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

Dosage

A variety of doses and schedules are used. To obtain optimum therapeutic results with minimum adverse effects, the dosage of cisplatin must be based on the clinical, renal and haematologic status of the patient.

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.

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.

Dosage Adjustment

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

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).

Hepatic impairment

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

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

Renal impairment

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 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 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. *Pre-treatment 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.

   Aluminium containing equipment should not be used for administration of cisplatin (see Section 6.2 Incompatibilities).

3. *Post-treatment Hydration:* It is important to maintain adequate hydration and urinary output for 24 hours following the infusion. It has been suggested that IV hydration continue after treatment with the aim to administer 2 litres of sodium chloride IV infusion 0.9% or glucose-saline over a period of 6-12 hours.

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). Care should be taken to prevent inhaling particles and exposing the skin to cisplatin. Protective gown, mask, gloves and appropriate eye protection should be worn while handling cisplatin. In the event of contact with the eyes, wash with water or saline; where solution accidentally contacts skin or mucosa, the affected area should be immediately washed thoroughly with soap and water and in both cases seek medical advice. Seek immediate medical attention if the drug is ingested or inhaled. It is recommended that pregnant personnel not handle cytotoxic agents such as cisplatin.

Luer-Lock fitting syringes and giving sets to avoid leakage 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 (refer to Section 4.2 Dose and method of administration)
- Hearing disorders (refer to Section 4.4 Special warnings and precautions for use, Ototoxicity)
- Bone marrow depression
- Generalised infections
- 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 is a highly toxic drug with a relatively narrow therapeutic index, and a therapeutic effect is unlikely to occur without some evidence of toxicity. 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 (magnesium, sodium, potassium and calcium) to detect hypomagnesaemia or hypocalcaemia; auditory function; red blood cells, white blood cells and platelets; liver function and neurological status.

Myelosuppression

This may occur in patients treated with cisplatin. 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.

Peripheral blood counts should be monitored frequently in patients receiving cisplatin. Although the haematologic toxicity is usually moderate and reversible, severe thrombocytopenia and leucopenia may occur. In patients who develop thrombocytopenia special precautions are recommended: care in performing invasive procedures; search for signs of bleeding or bruising; test of urine, stools and emesis for occult blood; avoiding aspirin and

other NSAIDs. Patients who develop leucopenia should be observed carefully for signs of infection and might require antibiotic support and blood product transfusions.

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/dL haemoglobin) occurs in a significant number of patients, usually after several courses of treatment. Anaemia occurs at approximately the same frequency but generally with a later onset than leucopenia and thrombocytopenia. Transfusions of packed red cells may be necessary in severe cases.

Rarely, the drug has caused haemolytic anaemia; Coombs-positive results have been reported in a few of these cases. Further courses with cisplatin in sensitised individuals may cause increased haemolysis.

A high incidence of severe anaemia requiring transfusion of packed red cells has been observed in patients receiving combination chemotherapy including cisplatin.

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.

Audiometric testing should be performed, if possible prior to initiation of therapy and at regular intervals thereafter, particularly if the clinical symptoms of tinnitus or hearing impairment occur. Radiotherapy may enhance ototoxicity. Clinically important deterioration of auditive function may require dosage modifications or discontinuation of therapy.

Hypomagnesaemia and hypocalcaemia

Hypomagnesaemia occurs quite frequently with cisplatin administration, while hypocalcaemia occurs less frequently. The loss of magnesium seems to be associated with renal tubular damage which prevents resorption of this cation. Where both electrolytes are deficient, tetany may result. It does not appear to be dose related. Monitoring of electrolytes is necessary.

Neurotoxicity

Cisplatin is known to induce neurotoxicity; therefore, neurologic examination is warranted in patients receiving a cisplatin-containing treatment. Peripheral neuropathy, postural

hypotension, myasthenic syndromes, seizures and visual loss may occur especially after prolonged cisplatin treatment. Since neurotoxicity may result in irreversible damage, cessation of cisplatin is recommended if these symptoms occur.

Anaphylaxis

Occasionally reactions secondary to cisplatin therapy have been reported in patients who were previously exposed to cisplatin. Patients with a prior history or family history of atopy are at particular risk. Facial oedema, wheezing, tachycardia, hypotension and skin rashes of urticarial non-specific maculopapular type can occur within a few minutes of administration. Serious reactions seem to be controlled by IV adrenaline, corticosteroids or antihistamines.

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

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)).

Immunosuppressant Effects/Increased Susceptibility to Infections

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including cisplatin, may result in serious or fatal infections. Extreme caution should be used where patients have recently been exposed to infections, particularly chicken pox and herpes zoster. Live vaccines should not be used in patients undergoing cisplatin therapy. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Dental

The bone marrow depressant effects of cisplatin may result in an increased incidence of microbial infection, delayed healing and gingival bleeding. Dental work should be avoided during cisplatin therapy.

Other

As patients undergoing treatment with cisplatin are at an increased risk of bleeding, bruising and infection, it is recommended that extreme care be used when performing necessary invasive procedures.

Alcohol and aspirin should be avoided because of the risk of gastrointestinal bleeding.

Use in hepatic impairment

Liver function should be monitored periodically.

Use in renal impairment

Cisplatin is contraindicated in patients with renal impairment (see Section 4.3 Contraindications).

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 (see Section 4.2 Dose and method of administration).

Special care has to be taken when cisplatin-treated patients are given concomitant therapies with other potentially nephrotoxic drugs (see Section 4.5 Interactions with other medicines and other forms of interactions).

Use in the elderly

No data available.

Paediatric use

Cisplatin can also be used in children. 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

Cisplatin is mostly used in combination with antineoplastic drugs having similar cytotoxic effects. In these circumstances additive toxicity is likely to occur.

Other known drug interactions are reported below.

Nephrotoxic drugs

Potentially nephrotoxic drugs such as aminoglycoside antibiotics or loop diuretics when given concurrently or within 1-2 weeks after cisplatin administration, may exacerbate the nephrotoxic effects of cisplatin. Concomitant use of other potentially nephrotoxic drugs (e.g., amphotericin B) is not recommended during cisplatin therapy.

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

Ototoxic drugs

Concurrent and/or sequential administration of potentially ototoxic drugs such as aminoglycoside antibiotics or loop diuretics may exacerbate the ototoxic effects of cisplatin, especially in the presence of renal impairment.

Ifosfamide may increase hearing loss due to cisplatin.

Renally excreted drugs

Literature data suggest that cisplatin may alter the renal elimination of bleomycin and methotrexate (possibly as a result of cisplatin-induced nephrotoxicity) and enhance their toxicity. 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. In patients receiving cisplatin and phenytoin, serum concentrations of the latter may be decreased, possibly as a result of decreased absorption and/or increased metabolism. In these patients, serum levels of antiepileptics should be monitored and dosage adjustments made as necessary.

Antigout agents

Cisplatin may raise the concentration of blood uric acid. Thus, in patients concurrently receiving antigout agents such as allopurinol, colchicine, probenecid or sulfinpyrazone, dosage adjustment of these drugs may be necessary to control hyperuricaemia and gout.

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 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. 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, and ovarian depletion.

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). Cisplatin caused testis damage and decreased sperm counts in mice, primarily through effects on differentiated spermatogonia. 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

The safety of cisplatin in pregnancy has not been established. Cisplatin can cross the placental barrier. In mice and rats, cisplatin is teratogenic and embryotoxic (at clinically relevant doses), and in both species, deformities have been reported. Studies in rodents have shown that exposure during pregnancy can cause tumours in adult offspring. Cisplatin may be toxic to the fetal urogenital tract. Therefore, cisplatin is considered to be potentially harmful to the fetus when administered to a pregnant woman and its use in pregnant women is not recommended. Patients should be advised to avoid becoming pregnant.

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.

Women of childbearing potential/contraception in males and females

Women of childbearing potential should use effective contraception during treatment with cisplatin and for at least 7 months 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 4 months after the last dose.

Use in lactation

Cisplatin and its active metabolites have been identified in human milk of treated mothers. Advise pregnant women not to breastfeed during treatment with cisplatin and for 1 month following last dose of treatment or to discontinue treatment, taking into account the importance of the drug to the mother.

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

Stomatitis, vomiting, nausea, anorexia, hiccups, diarrhoea.

Cisplatin induces severe nausea and vomiting in almost all patients. 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. The severity of these symptoms may be reduced by dividing the total dose per cycle into smaller doses given once daily for five days. 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

Thrombotic microangiopathy (haemolytic uraemic syndrome), bone marrow failure, neutropenia, Coombs positive haemolytic anaemia.

Myelosuppression often occurs during cisplatin therapy. 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. Leucopenia and thrombocytopenia are dose-related and more pronounced at doses greater than 50 mg/m^2. Leucocyte and platelet nadirs generally occur between days 18 and 23 of treatment, with recovery in most patients by day 39. Anaemia occurs at approximately the same frequency.

There have been rare reports of acute myelogenous leukaemias and myelodysplastic syndromes arising in patients who have been treated with cisplatin, mostly when given in combination with other potentially leukaemogenic agents.

Infections and Infestations

Infection (infectious complications have led to death), sepsis.

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 (>4000 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

Convulsion, leukoencephalopathy, reversible posterior leukoencephalopathy syndrome, haemorrhagic stroke, ischaemic stroke, ageusia, cerebral arteritis, myelopathy.

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. Retinal pigmentation has also been reported.

Cardiac Disorders

Cardiovascular abnormalities (coronary disease, congestive heart failure, arrhythmias, postural hypotension, thrombotic microangiopathy, bradycardia, tachycardia, cardiac arrest, cardiac disorder etc.).

Vascular Disorders

Raynaud's phenomenon.

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 embolism.

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. Liver injury has also been infrequently reported.

Skin and Subcutaneous Tissue Disorders

Mild alopecia. Rarely, urticarial or maculopapular skin rashes have also been observed.

Musculoskeletal and Connective Tissue Disorders

Myalgia, muscle spasm.

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 cause dehydration in patients. 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. Hypomagnesaemia and hypocalcaemia may develop during cisplatin therapy or following discontinuance of the drug. Other reported toxicities are hyperuricaemia, hyponatremia, hypophosphataemia, and syndrome of inappropriate antidiuretic hormone (SIADH). Hyperuricaemia may occur in patients receiving cisplatin, principally as a result of drug-induced nephrotoxicity. Hyperuricaemia is more pronounced with doses greater than 50 mg/m^2, with peak levels occurring between 3-5 days after administration of the drug. Allopurinol may be administered to reduce serum uric acid levels. Regular monitoring of serum electrolyte levels and replacement where necessary are advisable.

General Disorders and Administration Site Conditions

Pyrexia, asthenia, malaise. Local effects such as pain, oedema, erythema, phlebitis, tissue cellulitis, fibrosis and skin necrosis (following extravasation of the drug) may also occur. Extravasation may result from infusion of solutions greater than 0.5 mg/mL cisplatin.

4.9 Overdose

Acute overdosage with cisplatin may result in an enhancement of its expected toxic effects (e.g., kidney failure, severe myelosuppression, intractable nausea and vomiting, severe neurosensorial toxicities, liver failure etc.). Death may also occur. No proven antidotes are known for cisplatin overdosage. Haemodialysis is only effective, even then partially, up to 3 hours after administration because of the rapid and extensive binding of platinum to plasma proteins. Signs and symptoms of overdosage should be managed with supportive measures. Patients should be monitored for 3 to 4 weeks in case of delayed toxicity. See Section 4.8 Adverse effects (undesirable effects) for possible complications.

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 and has biochemical properties similar to those of bifunctional alkylating agents. 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.

Studies aiming at determining plasma elimination half-life of total platinum have shown a very large interindividual and interstudy variation. Most studies reported a half-life of total plasma platinum post cisplatin treatment of approximately 5 days or longer.

5.3 Preclinical safety data

Genotoxicity

Cisplatin has been shown to be genotoxic *in vitro*, in bacterial gene mutation assays, gene mutation assays in yeast (*Saccharomyces cerevisiae* D7) and mammalian cells (mouse lymphoma cells and Chinese hamster cells), *in vitro* chromosome aberration assays (in Chinese hamster cells and in human lymphocytes), *in vitro* DNA repair assays (*Saccharomyces cerevisiae* D7 and v79 Chinese hamster cells) and *in vivo* in a chromosome aberration assay in mouse bone marrow cells. Based on these studies, cisplatin is considered to present a genotoxic risk to humans.

Carcinogenicity

No formal carcinogenicity studies were performed. In a transplacental carcinogenicity study, a single IP injection of cisplatin (7.5 mg/kg) to pregnant mice on day 17 of gestation initiated and/or induced thymic lymphomas, lung tumours and proliferative kidney lesions in offsprings at week 25. In another transplacental carcinogenicity study, pregnant rats were given a single IP injection of cisplatin (5 mg/kg) on day 18 of gestation and resulted in significantly higher incidences (20/82 in treatment vs 3/75 in control) of hepatocellular adenoma in offspring rats at 79 weeks. Therefore, cisplatin has a high carcinogenic potential in mice and rats.

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

Refer to outer carton for expiration date.

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).

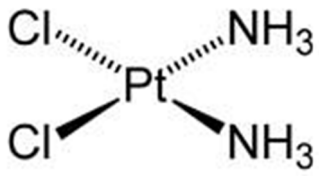
Not all presentations may be marketed.

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. MANUFACTURER

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