# Aritax

Paclitaxel USP

**COMPOSITION**

**Aritax 100 Injection:** Each vial contains Paclitaxel USP 100 mg, as 16.7 ml concentrated solution for IV infusion.
**Aritax 300 Injection:** Each vial contains Paclitaxel USP 300 mg, as 50 ml concentrated solution for IV infusion.

**CLINICAL PHARMACOLOGY**

**Mechanism of action:** Paclitaxel is a novel 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. In addition, Paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

**Pharmacokinetics:** Following intravenous administration, Paclitaxel plasma concentrations declines in a biphasic manner. The initial rapid decline represents distribution to the peripheral compartment and elimination of the drug. The later phase is due, in part, to a relatively slow efflux of Paclitaxel from the peripheral compartment.

In vitro studies of serum protein binding indicate that 89-98% of Paclitaxel is bound to proteins. Cimetidine, Ranitidine, Dexamethasone or Diphenhydramine were not found to affect the protein binding of Paclitaxel.

In vitro studies with human liver microsomes and tissue slices shows that Paclitaxel is metabolized primarily to 6a-hydroxypaclitaxel by the cytochrome P450 isozyme CYP2C8; and to 2 minor metabolites, 3'-p-hydroxypaclitaxel and 6a, 3'-p-dihydroxypaclitaxel, by CYP3A4.

Mean values for cumulative urinary recovery of unchanged Paclitaxel following intravenous administration as 1, 6, or 24-hour infusions ranged from 1.3% to 12.6% of the dose, indicating extensive non-renal clearance. Following 3-hour infusion of radiolabeled Paclitaxel, a mean of 71% of the radioactivity has been found excreted in the feces in 120 hours, and 14% in the urine. Paclitaxel represented a mean of 5% of the administered radioactivity recovered in the feces, while metabolites, primarily 6a-hydroxypaclitaxel, accounted for the balance.

**INDICATIONS**

**Ovarian Carcinoma:**

- Paclitaxel is indicated as first-line and subsequent therapy for the treatment of advanced carcinoma of the ovary. As first-line therapy, Paclitaxel is indicated in combination with Cisplatin.

**Breast Cancer:**

- Paclitaxel is indicated for the adjuvant treatment of node-positive breast cancer administered sequentially to standard Doxorubicin-containing combination chemotherapy.
- Paclitaxel 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 in combination with Cisplatin, is indicated for the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy.

**Kaposi's Sarcoma:**

- Paclitaxel is indicated for the second-line treatment of AIDS-related Kaposi's sarcoma.

**DOSAGE AND ADMINISTRATION**

**Ovarian Carcinoma:**

For previously untreated patients with carcinoma of the ovary-

- Paclitaxel 175 mg/m$^2$ IV administered over 3 hours followed by Cisplatin at a dose of 75 mg/m$^2$, every 3 weeks; or
- Paclitaxel 135 mg/m$^2$ administered over 24 hours followed by Cisplatin at a dose of 75 mg/m$^2$, every 3 weeks.

For patients previously treated with chemotherapy for carcinoma of the ovary-

- Paclitaxel 135 mg/m$^2$ or 175 mg/m$^2$ IV administered over 3 hours every 3 weeks.

**Breast Cancer:**

Adjuvant treatment of node-positive breast cancer-

- Paclitaxel 175 mg/m$^2$ IV administered over 3 hours every 3 weeks for 4 courses, given sequentially to Doxorubicin-containing combination chemotherapy.

After failure of initial chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy-

- Paclitaxel 175 mg/m$^2$ IV administered over 3 hours every 3 weeks.

**Non-Small Cell Lung Cancer:**

- Paclitaxel 135 mg/m$^2$ IV administered over 24 hours followed by Cisplatin 75 mg/m$^2$, given every 3 weeks.

**Kaposi's Sarcoma:**

- Paclitaxel 135 mg/m$^2$ IV administered over 3 hours every 3 weeks or at a dose of 100 mg/m$^2$ IV administered over 3 hours every 2 weeks (dose intensity 45-50 mg/m$^2$/week).

All patients should be premedicated prior to Paclitaxel administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of Dexamethasone 20 mg PO administered approximately 12 and 6 hours before Paclitaxel, Diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to Paclitaxel, and Cimetidine (300 mg) or Ranitidine (50 mg) IV 30 to 60 minutes before Paclitaxel.

**Dose modifications for HIV disease:** Based upon the immunosuppression in patients with advanced HIV disease, the following modifications are recommended in these patients-

- Reduce the dose of Dexamethasone as 1 of the 3 premedication drugs to 10 mg PO (instead of 20 mg PO)
- Initiate or repeat treatment with Paclitaxel only if the neutrophil count is at least 1000 cells/mm$^3$
- Reduce the dose of subsequent courses of Paclitaxel by 20% for patients who experience severe neutropenia (neutrophil <500 cells/mm$^3$ for a week or longer)
- Paclitaxel should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline or subsequent neutrophil count is less than 1000 cells/mm$^3$, and
- Initiate concomitant hematopoietic growth factor (G-CSF) as clinically indicated.

**Dosage adjustment for cancer patients:** For the therapy of patients with solid tumors, courses of Paclitaxel should not be repeated until the neutrophil count is at least 1500 cells/mm$^3$ and the platelet count is at least 100,000 cells/mm$^3$. Patients who experience severe neutropenia (neutrophil <500 cells/mm$^3$ for a week or longer) or severe peripheral neuropathy during Paclitaxel therapy should have dosage reduced by 20% for subsequent courses of Paclitaxel.

**Dosage adjustment for patients with Hepatic Impairment:** Patients with hepatic impairment may be at increased risk of toxicity, particularly grade III-IV myelosuppression. Recommendations for dosage adjustmentfor the first course of therapy are as follows-

| Degree of Hepatic Impairment | | Recommended Paclitaxel Dose (24-hour infusion) |
|---|---|---|
| Transaminase Levels | Bilirubin Levels | |
| <2 × ULN and | <1.5 mg/dL | 135 mg/m$^2$ |
| 2 to <10 × ULN and | <1.5 mg/dL | 100 mg/m$^2$ |
| <10 × ULN and | 1.6-7.5 mg/dL | 50 mg/m$^2$ |
| >10 × ULN or | >7.5 mg/dL | Not recommended |

| Degree of Hepatic Impairment | | Recommended Paclitaxel Dose (3-hour infusion) |
|---|---|---|
| Transaminase Levels | Bilirubin Levels | |
| <10 × ULN and | <1.25 × ULN | 175 mg/m$^2$ |
| <10 × ULN and | 1.26-2.0 × ULN | 135 mg/m$^2$ |
| <10 × ULN and | 2.01-5.0 × ULN | 90 mg/m$^2$ |
| >10 × ULN or | >5.0 × ULN | Not recommended |

Dosage recommendations are for the first course of therapy; further dose reduction in subsequent courses should be based on individual tolerance. Patients should be monitored closely for the development of profound myelosuppression.

**Preparation for Administration:** Contact of the undiluted concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl) phthalate], which may be leached from PVC infusion bags or sets, diluted Paclitaxel solutions should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Aritax injection must be diluted prior to infusion. Aritax should be diluted in 0.9% Sodium Chloride Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2 mg/ml. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25° C) and room lighting conditions. All parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle. The use of plasticized PVC containers and administration sets is not recommended. Paclitaxel should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns.

**Precautions during Handling:** Caution should be exercised in handling Paclitaxel solution. Procedures for proper handling and disposal of anticancer drugs should be utilized. To minimize the risk of dermal exposure, always wear impervious gloves when handling vials and IV sets containing Paclitaxel. If Paclitaxel contacts the skin or mucosa, immediately and thoroughly wash the skin with soap and water and flush the mucosa with water.

**CONTRAINDICATIONS**

Contraindicated in patients who have a history of hypersensitivity reactions to Paclitaxel or other drugs formulated in Polyoxyethylated castor oil. Paclitaxel should not be used in patients with solid tumors who have baseline neutrophil counts of <1500 cells/mm$^3$ or in patients with AIDS-related Kaposi's sarcoma with baseline neutrophil counts of <1000 cells/mm$^3$.

**ADVERSE REACTIONS**

**Patients with solid tumors receiving single-agent Paclitaxel:** Adverse events associated with bone marrow suppression were neutropenia, leukopenia, thrombocytopenia, anemia, infections and bleeding. Cardiovascular adverse events included bradycardia and hypotension. Gastrointestinal adverse events were nausea and vomiting, diarrhoea and mucositis. Hepatic adverse events were bilirubin elevations, alkaline phosphatase elevations and AST (SGOT) elevations. Other adverse events included hypersensitivity reaction, peripheral neuropathy, myalgia/arthralgia, alopecia and injection site reactions.

**Patients with AIDS-related Kaposi's Sarcoma:** Adverse events associated with bone marrow suppression were neutropenia, thrombocytopenia, anemia and febrile neutropenia. Cardiovascular adverse events included bradycardia and hypotension. Gastrointestinal adverse events were nausea and vomiting, diarrhoea and mucositis. Other adverse events included opportunistic infection (Cytomegalovirus, Herpes Simplex, Pneumocystis carinii, M. avium intracellulare, Candidiasis, Cryptosporidiosis, Cryptococcal meningitis, Leukoencephalopathy), Peripheral Neuropathy, Myalgia/Arthralgia, creatinine elevation and Hypersensitivity Reaction.

**PRECAUTIONS**

**Pregnancy:** Paclitaxel can cause fetal harm when administered to a pregnant woman. If Paclitaxel 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.

**Nursing mothers:** It is not known whether the drug is excreted in human milk. 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 therapy.

**Pediatric use:** The safety and effectiveness of Paclitaxel in pediatric patients have not been established.

**Geriatric use:** Severe myelosuppression and neuropathy has been observed more common in elderly patients. Elderly patients treated with Paclitaxel may also experience higher incidence of cardiovascular events.

**Hepatic impaired patients:** Patients with hepatic impairment may be at increased risk of toxicity, particularly grade III-IV myelosuppression. Recommended dosage adjustment to be done as mentioned in DOSAGE AND ADMINISTRATION.

**DRUG INTERACTIONS**

Pharmacokinetic data from clinical trials demonstrated a decrease in Paclitaxel clearance of approximately 33% when Paclitaxel was administered following Cisplatin. The metabolism of Paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when Paclitaxel is concomitantly administered with known substrates (eg, midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (eg, rifampin and carbamazepine) of CYP3A4. Caution should also be exercised when Paclitaxel is concomitantly administered with known substrates (eg, repaglinide and rosiglitazone), inhibitors (eg, gemfibrozil), and inducers (eg, rifampin) of CYP2C8. Plasma levels of Doxorubicin (and its active metabolite doxorubicinol) may be increased when Paclitaxel and Doxorubicin are used in combination.

**OVERDOSE**

There is no known antidote for Paclitaxel overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity, and mucositis. Overdoses in pediatric patients may be associated with acute ethanol toxicity.

**STORAGE**

Store in a dry place at a temperature below 25°C. Protect from light and do not refrigerate.
Keep out of the reach of children.

**PRESENTATION**

**Aritax 100 Injection:** Each box contains a single dose glass vial of Paclitaxel 100 mg.
**Aritax 300 Injection:** Each box contains a single dose glass vial of Paclitaxel 300 mg.

Manufactured for:
ARISTOPHARMA LTD.
Shampur-Kadamtali I/A, Dhaka-Bangladesh
by Healthcare Pharmaceuticals Limited, Rajendrapur, Gazipur

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