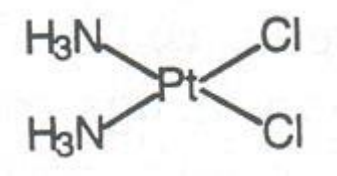
Product Information

CISPLATIN EBEWE® cisplatin 100 mg/100 mL Injection

NAME OF THE MEDICINE

Cisplatin Ebewe



Molecular formula: $Cl_2H_6N_2Pt$

Molecular weight: 300.06

CAS: 15663-27-1

DESCRIPTION

Cisplatin is a yellow to orange crystalline powder that is slightly soluble in water.

Cisplatin Ebewe is a sterile, isotonic, preservative-free solution containing cisplatin 1mg/mL, sodium chloride, hydrochloric acid and water for injections.

PHARMACOLOGY

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

Pharmacokinetics

Distribution: Cisplatin seems to concentrate in the liver, kidneys, small intestine and testes. It does not cross the blood-brain barrier so does not penetrate the cerebrospinal fluid (CSF) to any great extent. CSF levels of cisplatin are low although significant amounts can be detected in intracerebral tumours. Animal studies show good uptake into ovarian and uterine tissue.

Elimination: After intravenous injection, plasma decay is biphasic. The initial phase is rapid with a half-life of 25 to 49 minutes and this is followed by a prolonged elimination phase with a half-life of two to four 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: Excretion is predominantly renal. About 15 to 25% of a dose is rapidly excreted, mainly as intact drug, in the first two to four hours and 20 to 75% in the first 24 hours. The remainder represents drug bound to tissues or plasma proteins.

INDICATIONS

For use in the treatment of metastatic nonseminomatous germ cell carcinoma, advanced stage refractory ovarian carcinoma, advanced stage refractory bladder carcinoma and refractory squamous cell carcinoma of the head and neck, either singularly or in combination with other chemotherapeutic agents; or in appropriate circumstances, in addition to other treatments, such as radiotherapy or surgery.

CONTRAINDICATIONS

Cisplatin Ebewe is contraindicated in patients who:

- have a history of hypersensitivity to cisplatin or platinum-containing compounds
- are dehydrated (pre- and post-hydration is required to prevent serious renal dysfunction)
- have renal dysfunction
- are hearing impaired
- have marrow depression
- are pregnant or breast-feeding.
- have neuropathy caused by cisplatin
- are concurrently administered yellow fever vaccine

PRECAUTIONS

Cisplatin Ebewe should be administered only under constant supervision by physicians experienced in therapy with cytotoxic agents and only when potential benefits of cisplatin therapy outweigh the possible risks. Appropriate facilities should be available for adequate management of complications should they arise.

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 **CONTRAINDICATIONS** and **ADVERSE EFFECTS**).

To minimise the risk of nephrotoxicity, hydrate before, during and after therapy (see Dosage and Administration). Prior to initial therapy, then before subsequent doses, the following parameters should be monitored: renal function including GFR, BUN, serum creatinine and creatinine clearance; electrolytes to detect hypomagnesaemia or hypocalcaemia; auditory function; red blood cells, white blood cells and platelets; hepatic function and neurological status.

Patients receiving cisplatin should be observed carefully for possible anaphylactic like reactions and the necessary equipment and medication should be readily available to treat such reactions.

Patients should be advised to delay dental work while being treated with cisplatin because of bone marrow depressant effects that may result in an increased risk of microbial infection, delayed healing and gingival bleeding.

Nephrotoxicity. Cumulative and dose related renal insufficiency is the major dose limiting toxicity of cisplatin. The most commonly observed changes are a fall in glomerular filtration rate (GFR) reflected by a rise in serum creatinine and a reduction in effective renal plasma flow. Pretreatment and post-treatment hydration may reduce nephrotoxicity (see Dosage and Administration). Renal function must return to normal before further doses are given.

Myelosuppression. Haematological toxicity is also dose-related and cumulative. The lowest levels of circulating platelets and leucocytes generally occur between 18 to 23 days (range 7.3 to 45) with most patients recovering after 39 days (range 13 to 62). Leucopenia and thrombocytopenia are more pronounced at doses greater than 50 mg/ m^2. Subsequent courses of cisplatin should not be instituted until platelets are present at levels greater than 100,000/mm^3 and white cells greater than 4,000/mm^3.

Anaemia. Anaemia (decrease of greater than 2 g/100 mL haemoglobin) occurs in a significant number of patients, usually after several courses of treatment. Transfusions of packed red cells may be necessary in severe cases.

A Coombs' positive haemolytic anaemia has been reported with cisplatin. Further courses with cisplatin in sensitised individuals may cause increased haemolysis.

Nausea and vomiting. This cytostatic agent has a more marked toxicity than is usually found in antineoplastic chemotherapy. 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.

Ototoxicity. Ototoxicity is cumulative and occurs mainly with high dose regimes. Tinnitus or occasional decreased ability to hear normal conversation are indications of ototoxicity which have been frequently observed. Tinnitus is usually transient, lasting from a few hours to a week after cessation of therapy. Hearing loss is usually unilateral or bilateral and occurs in the 4,000 to 8,000 Hz range. Frequency and severity of these hearing disorders increase with repeated doses and severe impairment may not be reversible. Auditory function should be monitored to avoid these symptoms of ototoxicity.

Hypomagnesaemia and hypocalcaemia. Hypomagnesaemia occurs frequently and is probably due to renal tubular damage leading to wasting of magnesium ions. Secondary hypocalcaemia may occur with resulting tetany. Monitoring of electrolytes is necessary.

Neurotoxicity. Peripheral neuropathy, postural hypotension, myasthenic syndromes, seizures and visual loss may occur, especially after prolonged cisplatin treatment. Cessation of cisplatin is recommended if these symptoms occur.

Anaphylaxis. Occasionally reactions secondary to cisplatin therapy have been reported in patients previously exposed to cisplatin. Patients with a prior history or family history of atopy are at particular risk.

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

Renal toxicity, which is above-all cumulative and severe, requires particular precautions during administration (See **DOSAGE AND ADMINISTRATION** and **ADVERSE EFFECTS**).

Close supervision must also be carried out with regard to ototoxicity, myelodepression and anaphylactic reactions (see **ADVERSE EFFECTS**).

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.

Carcinogenic potential. There is a potential for carcinogenicity, in the rare cases where the appearance of acute leukaemia has coincided with use of cisplatin, as is generally associated with other leukaemogenic agents.

Use in pregnancy (Category D)

Australian Pregnancy Categorisation Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

Cisplatin has been shown to be mutagenic in bacterial cultures and produces chromosome aberrations in animal cells in tissue culture. In mice cisplatin is teratogenic and embryotoxic and its use in pregnant women is not recommended. Women of childbearing potential should use adequate contraception and cisplatin should only be used if the potential benefits outweigh the risk of therapy.

If the patient becomes pregnant while receiving the drug she should be advised of the hazard to the foetus.

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

Genetic counseling 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 cryo-conservation of their sperm prior to treatment (see **ADVERSE EFFECTS**).

Use in lactation. Cisplatin is excreted in breast milk. Therefore, because of the potential risk to the newborn infant it is recommended that breastfeeding be discontinued during therapy with cisplatin in breastfeeding women.

Infectious disease. Cisplatin should be administered with caution to patients with herpes zoster, existing or recent chicken pox, or recent exposure to chicken pox, due to the risk of severe generalised disease. It should also be administered with caution to patients with other infections. The myelosuppressive effects of cisplatin may adversely affect dental

procedures, resulting in an increased incidence of microbial infection, delayed healing and gingival bleeding. Where possible, dental work should be completed prior to cisplatin therapy, or deferred until blood counts return to normal. Patients should be instructed on proper dental hygiene during treatment, including caution in the use of toothbrushes, toothpicks and dental floss.

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.

Caution is essential in order to prevent an inadvertent overdose. An acute overdose of cisplatin 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 a cisplatin overdose. Even if haemodialysis is initiated 4 hours after the overdose it has little effect on the elimination of cisplatin from the body due to a strong and rapid fixation of cisplatin to proteins.

Treatment in the event of an overdose consists of general supportive measures (see **OVERDOSAGE**).

INTERACTIONS WITH OTHER MEDICINES

Potentially nephrotoxic and ototoxic drugs such as aminoglycoside antibiotics or loop diuretics may exacerbate the nephrotoxic and ototoxic effects of cisplatin.

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

Ifosfamide may increase hearing loss due to cisplatin.

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).

Attenuated live vaccines. Live vaccines should not be used in patients undergoing Cisplatin therapy. Yellow fever vaccine is strictly contraindicated because of the risk of fatal systemic vaccinal disease (see **CONTRAINDICATIONS**). In view of the risk of generalised illness, it is advisable to use an inactivated vaccine if available.

Incompatibilities: Cisplatin interacts with aluminium to form a black precipitate. Needles, syringes, catheters or intravenous administration sets that contain aluminium should not be used for the administration of cisplatin.

ADVERSE EFFECTS

Gastrointestinal disorders: Severe nausea and vomiting usually begin one to four hours after treatment and may persist for up to a week. This may necessitate stopping treatment. These side effects are only partially relieved by standard antiemetics. Rare occurrence of stomatitis has been reported.

Renal and urinary disorders: Nephrotoxicity is cumulative and dose-related and is the major limiting toxicity. Renal toxicity becomes more prolonged and severe and may produce irreversible renal insufficiency (sometimes fatal) with high or repeated courses of the drug.

Infections and infestations: Sepsis is commonly observed.

Blood and lymphatic system disorders: Mild bone marrow toxicity may occur with both leucopenia and thrombocytopenia and later, anaemia. These effects are usually reversible after ceasing treatment.

Neoplasm benign, malignant, and unspecified: Acute leukaemia has been reported as occurring uncommonly.

Immune system disorders: Anaphylactoid reactions such as flushing, facial oedema, wheezing, tachycardia, skin rash and hypotension have been reported in patients previously exposed to cisplatin. The reactions usually occur within a few minutes of cisplatin administration and may be controlled with intravenous adrenaline, corticosteroids and/or antihistamines.

Ear and labyrinth disorders: Unilateral or bilateral tinnitus and/or hearing loss in high frequencies (> 4,000 Hz) may occur in 10 % of patients and is usually reversible. The damage to the hearing system appears to be dose-related and cumulative, and it is reported more frequently in very young or very old patients. Auditory function should be monitored more closely during treatment.

Nervous system disorders: Peripheral neuropathies occur infrequently with usual doses of the drug. They are generally sensory in nature (e.g. paraesthesia of the upper and lower extremities), but can also include motor difficulties, reduced or absent reflexes and leg weakness. Autonomic neuropathy, seizures, slurred speech, loss of taste and memory loss have also been reported. These neuropathies usually appear after prolonged therapy, but have also developed after a single drug dose. Areflexia and loss of proprioception and vibratory sensation may be seen, especially if cisplatin is given at higher doses or more frequently than recommended. In some patients they may be irreversible however, they have been partially or completely reversible in others following discontinuance of cisplatin therapy. Cerebrovascular accident has been reported in patients treated with cisplatin. Convulsions, leukoencephalopathy and reversible posterior leukoencephalopathy syndrome have been rarely reported.

Eye disorders: Optic neuritis, papilloedema and cortical blindness have been rarely reported following the administration of cisplatin. These events are usually reversible after drug withdrawal.

Cardiac disorders: Cardiovascular abnormalities (e.g. coronary disease, congestive heart failure, arrhythmias, postural hypotension, thrombotic microangiopathy).

Respiratory, Thoracic and Mediastinal Disorders: Pulmonary toxicity has been reported in patients treated with cisplatin in combination with bleomycin or 5-fluorouracil.

Hepatobiliary Disorders: Mild and transient elevations of serum AST and ALT levels may occur infrequently.
Skin and Subcutaneous Tissue Disorders: Mild alopecia. Rarely, urticarial or maculopapular skin rashes have also been observed.

Musculoskeletal and Connective Tissue Disorders: Myalgia.

Reproductive System and Breast Disorders:
Cisplatin can affect male fertility. Impairment of spermatogenesis and azoospermia have been reported. Although the impairment of spermatogenesis can be reversible, males undergoing cisplatin treatment should be warned about the possible adverse effects on male fertility.

Metabolism and nutritional disorders: Cisplatin may cause serious electrolyte disturbances, mainly represented by hypomagnesaemia, hypocalcaemia, and hypokalaemia, and associated with renal tubular dysfunction. Hypomagnesaemia and hypocalcaemia may occur and are manifested by muscle irritability or cramps, clonus, tremor, carpopedal spasm and/or tetany.

Hyperuricaemia may occur particularly when doses greater than 50 mg/m^2 are administered. Peak levels occur three to five days after administration of the drug. Other reported toxicities are hyponatremia and syndrome of inappropriate antidiuretic hormone (SIADH). Allopurinol may be administered to reduce serum uric acid levels.

General Disorders and Administration Site Conditions: Pyrexia occurs very commonly. Local effects such as phlebitis, cellulitis and skin necrosis (following extravasation of the drug) may also occur.

Dental: The myelosuppressive effects of cisplatin may adversely affect dental procedures, resulting in an increased incidence of microbial infection, delayed healing and gingival bleeding. Where possible, dental work should be completed prior to cisplatin therapy, or deferred until blood counts return to normal. Patients should be instructed on proper dental hygiene during treatment, including caution in the use of toothbrushes, toothpicks and dental floss.

DOSAGE AND ADMINISTRATION

Adults, children. Single agent therapy. The usual dose when used as single agent therapy is 50 to 100 mg/m^2 as a single intravenous infusion every three to four weeks; or 15 to 20 mg/m^2 as a daily intravenous infusion for five days every three to four weeks.

Bone marrow depression: Dosage should be reduced in patients with depressed bone marrow function.

Impaired hepatic function. Human studies show a high uptake of cisplatin in the liver. An elevated AST has been reported in some cases and the adult dosage should be used with caution.

Impaired renal function. Cisplatin displays high tissue uptake in the kidneys, exhibits dose-related and cumulative nephrotoxicity and is excreted mainly in the urine. In addition, the plasma elimination half-life of cisplatin is prolonged in renal failure.

Caution should be exercised in patients with pre-existing renal dysfunction. Cisplatin is contraindicated in patients with serum creatinine levels greater than 0.2 mmol/L. Repeat courses are not advised until serum creatinine is below 0.14 mmol/L and/or blood urea below 9 mmol/L.

Administration: Patients should be adequately hydrated before and for 24 hours after administration of cisplatin to ensure good urinary output and minimise nephrotoxicity. Hydration may be achieved by intravenous infusion of 2 L of either sodium chloride IV infusion 0.9% or glucose-saline (e.g. glucose 4% in one-fifth sodium chloride IV infusion 0.9%) over a two-hour period. During the last 30 minutes of the pretreatment hydration or after the hydration, 375 mL of mannitol 10% injection may be administered via a sidearm drip.

Preparation of cisplatin infusion. Cisplatin Ebewe may be added to either 1 L of sodium chloride IV infusion 0.9%, a 1:1 mixture of 5% glucose and 0.9% sodium chloride or a 1:1 mixture of 5% mannitol and 0.9% sodium chloride. Cisplatin injection should not be added to solutions that do not contain at least 0.45% sodium chloride.

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

Treatment. Following prehydration, administer the cisplatin infusion over one to two hours. It has been proposed that a longer infusion time of six to eight hours may decrease gastrointestinal and renal toxicities.

The intravenous flask should be covered to preclude light.

Post-treatment hydration. Adequate hydration and urinary output must be maintained during the 24 hours following infusion. It has been suggested that intravenous hydration continue after treatment with the aim to administer 2 L of sodium chloride IV infusion 0.9% or glucose-saline over a period of 6 to 12 hours.

Handling precautions. As with all antineoplastic agents, trained personnel should prepare Cisplatin Injection. This should be performed in a designated area (preferably a cytotoxic laminar flow cabinet). Protective gown, mask, gloves and appropriate eye protection should be worn while handling cisplatin. Where solution accidentally contacts skin or mucosa, the affected area should be immediately washed thoroughly with soap and water. It is recommended that pregnant personnel not handle cytotoxic agents such as cisplatin.

Luer-Lok fitting syringes are recommended. Large bore needles are recommended to minimise pressure and possible formation of aerosols. Aerosols may also be reduced by using a venting needle during preparation. Items used to prepare cisplatin, or articles

associated with body waste should be disposed of by placing in a double-sealed polythene bag, and incinerating at 1,100 deg. C.

Spills and disposal. If spills occur, restrict access to the affected area. Wear two pairs of gloves (latex rubber), a respirator mask, a protective gown and safety glasses. Limit the spread of the spill by covering with a suitable material such as absorbent towel or adsorbent granules. Spills may also be treated with sodium hypochlorite 5%. Collect up absorbent/ adsorbent material and other debris from spill and place in a leakproof plastic container and label accordingly. Cytotoxic waste should be regarded as hazardous or toxic and clearly labelled 'CYTOTOXIC WASTE FOR INCINERATION AT 1,100 deg. C'. Waste material should be incinerated at 1,100 deg. C for at least one second. Cleanse the remaining spill area with copious amounts of water.

OVERDOSAGE

Contact the Poisons Information Centre on (telephone Australia 13 11 26 or New Zealand 0800 POISON or 0800 764766) for advice on management of overdose.

In the event of overdosage or toxic reactions, symptomatic or supportive measures should be taken. Patients should be monitored for three to four weeks in case of delayed toxicity.

PRESENTATION AND STORAGE CONDITIONS

Cisplatin Ebewe 100mg in 100mL glass vial; 1’s

Store between 15°C to 25°C. Do not refrigerate. Protect from light.

Solutions of Cisplatin Ebewe: Cisplatin Ebewe diluted to 0.10 mg/mL in either 0.9% sodium chloride, 1:1 mixture of 5% glucose and 0.9% sodium chloride or a 1:1 mixture of 5% mannitol and 0.9% sodium chloride is chemically stable for 24 hours when stored at room temperature and protected from light.

Cisplatin Ebewe is for single use in one patient only. Contains no antimicrobial agent. Discard any unused residue.

NAME AND ADDRESS OF THE SPONSOR

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Pyrmont NSW 2009

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POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 10/03/06

Date of most recent amendment: 15/08/11