

1. NAME OF THE MEDICINAL PRODUCT

PLATINOL Lyophilized 10 mg powder for solution for IV drip
PLATINOL Lyophilized 50 mg powder for solution for IV drip

4. CLINICAL PARTICULARS

4.3 Contraindications

Cisplatin (PLATINOL) is contraindicated in patients with a history of allergic reactions to cisplatin (PLATINOL) or other platinum containing compounds, or any component of the formulation.

Cisplatin (PLATINOL) is contraindicated in patients with myelosuppression, in patients who are dehydrated, and those with pre-existing renal impairment or hearing impairment due to the fact that cisplatin (PLATINOL) is nephrotoxic and neurotoxic (in particular ototoxic). These toxicities may be cumulative if disorders of this type pre-exist.

Patients receiving cisplatin should not breastfeed.

Concurrent administration of yellow fever vaccine is contraindicated

4.4 Special warnings and precautions for use

Cisplatin reacts with metallic aluminium to form a black precipitate of platinum. All aluminium containing IV sets, needles, catheters and syringes should be avoided.

Cisplatin (PLATINOL) must be administered under close supervision by a qualified doctor specialised in the use of chemotherapeutic agents.

Appropriate monitoring and management of the treatment and its complications are only possible if adequate diagnosis and exact treatment conditions are available.

1. Nephrotoxicity

PLATINOL causes severe cumulative nephrotoxicity. A urine output of 100 mL/hour or greater will tend to minimize cisplatin nephrotoxicity. This can be accomplished by prehydration with 2 litres of an appropriate intravenous solution, and similar post cisplatin hydration (recommended 2,500 mL/m²/24 hours). If vigorous hydration is insufficient to maintain adequate urinary output, an osmotic diuretic may be administered (eg, mannitol).

2. Neuropathies

Severe cases of neuropathies have been reported.

These neuropathies may be irreversible and may manifest by paresthesia, areflexia and a proprioceptive loss and a sensation of vibrations. A loss of motor function has also been reported. A neurologic examination must be carried out at regular intervals.

3. Ototoxicity

Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin 50mg/m², and is manifested by tinnitus and/or hearing loss in the high frequency range (4000 to 8000Hz). Decreased ability to hear conversational tones may occur occasionally. Ototoxic effect may be more pronounced in children receiving cisplatin. Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated doses; however,

deafness after initial dose of cisplatin has been reported rarely. Ototoxicity may be enhanced with prior simultaneous cranial irradiation and may be related to peak plasma concentration of cisplatin. It is unclear whether cisplatin induced ototoxicity is reversible. Careful monitoring by audiometry should be performed prior to initiation of therapy and prior to subsequent doses of cisplatin. Vestibular toxicity has also been reported. (see section "Undesirable Effects").

4. Allergic phenomena

As with other platinum-based products, hypersensitivity reactions appearing in most cases during perfusion may occur, and necessitate discontinuation of the perfusion and an appropriate symptomatic treatment. Cross reactions, sometimes fatal, have been reported with all the platinum compounds (See "Side Effects" and "Contraindications").

5. Hepatic function and haematological formula

The haematological formula and the hepatic function must be monitored at regular intervals.

6 **Carcinogenic potential**

In humans, in the rare cases the appearance of acute leukaemia has coincided with use of PLATINOL, which was in general associated with other leukaemogenic agents.

Cisplatin (PLATINOL) is a bacterial mutagen and causes chromosome aberrations in cultures on animal cells. Carcinogenicity is possible but has not been demonstrated. PLATINOL is teratogenic and embryo toxic in mice.

7. **Injection site reactions**

Injection site reactions may occur during the administration of cisplatin. 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.

WARNING

This cytostatic agent had a more marked toxicity than is usually found in antineoplastic chemotherapy.

Renal toxicity, which is above-all cumulative, is severe and requires particular precautions during administration (see "Side Effects" and "Administration").

Nausea and vomiting may be intense and require adequate antiemetic treatment.

Close supervision must also be carried out with regard to ototoxicity, myelodepression and anaphylactic reactions (see "Side Effects").

Preparation of the intravenous solution

Warning

As with all other potentially toxic products, precautions are essential when handling the cisplatin solution (PLATINOL). Skin lesions are possible in the event of accidental exposure to the product. It is advisable to wear gloves. In the event the cisplatin solution (PLATINOL)

comes into contact with the skin or mucous membranes, wash the skin or mucous membranes vigorously with soap and water.

Conforming to the procedures appropriate for the manipulation and elimination of cytostatic agents is recommended.

Before administering the solution to the patient, verify the clarity of the solution and the absence of particles.

4.5 Interaction with other medicinal products and other forms of interaction

Nephrotoxic substances:

Concomitant administration of nephrotoxic (e.g. cephalosporins, aminoglycosides, amphotericin B or contrast media) or ototoxic (e.g. aminoglycosides) medicinal products will potentiate the toxic effect of cisplatin on the kidneys. During or after treatment with cisplatin caution is advised with predominantly renal eliminated substances, e.g. cytostatic agents such as bleomycin and methotrexate, because of potentially reduced renal elimination.

The renal toxicity of ifosfamide may be greater when used with cisplatin or in patients who have previously been given cisplatin.

Reduction of the blood's lithium values was noticed in a few cases after treatment with cisplatin combined with bleomycin and etoposide. It is therefore recommended to monitor the lithium values.

Ototoxic substances:

Concomitant administration of ototoxic (e.g. aminoglycosides, loop diuretics) medicinal products will potentiate the toxic effect of cisplatin on auditory function. Except for patients receiving doses of cisplatin exceeding 60 mg/m^2 , whose urine secretion is less than 1000 ml per 24 hours, no forced diuresis with loop diuretics should be applied in view of possible damage to the kidney tract and ototoxicity.

Ifosfamide may increase hearing loss due to cisplatin.

Weakened live vaccines:

Yellow fever vaccine is strictly contraindicated because of the risk of fatal systemic vaccinal disease (see section 4.3.). In view of the risk of generalised illness, it is advisable to use an inactive vaccine if available.

Oral anticoagulants:

In the event of simultaneous use of oral anticoagulants, it is advisable regularly to check the INR.

Antihistamines, Phenothiazines and others:

Simultaneous use of antihistamines, buclizine, cyclizine, loxapine, meclozine, phenothiazines, thioxanthenes or trimethobenzamides may mask ototoxicity symptoms (such as dizziness and tinnitus).

Anticonvulsive substances:

Serum concentrations of anticonvulsive medicines may remain at subtherapeutic levels during treatment with cisplatin.

Pyroxidine + altretamine combination:

During a randomised study of the treatment of advanced ovarian cancer, the response time was unfavourably affected when pyridoxine was used in combination with altretamine (hexamethylmelamine) and PLATINOL.

Paclitaxel:

Treatment with cisplatin prior to an infusion with paclitaxel may reduce the clearance of paclitaxel by 33% and therefore can intensify neurotoxicity.

4.6 Pregnancy and lactation

PLATINOL may be toxic to the foetus when administered to a pregnant woman.

During treatment with PLATINOL and for a minimum of the following 6 months, appropriate measures must be taken to avoid pregnancy; this applies to patients of both sexes.

Genetic consultation is recommended if the patient wishes to have children after ending the treatment.

Since a treatment with cisplatin may cause irreversible infertility, it is recommended that men, who wish to become fathers in the future, ask for advice regarding cryoconservation of their sperm prior to treatment.

Breast-feeding

Cisplatin (PLATINOL) is excreted in breast milk. Patients treated with cisplatin must not breastfeed.

4.7 Effects on ability to drive and use machines

No studies on the effects on ability to drive and use machines have been performed. Nevertheless, the profile of undesirable effects (like nephrotoxicity) may influence the ability to drive vehicles and use machinery.

4.8 Undesirable effects

Undesirable effects depend on the used dose and may have cumulative effects.

The most frequently reported adverse events (>10%) of cisplatin were haematological (leukopenia, thrombocytopenia and anaemia), gastrointestinal (anorexia, nausea, vomiting and diarrhoea), ear disorders (hearing impairment), renal disorders (renal failure, nephrotoxicity, hyperuricaemia) and fever.

Serious toxic effects on the kidneys, bone marrow and ears have been reported in up to about one third of patients given a single dose of cisplatin; the effects are generally dose-related and cumulative. Ototoxicity may be more severe in children.

Frequencies are defined using the following convention: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $\leq 1/1,000$); very rare ($\leq 1/10,000$), not known (cannot be estimated from the available data).

**Table of Adverse Drug Events Reported During Clinical or Postmarketing Experience
(MedDRA terms).**

System Organ Class	Frequency	MedDRA Term
<i>Infections and infestations</i>	Not known	Infection ^a
	Common	Sepsis
<i>Blood and lymphatic system disorders</i>	Very common	Bone marrow failure, thrombocytopenia, leukopenia, anaemia
	Not known	Coombs positive haemolytic anaemia
<i>Neoplasm benign, malignant, and unspecified</i>	Rare	Acute leukaemia
<i>Immune system disorders</i>	Uncommon	Anaphylactoid ^b reaction
<i>Endocrine disorders</i>	Not known	Blood amylase increased, inappropriate antidiuretic hormone secretion
<i>Metabolism and nutrition disorders</i>	Not known	Dehydration, , hypokalaemia, hypophosphataemia, hyperuricaemia, hypocalcaemia, tetany
	Uncommon	Hypomagnesaemia
	Very common	Hyponatraemia
<i>Nervous system disorders</i>	Not known	Cerebrovascular accident, haemorrhagic stroke, ischaemic stroke ageusia, cerebral arteritis, Lhermitte's sign, myelopathy, autonomic neuropathy
	Rare	Convulsion, neuropathy peripheral, leukoencephalopathy, reversible posterior leukoencephalopathy syndrome
<i>Eye disorders</i>	Not known	Vision blurred, colour blindness acquired, blindness cortical, optic neuritis, papilloedema, retinal pigmentation
<i>Ear and labyrinth disorders</i>	Uncommon	Ototoxicity
	Not known	Tinnitus, deafness
<i>Cardiac disorders</i>	Not known	Cardiac disorder
	Common	Arrhythmia, bradycardia, tachycardia
	Rare	Myocardial infarction
	Very rare	Cardiac arrest
<i>Vascular disorders</i>	Not known	Thrombotic microangiopathy (haemolytic uraemic syndrome), Raynaud's phenomenon
<i>Gastrointestinal disorders</i>	Not known	Vomiting, nausea, anorexia, hiccups, diarrhoea
	Rare	Stomatitis
<i>Hepatobiliary disorders</i>	Not known	Hepatic enzymes increased, blood bilirubin increased
<i>Respiratory, thoracic and mediastinal disorders</i>	Not known	Pulmonary embolism
<i>Skin and subcutaneous tissue disorders</i>	Not known	Rash, alopecia
<i>Musculoskeletal, connective tissue and bone disorders</i>	Not known	Muscle spasms
<i>Renal and urinary disorders</i>	Not known	Renal failure acute, renal failure ^c , renal tubular disorder

System Organ Class	Frequency	MedDRA Term
<i>Reproductive system and breast disorders</i>	Uncommon	Abnormal spermatogenesis
<i>General disorders and administration site condition</i>	Not known	Pyrexia (very common) , asthenia, malaise, injection site extravasation ^d

* Source of frequencies: Cisplatin Injection Company Core Data Sheet (CCDS), BMS Pharmacovigilance & Epidemiology, 02 August 2010. Frequencies not reported in the CCDS, have been added from the assessment report

a: Infectious complications have led to death in some patients.

b: Symptoms reported for anaphylactoid reaction such as facial edema (PT-face oedema), wheezing, bronchospasm, tachycardia, and hypotension will be included in the parentheses for anaphylactoid reaction in the AE frequency table.

c: Elevations in BUN and creatinine, serum uric acid, and/or a decrease in creatinine clearance are subsumed under renal insufficiency/failure.

d: Local soft tissue toxicity including tissue cellulitis, fibrosis, and necrosis (common) pain (common), oedema (common) and erythema (common) as the result of extravasation.

4.9 Overdose

CAUTION IS ESSENTIAL IN ORDER TO PREVENT AN INADVERTENT OVERDOSE.

An acute overdose of PLATINOL 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 overdose of PLATINOL. 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 PLATINOL to proteins.

Treatment in the event of an overdose consists of general support measures.

7. MARKETING AUTHORISATION HOLDER