PACLINAB

Albumin bound paclitaxel

Paclinab ®

Paclitaxel albumin-bound particles 100 mg Powder for injectable Suspension

1. Name of the medicinam product

Paclinab® 100 mg powder for suspension for infusion

2. Qualitative and quantitative composition

Each vial contains 100 mg nano particles of paclitaxel and 900 mg human albumin

3. Pharmaceutical form

Powder for suspension for infusion. The powder id white to yellow.

4. Clinical particulars

4.1. Therapeutic indications

Paclinab as monotherapy is indicated for the treatment of adult paitients with metastatic breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy shoud have included an anthracycline unless clinically contraindicated.

Paclinab in combination with carboplatin is indicated as first-line therapy for the treatment of adult paitients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who are not candidates for curative surgery or radiation therapy.

Paclinab also in combination with gemcitabine is indicated as first-line therapy for treatment of adult patients with metastatic adenocarcinoma of pancreas.

4.2. Posology and method of administration

Paclinab® should only be administered under the supervision of a qualified oncologist in units specialized in the administration of cytotoxic agents. It should not be substituted for or with other paclitaxel

4.2.1. Breast cancer

The recommended dose of Paclinab® is 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks.

Dose adjustments during treatment of breast cancer

Patients who experience severe neutropenia (neutrophil count < 500 cells/mm^3 for a week or longer) or 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.

4.2.2. Pancreactic adenocarcinoma

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/m^2 administered intravenously over 30 minutes immediately after the completion of Paclinab® administration on Days 1, 8 and 15 of each 28-day cycle.

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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]	

4.2.3 Non-small cell lung cancer

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.

Dose adjustments during treatment of non-small cell lung cancer:

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/m2)[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

Non-hematologic Toxicity	Occurrence	Dose of Paclitaxel albumin-bound particles (mg/m^2)[1]	Dose of carboplatin (AUC mg*min/mL)[1]
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	First	75	4.5
	Second	50	3.0
	Third	Discontinue Treatment	
Grade 4 cutaneous toxicity, diarrhoea, or mucositis	First	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.

Method of administration

Administer reconstituted Paclinab® suspension intravenously using an infusion set incorporating a 15 μm filter. Following administration, it is recommended that the intravenous line be flushed with sodium chloride 9 mg/ mL (0.9%) solution for injection to ensure administration of the complete dose.

4.3. contraindications

Hypersensitivity to the active substance or to any of the excipients

Lactation

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

4.4. Special warnings and precautions for use

Hypersensitivity

Hematology

Neuropathy

Sepsis

Pneumonitis

Hepatic impairment

Cardiotoxicity

CNS metastases

Gastrointestinal symptoms

4.5. 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 (see section 5.2). 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

4.6 pregnancy and lactation

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.

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.

4.7. Effects on ability to drive and use machines

Paclitaxel albumin-bound particles has minor or moderate influence on the ability to drive and use machines. Paclinab® 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.

4.8. 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.

Table 5: 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 block 2
Vascular disorders	*Common*: Flushing, hot flushes, hypertension, lymphoedema *Uncommon*: Hypotension, peripheral coldness, orthostatic hypotension *Rare: Thrombosis*
Respiratory, thoracic and mediastinal disorders	*Common*: Interstitial 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*

Table 6: 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

Table 7: 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	97	13	96	12
Neutropenia	73	38	58	27
Thrombocytopenia	74	13	70	9

4.9. 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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, plant alkaloids and other natural products, taxanes, ATC Code: L01CD01

Mechanism of action

Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and 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

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetics of total paclitaxel following 30 and 180-minute infusions of ABRAXANE at dose levels of 80 to 375 mg/m^2 were determined in clinical studies. Dose levels of mg/m2 refer to mg of paclitaxel in Paclinab . Following intravenous administration of Paclinab, 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 drug exposure (AUCs) was dose proportional over 80 to 300 mg/m2 and the pharmacokinetics of paclitaxel for Paclinab were independent of the duration of intravenous administration

The pharmacokinetic data of 260 mg/m^2 Paclinab administered over a 30-minute infusion was compared to the pharmacokinetics of 175 mg/m2 paclitaxel injection over a 3-hour infusion. Clearance was larger (43%) and the volume of distribution was higher (53%) for Paclinab than for paclitaxel injection. There were no differences in terminal half-lives.

Distribution

Following Paclinab administration to patients with solid tumors, paclitaxel is evenly distributed into blood cells and plasma and is highly bound to plasma proteins (94%). In a within-patient comparison study, the fraction of unbound paclitaxel in plasma was significantly higher with Paclinab (6.2%) than with solvent-based paclitaxel (2.3%). This contributes to significantly higher exposure to unbound paclitaxel with Paclinab compared with solvent-based paclitaxel, when the total exposure is comparable. In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 µg/mL, indicated that the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel. The total volume of distribution is approximately 1741 L; the large volume of distribution indicates extensive extravascular distribution and/or tissue 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 6α-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found in vivo following normal therapeutic doses. Testosterone, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel in vitro. The pharmacokinetics of paclitaxel may also be altered in vivo as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4.

Elimination

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

After a 30-minute infusion of 260 mg/m2 doses of Paclinab, the mean values for cumulative urinary recovery of unchanged drug (4%) indicated extensive non-renal clearance. Less than 1% of the total administered dose wad excreted in urine as the metabolites 6α-hydroxypaclitaxel and 3'-p- hydroxypaclitaxe.

Fecal excretion was approximately 20% of the total dose administered

6- Pharmaceutical particulars

6.1 List of excipients

Excipients: Human serum albumin solution (containing sodium, sodium caprylate and N-acetyl DL tryptophanate)

6.2. Incompatibilities:

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3. Shelf life:

Unopened vials 2 years

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.

6.4. Special precautions for storage:

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.

Reconstituted suspension

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5. Nature and contents of container:

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

6.6. Special precautions for disposal and other handling administrative data:

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.

Reconstitution and administration of the product

Aseptically, reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP. 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 inside wall of the vial.Do not inject the 0.9% Sodium Chloride Injection, USP, directly onto the lyophilized cake as this will result in foaming. Once the injection is complete, allow the vial to sit for a minimum of 5 minutes to ensure proper wetting of the lyophilized cake/powder. Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs. Avoid generation of foam. If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.

Disposal

Paclinab is fors single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder

Manufacturing Authorization Holder:

Nano Daru Pajuhan Pardis Co.,

Address: Unit 2, NO. 33, East Baqerkhan St., Chamran Highway, Tehran, Iran

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8. Marketing authorization number(s):

+989122232579

9. Date of revision of the text:

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