AUSTRALIAN PRODUCT INFORMATION – CISPLATIN INJECTION (CISPLATIN)

1. NAME OF THE MEDICINE

Cisplatin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cisplatin Injection is a sterile, isotonic, preservative free solution containing cisplatin 1 mg/mL.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cisplatin Injection may be used singularly or in combination with other chemotherapeutic agents in the treatment of:

- Metastatic nonseminomatous germ cell carcinoma
- Advanced stage, refractory ovarian carcinoma
- Advanced stage, refractory bladder carcinoma
- Refractory squamous cell carcinoma of the head and neck.

4.2 Dose and method of administration

Adult and Children Single Agent Therapy

Typical doses and schedules are:

50-100 mg/m^2 as a single IV infusion every 3-4 weeks over 6-8 hours; or slow IV infusion of 15-20 mg/m^2/day for 5 days, every 3-4 weeks.

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

Combination Therapy

Cisplatin is commonly used in combination therapy with the following cytotoxic agents:

- *treatment of testicular cancer:* vinblastine, bleomycin, actinomycin D;

- *treatment of ovarian cancer:* cyclophosphamide, doxorubicin, hexamethylmelamine, 5-fluorouracil;

- *treatment of head and neck cancer:* bleomycin, methotrexate.

Subsequent Treatment with Cisplatin

A repeat course of cisplatin should not be given until:

- the serum creatinine is below 140 micromol/L and/or the plasma urea is below 9 mmol/L and

- circulating blood elements are at an acceptable level (platelets at least 100,000/mm^3, WBC at least 4000/mm^3).

A base line audiogram should be taken and the patient monitored periodically for auditory deterioration (see Section 4.4 Special warnings and precautions for use).

Impaired Hepatic Function

Human studies show a high uptake of cisplatin in the liver.

Elevated aspartate aminotransferase (AST) and alkaline phosphatase with clinical signs of liver toxicity have been reported. Cisplatin should be used with caution in patients with pre-existing hepatic dysfunction.

Impaired Renal Function

Cisplatin displays high tissue uptake in the kidneys and exhibits dose related and cumulative nephrotoxicity. It is excreted mainly in the urine. The plasma elimination half-life of cisplatin is prolonged and plasma levels are markedly elevated in renal function.

Caution should be exercised in patients with pre-existing renal dysfunction. Cisplatin is contraindicated in patients with serum creatinine levels greater than 200 micromol/L. Repeat courses are not advised until serum creatinine is below 140 micromol/L and/or blood urea below 9 mmol/L.

Administration: Patients should be adequately hydrated before and for 24 hours following administration of cisplatin to ensure good urinary output and minimise nephrotoxicity.

1. *Pretreatment Hydration:* Hydration may be achieved by intravenous infusion of 2 litres of 5% glucose in ½ to ⅓ normal saline infused over a 2-4 hour period.

2. *Administration:* Cisplatin Injection may be added to 1 litre of normal saline and infused over the desired time period.

3. *Post-treatment Hydration:* It is important to maintain adequate hydration and urinary output for 24 hours following the infusion.

The product and its admixtures contain no antimicrobial agent. In order to reduce microbiological hazards it is recommended that further dilution be effected immediately prior to use and infusion commenced as soon as practicable after preparation of the admixture. Infusion should be completed within 24 hours of preparation and the residue discarded.

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-Lock 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 1100°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 5% sodium hypochlorite. Collect up absorbent/adsorbent material and other debris from spill and place in a leak proof plastic container and label accordingly.

Cleanse the remaining spill area with copious amounts of water.

4.3 Contraindications

Cisplatin Injection is contraindicated in the following conditions:

- Renal impairment
- Hearing disorders
- Bone marrow depression
- During pregnancy or lactation
- In patients with a history of hypersensitivity to cisplatin or platinum containing compounds.

4.4 Special warnings and precautions for use

Cisplatin 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.

To minimise the risk of nephrotoxicity, hydrate before, during and after therapy (see Section 4.2 Dose and method of administration). Prior to initial therapy, then before subsequent doses, the following parameters should be monitored: renal function including Glomerular Filtration Rate (GFR), Blood Urea Nitrogen (BUN), serum creatinine and creatinine clearance;

electrolytes to detect hypomagnesaemia or hypocalcaemia; auditory function; red blood cells, white blood cells and platelets; liver function and neurological status.

Nephrotoxicity

Cumulative and dose-related renal insufficiency is the major dose-limiting toxicity of cisplatin. The most commonly observed changes are a fall in GFR reflected by a rise in serum creatinine and a reduction in effective renal plasma flow.

Pre and post treatment hydration may reduce nephrotoxicity (see Section 4.2 Dose and method of administration).

Renal function must return to normal before further doses are given.

Myelosuppression

Haematological toxicity is dose-related and cumulative. The lowest levels of circulating platelets and leucocytes generally occur between 18-23 days (range 7.3-45) with most patients recovering after 39 days (range 13-62). 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 2g % 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

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 4000 to 8000 Hz range. Frequency and severity of these hearing disorders increases 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. 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 with a family history of atopy are at particular risk.

Cardiovascular toxicity

Cisplatin has been found to be associated with cardiovascular toxicity (see Section 4.8 Adverse effects (undesirable effects)). Patients may experience clinically heterogeneous venous thromboembolic events, myocardial infarction, cerebrovascular accidents, thrombotic microangiopathy and cerebral arteritis. Cases of pulmonary embolism (including fatalities) have been reported (see Section 4.8 Adverse effects (undesirable effects)).

Live vaccines

Live vaccines should not be used in patients undergoing cisplatin therapy.

Use in the elderly

No data available.

Paediatric use

Cases of delayed-onset hearing loss have been reported in the paediatric population. Long term follow-up in this population is recommended.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

Nephrotoxic drugs

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

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

Ototoxic drugs

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

Ifosfamide may increase hearing loss due to cisplatin.

Renally excreted drugs

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

Anticonvulsant agents

Plasma levels of anticonvulsant agents may become subtherapeutic during cisplatin therapy.

Anticoagulants

It is advisable to check the international normalised ratio (INR) when oral anticoagulants such as coumarins/warfarin are used simultaneously with cisplatin.

Paclitaxel

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

4.6 Fertility, pregnancy and lactation

Effects on fertility

Female

Based on non-clinical (see Section 5.3 Preclinical safety data) and clinical findings, female fertility may be compromised by treatment with cisplatin. Use of cisplatin has been associated with cumulative dose-dependent ovarian failure, premature menopause and reduced fertility.

Male

Cisplatin can affect male fertility. Impairment of spermatogenesis and azoospermia have been reported (see Section 4.8 Adverse effects (undesirable effects) - Reproductive System and Breast Disorders). Although the impairment of spermatogenesis can be reversible, males undergoing cisplatin treatment should be warned about the possible adverse effects on male fertility.

Both men and women should seek advice on fertility preservation before treatment.

Use in pregnancy – Category D

In mice cisplatin is teratogenic and embryotoxic, and its use in pregnant women is not recommended.

Women of childbearing potential should use effective contraception during treatment with cisplatin and for at least 26 weeks following the last dose. Men with female partners of childbearing potential should be advised to use effective contraception during treatment with cisplatin and for at least 14 weeks after the last dose.

For patients with end-stage renal disease, the washout period of cisplatin will be longer (up to 7 weeks); effective contraception for men is advised for at least 19 weeks and for female patients, for at least 31 weeks after the last dose.

If the patient becomes pregnant whilst receiving the drug she should be advised of the hazard to the fetus. Cisplatin should only be used if the potential benefits outweigh the risk of therapy.

Use in lactation

Limited data from published literature report presence of cisplatin in human milk. Advise pregnant women not to breastfeed during treatment with cisplatin.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

Gastrointestinal Disorders

Severe nausea and vomiting usually begin 1-4 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. Reported toxicity includes gingival platinum line.

Renal and Urinary Disorders

Acute renal toxicity, which was highly frequent in the past and represented the major dose-limiting toxicity of cisplatin, has been greatly reduced by the use of 6 to 8 hour infusions as well as by concomitant intravenous hydration and forced diuresis. Cumulative toxicity, however, remains a problem and may be severe. Renal impairment, which is associated with tubular damage, may first be noted during the second week after a dose and is manifested by an increase in serum creatinine, BUN, serum uric acid and/or decrease in creatinine clearance. Renal insufficiency is generally mild to moderate and reversible at the usual doses of the drug, however, high or repeated doses can increase the severity and duration of renal impairment and may produce irreversible renal insufficiency (sometimes fatal). Renal failure has been reported following intraperitoneal instillation of the drug.

Blood and Lymphatic System Disorders

Mild bone marrow toxicity may occur with both leucopenia and thrombocytopenia. These effects are usually reversible after ceasing treatment. Cisplatin may also induce anaemia: this is not clearly dose related and is occasionally caused by haemolysis.

Immune System Disorders

Anaphylactic and anaphylactic like reactions such as flushing, facial oedema, wheezing, tachycardia, 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 IV adrenaline, corticosteroids and/or antihistamines.

Ear and Labyrinth Disorders

Unilateral or bilateral tinnitus and/or hearing loss in high frequencies (>4000Hz) 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. Lhermitte's sign has been reported.

Eye Disorders

Retinal toxicity manifests as blurred vision and altered colour perception. Optic neuritis, papilloedema and cortical blindness have been reported rarely following the administration of cisplatin. These events are usually reversible after drug withdrawal.

Cardiac Disorders

Cardiovascular abnormalities (coronary disease, congestive heart failure, arrhythmias, postural hypotension, thrombotic microangiopathy etc.).

Vascular Disorders

Venous thromboembolism

A significant increase in the risk of venous thromboembolic events has been reported in patients with advanced solid tumours and treated with cisplatin compared with non-cisplatin-based chemotherapy.

Vascular toxicity 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 (haemorrhagic and ischaemic stroke), thrombotic microangiopathy (haemolytic uremic syndrome) or cerebral arteritis. Various mechanisms have been proposed for these vascular complications.

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

Impairment of spermatogenesis and azoospermia have been reported (see Section 4.6 Fertility, pregnancy and lactation).

Metabolism and Nutrition Disorders

Cisplatin may also cause serious electrolyte disturbances, mainly represented by hypomagnesaemia, hypocalcaemia, and hypokalaemia, and associated with renal tubular dysfunction. Hypomagnesaemia and/or hypocalcaemia may become symptomatic, with muscle irritability or cramps, clonus, tremor, carpopedal spasm and/or tetany. Other reported toxicities are hyperuricaemia, 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, local effects such as phlebitis, cellulitis and skin necrosis (following extravasation of the drug) may also occur.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Treat symptomatically. See Section 4.8 Adverse effects (undesirable effects) for possible complications.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class

Antineoplastic agent.

Mechanism of Action

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

Clinical trials

No data available

5.2 Pharmacokinetic properties

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 and Excretion

After IV injection, plasma decay is biphasic. The initial phase is rapid with a half-life of 25-49 minutes and this is followed by a prolonged elimination phase with a half-life of 2-4 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 is predominantly renal. About 15-25% of a dose is rapidly excreted, mainly as intact drug, in the first 2-4 hours and 20-75% in the first 24 hours. The remainder represents drug bound to tissues or plasma proteins.

5.3 Preclinical safety data

Genotoxicity

Cisplatin has been shown to be mutagenic in bacterial cultures and produces chromosome aberrations in animal cells in tissue culture. Non-clinical findings in mice treated with cisplatin (5 mg/kg intraperitoneally) showed that cisplatin caused direct damage to primordial follicle oocytes, leading to apoptosis.

Carcinogenicity

Carcinogenicity of cisplatin is possible but not proven.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid

Sodium hydroxide

Sodium chloride

Mannitol

Water for Injections

6.2 Incompatibilities

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

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store between 15°C to 25°C. Do not refrigerate. Protect from light. Single use only. Discard unused portion.

6.5 Nature and contents of container

Cisplatin Injection 10 mg in 10 mL (sterile) Plastic Vial (1's and 5's).

Cisplatin Injection 50 mg in 50 mL (sterile) Plastic Vial (1's).

Cisplatin Injection 100 mg in 100 mL (sterile) Plastic Vial (1's).

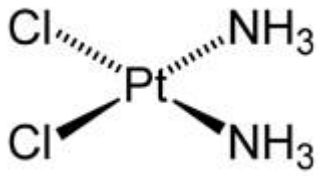
Not all presentations may be marketed.

6.6 Special precautions for disposal

Cytotoxic waste should be regarded as hazardous or toxic and clearly labelled 'CYTOTOXIC WASTE FOR INCINERATION AT 1100°C'. Waste material should be incinerated at 1100°C for at least 1 second.

6.7 Physicochemical properties

Chemical structure



CAS number

15663-27-1

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

Pfizer Australia Pty Ltd
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Toll Free Number: 1800 675 229
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9. DATE OF FIRST APPROVAL

13 August 1991

10. DATE OF REVISION

06 April 2020

Summary Table of Changes

Section changed	Summary of new information
4.4	Inclusion of a warning regarding delayed hearing loss in paediatrics.
4.5	Inclusion of drug-drug interaction information for ifosfamide, lithium, anticonvulsants, anticoagulants and paclitaxel.
4.6	Inclusion of new information regarding pregnancy, fertility and lactation.
4.8	Addition of Lhermitte's sign as an adverse effect.
5.3	Updated with information related to the updates in section 4.6 (female fertility). Inclusion of information on genotoxicity and carcinogenicity.