HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PACLINAB® safely and effectively. See full prescribing information for PACLINAB ®

PACLINAB® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound)

INDICATIONS AND USAGE

PACLINAB® is a microtubule inhibitor:

• Paclinab® (Paclitaxel albumin-bound particles) 100 mg Powder for Suspension monotherapy is indicated for the treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated. (1.1)

• Paclinab® in combination with carboplatin is indicated for the first-line treatment of non-small cell lung cancer in adult patients who are not candidates for potentially curative surgery and/or radiation therapy. . (1.2)

• Paclinab® in combination with gemcitabine is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas. . (1.3)

DOSAGE AND ADMINISTRATION

• Metastatic Breast Cancer: Recommended dosage of PACLINAB is 260 mg/m^2 intravenously over 30 minutes every 3 weeks. (2.1)

• Non-Small Cell Lung Cancer: Recommended dosage of PACLINAB is 100 mg/m^2 intravenously over 30 minutes on Days 1, 8, and 15 of each 21-day cycle; administer carboplatin on Day 1 of each 21-day cycle immediately after PACLINAB. (2.2)

• Adenocarcinoma of the Pancreas: Recommended dosage of PACLINAB is 125 mg/m^2 intravenously over 30-40 minutes on Days 1, 8 and 15 of each 28-day cycle; administer gemcitabine on Days 1, 8 and 15 of each 28-day cycle immediately after PACLINAB. (2.3)

• Do not administer PACLINAB to any patient with AST > 10 x ULN or bilirubin > 5 x ULN. Do not administer PACLINAB to patients with metastatic adenocarcinoma of the pancreas who have moderate to severe hepatic impairment. For diseases other than metastatic adenocarcinoma of the pancreas, reduce starting dose in patients with moderate to severe hepatic impairment. (2.4)

• Dose Reductions: Dose reductions or discontinuation may be needed based on severe hematologic, neurologic, cutaneous, or gastrointestinal toxicities. (2.5)

• Use caution when handling cytotoxic drugs. Closely monitor the infusion site for extravasation and infiltration. No premedication is required prior to administration. (2.6)

DOSAGE FORMS AND STRENGTHS

• Powder for suspension for infusion.The reconstituted suspension has a pH of 6-7.5 and an osmolality of 300-360 mOsm/kg. The powder is white to yellow. (3)

CONTRAINDICATIONS

• Patients who have baseline neutrophil counts <1500 cells/mm^3. (4)

- Lactation (4)

• Hypersensitivity to the active substance or to any of the excipients (4)

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WARNINGS AND PRECAUTIONS

• Bone marrow suppression (primarily neutropenia) occurs frequently with Paclitaxel albumin-bound particles. Neutropenia is dose-dependent and a dose-limiting toxicity. Frequent monitoring of blood cell counts should be performed during Paclinab® therapy. Patients should not be retreated with subsequent cycles of Paclinab® until neutrophils recover to >1500 cells/mm^3 and platelets recover to >100,000 cells/mm^3. (5.1)

• Sensory neuropathy occurs frequently with Paclitaxel albumin-bound particles, although development of severe symptoms is less common. The occurrence of Grade 1 or 2 sensory neuropathy does not generally require dose reduction. (5.2)

• Sepsis was reported at a rate of 5% in patients with or without neutropenia who received Paclitaxel albumin-bound particles 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 Paclinab® and gemcitabine until fever resolves and ANC ≥ 1500 cells/mm^3, then resume treatment at reduced dose levels. (5.3)

•Pneumonitis occurred in 1% of patients when Paclitaxel albumin-bound particles was used as monotherapy and in 4% of patients when Paclitaxel albumin-bound particles was used in combination with gemcitabine. Closely monitor all patients for signs and symptoms of pneumonitis. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with Paclinab® and gemcitabine and promptly initiate appropriate treatment and supportive measures. (5.4)

•Rare occurrences of severe hypersensitivity reactions, including very rare events of anaphylactic reactions with fatal outcome, have been reported. If a hypersensitivity reaction occurs, the medicinal product should be discontinued immediately, symptomatic treatment should be initiated, and the patient should not be rechallenged with paclitaxel. (5.5)

•Rare occurrences of severe hypersensitivity reactions, including very rare events of anaphylactic reactions with fatal outcome, have been reported. If a hypersensitivity reaction occurs, the medicinal product should be discontinued immediately, symptomatic treatment should be initiated, and the patient should not be rechallenged with paclitaxel. (5.6)

• Rare reports of congestive heart failure and left ventricular dysfunction have been observed among individuals receiving Paclitaxel albumin-bound. Most of the individuals were previously exposed to cardiotoxic medicinal products such as anthracyclines, or had underlying cardiac history. Thus patients receiving Paclinab® should be vigilantly monitored by physicians for the occurrence of cardiac events. (5.7)

• Fetal harm may occur when administered to a pregnant woman. Advise women of childbearing potential to avoid becoming pregnant while receiving PACLINAB. (5.8)

• Advise men not to father a child while on PACLINAB. (5.9)

ADVERSE REACTIONS

The most common clinically significant adverse reactions associated with the use of Paclitaxel albumin-bound particles have been neutropenia, peripheral neuropathy, arthralgia/myalgia and gastrointestinal disorders. (6)

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

• The most common adverse reactions (≥ 20%) in NSCLC are anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue. (6.2)

• The most common (≥ 20%) adverse reactions of PACLINAB in adenocarcinoma of the pancreas are neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration. (6.3)

DRUG INTERACTIONS

• Use caution when concomitantly administering PACLINAB with inhibitors or inducers of either CYP2C8 or CYP3A4. (7)

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

1 INDICATIONS AND USAGE

1.1 Metastatic Breast Cancer Paclinab® (Paclitaxel albumin-bound particles) 100 mg Powder for Suspension monotherapy is indicated for the treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated.

1.2 Non-Small Cell Lung Cancer Paclinab® in combination with carboplatin is indicated for the first-line treatment of non-small cell lung cancer in adult patients who are not candidates for potentially curative surgery and/or radiation therapy

1.3 Adenocarcinoma of the Pancreas Paclinab® in combination with gemcitabine is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas.

2 DOSAGE AND ADMINISTRATION

2.1 Metastatic Breast Cancer, The recommended dose of Paclinab® is 260 mg/m^2 administered

intravenously over 30 minutes every 3 weeks.

2.2 Non-Small Cell Lung The recommended dose of Paclinab® is 100 mg/m^2 administered as an intravenous infusion over 30 minutes on Days 1, 8 and 15 of each 21-day cycle. The recommended dose of carboplatin is AUC = 6 mg*min/mL on Day 1 only of each 21-day cycle, beginning immediately after the end of Paclinab® administration.

2.3 Adenocarcinoma of the Pancreas The recommended dose of Paclinab® in combination with gemcitabine is 125 mg/m^2 administered intravenously over 30 minutes on Days 1, 8 and 15 of each 28-day cycle. The concurrent recommended dose of gemcitabine is 1000 mg/m2 administered intravenously over 30 minutes immediately after the completion of Paclinab® administration on Days 1, 8 and 15 of each 28-day cycle.

2.4 Dose Reduction/Discontinuation Recommendations

2.4.1 Dose adjustments during treatment of pancreatic adenocarcinoma

Patients who experience severe neutropenia (neutrophil count < 500 cells/mm^3 for a week or longer) or severe sensory neuropathy during Paclinab® therapy should have the dose reduced to 220 mg/m^2 for subsequent courses. Following recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m^2. Paclinab® should not be administered until neutrophil counts recover to >1500 cells/mm^3. For Grade 3 sensory neuropathy, withhold treatment until resolution to Grade 1 or 2, followed by a dose reduction for all subsequent courses.

2.4.2. Dose adjustments during treatment of pancreatic adenocarcinoma

Table 1: Dose level reductions for patients with pancreatic adenocarcinoma

Dose Level	**Paclitaxel albumin-bound particles Dose (mg/m^2)**	**Gemcitabine Dose (mg/m^2)**
Full dose	125	1000
1st dose level reduction	100	800
2nd dose level reduction	75	600
If additional dose reduction required	Discontinue treatment	Discontinue treatment

Table 2: Dose modifications for neutropenia and/or thrombocytopenia at the start of a cycle or within a cycle for patients with pancreatic adenocarcinoma

Cycle Day	**ANC count (cells/mm^3)**		**Platelet count (cells/mm^3)**	**Paclitaxel albumin-bound particles** Dose	**Gemcitabine Dose**
Day 1	< 1500	OR	< 100,000	Delay doses until recovery	
Day 8	≥ 500 but < 1000	OR	≥ 50,000 but < 75,000	Reduce doses 1 dose level	
	< 500	OR	< 50,000	Withhold doses	
Day 15: If Day 8 doses were given without modification:					
Day 15	≥ 500 but < 1000	OR	≥ 50,000 but < 75,000	Treat with Day 8 dose level and follow with WBC Growth Factors OR Reduce doses 1 dose level from Day 8 doses	
	< 500	OR	< 50,000	Withhold doses	
Day 15: If Day 8 doses were reduced:					
Day 15	≥ 1000	AND	≥ 75,000	Return to the Day 1 dose levels and follow with WBC Growth Factors OR Treat with same doses as Day 8	
	≥ 500 but < 1000	OR	≥ 50,000 but < 75,000	Treat with Day 8 dose levels and follow with WBC Growth Factors OR Reduce doses 1 dose level from Day 8 doses	
	< 500	OR	< 50,000	Withhold doses	
Day 15: IF Day 8 doses were withheld:					
Day 15	≥ 1000	AND	≥ 75,000	Return to Day 1 dose levels and follow with WBC Growth Factors OR Reduce doses 1 dose level from Day 1 doses	

	≥ 500 but < 1000	OR	≥ 50,000 but < 75,000	Reduce 1 dose level and follow with WBC Growth Factors OR Reduce doses 2 dose levels from Day 1 doses
	< 500	OR	< 50,000	Withhold doses

Abbreviations: ANC=Absolute Neutrophil Count; WBC=white blood cell

Table 3: Dose modifications for other adverse drug reactions in patients with pancreatic adenocarcinoma

Adverse Drug Reaction (ADR)	**Paclitaxel albumin-bound particles Dose**	**Gemcitabine Dose**
Febrile Neutropenia: Grade 3 or 4	Withhold doses until fever resolves and ANC ≥ 1500; resume at next lower dose level. A	
Peripheral Neuropathy: Grade 3 or 4	Withhold dose until improves to ≤ Grade 1; Resume at next lower dose level. [a]	Treat with same dose
Cutaneous Toxicity: Grade 2 or 3	Reduce to next lower dose level [a]; discontinue treatment if ADR persists	
Gastrointestinal Toxicity: Grade 3 mucositis or diarrhoea	Withhold doses until improves to ≤ Grade 1; Resume at next lower dose level. [a]	

a See Table 1 for dose level reductions

2.4.3 Dose adjustments during treatment of pancreatic adenocarcinoma

Paclitaxel albumin-bound particles should not be administered on Day 1 of a cycle until absolute neutrophil count (ANC) is ≥1500 cells/mm^3 and platelet count is ≥100,000 cells/mm^3. For each subsequent weekly dose of Paclitaxel albumin-bound particles, patients must have an ANC ≥500 cells/mm^3 and platelets >50,000 cells/mm^3 or the dose is to be withheld until counts recover. When counts recover, resume dosing the following week according to the criteria in Table 4. Reduce subsequent dose only if criteria in Table 4 are met.

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

Hematologic Toxicity	Occurrence	Dose of Paclitaxel albumin-bound particles ® (mg/m^2)[1]	Dose of carboplatin (AUC mg*min/mL)[1]
Nadir ANC <500/mm^3 with neutropenic fever > 38°C OR Delay of next cycle due to persistent neutropenia2 (Nadir ANC <1500/mm^3) OR Nadir ANC <500/mm^3 for > 1 week	First	75	4.5
	Second	50	3.0
	Third	Discontinue Treatment	
Nadir platelets <50,000/mm^3	First	75	4.5
	Second	Discontinue Treatment	

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

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

For Grade 2 or 3 cutaneous toxicity, Grade 3 diarrhoea, or Grade 3 mucositis, interrupt treatment until the toxicity improves to ≤ Grade 1, then restart treatment according to the guidelines in Table 5. For ≥ Grade 3 peripheral neuropathy, withhold treatment until resolution to ≤ Grade 1. Treatment may be resumed at the next lower dose level in subsequent cycles according to the guidelines in Table 5. For any other Grade 3 or 4 non-hematologic toxicity, interrupt treatment until the toxicity improves to ≤ Grade 2, then restart treatment according to the guidelines in Table 5.

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

<table>
<tr><td>Non-hematologic Toxicity</td><td>Occurrence</td><td>Dose of Paclitaxel albumin-bound particles (mg/m^2)[1]</td><td>Dose of carboplatin (AUC mg*min/mL)[1]</td></tr>
<tr><td rowspan="3">Grade 2 or 3 cutaneous toxicity
Grade 3 diarrhoea
Grade 3 mucositis
≥ Grade 3 peripheral neuropathy
Any other Grade 3 or 4 non-hematologic toxicity</td><td>First</td><td>75</td><td>4.5</td></tr>
<tr><td>Second</td><td>50</td><td>3.0</td></tr>
<tr><td>Third</td><td colspan="2">Discontinue Treatment</td></tr>
<tr><td>Grade 4 cutaneous toxicity, diarrhoea, or mucositis</td><td>First</td><td colspan="2">Discontinue Treatment</td></tr>
</table>

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

2.5 Preparation and Administration Precautions

Paclitaxel is a cytotoxic anticancer medicinal product and, as with other potentially toxic compounds, caution should be exercised in handling Paclinab®. The use of gloves, goggles and protective clothing is recommended. If the suspension contacts the skin, the skin should be washed immediately and thoroughly with soap and water. If it contacts mucous membranes, the membranes should be flushed thoroughly with water. Paclinab® should only be prepared and administered by personnel appropriately trained in the handling of cytotoxic agents. Pregnant staff should not handle Paclinab®.

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

2.6 Reconstitution and administration of the product

Paclinab® is supplied as a sterile lyophilized powder for reconstitution before use. After reconstitution, each mL of suspension contains 5 mg of paclitaxel formulated as albumin bound nanoparticles

100mg vial: Using a sterile syringe, 20 mL of sodium chloride 9 mg/ mL (0.9%) solution for infusion should slowly be injected into a vial of Paclinab® over a minimum of 1 minute

250mg vial: Using a sterile syringe, 50 mL of sodium chloride 9 mg/ mL (0.9%) solution for infusion should slowly be injected into a vial of Paclinab® over a minimum of 1 minute

The solution should be directed onto the inside wall of the vial. The solution should not be injected directly onto the powder as this will result in foaming

Once the addition is complete, the vial should be allowed to stand for a minimum of 5 minutes to ensure proper wetting of the solid. Then, the vial should gently and slowly be swirled and/or inverted for at least 2 minutes until complete resuspension of any powder occurs. The generation of foam must be avoided. If foaming or clumping occurs, the solution must stand for at least 15 minutes until foam subsides

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

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

The exact total dosing volume of 5 mg/ mL suspension required for the patient should be calculated and the appropriate amount of reconstituted Paclinab® should be injected into an empty, sterile, PVC or non-PVC type intravenous bag. .

The use of medical devices containing silicone oil as a lubricant (i.e. syringes and IV bags) to reconstitute and administer Paclinab® may result in the formation of proteinaceous strands. Administer Paclinab® using an infusion set incorporating a 15 μm filter to avoid administration of these strands. Use of a 15 μm filter removes strands and does not change the physical or chemical properties of the reconstituted product.

Use of filters with a pore size less than 15 μm may result in blockage of the filter.

The use of specialized di (2-ethylhexyl) phthalate (DEHP)-free solution containers or administration sets is not necessary to prepare or administer Paclinab® infusions.

Following administration, it is recommended that the intravenous line be flushed with sodium chloride 9 mg/mL (0.9%) solution for

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

2.7 Stability

Unopened vials

Keep the vial in the outer carton in order to protect from light. Neither freezing nor refrigeration adversely affects the stability of the product. This medicinal product does not require any special temperature storage conditions.

Stability of reconstituted suspension in the vial

After first reconstitution, the suspension should be filled into an infusion bag immediately. However, chemical and physical in use stability has been demonstrated for 8 hours at 2°C-8°C in the original carton, and protected from bright light. Alternative light-protection may be used in the clean room.

Stability of the reconstituted suspension in the infusion bag

After reconstitution, the reconstituted suspension in the infusion bag should be used immediately. However chemical and physical in use stability has been demonstrated for 8 hours not above 25°C

.Nature and contents of container

Type 1 clear glass vial (Standard 50H vial) contains 1 g lyophilized powder of paclitaxel formulated as albumin bound nanoparticles were sealed by 20 mm bromobutylfluroTec rubber stopper with 20 mm pink flip off cap.

3 DOSAGE FORMS AND STRENGTHS

For injectable suspension: lyophilized powder containing 100 mg of paclitaxel formulated as albumin-bound particles in single-use vial for reconstitution.

4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients

Lactation

Patients who have baseline neutrophil counts <1500 cells/mm^3

5 WARNINGS AND PRECAUTIONS

Paclinab® is an albumin-bound nanoparticle formulation of paclitaxel, which may have substantially different pharmacological properties compared to other formulations of paclitaxel. It should not be substituted for or with other paclitaxel formulations.

5.1 Hypersensitivity

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

5.2 Hematology

Bone marrow suppression (primarily neutropenia) occurs frequently with Paclitaxel albumin-bound particles. Neutropenia is dose-dependent and a dose-limiting toxicity. Frequent monitoring of blood cell counts should be performed during Paclinab® therapy. Patients should not be retreated with subsequent cycles of Paclinab® until neutrophils recover to >1500 cells/mm^3 and platelets recover to >100,000 cells/mm^3.

5.3 Neuropathy

Sensory neuropathy occurs frequently with Paclitaxel albumin-bound particles, although development of severe symptoms is less common. The occurrence of Grade 1 or 2 sensory neuropathy does not generally require dose reduction. When Paclinab® 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 Paclinab® is recommended. For combination use of Paclinab® and gemcitabine, if Grade 3 or higher peripheral neuropathy develops, withhold Paclinab®; continue treatment with gemcitabine at the same dose. Resume Paclinab® at reduced dose when peripheral neuropathy improves to Grade 0 or 1. For combination use of Paclinab® and carboplatin, if Grade 3 or higher peripheral neuropathy develops, treatment should be withheld until improvement to Grade 0 or 1 followed by a dose reduction for all subsequent courses of Paclinab® and carboplatin.

5.4 Sepsis

Sepsis was reported at a rate of 5% in patients with or without neutropenia who received Paclitaxel albumin-bound particles 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 Paclinab® and gemcitabine until fever resolves and ANC $\geq$ 1500 cells/mm^3, then resume treatment at reduced dose levels.

5.5 Pneumonitis

Pneumonitis occurred in 1% of patients when Paclitaxel albumin-bound particles was used as monotherapy and in 4% of patients when Paclitaxel albumin-bound particles was used in combination with gemcitabine. Closely monitor all patients for signs and symptoms of pneumonitis. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with Paclinab® and gemcitabine and promptly initiate appropriate treatment and supportive measures.

5.6 Hepatic impairment

Because the toxicity of paclitaxel can be increased with hepatic impairment, administration of Paclinab® in patients with hepatic impairment should be performed with caution. Patients with hepatic impairment may be at increased risk of toxicity, particularly from myelosuppression; such patients should be closely monitored for development of profound myelosuppression.

Paclinab® is not recommended in patients that have total bilirubin > 5 x ULN or AST > 10 x ULN. In addition, Paclinab® is not recommended in patients with metastatic adenocarcinoma of the pancreas that have moderate to severe hepatic impairment (total bilirubin > 1.5 x ULN and AST $\leq$ 10 x ULN) .

5.7 Cardiotoxicity

Rare reports of congestive heart failure and left ventricular dysfunction have been observed among individuals receiving Paclitaxel albumin-bound. Most of the individuals were previously exposed to

cardiotoxic medicinal products such as anthracyclines, or had underlying cardiac history. Thus patients receiving Paclinab® should be vigilantly monitored by physicians for the occurrence of cardiac events.

5.8 CNS metastases

The effectiveness and safety of Paclitaxel albumin-bound in patients with central nervous system (CNS) metastases has not been established. CNS metastases are generally not well controlled by systemic chemotherapy.

5.9 Gastrointestinal symptoms

If patients experience nausea, vomiting and diarrhoea following the administration of Paclitaxel albumin-bound, they may be treated with commonly used anti-emetics and constipating agents.

5.10 Patients 75 years and older

For patients of 75 years and older, no benefit for the combination treatment of Paclitaxel albumin-bound and gemcitabine in comparison to gemcitabine monotherapy has been demonstrated. In the very elderly (≥75 years) who received Paclitaxel albumin-bound 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. Patients with pancreatic adenocarcinoma aged 75 years and older should be carefully assessed for their ability to tolerate Paclitaxel albumin-bound in combination with gemcitabine with special consideration to performance status, co-morbidities and increased risk of infections.

5.11 Other

Although limited data is available, no clear benefit in terms of prolonged overall survival has been demonstrated in pancreatic adenocarcinoma patients with normal CA 19-9 levels prior to start of treatment with Paclitaxel albumin-bound particles and gemcitabine

Erlotinib should not be coadministered with Paclitaxel albumin-bound particles plus gemcitabine.

6 UNDESIRABLE EFFECTS

Summary of the safety profile

The most common clinically significant adverse reactions associated with the use of Paclitaxel albumin bound particles have been neutropenia, peripheral neuropathy, arthralgia/myalgia and gastrointestinal disorders.

The frequencies of adverse reactions associated with the administration of Paclitaxel albumin-bound particles are listed in Table 6 (Paclitaxel albumin-bound particles as monotherapy) and Table 7 (Paclitaxel albumin-bound particles in combination with gemcitabine), and Table 9 (Paclitaxel albumin-bound particles in combination with carboplatin).

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

To <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Breast cancer (Paclitaxel albumin-bound particles administered as monotherapy)

Tabulated list of adverse reactions

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

6.1 ***Table 6: Adverse reactions reported with Paclitaxel albumin-bound particles monotherapy at any dose in clinical studies***

Infections and infestations	*Common*: Infection, urinary tract infection, folliculitis, upper respiratory tract infection, candidiasis, sinusitis *Uncommon*: Oral candidiasis, nasopharyngitis, cellulitis, herpes simplex, viral infection, pneumonia, catheter-related infection, fungal infection, herpes zoster, injection site infection, sepsis2, neutropenic sepsis2
Neoplasms benign, malignant and unspecified (including cysts and polyps)	*Uncommon:* Metastatic pain, tumor necrosis
Blood and lymphatic system disorders	*Very common*: Neutropenia, anemia, leukopenia, thrombocytopenia, lymphopenia, bone marrow suppression *Common*: Febrile neutropenia *Rare: Pancytopenia*
Immune system disorders	*Uncommon1:* Hypersensitivity *Rare:* Severe hypersensitivity
Metabolism and nutrition disorders	*Very common:* Anorexia *Common:* Dehydration, decreased appetite, hypokalemia *Uncommon:* Hypophosphatemia, fluid retention, hypoalbuminaemia, polydipsia, hyperglycemia, hypocalcaemia, hypoglycemia, hyponatremia
Psychiatric disorders	*Common*: Insomnia, depression, anxiety *Uncommon*: Restlessness
Nervous system disorders	*Very common*: Peripheral neuropathy, neuropathy, hypoesthesia, paresthesia *Common*: Peripheral sensory neuropathy, headache, dysgeusia, dizziness, peripheral motor neuropathy, ataxia, sensory disturbance, somnolence *Uncommon*: Polyneuropathy, areflexia, dyskinesia, hyporeflexia, neuralgia, sensory loss, syncope, postural dizziness, neuropathic pain, tremor
Eye disorders	*Common:* Increased lacrimation, blurred vision, dry eye, keratoconjunctivitis sicca, madarosis *Uncommon*: Eye irritation, eye pain, abnormal vision, reduced visual acuity, conjunctivitis, visual disturbance, eye pruritus, keratitis *Rare: Cystoid macular oedema*[2]
Ear and labyrinth disorders	*Common*: Vertigo *Uncommon*: Ear pain, tinnitus
Cardiac disorders	*Common*: Tachycardia, arrhythmia, supraventricular

	tachycardia *Rare:* bradycardia, cardiac arrest, left ventricular dysfunction, congestive heart failure, atrioventricular block2
Vascular disorders	*Common*: Flushing, hot flushes, hypertension, lymphoedema *Uncommon*: Hypotension, peripheral coldness, orthostatic hypotension *Rare: Thrombosis*
Respiratory, thoracic and mediastinal disorders	*Common*: Interstitial pneumonitis3, dyspnoea, epistaxis, pharyngolaryngeal pain, cough, rhinitis, rhinorrhea *Uncommon*: Productive cough, exertional dyspnoea, sinus congestion, decreased breath sounds, pleural effusion, allergic rhinitis, hoarseness, nasal congestion, nasal dryness, wheezing, pulmonary emboli, pulmonary thromboembolism
Gastrointestinal disorders	*Very common*: Nausea, diarrhoea, vomiting, constipation, stomatitis *Common*: Abdominal pain, abdominal distension, upper abdominal pain, dyspepsia, gastrooesophageal reflux disease, oral hypoesthesia *Uncommon*: Dysphagia, flatulence, glossodynia, dry mouth, gingival pain, loose stools, oesophagitis, lower abdominal pain, mouth ulceration, oral pain, rectal hemorrhage
Hepatobiliary disorders	*Uncommon*: Hepatomegaly
Skin and subcutaneous tissue disorders	*Very common*: Alopecia, rash *Common*: Nail disorder, pruritus, dry skin, erythema, nail pigmentation/discoloration, skin hyperpigmentation, onycholysis, nail changes *Uncommon*: Nail bed tenderness, urticaria, skin pain, photosensitivity reaction, pigmentation disorder, pruritic rash, skin disorder, hyperhidrosis, onychomadesis, erythematous rash, generalised rash, dermatitis, night sweats, maculo-papular rash, vitiligo, hypotrichosis, nail discomfort, generalized pruritus, macular rash, papular rash, skin lesion, swollen face *Very rare:* Stevens-Johnson syndrome[2], toxic epidermal necrolysis[2]
Hepatobiliary disorders	*Uncommon*: Hepatomegaly
Skin and subcutaneous tissue disorders	*Very common*: Alopecia, rash *Common*: Nail disorder, pruritus, dry skin, erythema, nail pigmentation/discolouration, skin hyperpigmentation, onycholysis, nail changes *Uncommon*: Nail bed tenderness, urticaria, skin pain, photosensitivity reaction, pigmentation disorder, pruritic rash, skin disorder, hyperhidrosis, onychomadesis, erythematous rash, generalised rash, dermatitis, night sweats, maculo-papular rash, vitiligo, hypotrichosis, nail discomfort, generalized pruritus, macular rash, papular rash, skin lesion, swollen face *Very rare:* Stevens-Johnson syndrome2, toxic epidermal necrolysis2
Hepatobiliary disorders	*Uncommon*: Hepatomegaly

Skin and subcutaneous tissue disorders	*Very common*: Alopecia, rash *Common*: Nail disorder, pruritus, dry skin, erythema, nail pigmentation/discolouration, skin hyperpigmentation, onycholysis, nail changes *Uncommon*: Nail bed tenderness, urticaria, skin pain, photosensitivity reaction, pigmentation disorder, pruritic rash, skin disorder, hyperhidrosis, onychomadesis, erythematous rash, generalised rash, dermatitis, night sweats, maculo-papular rash, vitiligo, hypotrichosis, nail discomfort, generalized pruritus, macular rash, papular rash, skin lesion, swollen face *Very rare:* Stevens-Johnson syndrome2, toxic epidermal necrolysis2
Investigations	*Common*: Decreased weight, increased alanine aminotransferase, increased aspartate aminotransferase, decreased hematocrit, decreased red blood cell count, increased body temperature, increased gamma-glutamyltransferase, increased blood alkaline phosphatase *Uncommon*: Increased blood pressure, increased weight, increased blood lactate dehydrogenase, increased blood creatinine, increased blood glucose, increased blood phosphorus, decreased blood potassium, increased bilirubin
Injury, poisoning and procedural complications	*Uncommon:* Contusion *Rare: Radiation recall phenomenon, radiation pneumonitis*

MedDRA = Medical Dictionary for Regulatory Activities.

SMQ = Standardized MedDRA Query; SMQ is a grouping of several MedDRA preferred terms to capture a medical concept.

[1] The frequency of hypersensitivity reactions is calculated based on one definitely related case in a population of 789 patients.

[2] As reported in the post-marketing surveillance of Paclitaxel albumin-bound particles.

[3] The frequency of pneumonitis is calculated based on pooled data in 1310 patients in clinical trials receiving Paclitaxel albumin-bound particles monotherapy for breast cancer and for other indications using MedDRA SMQ Interstitial lung disease. See section 4.4.

Description of selected adverse reactions

The following are the most common and clinically relevant adverse reactions related to 229 patients with metastatic breast cancer who were treated with 260 mg/m^2 Paclitaxel albumin-bound particles once every three weeks in the pivotal phase III clinical study.

Blood and lymphatic system disorders

Neutropenia was the most notable important hematological toxicity (reported in 79% of patients), and was rapidly reversible and dose dependent; leukopenia was reported in 71% of patients. Grade 4 neutropenia (< 500 cells/mm^3) occurred in 9% of patients treated with Paclitaxel albumin-bound particles. Febrile neutropenia occurred in four patients on Paclitaxel albumin-bound particles. Anemia (Hb < 10 g/dl) was observed in 46% of patients on Paclitaxel albumin-bound particles, and was severe (Hb < 8 g/dl) in three cases. Lymphopenia was observed in 45% of the patients.

Nervous system disorders

In general, the frequency and severity of neurotoxicity was dose-dependent in patients receiving Paclitaxel albumin-bound particles. Peripheral neuropathy (mostly Grade 1 or 2 sensory neuropathy) was observed in 68% of patients on Paclitaxel albumin-bound particles with 10% being Grade 3, and no cases of Grade 4.

Gastrointestinal disorders

Nausea occurred in 29% of the patients and diarrhoea in 25% of the patients.

Skin and subcutaneous tissue disorders

Alopecia was observed in >80% of the patients treated with Paclitaxel albumin-bound particles. The majority of alopecia events occurred less than one month after initiation of Paclitaxel albumin-bound particles. Pronounced hair loss ≥50% is expected for the majority of patients who experience alopecia.

Musculoskeletal and connective tissue disorders

Arthralgia occurred in 32% of patients on Paclitaxel albumin-bound particles and was severe in 6% of cases. Myalgia occurred in 24% of patients on Paclitaxel albumin-bound particles and was severe in 7% of cases. The symptoms were usually transient, typically occurred three days after Paclitaxel albumin-bound particles administration and resolved within a week.

General disorders and administration site conditions

Asthenia/Fatigue was reported in 40% of the patients.

Pancreatic adenocarcinoma (Paclitaxel albumin-bound particles administered in combination with gemcitabine)

Tabulated list of adverse reactions

Adverse reactions were assessed in 421 patients treated with Paclitaxel albumin-bound particles in combination with gemcitabine and 402 gemcitabine monotherapy-treated patients receiving first-line systemic treatment for metastatic adenocarcinoma of the pancreas in a phase III randomized,

controlled, open-label trial. Table 7 lists adverse reactions assessed in patients with pancreatic adenocarcinoma treated with Paclitaxel albumin-bound particles in combination with gemcitabine.

6.2 ***Table 7: Adverse reactions reported with Paclitaxel albumin-bound particles in combination with gemcitabine (N =421)***

Infections and infestations	*Common*: Sepsis, pneumonia, oral candidiasis
Blood and lymphatic system disorders	*Very common*: Neutropenia, anaemia, thrombocytopenia *Common:* Pancytopenia *Uncommon*: Thrombotic thrombocytopenic purpura
Metabolism and nutrition disorders	*Very common*: Dehydration, decreased appetite, hypokalemia
Psychiatric disorders	*Very common*: Insomnia, depression *Common*: Anxiety
Nervous system disorders	*Very common*: Peripheral neuropathy1, dysgeusia, headache, dizziness *Uncommon*: VIIth nerve paralysis
Eye disorders	*Common*: Lacrimation increased *Uncommon*: Cystoid macular edema
Cardiac disorders	*Common*: Cardiac failure congestive, tachycardia
Vascular disorders	*Common*: Hypotension, hypertension
Respiratory, thoracic and mediastinal disorders	*Very common*: Dyspnoea, epistaxis, cough *Common*: Pneumonitis2, nasal congestion *Uncommon*: Dry throat, nasal dryness
Gastrointestinal disorders	*Very common*: Nausea, diarrhoea, vomiting, constipation, abdominal pain, abdominal pain upper *Common*: Stomatitis, intestinal obstruction, colitis, dry mouth
Hepatobiliary disorders	*Common*: Cholangitis
Skin and subcutaneous tissue disorders	*Very common*: Alopecia, rash *Common*: Pruritus, dry skin, nail disorder, flushing
Musculoskeletal and connective tissue disorders	*Very common*: Pain in extremity, arthralgia, myalgia *Common*: Muscular weakness, bone pain
Renal and urinary disorders	*Common*: Acute renal failure *Uncommon*: Hemolytic uremic syndrome
General disorders and administration site conditions	*Very common*: Fatigue, edema peripheral, pyrexia, asthenia, chills *Common*: Infusion site reaction
Investigations	*Very common*: Weight decreased, alanine aminotransferase increased *Common*: Aspartate aminotransferase increased, blood bilirubin increased, blood creatinine increased

MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardized MedDRA Query (a grouping of several MedDRA preferred terms to capture a medical concept).

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

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

In this phase III randomized, controlled, open-label trial, adverse reactions resulting in death within 30 days of the last dose of study drug were reported for 4% of patients receiving Paclitaxel albumin-bound particles in combination with gemcitabine and for 4% of patients receiving gemcitabine monotherapy.

Description of selected adverse reactions

The following are the most common and important incidences of adverse reactions related to 421 patients with metastatic adenocarcinoma of the pancreas who were treated with 125 mg/m^2 Paclitaxel albumin-bound particles in combination with gemcitabine at a dose of 1000 mg/m2 given on Days 1, 8 and 15 of each 28-day cycle in the phase III clinical study.

Blood and lymphatic system disorders

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

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

	Paclitaxel albumin-bound particles (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 albumin-bound particles /gemcitabine-treated group
[b] 388 patients assessed in gemcitabine-treated group
[c] 404 patients assessed in Paclitaxel albumin-bound particles /gemcitabine-treated group

Peripheral neuropathy

For patients treated with Paclitaxel albumin-bound particles in combination with gemcitabine, the median time to first occurrence of Grade 3 peripheral neuropathy was 140 days. The median time to improvement by at least 1 grade was 21 days, and the median time to improvement from Grade 3 peripheral neuropathy to Grade 0 or 1 was 29 days. Of the patients with treatment interrupted due to peripheral neuropathy, 44% (31/70 patients) were able to resume Paclitaxel albumin-bound particles at a reduced dose. No patients treated with Paclinab® in combination with gemcitabine had Grade 4 peripheral neuropathy.

Sepsis

Sepsis was reported at a rate of 5% in patients with or without neutropenia who received Paclitaxel albumin-bound particles in combination with gemcitabine during the conduct of a trial in pancreatic adenocarcinoma. Complications due to the underlying pancreatic cancer, especially biliary obstruction or presence of biliary stent, were identified as significant contributing factors. If a patient becomes febrile (regardless of neutrophil count), initiate treatment with broad spectrum antibiotics. For febrile neutropenia, withhold Paclinab® and gemcitabine until fever resolves and ANC $\geq$ 1500 cells/mm^3, then resume treatment at reduced dose levels (see section 4.2).

Pneumonitis

Pneumonitis has been reported at a rate of 4% with the use of Paclitaxel albumin-bound particles in combination with gemcitabine. Of the 17 cases of pneumonitis reported in patients treated with Paclitaxel albumin-bound particles in combination with gemcitabine, 2 had a fatal outcome. Monitor patients closely for signs and symptoms of pneumonitis. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with Paclinab® and gemcitabine and promptly initiate appropriate treatment and supportive measures (see section 4.2).

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

Tabulated list of adverse reactions

Table 9 lists adverse reactions associated with the administration of Paclitaxel albumin-bound particles in combination with carboplatin.1

6.3 ***Table 9: Adverse reactions reported with Paclitaxel albumin-bound particles in combination with carboplatin (N = 514)***

Infections and infestations	*Common:* Pneumonia, bronchitis, upper respiratory tract infection, urinary tract infection *Uncommon:* Sepsis, oral candidiasis
Blood and lymphatic system disorders1	*Very common:* Neutropenia1, thrombocytopenia1, anaemia1, leukopenia1 *Common:* Febrile neutropenia, lymphopenia *Uncommon:* Pancytopenia
Immune system disorders	*Uncommon:* Drug hypersensitivity, hypersensitivity
Metabolism and nutrition disorders	*Very common:* Decreased appetite *Common:* Dehydration

Psychiatric disorders	*Common:* Insomnia
Nervous system disorders	*Very common:* Peripheral neuropathy2 *Common:* Dysgeusia, headache, dizziness
Eye disorders	*Common:* Vision blurred
Vascular disorders	*Common:* Hypotension, hypertension *Uncommon:* Flushing
Respiratory thoracic and mediastinal disorders	*Very common:* Dyspnoea *Common:* Hemoptysis, epistaxis, cough *Uncommon:* Pneumonitis3
Gastrointestinal disorders	*Very common:* Diarrhoea, vomiting, nausea, constipation *Common:* Stomatitis, dyspepsia, abdominal pain, dysphagia
Hepatobiliary disorders	*Common:* Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	*Very common:* Rash, alopecia *Common:* Pruritus, nail disorder *Uncommon:* Skin exfoliation, dermatitis allergic, urticaria
Musculoskeletal and connective tissue disorders	*Very common:* Arthralgia, myalgia *Common:* Back pain, pain in extremity, musculoskeletal pain
General disorders and administration site conditions	*Very common:* Fatigue, asthenia, edema peripheral *Common*: Pyrexia, chest pain *Uncommon:* Mucosal inflammation, infusion site extravasation, infusion site inflammation, infusion site rash
Investigations	*Common:* Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, weight decreased

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

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

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

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

For non-small cell lung cancer patients treated with Paclinab® and carboplatin, the median time to first occurrence of Grade 3 treatment related peripheral neuropathy was 121 days, and the median time to improvement from Grade 3 treatment related peripheral neuropathy to Grade 1 was 38 days. No patients treated with Paclinab® and carboplatin experienced Grade 4 peripheral neuropathy.

Anemia and thrombocytopenia were more commonly reported in the Paclinab® arm than in the Taxol arm (54% versus 28% and 45% versus 27% respectively).

Patient-reported taxane toxicity was assessed using the 4 subscales of the Functional Assessment of Cancer Therapy (FACT)-Taxane questionnaire. Using repeated measure analysis, 3 of the 4 subscales (peripheral neuropathy, pain hands/feet, and hearing) favored Paclitaxel albumin-bound particles and carboplatin ($p \leq 0.002$). For the other subscale (edema), there was no difference in the treatment arms.

6.4 Post-marketing experience

Cranial nerve palsies, vocal cord paresis, and rare reports of severe hypersensitivity reactions have been reported during post-marketing surveillance of Paclitaxel albumin-bound particles.

There have been rare reports of reduced visual acuity due to cystoid macular edema during treatment with Paclitaxel albumin-bound particles. Upon diagnosis of cystoid macular edema, treatment with Paclinab® should be discontinued.

In some patients previously exposed to capecitabine, reports of palmar-plantar erythrodysaesthesiae have been reported as part of the continuing surveillance of Paclitaxel albumin-bound particles. Because these events have been reported voluntarily during clinical practice, true estimates of frequency cannot be made and a causal relationship to the events has not been established.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

7 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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

Paclitaxel and gemcitabine do not share a common metabolic pathway. Paclitaxel clearance is primarily determined by CYP2C8 and CYP3A4 mediated metabolism followed by biliary excretion, while gemcitabine is inactivated by cytidine deaminase followed by

urinary excretion. Pharmacokinetic interactions between Paclitaxel albumin-bound particles and gemcitabine have not been evaluated in humans

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

Paclinab® is indicated as monotherapy for breast cancer, in combination with gemcitabine for pancreatic adenocarcinoma, or in combination with carboplatin for non-small cell lung cancer. Paclinab® should not be used in combination with other anticancer agents

8 USE IN SPECIFIC POPULATIONS

8.1 pregnancy

There are very limited data on the use of paclitaxel in human pregnancy. Paclitaxel is suspected to cause serious birth defects when administered during pregnancy. Studies in animals have shown reproductive toxicity (see section 5.3). Paclinab® should not be used in pregnancy, and in women of childbearing potential not using effective contraception, unless the clinical condition of the mother requires treatment with paclitaxel.

8.2 Breast-feeding

It is not known if paclitaxel is excreted in human milk. Because of potential serious adverse reactions in breast-feeding infants, Paclinab® 100 mg Powder for Suspension is contraindicated during lactation. Breast-feeding must be discontinued for the duration of therapy.

8.3 Fertility

Paclitaxel albumin-bound particles induced infertility in male rats (see section 5.3). Male patients should seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with Paclinab®

8.4 pediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Paclitaxel albumin-bound particles in all subsets of the pediatric population in the treatment of metastatic breast cancer, pancreatic adenocarcinoma and non-small cell lung cancer .

8.6 Patients with Hepatic Impairment

The exposure to paclitaxel may be higher in patients with hepatic impairment than in patients with normal hepatic function. Reduce PACLINAB® starting dose in patients with moderate to severe hepatic impairment. Do not administer PACLINAB® to patients with total bilirubin > 5 x ULN or AST > 10 x ULN .Do not administer to patients with metastatic adenocarcinoma of the pancreas who have moderate to severe hepatic impairment.

8.7 Patients with Renal Impairment

Adjustment of the starting PACLINAB® dose is not required for patients with mild to moderate renal impairment (estimated creatinine clearance ≥30 to)

9 overdose

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

10. description

PACLINAB® for Injectable Suspension (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.

PACLINAB® 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-use 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. PACLINAB® is free of solvents.

The active agent in PACLINAB is paclitaxel, a microtubule inhibitor. The chemical name for paclitaxel is 5β,20-Epoxy- 1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine.

Paclitaxel is a white to off-white crystalline powder with the empirical formula C47H51NO14 and a molecular weight of 853.91. It is highly lipophilic, insoluble in water, and melts at approximately 216°C to 217°C.

11. clinical pharmacology

11.1 Mechanism of Action

Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises 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. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Paclinab® contains human serum albumin-paclitaxel nanoparticles of approximately 130 nm in size, where the paclitaxel is present in a non-crystalline, amorphous state. Upon intravenous administration, the nanoparticles dissociate rapidly into soluble, albumin bound paclitaxel complexes of approximately 10 nm in size. Albumin is known to mediate endothelial caveolar transcytosis of plasma constituents, and in vitro studies demonstrated that the presence of albumin in Paclinab® enhances transport of paclitaxel across endothelial cells. It is hypothesized that this enhanced trans endothelial caveolar transport is mediated by the gp-60 albumin receptor, and that there is enhanced accumulation of paclitaxel in the area of tumor due to the albumin-binding protein Secreted Protein Acidic Rich in Cysteine (SPARC).

11.2 pharmacokinetics

The pharmacokinetics of total paclitaxel following 30- and 180-minute infusions of Paclitaxel albumin-bound particles at dose levels of 80 to 375 mg/m^2 were determined in clinical studies. The paclitaxel exposure (AUC) increased linearly from 2653 to 16736 ng.hr/ mL following dosing from 80 to 300 mg/m^2.

In a study in patients with advanced solid tumors, the pharmacokinetic characteristics of paclitaxel following Paclitaxel albumin-bound particles administered intravenously at 260 mg/m^2 over 30

minutes were compared with those following 175 mg/m^2 of the solvent-based paclitaxel injection administered over 3 hours. Based on non-compartmental PK analysis, the plasma clearance of paclitaxel with Paclitaxel albumin-bound particles was larger (43%) than that following a solvent-based paclitaxel injection and its volume of distribution was also higher (53%). There were no differences in terminal half-lives.

In a repeat dose study with 12 patients receiving Paclitaxel albumin-bound particles administered intravenously at 260 mg/m^2, intrapatient variability in AUC was 19% (range = 3.21%-27.70%). There was no evidence for accumulation of paclitaxel with multiple treatment courses.

Distribution

Following Paclitaxel albumin-bound particles administration to patients with solid tumors, paclitaxel is evenly distributed into blood cells and plasma and is highly bound to plasma proteins (94%).

The protein binding of paclitaxel following Paclitaxel albumin-bound particles was evaluated by ultrafiltration in a within-patient comparison study. The fraction of free paclitaxel was significantly higher with Paclitaxel albumin-bound particles (6.2%) than with solvent-based paclitaxel (2.3%). This resulted in significantly higher exposure to unbound paclitaxel with Paclitaxel albumin-bound particles compared with solvent-based paclitaxel, even though the total exposure is comparable. This is possibly due to paclitaxel not being trapped in Chromophore EL micelles as with solvent-based paclitaxel. Based on the published literature, in vitro studies of binding to human serum proteins, (using paclitaxel at concentrations ranging from 0.1 to 50 μg/ mL), indicate that the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

Based on population pharmacokinetic analysis, the total volume of distribution is approximately 1741 L; the large volume of distribution indicates extensive extravascular distribution and/or tissue binding of paclitaxel.

Biotransformation and elimination

Based on the published literature, in vitro studies with human liver microsomes and tissue slices show that paclitaxel is metabolized primarily to 6α-hydroxypaclitaxel; and to two minor metabolites, 3'-p-hydroxypaclitaxel and 6a-3'-p-dihydroxypaclitaxel. The formation of these hydroxylated metabolites is catalyzed by CYP2C8, CYP3A4, and both CYP2C8 and CYP3A4 isoenzymes, respectively.

In patients with metastatic breast cancer, after a 30-minute infusion of Paclitaxel albumin-bound particles at 260 mg/m^2, the mean value for cumulative urinary excretion of unchanged active substance accounted for 4% of the total administered dose with less than 1% as the metabolites 6α-

hydroxypaclitaxel and 3'-p-hydroxypaclitaxel, indicating extensive non-renal clearance. Paclitaxel is principally eliminated by hepatic metabolism and biliary excretion.

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

Hepatic impairment

The effect of hepatic impairment on population pharmacokinetics of Paclitaxel albumin-bound particles 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 hepatic function (as indicated by the baseline albumin or total bilirubin level) and neutropenia after adjusting for Paclitaxel albumin-bound particles exposure.

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

Renal impairment

Population pharmacokinetic analysis included patients with normal renal function (n=65), and pre-existing mild (n=61), moderate (n=23), or severe (n=l) renal impairment (according to draft FDA guidance criteria 2010). Mild to moderate renal impairment (creatinine clearance ≥30 to <90 mL /min) has no clinically important effect on the maximum elimination rate and systemic exposure (AUC and C_{max}) of paclitaxel. Pharmacokinetic data are insufficient for patients with severe renal impairment and not available for patients with end stage kidney disease.

Older people

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

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

Other intrinsic factors

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

13. PRECLINICAL SAFETY DATA:

The carcinogenic potential of paclitaxel has not been studied. However, based on the published literature, paclitaxel is a potentially carcinogenic and genotoxic agent at clinical doses, based upon its pharmacodynamic mechanism of action. Paclitaxel has been shown to be clastogenic in vitro (chromosome aberrations in human lymphocytes) and in vivo (micronucleus test in mice). Paclitaxel has been shown to be genotoxic in vivo (micronucleus test in mice), but it did not induce mutagenicity in the Ames test or the Chinese hamster ovary/hypoxanthine-guanine phosphoribosyl transferase (CHO/HGPRT) gene mutation assay.

Paclitaxel at doses below the human therapeutic dose was associated with low fertility and fetal toxicity in rats. Animal studies with Paclitaxel albumin-bound particles showed non-reversible, toxic effects on the male reproductive organs at clinically relevant exposure levels.

14. PATIENT COUNSELING INFORMATION

• Injection may cause fetal harm. Advise patients to avoid becoming pregnant while receiving this drug. Women of childbearing potential should use effective contraceptives while receiving PACLINAB®

• Advise men not to father a child while receiving PACLINAB®

• Patients must be informed of the risk of low blood cell counts and severe and life-threatening infections and instructed to contact their physician immediately for fever or evidence of infection.

• Patients should be instructed to contact their physician for persistent vomiting, diarrhea, or signs of dehydration.

- Patients must be informed that sensory neuropathy occurs frequently with PACLINAB® and patients should advise their physicians of numbness, tingling, pain or weakness involving the extremities
- Explain to patients that alopecia, fatigue/asthenia, and myalgia/arthralgia occur frequently with PACLINAB®
- Instruct patients to contact their physician for signs of an allergic reaction, which could be severe and sometimes fatal.
- Instruct patients to contact their physician immediately for sudden onset of dry persistent cough, or shortness of breath

Patient Information

PACLINAB®

(paclitaxel albumin-bound particles for injectable suspension)

Read this Patient Information before you start receiving PACLINAB® and before each infusion. This information does not take the place of talking with your doctor about your medical condition or your treatment.