

STERILE SOLUTION FOR SINGLE DOSE INTRAVENOUS INFUSION USE ONLY

COMPOSITION CISPLATIN 10 Cisplatin Injection BP 10 mg/10 mL Each mL contains Cisplatin Excipients CISPLATIN 50 Cisplatin Injection BP 50 mg/ 50 mL Each ml contains

CISPLATIN (Cisplatin Injection) is a clear colorless sterile aqueous solution, available in 10 and 50 mL multiple does

in water for injection. Hcl and/or sodium hydroxide added to

Cisplatin (cis-diamminedichloroplatinum) is a heavy metal complex containing central atom of platinum surrounded by two chloride atoms molecules in the cis position. It is a white powder with the molecular formula PtCl₂H₈N₂, and a molecular weight of 300.05. It is soluble in water or saline at 1 mg/mL and in dimethyl formamide at 24 mg/mL. It has a melting point

CLINICAL PHARMACLOGY

Plasma concentrations of parent compound, cisplatin, decay monoexponentially with a half-life of about 20 to 30 minutes following bolus administration of 50 or 100 mg/m² doses Monoexponential decay and plasma half- lives of about 0.5 hour are also seen following two hour or seven hour infusions of 100 mg/m². After the latter, total -body clearances and volumes of distribution at steady- state for cis –platin are about 15 to 16 L/h/m²and 11 to 12 L/m². Due to its unique chemical structure, the chlorine atoms of cisplatin are more subject to chemical displacement reactions by nucleophiles, such as water or sulfhydryl groups, than to enzyme catalyzed metabolism. At physiological pH in the presence of 0.1M NaCl, the predominant molecular species are cisplatin and monohydroxymonochloro cis –diammine platinum (II) in nearly equal concentrations. The latter, combined with the possible direct displacement of the chlorine atoms by

patients respond differently than younger patients. In four

clinical trials of combination chemotherapy for advanced

ovarian carcinoma, 1484 patients received cisplatin 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 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 leucopenia were also seen in

elderly compared with younger patients, although not in all

cisplatin-containing treatment arms. In the two trials where

nonhematologic 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,

Cisplatin is known to be substantially excreted by the kidney and is contraindicated in patients with pre existing renal

impairment. Because elderly patients are more likely to have

decreased renal function, care should taken in dose selection,

Nephrotoxicity - Dose related and cumulative renal

insufficiency is the major dose-limiting toxicity of cis-platin.

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 can be

given. Elderly patients may be more susceptible to nephrotoxicity (see PRECAUTIONS: Geriatric Use).

Impairment of renal function has been associated with renal tubular damage. The administration of cis-platin using a 6- to

8- hour infusion with intravenous hydration, and manntiol has

been used to reduce nephrotoxicity. However, renal toxicity

Ototoxicity- Ototoxicity has been observed in up to 31% of

patients treated with a single dose of cispatin 50 mg/m2, and is

manifested by tinnitus and/or hearing loss in the high

frequency range (4,000 to 8,000Hz). Decreased ability to hear

normal conversational tones may occur occasionally Deafness after the initial dose of cisplatin has been reported

rarely. Ototoxic effects may be more severe in children

receiving cisplatin. Hearing loss can be unilateral or bilateral

and tends to become more frequent and severe with repeated

doses. Ototoxicity may be enhanced with prior or simultaneous cranial irradiation. It is unclear whether cisplatin

induced ototoxicity is reversible. Ototoxic effects may be

related to the peak plasma concentration of cisplatin. Careful

monitoring of audiometry should be performed prior to

initiation of the rapy and prior to subsequent doses of cisplatin.

Ototoxicity may become more severe in patients being treated

still can occur after utilization of these procedures.

and nephrotoxicity than younger patients.

and renal function should monitored.

ADVERSE REACTIONS

sulfhydryl groups of amino acids or proteins, accounts for the instability of cisplatin in biological matrices. The ratios of cisplatin to total free (ultra filterable) platinum in the plasma vary considerably between patients and range from 0.5 to 1.1 after a dose of 100 mg/m². Cisplatin does not undergo the instantaneous and reversible binding to plasma proteins that is characteristic of normal drug-protein binding. However, the platinum from cisplatin, but not cisplatin itself, becomes bound to several plasma proteins including albumin, transterrin and gamma globulin. Three hours after a bolus injection and two hours after the end of a three- hour infusion, 90% of the plasma platinum is protein bound. The complexes between albumin and the platinum from cisplatin do not dissociate to significant extent and are slowly eliminated with a minimum half- life of

five days or more. Following cisplatin doses of 20 to 120 mg/m^2 , the concentrations of platinum are highest in liver, prostate, and kidney, somewhat lower in bladder, muscle, testicle pancreas, and spleen and lowest in bowel, adrenal, heart, lung, cerebrum, and cerebellum. Platinum is present in tissues for as long as 180 days after the last administration. With the exception of intracerebral tumors, platinum concentrations in tumors are generally somewhat lower than the concentrations in the organ where the tumor is located. Different metastatic sites in the same patient may have different platinum concentrations. Hepatic metastases have the highest platinum concentrations, but these are similar to the platinum concentrations in normal liver. Maximum red blood cell concentrations of platinum are reached within 90 to 150 minutes after a 100 mg/m² dose of cisplatin and decline in biphasic manner with a terminal half-life of 36 to 47 days.

Over ac dose rang of 40 to 140 mg cisplatin/m² given a bolus injection or as infusions varying in length from 1 hour to 24 hours, from 10% to about 40% of the administered platinum is excreted in the urine in 24 hours. Over five days following administration of 40 to 100 mg/m² doses given as rapid, 2 to 3 hour, or 6 to 8 hour infusions, a mean of 35% to 51% of the dosed platinum is excreted in the urine. Similar mean urinary recoveries of platinum of about 14% to 30% of the dose are found following five daily administrations of 20, 30, or 40 mg/m²/day. Only a small percentage of the administered platinum is excreted beyond 24 hours post-infusion and most of the platinum excreted in the urine in 24 hours is excreted within the first few hours. Platinum –containing species excreted in the urine are the same as those found following the incubation of cisplatin with urine healthy subjects, except that the proportions are different.

INDICATIONS

CISPLATIN (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 radiotherapeutic

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 radiotherapeutic procedures. An established combination consists of cisplating and cyclophosphamide. Cisplatin, 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 therapy.

Advanced Bladder Cancer - Cisplatin is indicated as a single agent for patients with transitional cell bladder cancer which is no longer amenable to local treatments such surgery and/ or

frequency and with the same timing as leukopenia and thrombocytopenia. Fever and infections have also been reported in patients with neutropenia. Elderly patients may be more susceptible to myelosuppression (see PRECAUTIONS: Geriatric Use).

In addition to anemia secondary to myelosuppression, a Coombs' positive hemolytic anemia has been reported. In the presence of cisplatin 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 has rarely been reported in humans. In these reports, cisplatin was generally given in combination with other leukemogenic agents.

Gastrointestinal—Marked nausea and vomiting occur in almost all patients treated with cisplatin, and are occasionally so severe that the drug must be discontinued. Nausea and vomiting usually begin within 1 to 4 hours after treatment and last up 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 therapy. Diarrhea has also been reported.

Other Toxicities

Vascular toxicities coincident with the use of cisplatin in combination with other antineoplastic agents have been reported rarely. The events are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident thrombotic microangiopathy (HUS), or cerebral atreritis. Various mechanisms have been proposed for these vascular complications. There are also reports of Reynaud's phenomenon occurring in patients treated with the combination of bleomycin, vinblastine with or without cisplatin. It has been suggested that hypomagnesemia developing coincident with the use of cisplatin may be an added, although not essential, factor associated with this event. However, it is currently unknown if the cause of Reynaud's phenomenon in these cases is the disease, underlying vascular compromise bleomycin, vin-blastin, hypomagnesemia, or a combination of any of these factors

Serum Electrolyte Disturbances - Hypomagnesemia hypocalcaemia, hyponatremia, hypokalemia, and hypophosphatemia have been reported to occur in patients treated with cisplatin and probably related to renal tubular damage. Tetany has occasionally been reported in those patients with hypocalcaemia and hyomagnesemia. Generally, normal serum electrolyte levels are restored by administering supplemental electrolytes and discontinuing cisplatin.

Inappropriate ant diuretic hormone syndrome has also been

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 50mg/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 sign of cis-platin neuropathy usually develop during treatment symptoms of neuropathy may begin 3 to 8 weeks after the last

CONTRAINDICATIONS

CISPLATIN (Cisplatin Injection) is contraindicated in patients with renal preexisting renal impairment. Cisplatin should not be employed in myelosuppressed patients, or patients with hearing impairment.

CISPLATIN (Cisplatin Injection) is contraindicated in patients with a history of allergic reactions to cisplatin or other platinum containing compounds.

DOSAGE AND ADMINISTRATION

Note: Needles or intravenous sets containing aluminum parts that may come in contact with cisplatin should not be used for preparation or administration. Aluminium reacts with cisplatin, causing precipitate formation and a loss of potency.

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

Metastatic Ovarian Tumors – The usual CISPLATIN (Cisplatin 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 (DAY 1). The dose of cyclophosphamide when used in combination with CISPLATIN (Cisplatin Injection) is 600 mg/m2 IV once every four weeks (DAY 1).

For directions for the administration of cyclophasphamide, refer to the cyclophasphamide package insert.

In combination therapy, cisplatin and cyclophasphamide are administered sequentially.

As a single agent, cisplatin should be administered at a dose of

100 mg/m² IV per cycle once every four weeks. Advanced bladder Cancer – CISPLATIN (Cisplatin 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 four weeks is

All Patients- Pretreatment hydration with 1 to 2 liters of fluid infused for 8 to 12 hours prior to a cisplatin does 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 should not be given until the serum

creatinine is below 1.5 mg/100mL, and/or the BUN is below 25 mg/ 100mL. A repeat course should not be given until circulating blood elements are at an acceptable level (platelets □ 100,000 / mm³, WBC ≥4,000 /mm³). Subsequent doses of cisplatin should not be given until an audiometric analysis indicates that auditory acuity is within normal limits.

As with other potentially toxic compounds, caution should be exercised in handling the aqueous solution. Skin reactions associated with accidental exposure to cisplatin may occur. The use of gloves is recommended. If cisplatin contacts the skin or mucosa, immediately and thoroughly wash the skin with soap and water and flush the mucosa with water

The aqueous solution should be used intravenously only and should be administered by IV infusion over a 6- to 8- hour period. The cisplatin remaining in the vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light.

Procedures for proper handling and disposal of anticancer drugs should be considered .Several guidelines on this subject have been published.^{1,7} there is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate

WARNINGS

CISPLATIN (Cisplatin Injection) produces cumulative nephrotoxicity which is potentiated by aminoglycoside antibiotics. The serum creatinine, 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 (Cisplatin Injection) should not be given more frequently than once every 3 to 4 weeks (see ADVERSE REACTIOS section). Elderly patients may be more susceptible to nephrotoxicity (see PRECAUTIONS: Geriatric

There are reports of severe neuropathies in patients in whom regimens are employed using higher doses of cisplatin 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 (see PRECAUTIONS: Geriatric Use).

Loss of motor function has also been reported.

Anaphylactic- like reactions to cisplatin have been reported. These reactions have occurred within minutes of administration to patients with prior exposure to cisplatin, and have been alleviated by administration of epinephrine, corticosteroids, and antihistamines.

Since ototoxicity of cisplatin is cumulative, audiometric testing should be performed prior to initiating therapy and prior to each subsequent dose of drug (see ADVERSE REACTIONS section)

Cisplatin can cause fetal harm when administered to a pregnant woman. Cisplatin is mutagenic in bacteria and produces chromosome aberrations in animal cells in tissue culture. In mice, cisplatin is teratogenic and embryotoxic. 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 carcinogenic effect of cisplatin was studied in BD IX rats. Cisplatin was administered i.p to 50 BD IX rats for 3 weeks, 3 x 1 mg/kg body weight per week. Four hundred and fifty-five days after the first application, 33 animals died, 13 of them related to malignancies: 12 leukemias and 1 renal fibrosarcoma.

The development of acute leukemia coincident with the use of cisplatin has rarely been reported in humans. In these reports, cisplatin was generally given in combination with other leukemogenic agents.

PRECAUTIONS

Peripheral blood counts should be monitored weekly. Liver function should be monitored periodically. Neurologic examination should also be performed regularly (see ADVERSE REACTIONS section).

Carcinogenesis, Mutagenesis, Impairment of Fertility see WARNINGS section.

Pregnancy: Teratogenic Effects, Pregnancy Category D- see WARNINGS section.

Nursing Mothers- Cisplatin has been reported to be found in human milk; patients receiving cisplatin should not breast

Pediatric Use - Safety and effectiveness in pediatric patients have not been established.

Geriatric Use -Insufficient data are available from clinical trials of cisplatin in the treatment of metastatic testicular tumors or advanced bladder cancer to determine whether elderly

after the overdosage, appears to have little effect on removing platinum from the body because of cisplatin'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.

Store at 15° to 25°C (59° to 77°F). Do not refrigerate. Protect

SHELF LIFE

HOW SUPPLIED

CISPLATIN 10 Cisplatin Injection BP 10mg/10mL

Each Sterile Single dose vial, packed in a individually carton.

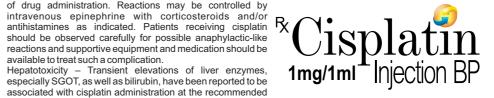
Cisplatin Injection BP 50mg/50mL

Each Sterile Multi Dose vial, packed in a individually carton.

Manufactured in India by: TAJ PHARMACEUTICALS LTD. at SURVEY NO.188/1 TO 189/1.190/1 TO 4 ATHIYAWAD, DABHEL, DAMAN- 396210 (INDIA)

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For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory



 $dose\ of\ cisplatin,\ although\ this\ is\ rare.\ Cisplatin\ the rapy\ should$ 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 (see PRECAUTIONS: Geriatric Use). Lhermitte's sign, dorsal column myelopathy, and autonomic

neuropathy have also been reported.

Loss of taste and seizures has 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 and with a relatively advanced symptomatic stage of peripheral neuropathy.

Ocular toxicity - Optic neuritis, papilledema, and cerebral

blindness have been reported infrequently in patients receiving standard recommended doses of cisplatin Improvement and / or total recovery usually occurs after discontinuing cisplatin. 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 or greater dose frequencies than those 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 occasionally reported in patients previously exposed to cisplatin. The reactions consist of facial edema, wheezing, tachycardia, and hypotension within a few minutes of drug administration. Reactions may be controlled by

associated with cisplatin administration at the recommended

Other Events – Other toxicities reported to occur infrequently are cardiac abnormalities, hiccups, elevated serum amylase, and rash. Alopecia, malaise, and asthenia have been reported as part of postmarketing surveillance.

Local soft tissue toxicity has rarely been reported following extravasation of cisplatin. Severity of the local tissue toxicity appears to be related to the concentration of the cisplatin solution. Infusion of solutions with a cisplatin concentration greater than 0.5 mg/mL may result in tissue cellulitis, fibrosis,

DRUG INTERACTIONS

Plasma levels of anticonvulsant agents may become subtherapeutic during cisplatin 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 Overdose

Caution should be exercised to prevent inadvertent overdosage with cisplatin. 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

TAJ PHARMA

Hematologic- Myelosuppression occurs in 25% to 30% of patients treated with cisplatin. 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). Leucopenia and thrombocytopenia are more pronounced at higher doses (>50mg/m2). Anemia (decrease of 2 g hemoglobin/100mL) occurs at approximately the same

Vestibular toxicity has also been reported.

with other drugs with nephrotoxic potential.

Cisplatin BP Excipients **DESCRIPTION**

vials, each mL containing 1 mg cisplatin 9 mg sodium chloride

 NH_3 NH₃ Cl Cis-diamminedichloroplatinum (II)