endpoint, based on independent radiologic assessment of tumor responses reconciled with investigator responses (which also included clinical information) for the first 6 cycles of therapy. The reconciled TLRR was lower than the investigator Reported Response Rates, which are based on all cycles of therapy.

<sup>b</sup>From Cochran-Mantel-Haenszel test stratified by 1<sup>st</sup>line vs. > 1<sup>st</sup>line therapy.

<sup>c</sup>Prior therapy included an anthracycline unless clinically contraindicated.

## 15 REFERENCES

1. OSHA Hazardous Drugs. OSHA  
<http://www.osha.gov/SLTC/hazardousdrugs/index.html>

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Paclitaxel protein-bound particles for injectable suspension (albumin-bound) is a white to yellow, sterile lyophilized powder supplied as:

NDC: 0781-3531-91 100 mg of paclitaxel in a single-dose vial, individually packaged in a carton.

Store the vials in original cartons at 20°C to 25°C (68°F to 77°F). Retain in the original package to protect from bright light.

Discard unused portion.

Paclitaxel protein-bound particles for injectable suspension (albumin-bound) is a cytotoxic drug. Follow applicable special handling and disposal procedures. <sup>1</sup>

## **17 PATIENT COUNSELING INFORMATION**

*Advise the patient to read the approved patient labeling (Patient Information).*

### Severe Myelosuppression

- Patients must be informed of the risk of low blood cell counts and severe and life-threatening infections and instructed to contact their healthcare provider immediately for fever or evidence of infection [see *Warnings and Precautions (5.1), (5.3)*].

### Severe Neuropathy

- Patients must be informed that sensory neuropathy occurs frequently with paclitaxel protein-bound particles for injectable suspension (albumin-bound) and patients should advise their healthcare providers of numbness, tingling, pain, or weakness involving the extremities [see *Warnings and Precautions (5.2)*].

### Pneumonitis

- Instruct patients to contact their healthcare provider immediately for sudden onset of dry persistent cough, or shortness of breath [see *Warnings and Precautions (5.4)*].

### Severe Hypersensitivity

- Instruct patients to contact their healthcare provider for signs of an allergic reaction, which could be severe and sometimes fatal [see *Warnings and Precautions (5.5)*].

### Common Adverse Reactions

- Explain to patients that alopecia, fatigue/asthenia, and myalgia/arthralgia occur frequently with paclitaxel protein-bound particles for injectable suspension (albumin-bound).
- Instruct patients to contact their healthcare providers for persistent vomiting, diarrhea, or signs of dehydration [see *Adverse Reactions (6)*].

### Embryo-Fetal Toxicity

- Paclitaxel protein-bound particles for injectable suspension (albumin-bound) injection can cause fetal harm. Advise patients to avoid becoming pregnant while receiving this drug. Females of reproductive potential should use effective contraception during treatment with paclitaxel protein-bound particles for injectable suspension (albumin-bound) and for at least six months after the last dose of paclitaxel protein-bound particles for injectable suspension (albumin-bound) [see *Warnings and Precautions (5.8) and Use in Specific Populations (8.1, 8.3)*].
- Advise male patients with female partners of reproductive potential to use effective contraception and avoid fathering a child during treatment with paclitaxel protein-bound particles for injectable suspension (albumin-bound) and for at least three months after the last dose of paclitaxel protein-bound particles for injectable suspension (albumin-bound) [see *Use in Specific Populations (8.3)*].

### Lactation

- Advise patients not to breastfeed while taking paclitaxel protein-bound particles for injectable suspension (albumin-bound) and for two weeks after receiving the last dose [see *Use in Specific Populations (8.2)*].

### Infertility

- Advise males and females of reproductive potential that paclitaxel protein-bound particles for injectable suspension (albumin-bound) may impair fertility [see *Use in*

*Specific Populations (8.3)].*

Manufactured by Jiangsu Hengrui Pharmaceuticals Co., Ltd.,

Lianyungang, Jiangsu 222047, China for

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**Patient Information**

**Paclitaxel (pak-li-TAX-el) Protein-Bound Particles for Injectable Suspension (Albumin-Bound)**

**What is paclitaxel protein-bound particles for injectable suspension (albumin-bound)?**

Paclitaxel protein-bound particles for injectable suspension (albumin-bound) is a prescription medicine used to treat:

- advanced breast cancer in people who have already received certain other medicines for their cancer.

It is not known if paclitaxel protein-bound particles for injectable suspension (albumin-bound) is safe or effective in children.

**Do not receive paclitaxel protein-bound particles for injectable suspension (albumin-bound) if:**

- your white blood cell count is below 1,500 cells/ mm<sup>3</sup>.
- you have had a severe allergic reaction to paclitaxel protein-bound particles for injectable suspension (albumin-bound).

**Before you receive paclitaxel protein-bound particles for injectable suspension (albumin-bound), tell your healthcare provider about all of your medical conditions, including if you:**

- have liver or kidney problems.
- had a prior allergic reaction to a taxane.
- are pregnant or plan to become pregnant. Paclitaxel protein-bound particles for injectable suspension (albumin-bound) can harm your unborn baby.

**Females who are able to become pregnant:**

- Your healthcare provider will check to see if you are pregnant before you start treatment with paclitaxel protein-bound particles for injectable suspension (albumin-bound).
- You should not become pregnant during your treatment and for at least six months after the last dose of paclitaxel protein-bound particles for injectable suspension (albumin-bound).
- You should use effective birth control (contraception) during your treatment and for at least six months after the last dose of paclitaxel protein-bound particles for injectable suspension (albumin-bound). Talk to your healthcare provider about birth control methods you can use during this time.

**Males with a female sexual partner who can become pregnant:**

- Paclitaxel protein-bound particles for injectable suspension (albumin-bound) can harm the unborn baby of your partner.
- You should not father a child during your treatment and for at least three months after the last dose of paclitaxel protein-bound particles for injectable suspension (albumin-bound).
- You should use effective birth control (contraception) during your treatment and for at least three months after the last dose of paclitaxel protein-bound particles for injectable suspension (albumin-bound).
- are breastfeeding or plan to breastfeed. Do not breastfeed during your treatment and for two weeks after the last dose of paclitaxel protein-bound particles for injectable suspension (albumin-bound).

**Tell your healthcare provider about all the medicines you take,** including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list to show your healthcare provider and pharmacist when you get a new medicine.

**How will I receive paclitaxel protein-bound particles for injectable suspension (albumin-bound)?**

- Your healthcare provider will prescribe paclitaxel protein-bound particles for injectable suspension (albumin-bound) in an amount that is right for you.
- Your healthcare provider may give you certain medicines to help prevent allergic reactions if you have had an allergic reaction to paclitaxel protein-bound particles for injectable suspension (albumin-bound) in the past.
- Paclitaxel protein-bound particles for injectable suspension (albumin-bound) will be given to you by intravenous (IV) infusion into your vein.
- Your healthcare provider should do blood tests regularly during treatment with paclitaxel protein-bound particles for injectable suspension (albumin-bound).
- Your healthcare provider may stop your treatment, delay your treatment, or change your dose of paclitaxel protein-bound particles for injectable suspension (albumin-bound) if you have certain side effects.

**What are the possible side effects of paclitaxel protein-bound particles for injectable suspension (albumin-bound)?**

**Paclitaxel protein-bound particles for injectable suspension (albumin-bound) may cause serious side effects, including:**

- **severe decreased blood cell counts.** Paclitaxel protein-bound particles for injectable suspension (albumin-bound) can cause a severe decrease in neutrophils, a type of white blood cell which helps fight infections, and blood cells called platelets which help to clot blood. Your healthcare provider will check your blood cell count during your treatment with paclitaxel protein-bound particles for injectable suspension (albumin-bound).
- **severe nerve problems (neuropathy).** Tell your healthcare provider if you have numbness, tingling, pain, or weakness in your hands or feet.
- **severe infection (sepsis).** If you receive paclitaxel protein-bound particles for injectable suspension (albumin-bound) in combination with gemcitabine, infections can be severe and lead to death. Tell your healthcare provider right away if you have a fever (temperature greater than 100.4° F) or develop signs of infection.
- **lung or breathing problems.** If you receive paclitaxel protein-bound particles for injectable suspension (albumin-bound) in combination with gemcitabine, lung or breathing problems may be severe and can lead to death. Tell your healthcare provider right away if you suddenly get a dry cough that will not go away or shortness of breath.
- **severe allergic reactions.** Severe allergic reactions are medical emergencies that can happen in people who receive paclitaxel protein-bound particles for injectable suspension (albumin-bound) and can lead to death. You may have an increased risk of having an allergic reaction to paclitaxel protein-bound particles for injectable suspension (albumin-bound) if you are allergic to other taxane medicines. Your healthcare provider will monitor you closely for allergic reactions during your infusion of paclitaxel protein-bound particles for injectable suspension (albumin-bound). Tell your healthcare provider right away if you get any of these signs of a serious allergic reaction: trouble breathing, sudden swelling of your face, lips, tongue, throat, or trouble swallowing, hives (raised bumps), rash, or redness all over your body.

**The most common side effects of paclitaxel protein-bound particles for injectable suspension (albumin-bound) in people with breast cancer include:**

- |                                                              |                                                                                                                                                                    |
|--------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| • hair loss                                                  | • decreased white blood cell count                                                                                                                                 |
| • numbness, tingling, pain, or weakness in the hands or feet | • abnormal heartbeat                                                                                                                                               |
| • tiredness                                                  | • joint and muscle pain                                                                                                                                            |
| • changes in your liver function tests                       | • low red blood cell count (anemia). Red blood cells carry oxygen to your body tissues. Tell your healthcare provider if you feel weak, tired, or short of breath. |
| • nausea                                                     |                                                                                                                                                                    |
| • diarrhea                                                   |                                                                                                                                                                    |
| • infections                                                 |                                                                                                                                                                    |

Tell your healthcare provider if you have vomiting, diarrhea, or signs of dehydration that does not go away.

Paclitaxel protein-bound particles for injectable suspension (albumin-bound) may cause fertility problems in males and females, which may affect your ability to have a child. Talk to your healthcare provider if this is a concern for you. These are not all of the possible side effects of paclitaxel protein-bound particles for injectable suspension (albumin-bound).

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**General information about the safe and effective use of paclitaxel protein-bound particles for injectable suspension (albumin-bound).**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your healthcare provider or pharmacist for information about paclitaxel protein-bound particles for injectable suspension (albumin-bound) that is written for health professionals.

**What are the ingredients in paclitaxel protein-bound particles for injectable suspension (albumin-bound)?**

**Active ingredient:**paclitaxel (bound to human albumin).

**Other ingredient:**human albumin (containing sodium caprylate and sodium acetyltryptophanate).

Manufactured by Jiangsu Hengrui Pharmaceuticals Co., Ltd., Lianyungang, Jiangsu 222047, China for Sandoz Inc., Princeton, NJ 08540

For more information, call 1-800-525-8747.

This Patient Information has been approved by the U.S. Food and Drug Administration.

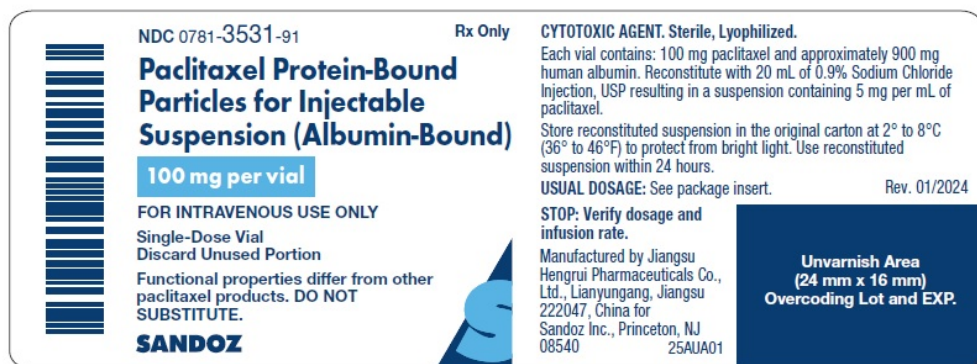
Revised: 01/2024

25AUF01

**PRINCIPAL DISPLAY PANEL - 100 mg Vial**

NDC 0781-3531-91

**Paclitaxel protein-bound particles for injectable suspension (albumin-bound)**



**PACLITAXEL**

paclitaxel injection, powder, lyophilized, for suspension

Product Information			
<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:0781-3531
<b>Route of Administration</b>	INTRAVENOUS		
Active Ingredient/Active Moiety			
	<b>Ingredient Name</b>	<b>Basis of Strength</b>	<b>Strength</b>
	PACLITAXEL (UNII: P88XT4IS4D) (PACLITAXEL - UNII:P88XT4IS4D)	PACLITAXEL	100 mg in 20 mL

Inactive Ingredients				
Ingredient Name				Strength
ALBUMIN HUMAN (UNII: ZIF514RVZR)				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0781-3531-91	1 in 1 CARTON	10/09/2024	
1		20 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category	Application Number or Monograph Citation		Marketing Start Date	Marketing End Date
ANDA	ANDA212700		10/08/2024	

**Labeler** - Sandoz Inc (005387188)

Revised: 10/2024

Sandoz Inc