PacliALL

Paclitaxel
(Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound))
Lyophilized powder for suspension for infusion 100 mg

WARNING : NEUTROPENIA

Do not administer PacliALL therapy to patients who have baseline neutrophil counts of less than 1,500 cells/$mm^{3.}$ In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell count be performed on all patients receiving PacliALL (see Contraindications, Warnings and Precautions and Adverse Reactions).

Note: An albumin form of paclitaxel may be substantially affect a drug's functional properties relative to those of drug in solution. DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS.

Composition
Each vial contains:

Paclitaxel	100 mg
Human Albumin	900 mg

Dosage form
Lyophilized powder for suspension for infusion

1 INDICATION AND USAGE
1.1 Metastatic Breast Cancer

PacliALL is indicated for the treatment of metastatic breast cancer after failure of firstline treatment for metastatic disease. Prior therapy should have included an anthracycline unless clinically contraindicated.

1.2 Non-Small Cell Lung Cancer

PacliALL is indicated for the first-line treatment of locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.

1.3 Adenocarcinoma of the Pancreas

PacliALL is indicated for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

2 DOSAGE AND ADMINISTRATION

2.1 Metastatic Breast Cancer

After failure of first line treatment, the recommended regimen for paclitaxel is 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks.

2.2 Non-Small Cell Lung Cancer

The recommended dose of paclitaxel is 100 mg/m^2 administered as an intravenous infusion over 30 minutes on Days 1, 8, and 15 of each 21-day cycle. Administer carboplatin on Day 1 of each 21-day cycle immediately after paclitaxel.

2.3 Adenocarcinoma of the Pancreas

The recommended dose of paclitaxel is 125 mg/m^2 administered as an intravenous infusion over 30-40 minutes on Days 1, 8, and 15 of each 28-day cycle. Administer gemcitabine immediately after paclitaxel on Days 1, 8, and 15 of each 28-day cycle.

2.4 Dosage in Patients with Hepatic Impairment

Hepatic impairment
For patients with mild hepatic impairment (total bilirubin > 1 to less than equal to (≤) 1.5 x ULN and aspartate aminotransferase [AST] less than equal to (≤) 10 x ULN), no dose adjustments are required, regardless of indication. Treat with same doses as patients with normal hepatic function. For metastatic breast cancer patients and non-small cell lung cancer patients with moderate to severe hepatic impairment (total bilirubin > 1.5 to less than equal to (≤) 5 x ULN and AST less than equal to (≤) 10 x ULN), a 20% reduction in dose is recommended. The reduced dose may be escalated to the dose for patients with normal hepatic function if the patient is tolerating the treatment for at least two cycles.
For patients with metastatic adenocarcinoma of the pancreas that have moderate to severe hepatic impairment, there are insufficient data to permit dosage recommendations. For patients with total bilirubin > 5 x ULN or AST > 10 x ULN, there are insufficient data to permit dosage recommendations regardless of indication.

Table 1: Recommendations for Starting Dose in Patients with Hepatic Impairment

	SGOT (AST) Levels		Bilirubin Levels	Paclitaxel Dose[a]		
				MBC	NSCLC[c]	Pancreatic[c] Adenocarcinoma
Mild	< 10 x ULN	AND	> ULN to ≤ 1.25 x ULN	260 mg/m^2	100 mg/m^2	125 mg/m^2
Moderate	< 10 x ULN	AND	1.26 to 2 x ULN	200 mg/m^2	75 mg/m^2	not recommended
Severe	< 10 x ULN	AND	2.01 to 5 x ULN	130 mg/m^2	50 mg/m^2	not recommended
	> 10 x ULN	OR	> 5 x ULN	not recommended	not recommended	not recommended

MBC= Metastatic Breast Cancer; NSCL = Non Small cell Lung Cancer

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

[b] A dose increase to 200 mg/m^2 in subsequent course should be considered based on individual tolerance.

[c] Patients with bilirubin levels above the upper limit of normal were excluded from clinical trials for pancreatic or lung cancer.

2.5 Dose Reduction/Discontinuation Recommendations

Metastatic Breast Cancer

Patients who experience severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer) or severe sensory neuropathy during paclitaxel therapy should have dosage reduced to 220 mg/m^2 for subsequent courses of paclitaxel. For recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m^2. For Grade 3 sensory neuropathy hold treatment until resolution to Grade 1 or 2, followed by a dose reduction for all subsequent courses of paclitaxel.

Non-Small Cell Lung Cancer

- Do not administer paclitaxel on Day 1 of a cycle until absolute neutrophil count (ANC) is at least 1500 cells/mm^3 and platelet count is at least 100,000 cells/mm^3.
- In patients who develop severe neutropenia or thrombocytopenia withhold treatment until counts recover to an absolute neutrophil count of at least 1500 cells/mm^3 and platelet count of at least 100,000 cells/mm^3 on Day 1 or to an absolute neutrophil count of at least 500 cells/mm^3 and platelet count of at least 50,000 cells/mm^3 on Days 8 or 15 of the cycle. Upon resumption of dosing, permanently reduce paclitaxel and carboplatin doses as outlined in Table 2.
- Withhold paclitaxel for Grade 3-4 peripheral neuropathy. Resume Paclitaxel and carboplatin at reduced doses (see Table 2) when peripheral neuropathy improves to Grade 1 or completely resolves.

Table 2: Permanent Dose Reduction for Hematologic and Neurologic Adverse Drug Reaction in NSCL

Adverse Drug Reaction	Occurrence	Weekly Paclitaxel Dose (mg/m^2)	Every 3-Week Carboplatin Dose (AUC mg•min/mL)
Neutropenic Fever (ANC less than 500/mm^3 with fever >38°C) OR Delay of next cycle by more than 7 days for ANC less than 1500/mm^3 OR ANC less than 500/mm^3 for more than 7 days	First	75	4.5
	Second	50	3
	Third	Discontinue Treatment	
Platelet count less than 50,000/mm^3	First	75	4.5
	Second	Discontinue Treatment	
Severe sensory Neuropathy – Grade 3 or 4	First	75	4.5
	Second	50	3
	Third	Discontinue Treatment	

Adenocarcinoma of the Pancreas
Dose level reductions for patients with adenocarcinoma of the pancreas, as referenced in Table 4 and 5, are provided in Table 3.

Table 3: Dose Level Reductions for Patients with Adenocarcinoma of the Pancreas

Dose Level	Paclitaxel (mg/m^2)	Gemcitabine (mg/m^2)
Full dose	125	1000
1st dose reduction	100	800
2nd dose reduction	75	600
If additional dose reduction required	Discontinue	Discontinue

Recommended dose modifications for neutropenia and thrombocytopenia for patients with adenocarcinoma of the pancreas are provided in Table 4.

Table 4: Dose Recommendation and Modifications for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or within a Cycle for Patients with Adenocarcinoma of the Pancreas

Cycle Day	ANC (cells/mm^3)		Platelet count (cells/mm^3)	Paclitaxel / Gemcitabine
Day 1	< 1500	OR	< 100,000	Delay doses until recovery
Day 8	500 to <1000	OR	50,000 to < 75,000	Reduce 1 dose level
	< 500	OR	< 50,000	Withhold doses
Day 15: IF Day 8 doses were reduced or given without modification:				
	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level from Day 8
	< 500	OR	< 50,000	Withhold doses
Day 15: IF Day 8 doses were withheld:				
	≥ 1000	OR	≥ 75,000	Reduce 1 dose level from Day 1
	500 to <1000	OR	50,000 to < 75,000	Reduce 2 dose levels drom Day 1
	< 500	OR	< 50,000	Withhold doses

Abbreviations: ANC = Absolute Neutrophil Count

Recommended dose modifications for other adverse drug reactions in patients with adenocarcinoma of the pancreas are provided in Table 5.

Table 5: Dose Modifications for Other Adverse Drug Reactions in Patients with Adenocarcinoma of the Pancreas

Adverse Drug Reaction	Paclitaxel	Gemcitabine
Febrile Neutropenia: Grade 3 or 4	Withhold until fever resolves and ANC ≥ 1500; resume at next dose level	
Peripheral Neuropathy: Grade 3 or 4	Withhold until improves to ≤ Grade 1; resume at next lower dose level	No dose reduction
Cutaneous Toxicity: Grade 3 or 4	Reduce to next lower dose level; discontinue treatment if toxicity persists	
Gastrointestinal Toxicity: Grade 3 mucositis or diarrhea	Withhold until improves to ≤ Grade 1; resume at next lower dose level	

2.6 Preparation and Administration Precautions

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

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

Premedication to prevent hypersensitivity reactions is generally not needed prior to the administration of Paclitaxel. Premedication may be needed in patients who have had prior hypersensitivity reactions to Paclitaxel. Patients who experience a severe hypersensitivity reaction to Paclitaxel should not be re-challenged with this drug.

Paclitaxel should only be prepared and administered by personnel appropriately trained in the handling of cytotoxic agents. Pregnant staff should not handle Paclitaxel.

2.7 Preparation for Intravenous Administration

Paclitaxel is supplied as a sterile lyophilized powder for reconstitution before use.

AVOID ERRORS, READ 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.

Calculate the exact total dosing volume of 5 mg/mL suspension required for the patient: Dosing volume (mL) = Total dose (mg)/5 (mg/mL).

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

Inject the appropriate amount of reconstituted paclitaxel 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 infusions. The use of an in-line filter is not recommended.

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

2.8 Stability

Unopened vials of paclitaxel are stable until the date indicated on the package when stored below 30°C in the original package. Neither freezing nor refrigeration adversely affects the stability of the product.

Stability of Reconstituted Suspension in the Vial

Reconstituted Paclitaxel 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 in the vial and in the infusion bas 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.

3 DOSAGE FORMS AND STRENGTHS

For injectable suspension: lyophilized powder containing 100 mg of paclitaxel in single-use vial for reconstitution.

4 CONTRAINDICATIONS

- Paclitaxel should not be used in patients who have baseline neutrophil counts of < 1,500 cells/mm^3.
- Patients who experience a severe hypersensitivity reaction to paclitaxel should not be rechallenged with the drug.

5 WARNING AND PRECAUTION

5.1 Hematological Effects

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

5.2 Nervous System

Sensory neuropathy is dose- and schedule-dependent. The occurrence of Grade 1 or 2 sensory neuropathy does not generally require dose modification. If ≥ Grade 3 sensory neuropathy develops, withhold Paclitaxel treatment until resolution to Grade 1 or 2 for metastatic breast cancer or until resolution to ≤ Grade 1 for NSCLC and pancreatic cancer followed by a dose reduction for all subsequent courses of paclitaxel.

For combination use of Paclitaxel and gemcitabine, if Grade 3 or higher peripheral neuropathy develops, withhold Paclitaxel; continue treatment with gemcitabine at the same dose. Resume Paclitaxel at reduced dose when peripheral neuropathy improves to Grade 0 or 1 (see section 4.2). For combination use of Paclitaxel and carboplatin, if Grade 3 or higher peripheral neuropathy develops, treatment should be withheld until improvement to Grade 0 or 1 followed by a dose reduction for all subsequent courses of Paclitaxel and carboplatin.

5.3 Sepsis

Sepsis occurred in 5% of patients with or without neutropenia who received Paclitaxel 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 ant biotics. For febrile neutropenia, interrupt Paclitaxel and gemcitabine until fever resolves and ANC ≥ 1500 cells/mm^3, then resume treatment at reduced dose levels.

5.4 Pneumonitis

Pneumonitis, including some cases that were fatal, occurred in 4% of patients receiving Paclitaxel in combination with gemcitabine. Monitor patients for signs and symptoms of pneumonitis and interrupt Paclitaxel and gemcitabine during evaluation of suspected pneumonitis. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with paclitaxel and gemcitabine.

5.5 Hypersensitivity

Severe and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, 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 Hepatic Impairment

Patients with hepatic impairment may be at increased risk of toxicity, particularly from myelosuppression; such patients should be closely monitored for development of profound myelosuppression. Paclitaxel is not recommended in patients that have total bilirubin > 5 x ULN or AST > 10 x ULN. In addition, Paclitaxel is not recommended in patients with metastatic adenocarcinoma of the pancreas that have moderate to severe hepatic impairment (total bilirubin > 1.5 x ULN and AST less than equal to (≤) 10 x ULN).

5.7 Human Albumin

Paclitaxel contains human albumin, 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 Pregnancy, Breast-feeding, Fertility

Pregnancy

Paclitaxel can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel protein-bound particles to rats during pregnancy at doses lower than the maximum recommended human dose, based on body surface area, caused embryofetal toxicities, including intrauterine mortality, increased resorptions, reduced numbers of live fetuses, and malformations. There are no adequate and well-controlled studies in pregnant women receiving Paclitaxel.

Paclitaxel should not be used in pregnancy, and in women of childbearing potential not using effective contraception, unless the clinical condition of the mother requires treatment with paclitaxel. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving paclitaxel.

Breast-feeding

Paclitaxel and/or its metabolites were excreted into the milk of lactating rats. It is not known if paclitaxel is excreted in human milk. Because of potential serious adverse reactions in breast-feeding infants, Paclitaxel is contraindicated during lactation. Breast-feeding must be discontinued for the duration of therapy.

Fertility

Paclitaxel induced infertility in male rats. Based on findings in animals, male and female fertility may be compromised. Male patients should seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with Paclitaxel.

5.9 Use in Men

Men should be advised not to father a child while receiving paclitaxel.

5.10 Effect on Ability to Drive and Use Machines

Paclitaxel has minor or moderate influence on the ability to drive and use machines. Paclitaxel may cause adverse reactions such as tiredness (very common) and dizziness (common) that may affect

the ability to drive and use machinery. Patients should be advised not to drive and use machines if they feel tired or dizzy.

6 ADVERSE REACTIONS

	Monotherapy	Combination therapy with gemcitabine	Combination therapy with carboplatin
Infections and infestations			
Common	Infection, urinary tract infection, folliculitis, upper respiratory tract infection, candidiasis, sinusitis	Sepsis, pneumonia, oral candidiasis	Pneumonia, bronchitis, upper respiratory tract infection, urinary tract infection
Uncommon	Sepsis, neutropenic sepsis, pneumonia, oral candidiasis, nasopharyngitis, cellulitis, herpes simplex, viral infection, herpes zoster, fungal infection, catheter-related infection, injection site infection		Sepsis, oral candidiasis
Neoplasm benign, malignant, and unspecified (including cysts and polyps)			
Uncommon	Tumour necrosis, metastatic pain		
Blood and lymphatic system disorders			
Very common	Bone marrow suppression, neutropenia, thrombocytopenia, anaemia, leukopenia, lymphopenia	Neutropenia, thrombocytopenia, anaemia	Neutropenia, thrombocytopenia, anaemia, leukopenia
Common	Febrile neutropenia	Pancytopenia	Febrile neutropenia, lymphopenia
Uncommon		Thrombotic thrombocytopenic purpura	Pancytopenia
Rare	Pancytopenia		
Immune system disorders			
Uncommon	Hypersensitivity		Drug hypersensitivity, hypersensitivity
Rare	Severe hypersensitivity		
Metabolism and nutrition disorders			
Very common	Anorexia	Dehydration, decreased appetite, hypokalaemia	Decreased appetite
Common	Dehydration, decreased appetite, hypokalaemia		Dehydration
Uncommon	Hypophosphataemia, fluid retention, hypoalbuminaemia, polydipsia, hyperglycaemia, hypocalcaemia, hypoglycaemia,		

	Monotherapy	Combination therapy with gemcitabine	Combination therapy with carboplatin
	hyponatraemia		
Not known	Tumour lysis syndrome		
Psychiatric disorders			
Very common		Depression, insomnia	
Common	Depression, insomnia, anxiety	Anxiety	Insomnia
Uncommon	Restlessness		
Nervous system disorders			
Very common	Peripheral neuropathy, neuropathy, hypoaesthesia, paraesthesia	Peripheral neuropathy, dizziness, headache, dysgeusia	Peripheral neuropathy
Common	Peripheral sensory neuropathy, dizziness, peripheral motor neuropathy, ataxia, headache, sensory disturbance, somnolence, dysgeusia		Dizziness, headache, dysgeusia
Uncommon	Polyneuropathy, areflexia, syncope, postural dizziness, dyskinesia, hyporeflexia, neuralgia, neuropathic pain, tremor, sensory loss	VIIth nerve paralysis	
Not known	Cranial nerve palsies multiple		
Eye disorders			
Common	Vision blurred, lacrimation increased, dry eye, keratoconjunctivitis sicca, madarosis	Lacrimation increased	Vision blurred
Uncommon	Reduced visual acuity, abnormal vision, eye irritation, eye pain, conjunctivitis, visual disturbance, eye pruritus, keratitis	Cystoid macular oedema	
Rare	Cystoid macular oedema		
Ear and labyrinth disorders			
Common	Vertigo		
Uncommon	Tinnitus, ear pain		
Cardiac disorders			
Common	Arrhythmia, tachycardia, supraventricular tachycardia	Cardiac failure congestive, tachycardia	
Rare	Cardiac arrest, cardiac failure congestive, left ventricular dysfunction, atrioventricular block, bradycardia		
Vascular disorders			
Common	Hypertension,	Hypotension,	Hypotension,

	Monotherapy	Combination therapy with gemcitabine	Combination therapy with carboplatin
	lymphoedema, flushing, hot flushes	hypertension	hypertension
Uncommon	Hypotension, orthostatic hypotension, peripheral coldness	Flushing	Flushing
Rare	Thrombosis		
Respiratory, thoracic and mediastinal disorders			
Very common		Dyspnoea, epistaxis, cough	Dyspnoea
Common	Interstitial pneumonitis, dyspnoea, epistaxis, pharyngolaryngeal pain, cough, rhinitis, rhinorrhoea	Pneumonitis, nasal congestion	Haemoptysis, epistaxis, cough
Uncommon	Pulmonary emboli, pulmonary thromboembolism, pleural effusion, exertional dyspnoea, sinus congestion, decreased breath sounds, productive cough, allergic rhinitis, hoarseness, nasal congestion, nasal dryness, wheezing	Dry throat, nasal dryness	Pneumonitis
Not known	Vocal cord paresis		
Gastrointestinal disorders			
Very common	Diarrhoea, vomiting, nausea, constipation, stomatitis	Diarrhoea, vomiting, nausea, constipation, abdominal pain, abdominal pain upper	Diarrhoea, vomiting, nausea, constipation
Common	Gastrooesophageal reflux disease, dyspepsia, abdominal pain, abdominal distension, abdominal pain upper, oral hypoaesthesia	Intestinal obstruction, colitis, stomatitis, dry mouth	Stomatitis, dyspepsia, dysphagia, abdominal pain
Uncommon	Rectal haemorrhage, dysphagia, flatulence, glossodynia, dry mouth, gingival pain, loose stools, oesophagitis, abdominal pain lower, mouth ulceration, oral pain		
Hepatobiliary disorders			
Common		Cholangitis	Hyperbilirubinaemia
Uncommon	Hepatomegaly		
Skin and subcutaneous tissue disorders			
Very common	Alopecia, rash	Alopecia, rash	Alopecia, rash
Common	Pruritus, dry skin, nail disorder, erythema, nail pigmentation/discolouration,	Pruritus, dry skin, nail disorder	Pruritus, nail disorder

	Monotherapy	Combination therapy with gemcitabine	Combination therapy with carboplatin
	skin hyperpigmentation, onycholysis, nail changes		
Uncommon	Photosensitivity reaction, urticaria, skin pain, generalised pruritus, pruritic rash, skin disorder, pigmentation disorder, hyperhidrosis, onychomadesis, erythematous rash, generalised rash, dermatitis, night sweats, maculo-papular rash, vitiligo, hypotrichosis, nail bed tenderness, nail discomfort, macular rash, papular rash, skin lesion, swollen face		Skin exfoliation, dermatitis allergic, urticaria
Very rare	Steven-Johnson syndrome, toxic epidermal necrolysis		
Not known	Palmar – plantar erythrodysaesthesiae syndrome, scleroderma		
Musculoskeletal and connective tissue disorders			
Very common	Arthralgia, myalgia	Arthralgia, myalgia, pain in extremity	Arthralgia, myalgia
Common	Back pain, pain in extremity, bone pain, muscle cramps, limb pain	Muscular weakness, bone pain	Back pain, pain in extremity, musculoskeletal pain
Uncommon	Chest wall pain, muscular weakness, neck pain, groin pain, muscle spasms, musculoskeletal pain, flank pain, limb discomfort, muscle weakness		
Renal and urinary disorders			
Common		Acute renal failure	
Uncommon	Haematuria, dysuria, pollakiuria, nocturia, polyuria, urinary incontinence	Haemolytic uraemic syndrome	
Reproductive system and breast disorders			
Uncommon	Breast pain		
General disorders and administration site conditions			
Very common	Fatigue, asthenia, pyrexia	Fatigue, asthenia, pyrexia, oedema peripheral, chills	Fatigue, asthenia, oedema peripheral
Common	Malaise, lethargy, weakness, peripheral oedema, mucosal inflammation, pain, rigors,	Infusion site reaction	Pyrexia, chest pain

	Monotherapy	Combination therapy with gemcitabine	Combination therapy with carboplatin
	oedema, decreased performance status, chest pain, influenza-like illness, hyperpyrexia		
Uncommon	Chest discomfort, abnormal gait, swelling, injection site reaction		Mucosal inflammation, infusion site extravasation, infusion site inflammation, infusion site rash
Rare	Extravasation		
Investigations			
Very common		Weight decreased, alanine aminotransferase increased	
Common	Decreased weight, increased alanine aminotransferase, increased aspartate aminotransferase, decreased haematocrit, decreased red blood cell count, increased body temperature, increased gamma-glutamyltransferase, increased blood alkaline phosphatase	Aspartate aminotransferase increased, blood bilirubin increased, blood creatinine increased	Weight decreased, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased
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		

7 DRUG INTERACTIONS

The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering paclitaxel 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, and nevirapine) either CYP2C8 or CYP3A4.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D.

There are no adequate and well-controlled studies in pregnant women using paclitaxel. Based on its mechanism of action and findings in animals, paclitaxel can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving paclitaxel.

8.2 Nursing Mothers

It is not known whether paclitaxel is excreted in human milk. Paclitaxel and/or its metabolites were excreted into the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.3 Pediatric Use

The safety and effectiveness of paclitaxel in pediatric patients have not been evaluated.

8.4 Patients with Hepatic Impairment

Because the exposure and toxicity of paclitaxel can be increased in patients with hepatic impairment, the administration of paclitaxel should be performed with caution in patients with hepatic impairment Paclitaxel has not been studied in combination with gemcitabine for the treatment of pancreatic cancer in patients with a bilirubin greater than the upper limit of normal.

8.5 Patients with Renal Impairment

The use of paclitaxel has not been studied in patients with renal impairment.

9 OVERDOSAGE

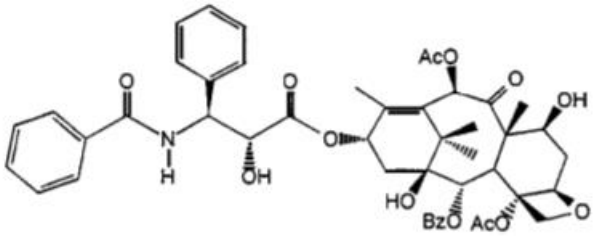
There is no known antidote for paclitaxel overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, sensory neurotoxicity, and mucositis.

10 DESCRIPTION

PacliALL for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. Paclitaxel exists in the particles in a noncrystalline, amorphous state. PacliALL 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, potassium, N-acetyl-DL-tryptophan, and caprylic acid). Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. PacliALL is free of solvents.

The active agent in PacliALL is paclitaxel, a microtubule inhibitor. The chemical name for paclitaxel is 5β,20-Epoxy1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine.

Paclitaxel has the following structural formula:



Paclitaxel is a white to off-white crystalline powder with the empirical formula $C_{47}H_{51}NO_{14}$ 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 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.

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

11.2 Pharmacokinetics

Absorption

The pharmacokinetics of total paclitaxel following 30 and 180-minute infusions of Paclitaxel at dose levels of 80 to 375 mg/m^2 were determined in clinical studies. Dose levels of mg/m^2 refer to mg of paclitaxel. Following intravenous administration of paclitaxel plasma concentrations declined in a biphasic manner, the initial rapid decline representing distribution to the peripheral compartment and the slower second phase representing drug elimination. The terminal half-life was approximately 27 hours.

The drug exposure (AUCs) was dose proportional over 80 to 375 mg/m^2 and the pharmacokinetics of paclitaxel were independent of the duration of Paclitaxel administration. At the dose of 260 mg/m^2 for metastatic breast cancer, the mean maximum concentration of paclitaxel, which occurred at the end of the infusion, was 18,741 ng/mL. The mean total clearance was 15 L/hr/m^2. The mean volume of distribution was 632 L/m^2 indicating extensive extravascular distribution and/or tissue binding of paclitaxel.

The pharmacokinetic data of 260 mg/m^2 paclitaxel protein bound particles administered over a 30-minute infusion was compared to the pharmacokinetics of 175 mg/m^2 paclitaxel injection over a 3-

hour infusion. The clearance was larger (43%) and the volume of distribution was also higher (53%) for PacliALL than for paclitaxel injection. Differences in the maximum concentration (C_{max}) and dose-corrected C_{max} reflected differences in total dose and rate of infusion. There were no differences in terminal half-lives.

Distribution
In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 µg/mL, indicated that between 89% to 98% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

Metabolism
In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6α-hydroxypaclitaxel by CYP2C8; and to two minor metabolites, 3'-p-hydroxypaclitaxel and 6α, 3'-*p*-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6 α-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 α -ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α -hydroxypaclitaxel *in vitro*. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inh bitors of CYP2C8 and/or CYP3A4.

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

Fecal excretion was approximately 20% of the total dose administered.

Effect of Hepatic Impairment
Based on published paper, the pharmacokinetic profile of paclitaxel administered as a 30-minute infusion was evaluated in 15 out of 30 solid tumor patients with mild to severe hepatic impairment defined by serum bilirubin levels and AST levels. Patients with AST > 10 x ULN or bilirubin > 5 x ULN were not enrolled. Paclitaxel doses were assigned based on the degree of hepatic impairment as described:

- Mild (bilirubin > ULN to 1.25 x ULN and AST > ULN and less than 10 x ULN): 260 mg/m^2
- Moderate (bilirubin 1.26 to 2 x ULN and AST > ULN and less than 10 x ULN): 200 mg/m^2
- Severe (bilirubin 2.01 to 5 x ULN and AST > ULN and less than 10 x ULN): 130 mg/m^2
- The 260 mg/m^2 dose for mild hepatic impairment and the 200 mg/m^2 dose for moderate hepatic impairment resulted in paclitaxel exposures within the range seen in patients with normal hepatic function. The 130 mg/m^2 dose in patients with severe hepatic impairment resulted in lower paclitaxel exposures than those seen in normal subjects. In addition, patients with severe hepatic impairment had higher mean cycle 1 absolute neutrophil count (ANC) nadir values than those with mild and moderate hepatic impairment. The 200 mg/m^2 dose has not been evaluated in patients with severe hepatic impairment, but it is predicted to adjust the paclitaxel AUC to the range observed in patients with normal hepatic function. There are no data for patients with AST >10 x ULN or bilirubin >5 x ULN.

Effect of Renal Impairment
The effect of renal impairment on the disposition of paclitaxel has not been studied.

Pharmacokinetic Interactions between Paclitaxel and Carboplatin
Administration of carboplatin immediately after the completion of the PacliALL infusion to patients with NSCLC did not cause clinically meaningful changes in paclitaxel exposure. The observed mean AUC_{inf} of free carboplatin was approximately 23% higher than the targeted value (6 min*mg/mL), but its mean half-life and clearance were consistent with those reported in the absence of paclitaxel.

Pharmacokinetic Interactions between and Paclitaxel and Gemcitabine
Pharmacokinetic interactions between paclitaxel and gemcitabine have not been studied in humans.

12 NONCLINICAL TOXICOLOGY
12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
The carcinogenic potential of paclitaxel has not been studied.

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

Administration of paclitaxel protein-bound particles to male rats at 42 mg/m^2 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 low incidence of skeletal and soft tissue fetal anomalies was also observed at doses of 3 and 12 mg/m^2 /week in this study (approximately 1 to 5% of the daily maximum recommended human exposure on a mg/m^2 basis). Testicular atrophy/degeneration was observed in single-dose toxicology studies in rodents administered paclitaxel protein-bound particles at doses lower than the recommended human dose; doses were 54 mg/m^2 in rodents and 175 mg/m^2 in dogs.

13. REPORTING OF SUSPECTED ADVERSE REACTIONS
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Healthcare professionals are asked to report any suspected adverse reactions via:
Pusat Farmakovigilans/MESO Nasional Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Phone: +62-21-4244691 Ext.1079
Website: https://e-meso.pom.go.id/ADR

For adverse event and product quality complaint, please contact pv.soho@sohoglobalhealth.com or (021) 460-555.

14 HOW SUPPLIED/STORAGE AND HANDLING
14.1 How Supplied
100 mg of paclitaxel in a single-use vial, individually packaged in a carton.
14.2 Storage

Do not store above 30°C. Reconstituted suspension should be stored in the original carton at 2°C to 8°C (36° F to 46° F). (See USP Controlled Room Temperature). Protect from bright light.
Use reconstituted suspension within 24 hours. Discard any unused portion

14.3 Handling and Disposal
Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published [*see References* (13)]. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

15 SHELF LIFE
2 years from the date of manufacture.

16 INCOMPATIBILITIES
Not known.

17 PATIENT COUNSELING INFORMATION

- Paclitaxel 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 paclitaxel.
- Advise men not to father a child while receiving paclitaxel.
- 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 paclitaxel 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 paclitaxel.
- 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

ON MEDICAL PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

DKIXXXXXXXXXXXX

Manufactured by :
Panacea Biotec Pharma Ltd.
Malpur, Baddi, Distt. Solan (H.P)
173205, India

Imported and Marketed by :
PT SOHO Industri Pharmasi
a **SOHO Global Health** Company
Jakarta - Indonesia

PacliALL

Paclitaxel
Paclitaxel Protein – Bound Particles for Injectable Suspension (Albumin Bound) 100 mg
Serbuk Liofilisasi untuk Infus Suspensi

Baca seluruh brosur ini dengan seksama sebelum Anda mulai menggunakan obat ini karena terdapat informasi penting untuk Anda.

- Simpan brosur ini. Anda mungkin perlu untuk membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter atau apoteker Anda.
- Obat ini hanya diresepkan untuk Anda. Jangan berikan obat ini kepada orang lain. Obat ini dapat membahayakan mereka, meskipun gejala penyakit mereka sama dengan Anda.
- Jika Anda mengalami efek samping, bicarakan dengan dokter, apoteker, atau perawat Anda. Hal ini termasuk kemungkinan efek samping lainnya yang tidak tercantum dalam brosur ini.

Apa yang ada dalam brosur ini?

1. Apa itu *PacliALL* dan apa kandungannya?

- *PacliALL* adalah obat yang mengandung zat aktif Paclitaxel *(Paclitaxel Protein – Bound Particles for Injectable Suspension (Albumin Bound))* dengan kekuatan 100 mg. Paclitaxel yang menempel pada albumin manusia (human albumin), dalam bentuk partikel kecil yang dikenal sebagai nanopartikel. Paclitaxel termasuk dalam kelompok obat *taxanes* yang digunakan pada pengobatan kanker.

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- Paclitaxel adalah bagian dari obat yang mempengaruhi sel kanker, bekerja dengan menghentikan pembelahan sel kanker – ini berarti sel kanker mati.
- Albumin adalah bagian dari obat yang membantu Paclitaxel larut dalam darah dan menembus dinding pembuluh darah menuju tumor. Ini berarti bahwa bahan kimia lain yang dapat menyebabkan efek samping yang mengancam jiwa tidak diperlukan. Efek samping seperti itu terjadi jauh lebih sedikit dengan *PacliALL*.
- Albumin yang digunakan adalah larutan Human Albumin 25% yang mengandung bahan tambahan Sodium, Potassium, N-acetyl-DL-tryptophan, dan Caprylic acid.

2. Untuk apa *PacliALL* digunakan?

PacliALL digunakan untuk mengobati jenis kanker berikut:

Kanker Payudara
- Kanker payudara yang telah menyebar ke bagian tubuh lain (ini disebut kanker payudara "metastatik").
- *PacliALL* digunakan pada kanker payudara metastatik ketika setidaknya terapi lini pertama telah dicoba tetapi tidak berhasil dan pada terapi sebelumnya Anda harus sudah menggunakan pengobatan yang mengandung kelompok obat anthracyclines kecuali dikontraindikasikan.

Kanker Pankreas
- *PacliALL* digunakan bersama dengan obat *gemcitabine* jika Anda menderita kanker pankreas metastatik.

Kanker Paru
- *PacliALL* juga digunakan bersama dengan *carboplatin* jika Anda menderita jenis kanker paru non-sel kecil (NSCLC) tingkat lanjut atau metastatik tapi pembedahan atau radioterapi tidak cocok untuk mengobati kanker tersebut.

3. Berapa banyak dan seberapa sering *PacliALL* harus diberikan, dan berapa lama pengobatan akan berlangsung?

Berapa banyak PacliALL harus diberikan?
PacliALL akan diberikan kepada Anda oleh dokter atau perawat ke dalam vena melalui infus. Dosis yang Anda terima didasarkan pada luas permukaan tubuh anda dan hasil tes darah. Dosis umum untuk kanker payudara adalah 260 mg/m^2 luas permukaan tubuh yang diberikan selama periode 30 menit. Dosis umum untuk kanker pankreas stadium lanjut adalah 125mg/m^2 luas permukaan tubuh yang diberikan selama periode 30 menit. Dosis umum untuk kanker paru non-sel kecil adalah 100 mg/m^2 luas permukaan tubuh yang diberikan selama periode 30 menit.

Seberapa sering Anda akan diberikan PacliALL?
Untuk pengobatan kanker payudara metastatik, *PacliALL* biasa diberikan setiap tiga minggu sekali (pada hari ke-1 dari siklus 21 hari).

Untuk pengobatan kanker pankreas stadium lanjut, *PacliALL* diberikan pada hari ke-1, 8, dan 15 dari setiap siklus pengobatan 28 hari dengan *gemcitabine* diberikan segera setelah *PacliALL.*

Untuk pengobatan kanker paru non-sel kecil *PacliALL* diberikan seminggu sekali (yaitu pada hari ke-1, 8, dan 15 dari siklus 21 hari), dengan *carboplatin* diberikan setiap tiga minggu sekali (yaitu hanya pada hari ke-1 setiap siklus 21 hari), segera setelah dosis *PacliALL* diberikan.

Apa yang harus dilakukan jika dosis terlewat?

Jangan mengambil dosis ganda untuk memenuhi dosis yang terlupakan. Ambil dosis berikutnya pada waktu yang biasanya dengan berkonsultasi dengan dokter Anda. (Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan produk ini, tanyakan kepada dokter atau apoteker Anda).

Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan kepada dokter atau perawat Anda.

4. Apa yang harus Anda ketahui sebelum menggunakan *PacliALL*?

Jangan gunakan PacliALL

- Jika anda alergi (hipersensitif) terhadap *Paclitaxel* atau bahan lain yang terkandung dalam *PacliALL*
- Jika Anda sedang menyusui
- Jika Anda memiliki jumlah sel darah putih yang rendah (jumlah neutrofil dasar <1500 sel/mm^3 – dokter Anda akan memberitahu Anda tentang ini)

Kapan *PacliALL* tidak boleh digunakan?

Jika Anda mengalami salah satu dari kondisi yang tercantum di bawah ini pada pemberian *PacliALL*, hentikan pengobatan atau kurangi dosis setelah berkonsultasi dengan dokter Anda.

- Jika Anda mengalami memar, pendarahan, atau tanda-tanda infeksi yang abnormal seperti sakit tenggorokan atau demam
- Jika Anda mengalami mati rasa, kesemutan, sensasi tertusuk, kepekaan terhadap sentuhan, atau kelemahan otot
- Jika Anda mengalami masalah pernapasan, seperti sesak napas atau batuk kering

Anak-anak dan remaja

PacliALL hanya digunakan untuk pasien dewasa dan tidak boleh digunakan pada anak dan remaja di bawah 18 tahun.

PacliALL mengandung natrium

Setiap ml *PacliALL* mengandung sekitar 4,2 mg natrium. Hal ini harus dipertimbangkan jika Anda menjalani diet natrium terkontrol.

Mengemudi dan menggunakan mesin

Beberapa orang mungkin merasa lelah atau pusing setelah diberikan *PacliALL.* Jika ini terjadi pada Anda, jangan mengemudi atau menggunakan alat atau mesin apa pun.

Jika Anda diberikan obat lain sebagai bagian dari perawatan, Anda harus meminta saran dokter tentang mengemudi dan menggunakan mesin.

Obat atau makanan lain yang harus dihindari dengan penggunaan *PacliALL*

Beri tahu dokter Anda jika sedang mengonsumsi atau baru saja mengonsumsi obat lain. Ini termasuk obat-obatan yang diperoleh tanpa resep, termasuk obat-obatan herbal. Ini karena *PacliALL* dapat mempengaruhi cara kerja beberapa obat lain. Selain itu, beberapa obat lain juga dapat mempengaruhi cara kerja *PacliALL*.

Berhati-hatilah dan bicarakan dengan dokter Anda saat menggunakan *PacliALL* bersamaan dengan salah satu dari berikut ini:

- Obat-obatan untuk mengobati infeksi (yaitu antibiotik seperti *erythromycin*, *rifampicin*, dll.; tanyakan kepada dokter, perawat atau apoteker Anda jika tidak yakin apakah obat yang Anda minum adalah antibiotik), dan termasuk obat-obatan untuk mengobati infeksi jamur (misalnya *Ketoconazol*)
- Obat-obatan untuk menstabilkan suasana hati Anda yang kadang disebut sebagai antidepresan (misalnya *Fluoxetine*)
- Obat-obatan untuk mengobati kejang (epilepsi) (misalnya *Carbamazepine*, *Phenytoin*)
- Obat-obatan untuk membantu menurunkan kadar lipid darah (misalnya *Gemfibrozil*)
- Obat-obatan untuk nyeri ulu hati atau ulkus lambung (misalnya *cimetidine*)
- Obat-obatan untuk HIV dan AIDS (misalnya *Ritonavir*, *Saquinavir*, *Indinavir*, *Nelfinavir*, *Efavirenz*, *Nevirapine*)
- Obat *Clopidogrel* yang digunakan untuk mencegah pembekuan darah

Peringatan dan Pencegahan
Bicarakan dengan dokter atau perawat Anda sebelum menggunakan *PacliALL*
- Jika Anda memiliki fungsi ginjal yang buruk
- Jika Anda memiliki gangguan hati yang parah
- Jika Anda memiliki gangguan jantung

Kehamilan, menyusui dan kesuburan
PacliALL dapat menyebabkan cacat lahir yang serius dan karenanya tidak boleh digunakan jika Anda sedang hamil.

Wanita usia subur harus menggunakan kontrasepsi yang efektif selama dan hingga 1 bulan setelah menerima pengobatan *PacliALL*.

Jangan menyusui saat dalam pengobatan *PacliALL* karena tidak diketahui apakah zat aktif *PacliALL* masuk ke dalam ASI.

Pasien pria disarankan untuk tidak memiliki anak selama dan hingga enam bulan setelah perawatan dan harus mencari konsultasi terkait konservasi sperma sebelum perawatan karena kemungkinan infertilitas ireversibel akibat terapi dengan *PacliALL*.

Mintalah saran dokter Anda sebelum menggunakan obat ini

5. Apa gejala efek samping yang mungkin terjadi?

Layaknya semua obat-obatan, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya.

	Monoterapi	**Terapi kombinasi dengan gemcitabine**	**Terapi kombinasi dengan carboplatin**
Infeksi dan Infestasi			
Umum	Infeksi, infeksi saluran kemih, infeksi folikel rambut, infeksi saluran pernapasan atas, infeksi jamur kandida, infeksi sinus	Infeksi berat, pneumonia, infeksi jamur kandida pada mulut	Pneumonia, bronkitis, infeksi saluran pernapasan atas, infeksi saluran kemih
Tidak umum	Infeksi berat, kadar neutrofil di dalam darah		Infeksi berat, infeksi jamur kandida pada

	Monoterapi	Terapi kombinasi dengan gemcitabine	Terapi kombinasi dengan carboplatin
	rendah, pneumonia, infeksi jamur kandida pada mulut, infeksi saluran pernafasan atas, infeksi kulit, herpes, infeksi virus, herpes zoster, infeksi jamur, infeksi terkait kateter, infeksi tempat suntikan		mulut
Neoplasma jinak, ganas dan tidak spesifik (termasuk kista dan polip)			
Tidak umum	Kematian sel tumor, nyeri akibat penyebaran sel kanker		
Gangguan sistem darah dan limfatik			
Sangat umum	Penekanan sumsum tulang, jumlah neutrofil dalam darah rendah, jumlah trombosit dalam darah rendah, anemia, jumlah sel leukosit dalam darah rendah, jumlah sel limfosit dalam darah rendah	Jumlah neutrofil di dalam darah rendah, jumlah trombosit dalam darah rendah, anemia	Jumlah neutrofil dalam darah rendah, jumlah trombosit dalam darah rendah, anemia, jumlah sel leukosit dalam darah rendah
Umum	Jumlah neutrofil dalam darah rendah yang disertai demam	Jumlah sel darah merah, sel darah putih, dan trombosit berada di bawah batas normal	Jumlah neutrofil dalam darah rendah yang disertai demam, jumlah sel limfosit dalam darah rendah
Tidak umum		Darah lebih cepat menggumpal	Jumlah sel darah merah, sel darah putih, dan trombosit berada di bawah batas normal
Jarang	Jumlah sel darah merah, sel darah putih, dan trombosit berada di bawah batas normal		
Gangguan sistem imun			
Tidak umum	Reaksi alergi		Reaksi alergi terhadap obat, reaksi alergi
Jarang	Reaksi alergi berat		
Gangguan metabolisme dan nutrisi			
Sangat umum	Nafsu makan menurun	Kehilangan cairan, nafsu makan menurun, kekurangan kalium	Nafsu makan menurun
Umum	Kehilangan cairan, nafsu makan menurun, kekurangan kalium		Kehilangan cairan
Tidak umum	Kekurangan kadar fosfat, kelebihan cairan, kekurangan albumin, haus berlebihan, gula darah meningkat, kekurangan kalsium, kekurangan gula darah, kekurangan natrium/garam		

	Monoterapi	Terapi kombinasi dengan gemcitabine	Terapi kombinasi dengan carboplatin
Tidak diketahui	Kelainan akibat kematian sel tumor		
Gangguan kejiwaan			
Sangat umum		Depresi, kesulitan tidur	
Umum	Depresi, kesulitan tidur, kecemasan	Kecemasan	Kesulitan tidur
Tidak umum	Gelisah		
Gangguan sistem saraf			
Sangat umum	Kerusakan saraf perifer, kerusakan saraf, berkurangnya sensitivitas terhadap sentuhan, kesemutan	Kerusakan saraf perifer, pusing, sakit kepala, gangguan persepsi rasa di lidah	Kerusakan saraf perifer
Umum	Kerusakan saraf sensorik perifer, pusing, kerusakan saraf motorik perifer, gangguan gerakan tubuh, sakit kepala, gangguan sensorik, penurunan kesadaran, gangguan persepsi rasa di lidah		Pusing, sakit kepala, gangguan persepsi rasa di lidah
Tidak umum	Kerusakan saraf, kehilangan reflex pada otot, pingsan, pusing saat tubuh berubah posisi, gerakan tubuh yang cepat dan tidak terkendali, otot kurang responsif, nyeri berat pada saraf, nyeri akibat kerusakan saraf, tremor, kehilangan sensori	Kelumpuhan saraf VII	
Tidak diketahui	Kelumpuhan saraf kranial multipel		
Gangguan mata			
Umum	Penglihatan kabur, produksi air mata meningkat, mata kering, kerontokan bulu mata	Produksi air mata meningkat	Penglihatan kabur
Tidak umum	Ketajaman penglihatan berkurang, penglihatan abnormal, iritasi mata, sakit mata, mata merah, gangguan penglihatan, mata gatal, infeksi pada kornea mata	Pembengkakan pada retina	
Jarang	Pembengkakan pada retina		
Gangguan telinga dan labirin			
Umum	Vertigo		
Tidak umum	Telinga berdenging, sakit telinga		
Gangguan jantung			
Umum	Gangguan irama jantung, denyut jantung cepat	Gagal jantung kongestif, denyut jantung cepat	
Jarang	Henti jantung, jantung gagal memompa darah, ketidaknormalan bilik		

	Monoterapi	Terapi kombinasi dengan gemcitabine	Terapi kombinasi dengan carboplatin
	jantung kiri, denyut jantung terhambat, denyut jantung lambat		
Gangguan pembuluh darah			
Umum	Peningkatan tekanan darah, pembengkakan getah bening, muka memerah, sensasi panas	Penurunan tekanan darah, peningkatan tekanan darah	Penurunan tekanan darah, peningkatan tekanan darah
Tidak umum	Penurunan tekanan darah, penurunan tekanan darah akibat perubahan posisi duduk, akral dingin	Muka memerah	Muka memerah
Jarang	Penyumbatan pembuluh darah		
Gangguan pernapasan, toraks dan rongga dada			
Sangat umum		Sesak napas, mimisan, batuk	Sesak napas
Umum	Peradangan paru bawah bagian intertisial, sesak napas, mimisan, sakit tenggorokan, batuk, radang pada rongga hidung, hidung berair	Peradangan paru bawah, hidung tersumbat	Batuk darah, mimisan, batuk
Tidak umum	Penyumbatan pembuluh darah di paru, terbentuknya bekuan darah (trombus) yang menyumbat pembuluh darah paru, penumpukan cairan pada rongga selubung luar paru, sesak napas saat beraktivitas, hidung tersumbat, penurunan suara napas, batuk berdahak, alergi pada hidung, suara serak, hidung tersumbat, hidung kering, mengeluarkan suara mengi	Tenggorokan kering, hidung kering	Peradangan paru bawah
Tidak diketahui	Kelumpuhan pita suara		
Gangguan saluran pencernaan			
Sangat umum	Diare, muntah, mual, sembelit, sariawan	Diare, muntah, mual, sembelit, nyeri perut, nyeri perut bagian atas	Diare, muntah, mual, sembelit
Umum	Penyakit asam lambung naik ke tenggorokan, perut terasa tidak nyaman, nyeri perut, penumpukan gas didalam perut, nyeri perut bagian atas, penurunan sensitivitas pada daerah mulut	Penyumbatan pada usus, peradangan usus besar, sariawan, mulut kering	Sariawan, perut terasa tidak nyaman, kesulitan menelan, nyeri perut
Tidak umum	Perdarahan pada rektum, kesulitan menelan, buang gas dari anus, sensasi panas pada mulut, mulut kering, nyeri gusi, diare,		

	Monoterapi	Terapi kombinasi dengan gemcitabine	Terapi kombinasi dengan carboplatin
	peradangan pada kerongkongan, nyeri perut bagian bawah, luka pada mulut, nyeri mulut		
Gangguan pada hati dan empedu			
Umum		Infeksi pada saluran empedu	Peningkatan kadar bilirubin di dalam darah
Tidak umum	Pembesaran organ hati		
Gangguan kulit dan jaringan subkutan			
Sangat umum	Kerontokan rambut, ruam kulit	Kerontokan rambut, ruam kulit	Kerontokan rambut, ruam kulit
Umum	Gatal, kulit kering, kelainan kuku, kemerahan pada kulit, pigmentasi/perubahan warna kuku, warna kulit menggelap, kuku lepas, perubahan kuku	Gatal, kulit kering, kelainan kuku	Gatal, kelainan kuku
Tidak umum	Reaksi tubuh berlebihan saat terkena radiasi ultraviolet, infeksi kulit lapisan atas, nyeri kulit, gatal menyeluruh, ruam gatal, kelainan kulit, kelainan pigmentasi, keringat berlebih, pelepasan kuku, ruam kemerahan, ruam umum, dermatitis, keringat malam, ruam bercak-bruntus, kelainan ada bercak putih pada kulit, kerontokan, nyeri tekan dasar kuku, rasa tidak nyaman pada kuku, ruam bercak, ruam bruntus, lecet pada kulit, wajah bengkak		Pengelupasan kulit, dermatitis alergi, infeksi kulit lapisan atas.
Sangat jarang	Sindrom Steven-Johnson, kerusakan kulit		
Tidak diketahui	Sindrom eritrodisestesia palmar-plantar , scleroderma/ kelainan pada kulit		
Gangguan muskuloskeletal dan jaringan ikat			
Sangat umum	Nyeri sendi, nyeri otot	Nyeri sendi, nyeri otot, nyeri pada anggota gerak tubuh	Nyeri sendi, nyeri otot
Umum	Nyeri punggung, nyeri pada anggota gerak tubuh, nyeri tulang, kram otot, nyeri tungkai	Kelemahan otot, nyeri tulang	Nyeri punggung, nyeri pada anggota gerak tubuh, nyeri muskuloskeletal
Tidak umum	Nyeri dinding dada, kelemahan otot, nyeri leher, nyeri selangkangan, kejang otot, nyeri muskuloskeletal, nyeri		

	Monoterapi	Terapi kombinasi dengan gemcitabine	Terapi kombinasi dengan carboplatin
	panggul, ketidaknyamanan tungkai, kelemahan otot		
Gangguan ginjal dan saluran kemih			
Umum		Gagal ginjal akut	
Tidak umum	Adanya darah dalam urin, nyeri saat buang air kecil, gangguan buang air kecil, sering buang air kecil berlebih di malam hari, sering buang air kecil, sulit menahan buang air kecil.	Infeksi pembuluh darah pada ginjal	
Gangguan sistem reproduksi dan payudara			
Tidak umum	Nyeri payudara		
Gangguan umum dan kondisi tempat administrasi			
Sangat umum	Kelelahan, kelemahan fisik, demam	Kelelahan, kelemahan fisik, demam, pembengkakan pada kaki dan tangan, menggigil	Kelelahan, kelemahan fisik, pembengkakan pada kaki dan tangan
Umum	Lelah, lesu, lemah, pembengkakan pada kaki dan tangan, radang mukosa, nyeri, kekakuan, bengkak, status kinerja menurun, nyeri dada, penyakit seperti influenza, demam tinggi	Reaksi tempat infus	Demam, nyeri dada
Tidak umum	Ketidaknyamanan dada, gaya berjalan abnormal, pembengkakan, reaksi di tempat suntikan		Peradangan mukosa, kebocoran cairan pada lokasi infus, peradangan lokasi infus, ruam lokasi infus
Jarang	Kebocoran cairan dari pembuluh darah		
Investigasi			
Sangat umum		Penurunan berat badan, peningkatan alanin aminotransferase	
Umum	Penurunan berat badan, peningkatan alanin aminotransferase, peningkatan aspartat aminotransferase, penurunan hematokrit, penurunan jumlah sel darah merah, peningkatan suhu tubuh, peningkatan gamma-glutamiltransferase, peningkatan alkali fosfatase darah	Peningkatan aspartate aminotransferase, peningkatan bilirubin darah, peningkatan kreatinin darah	Penurunan berat badan, peningkatan alanin aminotransferase, peningkatan aspartat aminotransferase, peningkatan alkaline phosphatase darah
Tidak umum	Peningkatan tekanan darah, peningkatan berat badan, peningkatan laktat dehidrogenase darah,		

	Monoterapi	Terapi kombinasi dengan gemcitabine	Terapi kombinasi dengan carboplatin
	peningkatan kreatinin darah, peningkatan guladarah, peningkatan fosfor darah, penurunan kalium darah, peningkatan bilirubin		
Cedera, keracunan dan komplikasi prosedural			
Tidak umum	Luka memar		
Jarang	Fenomena penarikan radiasi, infeksi paru-paru akibat radiasi		

Pelaporan efek samping
Jika Anda mengalami efek samping, bicarakan dengan dokter atau perawat Anda. Hal ini termasuk kemungkinan efek samping lainnya yang tidak tercantum dalam *leaflet* ini.

Untuk pelaporan efek samping dan keluhan kualitas produk, dapat menghubungi pv.soho@sohoglobalhealth.com or (021) 460-5550.

Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

6. Jika diberikan dengan dosis lebih tinggi, apa saja tanda/gejala overdosis?

Overdosis
Jika terjadi overdosis, segera laporkan pada dokter Anda atau datangi Unit Gawat Darurat terdekat.

7. Bagaimana cara penyimpanan *PacliALL*?

Jauhkan obat ini dari jangkauan anak-anak.
Jangan gunakan obat melewati tanggal kadaluwarsa yang tertera pada label botol dan karton kemasan.
Tanggal kadaluwarsa mengacu pada hari terakhir bulan yang tertera. Simpan pada suhu tidak melebihi 30°C, lindungi dari cahaya dan kelembapan.
Simpan vial di dalam karton kemasan, untuk melindungi dari cahaya. Cairan infus harus jernih dan tidak berwarna hingga kuning pucat. Cairan infus yang mengandung partikel bening atau sangat berwarna tidak boleh digunakan.

Suspensi yang telah direkonstitusi harus disimpan dalam kemasan asli pada suhu 2ºC sampai 8ºC. Terlindung dari cahaya. Gunakan suspensi yang telah direkonstitusi dalam waktu 24 jam.

8. Informasi lainnya

Pemerian

Sebelum rekonstitusi	:	Serbuk berwarna putih hingga putih pucat dalam vial 50 ml.
Setelah rekonstitusi	:	Suspensi homogen berwarna putih keruh tanpa terlihat adanya partikel asing.

HARUS DENGAN RESEP DOKTER

Nomor: DKIXXXXXXX

SIMPAN DI BAWAH SUHU 30^{0}C
TERLINDUNG DARI CAHAYA
JAUHKAN DARI JANGKAUAN ANAK-ANAK

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Diimpor dan dipasarkan oleh :
PT SOHO Industri Pharmasi
a **SOHO Global Health** Company
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