

Cisplatin solution in a 100 ml glass vial

occurring in patients treated with the combination of bleomycin , vincristine with or without cisplatin. Foot or leg edemas (nephrotoxicity, hyperuricemia, neuropathy).

Serum electrolyte disturbances: Hypomagnesemia, hypocalcemia, hyponatremia, hypocalcemia, and hypophosphatemia have been reported to occur in patients treated with cisplatin and are also probably related to renal tubular damage. Tetany has occasionally been reported in patients with hypocalcemia and hypomagnesemia. Generally, normal serum electrolyte levels are restored by administering supplemental electrolytes and discontinuing cisplatin treatment. Antidiuretic hormone syndrome has also been reported. **Neurotoxicity:** neurotoxicity has been reported, usually characterized by peripheral neuropathy. The neuropathy usually occurs after prolonged therapy (4 to 7 months); however, neurologic symptoms also occur after a single dose. Although, symptoms and signs of neuropathy caused by cisplatin usually develop during treatment, neuropathy symptoms may begin 3 to 8 weeks after the last dose of cisplatin. Cisplatin therapy should be interrupted when the symptoms are first observed. However, neuropathy may progress further after stopping treatment.

Preliminary evidence suggest that peripheral neuropathy may be irreversible in some patients.

Lhermitte’s sign, dorsal spinal myelopathy, and autonomic neuropathy have also been reported.

Localized and painful muscle cramps, involuntary musculoskeletal contractions of sudden onset and short duration have been reported and were usually associated with patients receiving relatively high cumulative doses of cisplatin, and with a relatively advanced symptomatic stage of peripheral neuropathy.

Ocular toxicity: optic neuritis, papilledema and blindness have been rarely reported in patients receiving standard recommended doses of cisplatin. Improvement and/or total or partial recovery occur after discontinuing cisplatin therapy. Altered color perception has been reported, which manifests as a loss of blue and yellow color discrimination. With the fundoscopic exam it was found that retinal pigmentation is irregular in the macular area.

Anaphylactic reactions: they were occasionally reported in patients previously treated with cisplatin. These reactions consist of facial edema, tachycardia, and hypotension within a few minutes after drug administration. They may be controlled by intravenous epinephrine with corticosteroids and/or antihistamines. Supportive equipment and these medications should be available in case an anaphylactic reaction occurs.

Hepatotoxicity: transient elevations of liver enzymes, particularly SGOT, and bilirubin may be associated with the administration of cisplatin at recommended doses.

Nephrotoxicity: it is dose-related and cumulative. It is usually reversible, but it may become irreversible at high doses or with repeated treatments; occasionally it may be fatal. Hyperuricemia: hyperuricemia occurs at approximately the same frequency as the increases in BUN and creatinine values.

These increases are more pronounced at cisplatin doses greater than 50 mg/m²; peak uric acid concentrations occur during days 3 and 5 after dose administration. Allopurinol therapy effectively reduces uric acid levels in hyperuricemia. **Note:** hyperuricemia usually occurs during initial treatment of patients with leukemia or lymphomas as a result of the tumor lysis syndrome. This produces an increase of uric acid concentrations. Abnormalities in laboratory tests: they may appear during the second week after receiving a cisplatin dose. Peak uric acid concentrations occur 3 to 5 days after receiving cisplatin.

Other adverse reactions: other adverse reactions rarely occurring are: cardiac abnormalities, hiccups, elevation of serum amylase and rash. Alopecia have also been reported. Local soft tissue toxicity has rarely been reported. Its severity is related to the concentration of the cisplatin solution. Infusion of solutions with a cisplatin concentration greater than 0.5 mg/ml may result in cellulitis, fibrosis, and necrosis.

Incidence of less frequent adverse reactions: loss of taste or numbness in fingers and toes or in the face (peripheral neuropathy).

They indicate the need for medical attention if they occur after the medication has been discontinued.

Sores in mouth and on lips (stomatitis) and loss of appetite. They indicate the need for medical attention only if they continue.

Note: they may occur after a single dose or a prolonged therapy (4 to 7 months) and may be irreversible.

Pain at site of injection (extravasation). Face swelling or unusual tachycardia, anaphylactic reaction.

Blurred vision or Altered color perception (optic neuritis, papilledema, blindness)

Note: usually they are reversible after cisplatin discontinuation.

Incidence of more frequent adverse reactions (they occur in most patients); severe nausea and vomiting.

Note: usually, within 1 to 4 hours after dose administration vomiting occurs, and it may persist for 24 hours. Cases of nausea and anorexia may persist for up to 1 week. Ondansetron and/or adrenocorticosteroids have demonstrated to effectively prevent severe nausea and vomiting. Their severity will determine whether cisplatin treatment should be discontinued.

OVERDOSAGE: Caution should be exercised to prevent overdosage with cisplatin.

Acute overdosage with this drug may cause liver failure, deafness, ocular toxicity (including detachment of the retina), significant myelosuppression, nausea, vomiting and/or neuritis. Death can occur following overdosage. No antidotes have been found to counteract cisplatin overdosage. Hemodialysis commenced four hours after overdosage has a little effect, removing cumulated platinum from the body. Management of overdosage should include supportive therapeutic measures to sustain the patient in an appropriate clinical state throughout any period of overdosage that may occur.

In case of overdosage, go to the nearest Hospital.

PATIENT INFORMATION:

Before receiving treatment with cisplatin, you should take the following into account:

If you are being treated with other medication(s), tell your doctor and stick to the medication(s) schedules.

It is important to drink plenty of fluids.

Severe nausea and vomiting are usual effects.

Your doctor will recommend you a medicine to lessen these effects.

PRECAUTIONS:

*It is very important that your doctor check your progress.

*Avoid vaccinations unless they are approved by your doctor.

*Avoid contact with people who have viral or bacterial infections, especially during periods of low blood counts.

*Tissue may be locally damaged if intravenous solution infiltration occurs.

ADVERSE EFFECTS:

This medication may cause adverse effects such us auditory, renal and blood problems. (See Dosage and Administration).

STABILITY: Unreconstituted vials are stable until the expiration appearing on the packing (see storage).

Keep between 15 °C and 25 °C, avoiding exposure to temperatures below 5 °C. Protect from light.

Keep out from the reach of children.

PRESENTATION: Cisplatinio Servycal 10 and 50 mg, carton with 1 vial containing lyophilized powder.

Cisplatinio Servycal 10 mg and 50 mg

This medicine must be used under medical prescription and supervision, and it must not be repeated without a new prescription.

Cisplatinio Servycal 10 mg and 50 mg

Medicinal Specialty authorized by Argentine Ministry of Health (ANMAT). Certificate N° 50.130

Cisplatinio Servycal 10 mg and 50 mg

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Cisplatinio Servycal

Cisplatin 10 mg and 50 mg

LYOPHILIZED POWDER FOR INJECTION

Salé under filed prescription

Made in Argentina

Cisplatinio Servycal 10 mg and 50 mg

QUALI-QUANTITATIVE COMPOSITION:
Each vial of Cisplatinio Servycal 10 mg contains:
 Cisplatin 10 mg
 Mannitol 100 mg
 Sodium chloride 90 mg
 Hydrochloric acid q.s. to adjust pH 3.4

Each vial of Cisplatinio Servycal 50 mg contains:
 Cisplatin 50 mg
 Mannitol 500 mg
 Sodium chloride 450 mg
 Hydrochloric acid q.s. to adjust pH 3.4

Cisplatinio Servycal 10 mg and 50 mg

PHARMACOLOGIC ACTION:

Cisplatin acts by crosslinking DNA in several different ways.

THERAPEUTIC ACTION:
 Antineoplastic.

INDICATIONS:

Metastatic testicular tumors:

In combination therapy with other approved chemotherapeutic agent in patients with metastatic testicular tumors who have received appropriate surgery and/or radiotherapeutic procedures.

Metastatic ovarian tumors:

In combination therapy with other approved chemotherapeutic agent in patients with metastatic ovarian tumors who have received appropriate surgery. The combination consists of cisplatin and cyclophosphamide. Cisplatin as 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 single agent in patients with bladder cancer which is no longer amenable to surgery and/or radiotherapy.

DOSAGE AND ADMINISTRATION:
 General information: cisplatin should be administered in patients under the supervision of physicians experienced in cancer and chemotherapy. The following equipment and medicines should be readily available in case an anaphylactic reaction occurs: epinephrine, oxygen, antihistamines and intravenous adrenocorticosteroids. There is a wide range of dosage regimens, whether with cisplatin as single agent or in combination with other antineoplastic agents. Low doses of cisplatin are recommended in patients with renal impairment.

Cisplatin courses should not be repeated more frequently than every 3 or 4 weeks in order to reduce the risk of cumulative nephrotoxicity.

Subsequent doses of cisplatin should not be given until the renal function returns to normal (creatinine clearance over 90 ml/min, serum creatinine below 1.3 mg/100 ml or BUN below 20 mg/100 ml), and until platelets and WBC are at acceptable levels, 100,000/mm³ and at least 4,000/mm³ respectively.

Cisplatin should be administered intravenously to increase hydration, maintain an appropriate renal function, and reduce nephrotoxicity and ototoxicity, although this form of administration does not prevent them.

The following is recommended: pre-treatment intravenous hydration with 2 litres of fluid for 8 to 12 hours prior to administering a cisplatin dose diluted in 2 litres of Sodium chloride and 1/2 or 1/3 sodium chloride containing 37.5 g of mannitol, and infused over a 6 to 8 hour period. Adequate hydration and urinary output control should be maintained during the following 24 hours.

Cisplatin has also been administered as continuous IV infusion over periods ranging from 24 hours to 5 days. This method reduces nausea and vomiting but nephrotoxicity or ototoxicity are not modified.

Cisplatin therapy should be discontinued when the symptoms of peripheral neuropathy are first observed, as it may be irreversible in some patients.

Combined chemotherapy: cisplatin may be used in combination with other agents in varied regimes. Different doses may be used depending on the results, incidence and/or severity of side effects. For example, cisplatin is part of the following combinations: cyclophosphamide, doxorubicin and cisplatin (CISCA); vinblastine, cisplatin and bleomycin (VBP). **Note:** needles or intravenous sets containing aluminum parts that may come in contact with cisplatin should not be used for this drug preparation or administration. Aluminum reacts with cisplatin, causing a precipitate formation and a loss of potency.

Testicular metastatic tumor: the usual cisplatin dose for the treatment of this type of cancer in combination with other approved chemotherapeutic agents is 20 mg/m² IV daily for a 5 day cycle.

Ovarian metastatic tumor: the usual cisplatin dose for the treatment of this type of cancer in combination with other agents is 75 to 100 mg/m² IV every 4 weeks.

Advanced bladder cancer: cisplatin should be administered as single agent at a dose of 50 to 70 mg/m² IV once every 3 to 4 weeks, depending on the duration of prior chemotherapy. The initial dose for heavily pretreated patients is 50 mg/m² to be repeated every 4 weeks. Pre-treatment hydration with 1 to 2 litres of fluid for 8 to 12 hours prior to administering cisplatin dose is recommended. The drug is then diluted in 2 litres of Sodium chloride in 1/2 or 1/3 physiological salt solution 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 it from light. Adequate hydration and renal function control should be maintained during the following 24 hours.

A new course of cisplatin should not be repeated until the serum creatinine is about 1.5 mg/100 ml and/or the BUN is about 25 mg/100 ml; it should neither be repeated 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 test indicates that auditory acuity is within normal limits.

As with other potentially toxic compounds, caution should be exercised in handling the lyophilized powder and in preparing the cisplatin solution.

Skin reactions associated with accidental exposure to cisplatin may occur. The use of gloves is recommended.

If the lyophilized powder or the cisplatin solution come in contact with the skin or mucosa, wash them immediately with water and soap.

Preparation of IV solution:

Vials containing 10 mg or 50 mg of cisplatin should be reconstituted with, respectively, 10 ml or 50 ml of sterile water for injection. Each ml of the resulting solution will contain 1 mg of cisplatin. The reconstituted solution is clear and colorless. This solution should only be infused intravenously over a 6 to 8 hour period.

PRECAUTIONS:
Carcinogenicity: this is one of the side effects produced by cisplatin. The dose effect and therapy duration are unknown, but risks seem to increase with long-term use.

Mutagenicity: it has been demonstrated that cisplatin is mutagenic in bacteria; it produces chromosome aberrations in tissue cultures of animal cells.

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Reproduction:

Fertility: gonadal suppression resulting in amenorrhea and azoospermia may occur in patients under antineoplastic therapy, especially alkylating agents.

In general, these effects seem to be related to dose and length of therapy, and appear to be irreversible. Prediction of the degree of testicular and ovarian function impairment is complicated due to the common use of combinations of several antineoplastics, which make it difficult to determine the effects of individual agents.

Pregnancy: cisplatin is embryotoxic and teratogenic. *During the first quarter of pregnancy:* it is recommended that the use of antineoplastics be avoided. However, the risk-benefit relation should be considered due to the teratogenicity, mutagenicity and carcinogenicity of this medication.

Breast-feeding: although there is little information available regarding the excretion of antineoplastics agents into breast milk, breast-feeding is not recommended during cisplatin administration due to the risk to the baby (adverse effects, mutagenicity, carcinogenicity).

Pediatrics: the toxic effects of cisplatin may be more severe in children.

Dental pieces: myelodepressant effects of cisplatin may result in an increased incidence of microbial infections. Dental treatments, if possible, should be completed before therapy is initiated, or should be postponed until blood counts have returned to normal values. Patients should be instructed in proper dental hygiene during treatment, including care in the regular use of topical substances, toothbrushes, etc. Cisplatin

may also rarely cause stomatitis associated with considerable upset.

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Drug interactions and/or related problems: the following interactions and/or related problems have been selected on the basis of their potential clinical significance.

Note: combinations containing any of the following medications, depending on the amount present, may interact with cisplatin:

Allopurinol, colchicines, probenecid, sulfipyrazone, anthistamines, budizine, cycizine, loxapine, meclizine, phenothiazines, thioxanthenes, trimethobenzamide and bleomycin.

Blood dyscrasia-causing medications or bone marrow depressants, or other.

Radiotherapy. Nephrotoxic medications, or other. Toxic medications, or other. Live virus vaccines.

Because normal defense mechanisms may be suppressed by the concurrent use of this medication and the administration of live virus vaccines, this may potentiate the replication of the vaccine virus in this type of patients. It may also increase the adverse effects of the vaccine and/or may decrease the patient's antibodies response to the vaccine; immunization of these patients must be carried out with extreme care after carefully checking the patient's hematological status and with the knowledge and consent of the physician in charge of the cisplatin therapy.

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Laboratory tests interactions:
 With physiological values. BUN concentrations and serum creatinine concentrations. Serum uric acid concentrations (may be increased thus indicating nephrotoxicity). Creatinine clearance, Serum calcium, magnesium, potassium and phosphate concentrations (may be decreased due to renal toxicity).

CONTRAINDICATIONS:
 This medication should not be used if any of the following medical problems exist:

- Existing or recent rubella (including recent exposure).
- Herpes zoster (risk of generalized severe disease).
- Bone marrow depression.
- History of gout or urate renal stones (risk of hyperuricemia).
- Hearing impairment.
- Infection.
- Renal function impairment.
- Cautious use is required in patients who have been previously treated with cytotoxic drugs and radiotherapy.

Mild to severe Peripheral Neurotoxicity.

Patient monitoring: the following determinations may be especially important in patient monitoring (other tests may be required in some patients, depending on their condition).

- Audiometric test.
- Neurologic function study (recommended prior to the initiation of therapy and at periodic intervals during therapy).
- Blood urea
- Urine and serum nitrogen
- Creatinine and uric acid clearance (determinations recommended before starting therapy and prior to each

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course of cisplatin to establish renal toxicity)

Live enzymes:
 Alanine aminotransferase (ALT [S-GPT]) and aspartate aminotransferase (AST [S-GOT]) and serum bilirubin. Differential and total leukocyte count.

Red blood cells and platelets counts, and leukocyte formula (determinations are recommended before commencing therapy, at periodic intervals during therapy; frequency varies according to the clinical state, dosing and other agents being used concurrently).

Serum and urine ions: calcium, magnesium, phosphorus and potassium (determinations recommended at periodic intervals during therapy).

ADVERSE EFFECTS:
Note: many of these effects occurring during chemotherapy are unavoidable and represent the medication's pharmacologic action. Some of them, for example leukopenia and thrombocytopenia, are actually used as parameters to assess effectiveness and to monitor dosing.

Cisplatin often causes renal toxicity in the form of acute renal dysfunction, which may be detected initially only by means of renal function tests. The effects are more pronounced at doses of cisplatin greater than 50 mg/m² of body surface area.

Hematologic system: myelosuppression occurs in 25% to 30% of patients treated with cisplatin.

Leukopenia and thrombocytopenia are more pronounced at higher doses of cisplatin (> 50 mg/m²). Anemia (less than 8 g Hb/100 ml) occurs approximately at the same frequency and with the same timing as leukopenia and thrombocytopenia. Fever and infections have been reported in patients with neutropenia.

In addition to anemia secondary to myelosuppression, a Coombs positive hemolytic anemia has also been reported. In the presence of hemolytic anemia caused by cisplatin, a further course of treatment may be accompanied by increased hemolysis and the risk should be weighed by physicians. The development of acute anemia during the use of cisplatin has rarely been reported in humans. In these reports, cisplatin was generally administered in combination with other leukemogenic agents.

Unusual bleeding (thrombocytopenia). Unusual tiredness (anemia).

Gastrointestinal: severe nausea and vomiting occur in most patients treated with cisplatin, and are occasionally so severe that the drug must be discontinued. Nausea and vomiting usually occur 1 to 4 hours after treatment and last up to 24 hours. Several degrees of nausea, vomiting and anorexia may persist for up to one week after treatment. Stomachache.

Vascular toxicities: the use of cisplatin in combination with other antineoplastic agents may produce clinically heterogeneous events which may include: myocardial infarction, cerebrovascular accidents, thrombotic microangiopathy (HUS), or cerebral arteritis. Several mechanisms have been proposed for these vascular complications. There are reports of Raynaud's phenomenon