Cispatin 50mg/50ml Injection

(C i s p l a t i n)

سسپیٹن ۵۰ ملی گرام/۵۰ ملی لیٹر انجیکشن

(سسپلاٹن)

COMPOSITION:

CISPATIN 50mg/50ml

Each 50ml vial contains:

Cisplatin.....50mg

(BP Specifications)

INDICATIONS:

Cispatin (CISPLATIN) 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

Cisplatin (CISPATIN) 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 (CISPATIN) Injection therapy.

Advanced Bladder Cancer

Cisplatin (CISPATIN) 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

DESCRIPTION

Cisplatin (CISPATIN) Injection infusion concentrate is a clear, colorless to slightly yellow sterile aqueous solution. Cisplatin (CISPATIN) Injection infusion concentrate must be further diluted prior to administration. The active ingredient, Cisplatin (CISPATIN), is a yellow to orange crystalline powder with the molecular formula PtCl2H6N2, and a molecular weight of 300.1. Cisplatin (CISPATIN) is a heavy metal complex containing a central atom of platinum surrounded by two chloride atoms and two ammonia molecules in the cis position. It is soluble in water or saline at 1 mg/mL and in dimethylformamide at 24 mg/mL. It has a melting point of 207° C.

CONTRAINDICATIONS

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

DOSAGE AND ADMINISTRATION

Cisplatin (CISPATIN) Injection is administered by slow intravenous infusion. **CISPLATIN (CISPATIN) INJECTION SHOULD NOT BE GIVEN BY RAPID INTRAVENOUS INJECTION**. **Note:** Needles or intravenous sets containing aluminum parts that may come in contact with Cisplatin (CISPATIN) Injection should not be used for preparation or administration. Aluminum reacts with Cisplatin (CISPATIN) Injection, causing precipitate formation and a loss of potency.

Metastatic Testicular Tumors

The usual **Cisplatin (CISPATIN)** Injection dose for the treatment of testicular cancer in combination with other approved chemotherapeutic agents is 20 mg/m2 IV daily for 5 days per cycle.

Metastatic Ovarian Tumors

The usual **Cisplatin (CISPATIN)** Injection dose for the treatment of metastatic ovarian tumors in combination with cyclophosphamide is 75 to 100 mg/m2 IV per cycle once every four weeks (DAY1). The dose of cyclophosphamide when used in combination with Cisplatin (CISPATIN) Injection is 600 mg/m2 IV once every 4 weeks (DAY 1). In combination therapy, Cisplatin (CISPATIN) Injection and cyclophosphamide are administered sequentially. As a single agent, Cisplatin (CISPATIN) Injection should be administered at a dose of 100 mg/m2 IV per cycle once every four weeks.

Advanced Bladder Cancer

Cisplatin (CISPATIN) Injection should be administered as a single agent at a dose of 50 to 70 mg/m2 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/m2 per cycle repeated every 4 weeks is recommended.

All Patients

Pretreatment hydration with 1 to 2 liters of fluid infused for 8 to 12 hours prior to a Cisplatin (CISPATIN) 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. Adequate hydration and urinary output must be maintained during the following 24 hours. A repeat course of Cisplatin (CISPATIN) 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/mm3, WBC≥4000/mm3). Subsequent doses of Cisplatin (CISPATIN) Injection should not be given until an audiometric analysis indicates that auditory acuity is within normal limits.

WARNINGS

Cisplatin (CISPATIN) produces cumulative nephrotoxicity which is potentiated by aminoglycoside antibiotics. The serum creatinine, blood urea nitrogen (BUN), creatinine clearance, and magnesium, sodium, potassium, and calcium levels should be measured prior to initiating therapy, and prior to each subsequent course. At the recommended dosage, Cisplatin (CISPATIN) should not be given more frequently than once every 3 to 4 weeks. Elderly patients may be more susceptible to nephrotoxicity. There are reports of severe neuropathies in patients in whom regimens are employed using higher doses of Cisplatin (CISPATIN) or greater dose frequencies than those recommended. These neuropathies may be irreversible and are seen as paresthesias in a stocking- glove distribution, areflexia, and loss of proprioception and vibratory sensation. Elderly patients may be more susceptible to peripheral neuropathy. Loss of motor function has also been reported.

Anaphylactic-like reactions to Cisplatin (CISPATIN) have been reported. These reactions have occurred within minutes of administration to patients with prior exposure to Cisplatin (CISPATIN), and have been alleviated by administration of epinephrine, corticosteroids, and antihistamines. Cisplatin (CISPATIN) can commonly cause ototoxicity which is cumulative and may be severe. Audiometric testing should be performed prior to initiating therapy and prior to each subsequent dose of drug. All pediatric patients receiving Cisplatin (CISPATIN) should have audiometric testing at baseline, prior to each subsequent dose, of drug and for several years post therapy. Cisplatin (CISPATIN) can cause fetal harm when administered to a pregnant woman. Cisplatin (CISPATIN) is mutagenic in bacteria and produces chromosome aberrations in animal cells in tissue culture.

In mice Cisplatin (CISPATIN) is teratogenic and embryo toxic. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Patients should be advised to avoid becoming pregnant. The development of acute leukemia coincident with the use of Cisplatin (CISPATIN) has been reported. In these reports, Cisplatin (CISPATIN) was generally given in combination with other leukemogenic agents. Injection site reactions may occur during the administration of Cisplatin (CISPATIN). Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during drug administration. A specific treatment for extravasation reactions is unknown at this time.

PRECAUTIONS

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 sub therapeutic during Cisplatin (CISPATIN) therapy.

In a randomized trial in advanced ovarian cancer, response duration was adversely affected when Pyridoxine was used in combination with altretamine (hexamethylmelamine) and Cisplatin (CISPATIN).

Pregnancy

Pregnancy Category D

Nursing Mothers

Cisplatin (CISPATIN) has been reported to be found in human milk; patients receiving Cisplatin (CISPATIN) should not breast-feed.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. All children should have audiometric monitoring performed prior to initiation of therapy prior to each subsequent dose, and for several years post therapy. Advanced testing methods may allow for earlier detection of hearing loss in an attempt to facilitate the rapid initiation of interventions that can limit the potential adverse impact of hearing impairment on a child's cognitive and social development.

Geriatric Use

Insufficient data are available from clinical trials of Cisplatin (CISPATIN) in the treatment of metastatic testicular tumors or advanced bladder cancer to determine whether elderly patients respond differently than younger patients. In four clinical trials of combination chemotherapy for advanced ovarian carcinoma, 1484 patients received Cisplatin (CISPATIN) either in combination with cyclophosphamide or paclitaxel. Of these, 426 (29%) were older than 65 years. In these trials, age was not found to be a prognostic factor for survival. However, in a later secondary analysis for one of these trials, elderly patients were found to have shorter survival compared with younger patients. In all four trials, elderly patients experienced more severe neutropenia than younger patients. Higher incidences of severe thrombocytopenia and leukopenia were also seen in elderly compared with younger patients, although not in all Cisplatin (CISPATIN)-containing treatment arms. In the two trials where no hematologic toxicity was evaluated according to age, elderly patients had a numerically higher incidence of peripheral neuropathy than younger patients. Other reported clinical experience suggests that elderly patients may be more susceptible to myelosuppression, infectious complications, and nephrotoxicity than younger patients. Cisplatin (CISPATIN) is known to be substantially excreted by the kidney and is contraindicated in patients with preexisting renal impairment. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored.

ADVERSE REACTIONS

Nephrotoxicity

Dose-related and cumulative renal insufficiency, including acute renal failure, is the major dose limiting toxicity of Cisplatin (CISPATIN). Renal toxicity has been noted in 28% to 36% of patients treated with a single dose of 50 mg/m2. It is first noted during the second week after a dose and is manifested by elevations in BUN and creatinine,

serum uric acid and/or a decrease in creatinine clearance. Renal toxicity becomes more prolonged and severe with repeated courses of the drug. Renal function must return to normal before another dose of Cisplatin (CISPATIN) can be given. Elderly patients may be more susceptible to nephrotoxicity. Impairment of renal function has been associated with renal tubular damage. The administration of Cisplatin (CISPATIN) using a 6-to 8-hour infusion with intravenous hydration, and mannitol has been used to reduce nephrotoxicity. However, renal toxicity still can occur after utilization of these procedures.

Ototoxicity

Ototoxicity has been observed in up to 31% of patients treated with a single dose of Cisplatin (CISPATIN) 50 mg/m2, and is manifested by tinnitus and/or hearing loss in the high frequency range (4000 to 8000 Hz). The prevalence of hearing loss in children is particularly high and is estimated to be 40-60%. Decreased ability to hear normal conversational tones may occur. Deafness after the initial dose of Cisplatin (CISPATIN) has been reported. Ototoxic effects may be more severe in children receiving Cisplatin (CISPATIN). Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated Cisplatin (CISPATIN) doses. It is unclear whether Cisplatin (CISPATIN)-induced ototoxicity is reversible. Vestibular toxicity has also been reported. Ototoxic effects may be related to the peak plasma concentration of Cisplatin (CISPATIN). Ototoxicity can occur during treatment or be delayed. Audiometric monitoring should be performed prior to initiation of therapy, prior to each subsequent dose, and for several years post therapy. The risk of ototoxicity may be increased by prior or simultaneous cranial irradiation, and may be more severe in patients less than 5 years of age, patients being treated with other ototoxic drugs (e.g. aminoglycosides and vancomycin), and in patients with renal impairment. Genetic factors (e.g. variants in the thiopurine S-methyltransferase [TPMT] gene) may contribute to Cisplatin (CISPATIN)-induced ototoxicity; although this association has not been consistent across populations and study designs.

Hematologic

Myelosuppression occurs in 25% to 30% of patients treated with Cisplatin (CISPATIN). The nadirs in circulating platelets and leukocytes occur between days 18 to 23 (range 7.5 to 45) with most patients recovering by day 39 (range 13 to 62). Leukopenia and thrombocytopenia are more pronounced at higher doses (>50 mg/m2). Anemia (decrease of 2 g hemoglobin/100 mL) occurs at approximately the same frequency and with the same timing as leukopenia and thrombocytopenia. Fever and infection have also been reported in patients with neutropenia. Potential fatalities due to infection (secondary to myelosuppression) have been reported. Elderly patients may be more susceptible to myelosuppression. In addition to anemia secondary to myelosuppression, a Coombs' positive hemolytic anemia has been reported. In the presence of Cisplatin (CISPATIN) hemolytic anemia, a further course of treatment may be accompanied by increased hemolysis and this risk should be weighed by the treating physician. The development of acute leukemia coincident with the use of Cisplatin (CISPATIN) has been reported. In these reports, Cisplatin (CISPATIN) was generally given in combination with other leukemogenic agents.

Gastrointestinal

Marked nausea and vomiting occur in almost all patients treated with Cisplatin (CISPATIN), and may be so severe that the drug must be discontinued. Nausea and vomiting may begin within 1 to 4hours after treatment and last up to 24 hours. Various degrees of vomiting, nausea and/or anorexia may persist for up to 1 week after treatment. Delayed nausea and vomiting (begins or persists 24 hours or more after chemotherapy) has occurred in patients attaining complete emetic control on the day of Cisplatin (CISPATIN) therapy. Diarrhea has also been reported.

OTHER TOXICITIES

Vascular toxicities coincident with the use of Cisplatin (CISPATIN) in combination with other antineoplastic agents have been reported. The events are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (hemolytic- uremic syndrome [HUS]), or cerebral arteritis. Various mechanisms have been proposed for these vascular complications. There are also reports of Raynaud's phenomenon occurring in patients treated with the combination of bleomycin, vinblastine with or without Cisplatin (CISPATIN). It has been suggested that hypomagnesemia developing coincident with the use of Cisplatin (CISPATIN) may be an added, although not essential, factor associated with this event. However, it is currently unknown if the cause of Raynaud's phenomenon in these cases is the disease, underlying vascular compromise, bleomycin, vinblastine, hypomagnesemia, or a combination of any of these factors. Serum Electrolyte Disturbances Hypomagnesemia, hypocalcemia, hyponatremia, hypokalemia, and hypophosphatemia have been reported to occur in patients treated with Cisplatin (CISPATIN) and are probably related to renal tubular damage. Tetany has been reported in those patients with hypocalcemia and hypomagnesemia. Generally, normal serum electrolyte levels are restored by administering supplemental electrolytes and discontinuing Cisplatin (CISPATIN). Inappropriate antidiuretic hormone syndrome has also been reported.

Hyperuricemia

Hyperuricemia has been reported to occur at approximately the same frequency as the increases in BUN and serum creatinine. It is more pronounced after doses greater than 50 mg/m2, and peak levels of uric acid generally occur between 3 to 5 days after the dose. Allopurinol therapy for hyperuricemia effectively reduces uric acid levels.

Neurotoxicity.

Neurotoxicity, usually characterized by peripheral neuropathies, has been reported. The neuropathies usually occur after prolonged therapy (4 to 7 months); however, neurologic symptoms have been reported to occur after a single dose. Although symptoms and signs of Cisplatin (CISPATIN) neuropathy usually develop during treatment, symptoms of neuropathy may begin 3 to 8 weeks after the last dose of Cisplatin (CISPATIN). Cisplatin (CISPATIN) therapy should be discontinued when the symptoms are first observed. The neuropathy, however, may progress further even after stopping treatment. Preliminary evidence suggests peripheral neuropathy may be irreversible in some patients. Elderly patients may be more susceptible to peripheral neuropathy. Loss of taste, seizures, leukoencephalopathy, and reversible posterior leukoencephalopathy syndrome (RPLS) have also been reported. Muscle cramps, defined as localized, painful, involuntary skeletal muscle contractions of sudden onset and short duration, have been reported and were usually associated in patients receiving a relatively high cumulative dose of Cisplatin (CISPATIN) and with a relatively advanced symptomatic stage of peripheral neuropathy.

Ocular Toxicity

Optic neuritis, papilledema, and cerebral blindness have been reported in patients receiving standard recommended doses of Cisplatin (CISPATIN). Improvement and/or total recovery usually occurs after discontinuing Cisplatin (CISPATIN). Steroids with or without mannitol have been used; however, efficacy has not been established. Blurred vision and altered color perception have been reported after the use of regimens with higher doses of Cisplatin (CISPATIN) or greater dose frequencies than recommended in the package insert. The altered color perception manifests as a loss of color discrimination, particularly in the blue-yellow axis. The only finding on funduscopic exam is irregular retinal pigmentation of the macular area.

Anaphylactic-Like Reactions

Anaphylactic-like reactions have been reported in patients previously exposed to Cisplatin (CISPATIN). The reactions consist of facial edema, wheezing, tachycardia, and hypotension within a few minutes of drug administration. Reactions may be controlled by intravenous epinephrine with corticosteroids and/or antihistamines as indicated. Patients receiving Cisplatin (CISPATIN) should be observed carefully for possible anaphylactic-like reactions and supportive equipment and medication should be available to treat such a complication.

Hepatotoxicity

Transient elevations of liver enzymes, especially SGOT, as well as bilirubin, have been reported to be associated with Cisplatin (CISPATIN) administration at the recommended doses.

Other Events

Cardiac abnormalities, hiccups, elevated serum amylase, rash, alopecia, malaise, asthenia, and dehydration have been reported. Local soft tissue toxicity has been reported following extravasation of Cisplatin (CISPATIN). Severity of the local tissue toxicity appears to be related to the concentration of the Cisplatin (CISPATIN) solution. Infusion of solutions with a Cisplatin (CISPATIN) concentration greater than 0.5 mg/mL may result in tissue cellulitis, fibrosis, necrosis, pain, edema, and erythema.

OVERDOSAGE

Caution should be exercised to prevent inadvertent overdosage with Cisplatin (CISPATIN). 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.

Storage & Instructions:

Cisplatin (CISPATIN) Injection is a sterile vial without preservatives. Store at 15° C to 25°C. Do not refrigerate, it may cause precipitation. Protect from sunlight, heat and moisture. The Cisplatin (CISPATIN) remaining in the amber vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light.

To be sold on the prescription of a registered oncologist or on demand from cancer hospitals, institutions and oncologists only.

HOW SUPPLIED

Cispatin 50mg/50ml:

1 vial

خوراک وطریقہ استعمال:

سرطان کے ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

دوا کو ۱۵-۲۵ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔

دھوپ، گرمی اور نمی سے محفوظ رکھیں۔

بچوں کی پہنچ سے دور رکھیں۔

صرف مستند اونکولوجسٹ یا کینسر ہسپتال کے نسخے پر فروخت کریں۔

Manufactured by:
PHARMASOL
PRIVATE LIMITED
Plot # 549,Sundar Industrial Estate,
Lahore, Pakistan.