Ariplat

Cisplatin BP

COMPOSITION
Ariplat 10 Injection: Each vial contains Cisplatin BP 10 mg, as sterile preservative free 10 ml concentrated solution for IV Infusion.
Ariplat 50 Injection: Each vial contains Cisplatin BP 50 mg, as sterile preservative free 50 ml concentrated solution for IV Infusion.

CLINICAL PHARMACOLOGY
Mechanism of action: Cisplatin is a heavy metal complex which binds with DNA to form intrastrand crosslinks and adducts that cause changes in the conformation of the DNA and affect DNA replication. In the blood, Cisplatin is present in an inactive, uncharged state. Cisplatin enters cells by passive diffusion. Intracellularly, Cisplatin loses its two chloride groups and becomes a positively charged electrophilic compound. Cisplatin then binds with DNA, RNA, or other macromolecules at two sites to form interstrand and intrastrand links. Intrastrand links account for > 90% of the platinum binding to DNA. Cisplatin binds preferentially to the N-7 positions of guanine and adenine due to the high nucleophilicity of the imidazole ring at this position. These intrastrand adducts significantly alter the conformation of DNA and inhibit DNA polymerase, RNA polymerase, RNA translocation, and other key enzymes. Cisplatin causes cell cycle arrest in the G2-phase and then induces programmed cell death or apoptosis.
Pharmacokinetics: Cisplatin following IV administration distributes widely throughout body tissues, with high concentrations in the prostate, liver, and kidneys. It binds extensively to plasma proteins and to the surfaces of red blood cells. Cisplatin is believed to undergo spontaneous degradation in the bloodstream and is not hepatically metabolized. Unchanged drug is excreted via the kidneys by both filtration and secretion. Elimination is triphasic, with the half-life of the initial phase lasting 20 minutes, the second phase 48-70 minutes, and the terminal phase 24 hours. The first two phases of elimination represent binding to plasma and tissue proteins. The third phase represents the slow removal from tissues. Only 10% of a dose is eliminated in the bile. Twenty-three to seventy-five percent of a dose is eliminated in the first 24 hours. Traces of the drug can be found in the urine up to 6 months after discontinuance of therapy.

INDICATIONS
Metastatic Testicular Tumors: In established combination therapy with other approved chemotherapeutic agents in patients with metastatic testicular tumors who have already received appropriate surgical and/or radiotherapeutic procedures.
Metastatic Ovarian Tumors: In established combination therapy (e.g.Cisplatin with Cyclophosphamide) with other approved chemotherapeutic agents in patients with metastatic ovarian tumors who have already received appropriate surgical and/or radiotherapeutic procedures.
Cisplatin Injection, as a single agent, is indicated as secondary therapy in patients with metastatic ovarian tumors refractory to standard chemotherapy who have not previously received Cisplatin Injection therapy.
Advanced Bladder Cancer: Cisplatin Injection is indicated as a single agent for patients with transitional cell bladder cancer which is no longer amenable to local treatments, such as surgery and/or radiotherapy.

DOSAGE AND ADMINISTRATION
Cisplatin Injection is administered by slow intravenous infusion. Pretreatment hydration with 1 to 2 liters of fluid infused for 8 to 12 hours prior to a Cisplatin Injection dose is recommended.
Needles or intravenous sets containing aluminum parts that may come in contact with Cisplatin Injection should not be used for preparation or administration. Aluminum reacts with Cisplatin Injection, causing precipitate formation and a loss of potency. All parenteral drug products should be inspected visually prior to administration and should not be used if precipitates, visible particles and/or discoloration is present.
Metastatic Testicular Tumors: The usual dose for the treatment of testicular cancer in combination with other approved chemotherapeutic agents is 20 mg/m^2 IV daily for 5 days per cycle.
Metastatic Ovarian Tumors: The usual dose for the treatment of metastatic ovarian tumors is 75 to 100 mg/m^2 IV in combination with Cyclophosphamide 600 mg/m^2 IV per cycle once every 4 weeks. In combination therapy, Cisplatin Injection and Cyclophosphamide are administered sequentially.
As a single agent, Cisplatin Injection should be administered at a dose of 100 mg/m^2 IV per cycle once every four weeks.
Advanced Bladder Cancer: Administered as a single agent at a dose of 50 to 70 mg/m^2 IV per cycle once every 3 to 4 weeks depending on the extent of prior exposure to radiation therapy and/or prior chemotherapy. For heavily pretreated patients an initial dose of 50 mg/m^2 per cycle repeated every 4 weeks is recommended.
Preparation for Administration: To prepare for administration Cisplatin is diluted in 2 liters of 5% Dextrose in 1/2 or 1/3 normal saline containing 37.5 g of mannitol, and infused over a 6-to 8-hour period. If diluted solution is not to be used within 6 hours, protect solution from light. The diluted solution is intended to be used within 24 hours and any unused portion should be discarded after this period.
Precautions during Handling: Caution should be exercised in handling the aqueous 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 Cisplatin. If Cisplatin contacts the skin or mucosa, immediately and thoroughly wash the skin with soap and water and flush the mucosa with water.

CONTRAINDICATIONS
Cisplatin is contraindicated in patients with preexisting renal impairment. Cisplatin should not be employed in myelosuppressed patients, or in patients with hearing impairment. Cisplatin is contraindicated in patients with a history of allergic reactions to Cisplatin or other platinum-containing compounds.

ADVERSE EFFECTS
Nephrotoxicity: Dose-related and cumulative renal insufficiency, including acute renal failure.
Ototoxicity: Tinnitus and/or hearing loss in the high frequency range.
Hematologic: Myelosuppression, leukopenia, thrombocytopenia, anemia, neutropenia.
Gastrointestinal: Nausea and vomiting, anorexia, diarrhoea.
Other Toxicities: Serum electrolyte disturbances, hyperuricemia, neurotoxicity, ocular toxicity, anaphylactic-like reactions, hepatotoxicity.

PRECAUTIONS
Pregnancy: Pregnancy category D, Cisplatin can cause fetal harm. Pregnancy should be avoided during Cisplatin treatment and for at least 14 months after the last dose.
Nursing mothers: Cisplatin has been reported to be found in human milk; patients receiving Cisplatin should not breast-feed.
Pediatric use: Safety and effectiveness in pediatric patients have not been established.
Geriatric use: Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored.
Renal impaired patients: Cisplatin is known to be substantially excreted by the kidney and is contraindicated in patients with preexisting renal impairment.
Peripheral blood counts should be monitored weekly. Liver function should be monitored periodically. Neurologic examination should also be performed regularly.

DRUG INTERACTIONS
Plasma levels of anticonvulsant agents may become subtherapeutic during Cisplatin therapy.
Response duration can be adversely affected when pyridoxine is used in combination with hexamethylmelamine and Cisplatin.

OVERDOSE
Caution is essential in order to prevent an inadvertent overdose. An acute overdose of Cisplatin may result in renal failure, liver failure, deafness, ocular toxicity (including detachment of the retina), significant myelosuppression, untreatable nausea and vomiting and/or neuritis. An overdose may be fatal. There is no specific antidote in the event of an over dosage of Cisplatin. Even if haemodialysis is initiated 4 hours after the overdose it has little effect on the elimination of Cisplatin from the body following a strong and rapid fixation of Cisplatin to proteins. Treatment in the event of an overdose consists of general support measures.

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

PRESENTATION
Ariplat 10 Injection: Each box contains a single dose glass vial of Cisplatin 10 mg.
Ariplat 50 Injection: Each box contains a single dose glass vial of Cisplatin 50 mg.

Manufactured for:
ARISTOPHARMA LTD.
Shampur-Kadamtali I/A, Dhaka-Bangladesh
by Healthcare Pharmaceuticals Limited, Rajendrapur, Gazipur
2000514900