

To be sold by retail on prescription of an Oncologist/Cancer Hospital/ Institution only.

8103885-9093

Paclitaxel Protein Bound Particles for Injectable Suspension 100 mg

NAB TORTAXEL™ 100 Lyophilized vial 100 mg/vial

Rx only

COMPOSITION

Each lyophilized vial contains :
Paclitaxel I.P. 100 mg
Human Albumin I.P. 900 mg
Excipients q.s.

DESCRIPTION :

Paclitaxel protein-bound particles for Injectable suspension is an albumin-bound form of Paclitaxel with a mean particle size of approximately 130 nanometers.

Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin.

Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. Paclitaxel Protein bound particles for injectable suspension is free of solvents. The active agent in Paclitaxel protein-bound particles for injectable suspension is paclitaxel, a natural product with antitumor activity. Paclitaxel is obtained from Taxus media. The chemical name for paclitaxel is 5 β,20-Epoxy-1,2α,4,7β,10β,13αhexahydroxytax-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.

CLINICAL PHARMACOLOGY

Mechanism of Action: A Paclitaxel protein-bound particle for injectable suspension is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. Paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Pharmacokinetics:

The pharmacokinetics of total Paclitaxel following 30 and 180-minute infusions of Paclitaxel protein-bound particles for injectable suspension at dose levels of 80 to 375 mg/m² were determined in clinical studies. Dose levels of mg/m² refer to mg of Paclitaxel in Paclitaxel protein-bound particles for injectable suspension. Following intravenous administration of Paclitaxel protein-bound particles for injectable suspension, 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 about 27 hours.

The drug exposure (AUCs) was dose proportional over 80 to 375 mg/m² and the pharmacokinetics of Paclitaxel protein-bound particles for injectable suspension was independent of the duration of administration. At the recommended Paclitaxel protein-bound particles for injectable suspension clinical dose, 260 mg/m², 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/m². The mean volume of distribution was 632 L/m²; the large volume of distribution indicates extensive extravascular distribution and/or tissue binding of Paclitaxel.

The pharmacokinetic data of 260 mg/m² Paclitaxel protein-bound particles for injectable suspension administered over 30 minutes was compared to the pharmacokinetics of 175 mg/m² paclitaxel injection over 3 hours. The clearance of Paclitaxel protein-bound particles for injectable suspension was larger (43%) than for the clearance of paclitaxel injection and the volume of distribution of Paclitaxel protein-bound particles for injectable suspension was also higher (53%). Differences in C_{max} and C_{max} corrected for dose reflected differences in total dose and rate of infusion. There were no differences in terminal half-lives.

INDICATIONS AND USAGE

Metastatic Breast Cancer : A Paclitaxel protein-bound particle for injectable suspension is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

Non-Small cell Lung Cancer : Paclitaxel protein-bound particles for injectable suspension 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.

Adenocarcinoma of the Pancreas : Paclitaxel protein-bound particles for injectable suspension is indicated for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

CONTRAINDICATIONS

Paclitaxel protein-bound particles for injectable suspension should not be used in patients who have baseline neutrophil counts of < 1,500 cells/mm³.

DOSAGE AND ADMINISTRATION

After failure of combination chemotherapy for metastatic breast cancer or relapse within 6 months of adjuvant chemotherapy, the recommended regimen for Paclitaxel protein-bound particles for injectable suspension is 260 mg/m² administered intravenously over 30 minutes every 3 weeks.

Hepatic Impairment : No dose adjustment is necessary for patients with mild hepatic impairment. Patients with moderate and severe hepatic impairment treated with Paclitaxel protein-bound particles for injectable suspension may be at increased risk of toxicities known to paclitaxel. Patients should not receive Paclitaxel protein-bound particles for injectable suspension if AST > 10 x ULN or bilirubin > 5.0 x ULN. Recommendations for dosage adjustment for the first course of therapy are shown in Table 1. The dose of Paclitaxel protein-bound particles for injectable suspension can be increased up to 200 mg/m² in patients with severe hepatic impairment in subsequent cycles based on individual tolerance.

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

| | SGOT (AST) Levels | Bilirubin Levels | NAB TORTAXEL™ 100 ^a |
|-----------------|-------------------|-----------------------|------------------------------------|
| Mild | < 10 x ULN | > ULN to ≤ 1.25 x ULN | 260 mg/m ² |
| Moderate | < 10 x ULN | 1.26 to 2.0 x ULN | 200 mg/m ² |
| | < 10 x ULN | 2.01 to 5.0 x ULN | 130 mg/m ² ^b |
| Severe | > 10 x ULN | > 5.0 x ULN | not eligible |

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/m² in subsequent courses should be considered based on individual tolerance.

Dose Reduction: Patients who experience severe neutropenia (neutrophil < 500 cells/mm³ for a week or longer) or severe sensory neuropathy during Paclitaxel protein-bound particles for injectable suspension therapy should have dosage reduced to 220 mg/m² for subsequent courses of Paclitaxel protein-bound particles for injectable suspension. For recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m². For grade 3 sensory neuropathy hold treatment until resolution to grade 1 or 2, followed by a dose reduction for all subsequent courses of Paclitaxel protein-bound particles for injectable suspension.

Preparation for Intravenous Administration : A Paclitaxel protein-bound particle for injectable suspension is supplied as a sterile lyophilized powder for reconstitution before use. AVOID ERRORS, READ ENTIRE PREPARATION INSTRUCTIONS PRIOR TO RECONSTITUTION.

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

DO NOT INJECT the 0.9% Sodium Chloride Injection, I.P., 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.

OVERDOSAGE

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

WARNINGS

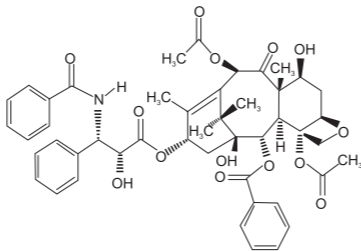
Bone marrow suppression : Primarily neutropenia is dose dependent and a dose limiting toxicity. Paclitaxel protein-bound particles for injectable suspension should not be administered to patients with baseline neutrophil counts of < 1,500 cells/mm³. Frequent monitoring of blood counts should be instituted during Paclitaxel protein-bound particles for injectable suspension treatment. Patients should not be retreated with subsequent cycles of Paclitaxel protein-bound particles for injectable suspension until neutrophils recover to a level >1,500 cells/mm³ and platelets recover to a level >100,000 cells/mm³. The use of Paclitaxel protein-bound particles for injectable suspension has not been studied in patients with renal dysfunction. In the randomized controlled trial, patients were excluded for baseline serum bilirubin >1.5 mg/dL or baseline serum creatinine >2 mg/dL.

Pregnancy-Teratogenic Effects:

Pregnancy Category D : There are no adequate and well-controlled studies in pregnant women using Paclitaxel protein-bound particles for injectable suspension. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Paclitaxel protein-bound particles for injectable suspension.

PRECAUTIONS

Carcinogenesis, Mutagenesis, Impairment of Fertility : The carcinogenic potential of Paclitaxel protein-bound particles for injectable suspension has not been studied. Paclitaxel has been shown to be clastogenic in vitro (chromosome aberrations in human lymphocytes) and in vivo (micronucleus test in mice). A Paclitaxel protein-bound particle for injectable suspension was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay.



Hematology : Paclitaxel protein-bound particles for injectable suspension therapy should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm³. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving Paclitaxel protein-bound particles for injectable suspension. Patients should not be retreated with subsequent cycles of Paclitaxel protein-bound particles for injectable suspension until neutrophils recover to a level >1,500 cells/mm³ and platelets recover to a level >100,000 cells/mm³. In the case of severe neutropenia (<500 cells/mm³ for seven days or more) during a course of Paclitaxel protein-bound particles for injectable suspension therapy, a dose reduction for subsequent courses of therapy is recommended.

Nervous System : Sensory neuropathy occurs frequently with Paclitaxel protein-bound particles for injectable suspension. The occurrence of grade 1 or 2 sensory neuropathy does not generally require dose modification. If grade 3 sensory neuropathy develops, treatment should be withheld until resolution to grade 1 or 2 followed by a dose reduction for all subsequent courses of Paclitaxel protein-bound particles for injectable suspension.

Hepatic Impairment: Because the exposure and toxicity of Paclitaxel can be increased with hepatic impairment, administration of Paclitaxel protein-bound particles for injectable suspension in patients with hepatic impairment should be performed with caution. The starting dose should be reduced for patients with moderate and severe hepatic impairment.

Nursing Mothers : It is not known whether Paclitaxel is excreted in human milk. Following intravenous administration of carbon-14 labeled Paclitaxel to rats on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving Paclitaxel protein-bound particles for injectable suspension therapy.

Pediatric Use : The safety and effectiveness of Paclitaxel protein-bound particles for injectable suspension in pediatric patients have not been evaluated.

Geriatric use : Of the 229 patients in the randomized study who received Paclitaxel protein-bound particles for injectable suspension, 11% were at least 65 years of age and < 2% were 75 years or older. No toxicities occurred notably more frequently among elderly patients who received Paclitaxel protein-bound particles for injectable suspension.

DRUG INTERACTIONS :

No drug interaction studies have been conducted with Paclitaxel Protein bound Particles for Injectable Suspension.

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 Protein bound particles for Injectable suspension 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. rifampin, carbamazepine, Phenytoin, efavirenz, nevirapine) either CYP2C8 or CYP3A4.

ADVERSE REACTIONS :

The following table shows the frequency of important adverse events in the randomized comparative trial for the patients who received either single-agent Paclitaxel protein-bound particles for injectable suspension or Paclitaxel injection for the treatment of metastatic breast cancer.

Table 2 : Frequency of Important Treatment Emergent Adverse Events in the Randomized Study on an Every-3-Weeks Schedule

| | Percent of Patients | |
|----------------------------------|---|--|
| | NAB TORTAXEL 100 260 mg/m ² over 30 min (n=229) | Paclitaxel Injection 175 mg/m ² over 30 hb (n=225) |
| Bone Marrow | | |
| Neutropenia | | |
| < 2.0 x 10 ⁹ /L | 80 | 82 |
| < 0.5 x 10 ⁹ /L | 9 | 22 |
| Thrombocytopenia | | |
| < 100 x 10 ⁹ /L | 2 | 3 |
| < 50 x 10 ⁹ /L | < 1 | < 1 |
| Anemia | | |
| < 11 g/dL | 33 | 25 |
| < 8 g/dL | 1 | < 1 |
| Hypersensitivity Reaction | | |
| All | 4 | 12 |
| Severe | 0 | 2 |
| Cardiovascular | | |
| Bradycardia | < 1 | < 1 |
| Hypotension | 5 | 5 |
| Severe cardiovascular events | 3 | 4 |
| Abnormal ECG | | |
| All patients | 60 | 52 |
| Patients with normal baseline | 35 | 30 |
| Respiratory | | |
| Cough | 7 | 6 |
| Dyspnea | 12 | 9 |

Hematologic : Neutropenia, the most important hematologic toxicity, was dose dependent and reversible. Among patients with metastatic breast cancer in the randomized trial, neutrophil counts declined below 500 cells/mm³ (Grade 4) in 9 % of the patients treated with a dose of 260 mg/m² compared to 22% in patients receiving paclitaxel injection at a dose of 175 mg/m².

Anemia : Anemia (Hb < 11 g/dL) was observed in 33% of patients treated with Paclitaxel protein-bound particles for injectable suspension in the randomized trial and was severe (Hb < 8 g/dL) in 1% of the cases. Among all patients with normal baseline hemoglobin, 31% became anemic on study and 1% had severe anemia.

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

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

Respiratory : Reports of dyspnea (12 %) and cough (6%) were reported after treatment with Paclitaxel protein-bound particles for injectable suspension in the randomized trial. Rare reports (< 1%) of pneumothorax were reported after treatment with Paclitaxel protein-bound particles for injectable suspension. Rare reports of interstitial pneumonia, lung fibrosis, and pulmonary embolism have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following Paclitaxel protein-bound particles for injectable suspension treatment. Rare reports of radiation pneumonitis have been received in paclitaxel injection patients receiving concurrent radiotherapy. There is no experience with the use of Paclitaxel protein-bound particles for injectable suspension with concurrent radiotherapy.

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

Other Clinical Events : Rare cases of cardiac ischemia/infarction and thrombosis/embolism possibly related to Paclitaxel protein-bound particles for injectable suspension treatment have been reported. Alopecia was observed in almost all of the patients. Nail changes (changes in pigmentation or discoloration of nail bed) were uncommon. Edema (fluid retention) was infrequent (10% of randomized trial patients); no patients had severe edema.

Reporting of 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. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com.

STORAGE : Store at 20° C to 25° C. Protect from light.

HOW SUPPLIED : Paclitaxel Protein bound particles for Injectable suspension 100 mg.

NAB TORTAXEL™ 100 Single dose vial individually packed in a carton.

SHELF LIFE : 24 Months

TORRENT[®]

PHARMA

Marketed by :
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.

TM - Trade mark under registration.

Manufactured by :
SPAL Private Limited.
Plot No.12, Biotech Park, Phase-II,
Lalgadi Malakpet, Shmeerpet,
Medchal-Malakjiri District, Telangana State - 500 101.

IN/NAB TORTAXEL/100mg/Dec-2018/03/CCDS

Size : 215 x 300 mm (Front Side)

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|------------------------|--|-------------------------------|--|-----------------------------|-------------|------------------|-------------|
| PRODUCT NAME | : NAB TORTAXEL | COUNTRY : Domestic P2P | LOCATION : Panacea Biotec | SUPERSEDES A/W NO. : | | | |
| ITEM / PACK | : Insert | NO. OF COLORS: 1 | REMARK : | | | | |
| DESIGN STYLE | : Front/Back | PANTONE SHADE NOS.: | SUBSTRATE : Mapliitho or bible paper and GSM. | | | | |
| CODE | : 8103885-9093 | Black | Activities | Department | Name | Signature | Date |
| DIMENSIONS (MM) | : 215 x 300 mm (Folded dimensions as 45 x 70 mm) | | Prepared By | Pkg.Dev | | | |
| ART WORK SIZE | : S/S | | Prepared By | Pkg.Dev | | | |
| DATE | : 27-10-2025 | | Reviewed By | CR | | | |
| | | | Approved By | Quality | | | |
| | | | Approved By | Quality | | | |

This colour proof is not colour binding. Follow Pantone shade reference for actual colour matching.

Size : 215 x 300 mm (Back Side)