Neoplat

Injection

DRUG INTERNATIONAL LTD.

Composition:

Neoplat 10 - Each vial contains Cisplatin BP 10 mg (1 mg/ ml).

Neoplat 50 - Each vial contains Cisplatin BP 50 mg (1 mg/ ml).

PHARMACOLOGICAL INFORMATION:

Mechanism of Action:

Cisplatin is a platinum compound of which only the cis-isomer is active. It appears to produce intra-and interstrand cross links which modify DNA structure and inhibit DNA synthesis. In addition and to a lesser extent Cisplatin inhibits protein and RNA synthesis. It does not appear to be phase-specific in the cell cycle.

Pharmacokinetics:

Distribution: Cisplatin seems to concentrate in the liver and kidneys. It does not cross the blood brain barrier so does not penetrate the CSF to any great extent. **Elimination and Excretion:** After IV injection, plasma decay is biphasic. The initial phase is rapid with a half-life of 25-49 minutes and this is followed by a prolonged elimination phase with a half-life of 2-4 days. This long elimination phase is probably due to a high degree of protein binding. Normally more than 90% is bound to plasma proteins, but this may be more during a slow infusion. Excretion is predominantly renal. About 15-25% of a dose is rapidly excreted, mainly as intact drug, in the first 2-4 hours and 20-75% in the first 24 hours. The remainder represents drug bound to tissues or plasma proteins.

Indications and dosages:

Neoplat injection is indicated as therapy to be employed as follows: **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 radio therapeutic procedures. **Metastatic Ovarian Tumors**- In established combination therapy with other approved chemotherapeutic agents in patients with metastatic ovarian tumors who have already received appropriate surgical and/or radio therapeutic procedures. An established combination consists of Neoplat (Cisplatin) and cyclophosphamide. Neoplat, 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** - Neoplat (Cisplatin) 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. **Non Small Cell Lung Carcinoma-** Neoplat (Cisplatin) in combination with other chemotherapeutic agent is indicated for the treatment of non small cell lung cancer in patients who are not candidates for potential curative surgery and/ or radiation therapy.

Dosage and Administration:

Cisplatin injection is administered by slow intravenous infusion. It should not be given by rapid intravenous injection.

Note: 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. **Metastatic Testicular Tumors -** The usual Cisplatin Injection 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 Cisplatin Injection dose for the treatment of metastatic ovarian tumors in combination with cyclophosphamide is 75 to 100 mg/m^2 IV per cycle once every 4 weeks (DAY 1). The dose of cycloposphamide when used in combination with cisplatin is 600 mg/m^2 IV once every four weeks (DAY 1). 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-** Cisplatin Injection should be 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.

Non Small Cell Lung Carcinoma- Cisplatin Injection (75 mg/m^2) should be administered in combination with Paclitaxel (135 mg/m^2) in every three weeks. Or, as directed by the registered physicians.

Preparation for Intravenous Administration:

Pretreatment hydration with 1 to 2 liters of fluid infused for 8 to 12 hours prior to a Cisplatin Injection dose is recommended. The drug is then 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. Do not dilute cisplatin in just 5% Dextrose Injection. Adequate hydration and urinary output must be maintained during the following 24 hours. A repeat course of Cisplatin Injection should not be given until the serum creatinine is below 1.5 mg/100 mL, and/or the BUN is below 25 mg/100 mL. A repeat course should not be given until circulating blood elements are at an acceptable level (platelets > 100,000/mm^3, WBC > 4,000/mm^3). Subsequent doses of Cisplatin Injection should not be given until aaudiometric analysis indicates that auditory acuity is within normal limits. **Special Instruction for Uses, Handling, and Disposal:** Neoplat is a cytotoxic drug and, as with other potentially toxic compounds caution should be exercised in handling Neoplat. The use of gloves is recommended. If Neoplat solution contacts the skin, wash the skin immediately and thoroughly with soap and water.

Contraindications:

Neoplat is contraindicated in patients with pre-existing renal impairment, or in patients with a history of hypersensitivity to Cisplatin or Platinum containing compounds. Cisplatin injection should not be employed in myelosuppresed patients or in patients with hearing impairment.

Precautions:

Renal function: Cisplatin produces cumulative nephrotoxicity. Renal function and serum electrolyte (magnesium, sodium, potassium and calcium) should be evaluated prior to initiating cisplatin treatment and prior to each subsequent course of therapy. To maintain urine output and reduce renal toxicity it is recommended that cisplatin be administered as an intravenous infusion ovar 6 to 8 hours. Moreover, per-treatment intravenous hydration with 1-2 litres of fiuid over 8-12 hours followed by adequate hydration for the next 24 hours is recommended. Repeat courses of cisplatin should not be given unless the level of serum creatinine is below 1.5 mg/100 ml, or the BUN is below 25 mg/100 ml. Special care has to be taken when cisplatin-treated patients **Bone marrow function:** Peripheral blood counts should be monitored frequently in patients receiving Cisplatin. Although the hematologic toxicity is usually moderate and reversible, severe thrombocytopenia and leukopenia may occur. In patients who develop thrombocytopenia special precautions are recommended: care in performing invasive procedures; search for signs of bleeding or bruising; test of urine, stools and emesis for occult blood; avoiding aspirin and other NSAIDs. Patients who develop leukopenia should be observed carefully for signs of infection and might require antibiotic support and blood product transfusions. **Hearing function:** Cisplatin may produce cumulative ototoxicity, which is more likely to occur with high-dose regimens. Audiometry should be performed prior to initiating therapy, and repeated audiograms should be performed when auditory symptoms occur or clinical hearing changes become apparent. Clinically important deterioration of auditive function may require dosage modifications or discontinuation of therapy. **CNS functions:** Cisplatin is known to induce neurotoxicity; therefore, neurologic examination is warranted in patients receiving a Cisplatin-containing treatment. Since neurotoxicity may result in irreversible damage, it is recommended to discontinue therapy with Cisplatin when neurologic toxic signs or symptoms become apparent. In addition, patients receiving Cisplatin should be observed for possible anaphylactoid reactions, and appropriate equipment and medication should be readily available to treat such reactions. **Nausea and Vomiting:** Marked nausea and vomiting occur in almost all patients treated with Cisplatin and are occasionally so severe that dosage reduction or discontinuance of treatment is necessary. Cisplatin should be administered only by physicians experienced in the use of chemotherapeutic agents. **Carcinogenicity:** Secondary malignancies are potential delayed effects of many antineoplastic agents, although it is not clear whether the effect is related to their mutagenic or immunosuppressive action. The effect of dose and duration of therapy is also unknown, although risk seems to increase with long-term use. Although information is limited, available data seems to indicate that the carcinogenic risk is greatest with the alkylating agents. **Dental:** The bone marrow depressant effects of Cisplatin may result in an increased incidence of microbial infection,delayed healing, and gingival bleeding. Dental work, wherever possible, should be completed prior to initiation of therapy or deferred until blood counts have returned to normal.

Use in Pregnancy and Lactation:

Pregnancy Category D. There are no adequate and well controlled studies in pregnant women. Cisplatin has been reported to be found in human milk. It is not known whether cisplatin is excreted in human.

Side Effects:

Severe nausea and vomiting usually begins 1-4 hours after treatment and may persist for up to a week. Cisplatin may also cause serious electrolyte disturbances, mainly represented by hypomagnesemia, hypocalcemia, and hypokalemia, and associated with renal tubular dysfunction. Hypomagnesemia and/or hypocalcemia may become symptomatic, with muscle irritability or cramps, clonus, tremor, carpopedal spasm, and/or tetany.

Drug Interactions:

Cisplatin is mostly used in combination with antineoplastic drugs having similar cytotoxic effects. In these circumstances additive toxicity is likely to occur. Other known drug interactions are reported below: **Nephrotoxic drugs:** Aminoglycoside antibiotics, when given concurrently or within 1-2 weeks after Cisplatin administration, may potentiate its nephrotoxic effects. Concomitant use of other potentially nephrotoxic drugs (eg Amphotericin B) is not recommended during Cisplatin therapy. **Ototoxic drugs:** Concurrent and/or sequential administration of ototoxic drugs such as aminoglycoside antibiotics or loop diuretics may increase the potential of Cisplatin to cause ototoxicity, especially in the presence of renal impairment. **Renally excreted drugs:** Cisplatin may alter the renal elimination of bleomycin and methotrexate (possibly as a result of Cisplatin-induced nephrotoxicity) and enhance their toxicity. **Anticonvulsant agents:** In patients receiving Cisplatin and Phenytoin, serum concentrations of the latter may be decreased, possibly as a result of decreased absorption and/or increased metabolism. In these patients, serum levels of phenytoin should be monitored and dosage adjustments made as necessary. **Antigout agents:** Cisplatin may raise the concentration of blood uric acid. Thus, in patients concurrently receiving antigout agents such as Allopurinol, Colchicine, Probenecid or Sulfinpyrazone, dosage adjustment of these drugs may be necessary to control hyperuricemia and gout.

Over dosage:

Acute overdosage with this drug may result in kidney failure, liver failure, deafness, ocular toxicity (including detachment of the retina), significant myelosuppression, intractable nausea and vomiting and/or neuritis. In addition, death can occur following overdosage. No proven antidotes have been established for Cisplatin overdosage. Hemodialysis, even when initiated four hours after the overdosage, appears to have little effect on removing platinum from the body because of Platinol's rapid and high degree of protein binding. Management of overdosage should include general supportive measures to sustain the patient through any period of toxicity that may occur.

Storage:

Store the vial in original carton at 25° C. Do not refrigerate. Protect from light and keep out of the reach of children.

Packing:

Neoplat 10 - Each box contains one vial of 10 ml solution.

Neoplat 50 - Each box contains one vial of 50 ml solution.