

# NEW ZEALAND DATA SHEET

## CISPLATIN ACCORD (CISPLATIN) SOLUTION FOR INJECTION

### 1 PRODUCT NAME

Cisplatin Accord 1 mg/1 mL solution for injection

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Cisplatin Accord 1 mg/1 mL is available as a 10 mg/10 mL, 25 mg/25 mL, 50 mg/50 mL and 100 mg/100 mL solution for injection.

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

### 3 PHARMACEUTICAL FORM

Solution for injection

Cisplatin Accord injection is a clear, colourless to pale yellow sterile solution of cisplatin 1 mg/mL and sodium chloride 9 mg/mL in water for injections.

### 4 CLINICAL PARTICULARS

#### 4.1 THERAPEUTIC INDICATIONS

Cisplatin Accord is indicated for the palliative treatment of:

- Metastatic non-seminomatous germ cell carcinoma;
- Advanced-stage refractory ovarian carcinoma;
- Advanced-stage refractory bladder carcinoma; and
- Refractory squamous cell carcinoma of the head and neck.

It may be used as a single agent or in combination with other chemotherapeutic agents.

It may be employed, in appropriate circumstances, in addition to other modalities, e.g. radiotherapy or surgery.

#### 4.2 DOSE AND METHOD OF ADMINISTRATION

The usual dose in adults and children when used as single agent therapy is 50 - 100 mg/m<sup>2</sup> as a single IV infusion every 3 - 4 weeks, or 15 - 20 mg/m<sup>2</sup> as a daily IV infusion for 5 days every 3 - 4 weeks.

#### Combination therapy:

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

1. For the treatment of testicular cancer: vinblastine, bleomycin, actinomycin D.
2. For treatment of ovarian cancer: cyclophosphamide, doxorubicin, (adriamycin), hexamethylmelamine, fluorouracil.
3. For 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:

1. The serum creatinine is below 140 micromol/L and/or the plasma urea is below 9 mmol/L, and
2. Circulating blood elements are at an acceptable level (platelets at least 100,000/mm<sup>3</sup>, WBC at least 4,000/mm<sup>3</sup>).

A baseline audiogram should be taken and the patient monitored periodically for auditory deterioration.

### **With impaired liver function**

Human studies show a high uptake of cisplatin in the liver. An elevated aspartate aminotransferase (AST) and alkaline phosphatase with clinical signs of liver toxicity has been reported in some cases and the adult dosage should be used with caution in patients with pre-existing hepatic dysfunction.

### **With 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.

- a. **Pretreatment hydration:** 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 IV infusion of 2 litres 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 2-hour period. During the last 30 minutes of the pretreatment hydration or after the hydration, 375 mL of 10% mannitol injection may be administered via a side-arm drip.
- b. **Preparation of cisplatin infusion:** Cisplatin injection should be added to 1 litre of sodium chloride IV infusion 0.9%.

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

- c. **Treatment:** Following prehydration, administer the cisplatin infusion over 1 - 2 hours. It has been proposed that a longer infusion time of 6 - 8 hours may decrease gastrointestinal and renal toxicities. The IV flask should be covered to preclude light.
- d. **Post-treatment hydration:** Adequate hydration and urinary output must be maintained during the 24 hours following 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.

### **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.

### **4.3 CONTRAINDICATIONS**

Use of cisplatin is contraindicated in patients with a history of hypersensitivity to cisplatin or other platinum-containing compounds, in pregnancy or lactation, bone marrow depression, generalised infections and in patients with renal impairment. Cisplatin should not be used in patients with hearing impairment or myelosuppression.

#### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Cisplatin is a highly toxic drug with a relatively narrow therapy 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.

##### **Use in renal function**

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 change in renal function has been a fall in glomerular filtration rate 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**).

##### **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. Abnormalities of audiometric testing are more common and hearing loss can be unilateral or bilateral; frequency and severity increase with repeated doses, and may not be reversible, but mostly occur in the 4,000 - 8,000 Hz range.

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.

##### **Myelosuppression**

This may occur in patients treated with cisplatin. Haematological toxicity is dose-related and cumulative. The nadirs in circulating platelets and leucocytes generally occur between days 18 - 23 (range 7.3 - 45) with most patients recovering by day 39 (range 13 - 62). Leucopenia and thrombocytopenia are more pronounced at doses greater than 50 mg/m<sup>2</sup>.

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<sup>3</sup> and white cells greater than 4,000/mm<sup>3</sup>.

Peripheral blood counts should be performed at regular intervals for the duration of cisplatin treatment.

### **Anaemia**

Anaemia (decrease of greater than 2 g% 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; direct 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.

### **Anaphylaxis**

Reactions, possibly secondary to cisplatin therapy, have been occasionally reported in patients who were previously exposed to cisplatin. Patients who are at particular risk are those with a prior history or family history of atopy. 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 a complication.

### **Cardiovascular toxicity**

Cisplatin has been found to be associated with cardiovascular toxicity (see **Section 4.8 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 Undesirable Effects**).

### **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 and seizures**

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 with cisplatin administration. This appears to be more common after prolonged administration. Since neurotoxicity may result in irreversible damage, the development of clinically significant symptoms should generally contraindicate further cisplatin usage.

### **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.

Vaccination with a live vaccine should be avoided in patients receiving cisplatin. 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.

### **Others**

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 the Elderly**

No data available.

### **Paediatric population**

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 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION**

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 or ototoxic drugs, e.g. aminoglycoside antibiotics and loop diuretics when given concurrently or within 1-2 weeks after cisplatin administration, may potentiate the nephrotoxic and ototoxic 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 and loop diuretics, potentiate 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.

### **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 hyperuricemia and gout.

### **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.

### **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.

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.

## **4.6 FERTILITY, PREGNANCY AND LACTATION**

### **Pregnancy (Category D)<sup>1</sup>**

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

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.

#### *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.

### **Breastfeeding**

Cisplatin is excreted in breast milk. To avoid possible harmful effects in the infant, patients treated with cisplatin must not breastfeed.

### **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. 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.

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<sup>1</sup> *Category D: Drugs which have caused, are suspected to have caused or be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.*

## **Male**

Cisplatin can affect male fertility. Impairment of spermatogenesis and azoospermia have been reported (see **Section 4.8 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. Cisplatin caused testis damage and decreased sperm counts in mice, primarily through effects on differentiated spermatogonia.

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

## **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 effect of cisplatin on the ability to drive and use machinery has not been established.

## **4.8 UNDESIRABLE EFFECTS**

Cumulative and dose-related renal impairment is the major limiting toxicity of cisplatin. Renal toxicity becomes more prolonged and severe with repeated courses of the drug. Regimes of IV hydration, mannitol diuresis and 6 - 8 hour infusions of cisplatin have been used to reduce the incidence and severity of nephrotoxicity.

### **Infections and infestations**

Infection (infectious complications have led to death), sepsis

### **Neoplasms benign, malignant and unspecified**

Secondary malignancies and acute leukaemia have been known to develop.

### **Blood and lymphatic system disorders**

Thrombotic microangiopathy (hemolytic uremic syndrome), bone marrow failure, neutropenia, thrombocytopenia, leukopenia, anemia, Coombs positive hemolytic anemia.

Myelosuppression often occurs during cisplatin therapy. Mild bone marrow toxicity may occur with both leukopenia 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<sup>2</sup>. 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 leukemias and myelodysplastic syndromes arising in patients who have been treated with cisplatin, mostly when given in combination with other potentially leukemogenic agents.

### **Immune system disorders**

Anaphylactic and anaphylactic-like reactions, consisting principally of 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 by IV adrenaline, corticosteroids and/or antihistamines.

### **Metabolism and nutritional disorders**

Cisplatin may cause dehydration in patients. Cisplatin may also cause serious electrolyte disturbances, mainly represented by hypomagnesemia, hypocalcemia, and hypokalemia, 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 hyperuricemia, 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<sup>2</sup>, with peak levels occurring between 3-5 days after administration of the drug. Allopurinol may be used to reduce serum uric acid levels. Regular monitoring of serum electrolyte levels and replacement where necessary are advisable.

### **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.

### **Ear and labyrinth disorders**

Unilateral or bilateral tinnitus and/or high frequency hearing loss (>4000Hz) has been observed in up to 31% of patients treated with cisplatin 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.

### **Cardiac disorders**

Cardiovascular abnormalities (coronary disease, congestive heart failure, postural hypotension, thrombotic microangiopathy, arrhythmia, myocardial infarction, 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 uraemic 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 fluorouracil.

### **Gastrointestinal disorders**

Stomatitis, vomiting, nausea, anorexia, hiccups, diarrhoea

Cisplatin induces severe nausea and vomiting in almost all patients. Severe nausea and vomiting usually begin within 1-4 hours after treatment and may persist for up to a week after 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.

### **Hepatobiliary disorders**

Mild and transient elevations of serum AST and ALT levels may occur infrequently. Liver damage 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 spasms.

### **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 be first noted during the second week after a dose and is manifested by an increase in serum creatinine, BUN, serum uric acid and/or a decrease in creatinine clearance.

Renal insufficiency is generally mild to moderate and reversible at the usual doses of the drug (recovery occurring as a rule within 2-4 weeks); however, high or repeated cisplatin doses can increase the severity and duration of renal impairment and may produce irreversible renal insufficiency (sometimes fatal). Renal failure has been reported also following intraperitoneal instillation of the drug.

### **Reproductive system and breast disorders**

Impairment of spermatogenesis and azoospermia have been reported (see **Section 4.6 Fertility, Pregnancy and Lactation**).

### **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.

### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://pophealth.my.site.com/carmreportnz/s/>

## **4.9 OVERDOSE**

Acute overdosage with cisplatin may result in an enhancement of its expected toxic effects (eg 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 PHARMACODYNAMIC PROPERTIES**

Pharmacotherapeutic group: antineoplastic agent

ATC code: L01XA01

#### **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. The drug inhibits DNA synthesis by producing intrastrand and interstrand crosslinks in DNA. Protein and RNA synthesis are also inhibited to a lesser extent. Cisplatin does not appear to be cell-cycle specific.

### **5.2 PHARMACOKINETIC PROPERTIES**

#### **Distribution**

There is good uptake of cisplatin by the kidneys, liver and intestine. More than 90% of platinum-containing species remaining in the blood are bound (possibly irreversibly) to plasma proteins.

The clearance of total platinum from plasma is rapid during the first four hours after intravenous administration, but then proceeds more slowly because of covalent binding to serum proteins. Levels of unbound platinum fall with a half-life of 20 minutes to 1 hour depending on the rate of drug infusion

#### **Elimination**

The elimination of intact drug and various platinum-containing biotransformation products is via the urine. About 15 - 25% of administered platinum is rapidly excreted in the first 2 - 4 hours after administration of cisplatin. This early excretion is mostly of intact cisplatin. In the first 24 hours after administration, 20 - 80% is excreted, the remainder representing drug bound to tissues or plasma protein.

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. The half-life of total platinum was observed at 1 to 240 hours in end-stage renal disease patient.

### **5.3 PRECLINICAL SAFETY DATA**

#### **Genotoxicity**

Cisplatin is mutagenic in bacteria and produces chromosome aberrations in animal cells in tissue culture. In mice, cisplatin is teratogenic and embryotoxic. Cisplatin may be toxic to the foetal urogenital tract.

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 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

Sodium chloride  
 Hydrochloric acid  
 Sodium hydroxide  
 Water for injections

The solution does not contain any preservative.

### 6.2 INCOMPATIBILITIES

Cisplatin may interact with aluminium to form a black precipitate. Needles, syringes, catheters or IV administration sets that contain aluminium parts which may come in contact with cisplatin should not be used for preparation or administration of the drug. The stability of cisplatin is adversely affected by the presence of bisulphite, metabisulphite, sodium bicarbonate and fluorouracil.

### 6.3 SHELF LIFE

3 years

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light. Do not refrigerate or freeze.

If a precipitate has formed because of exposure to low temperatures, redissolve by storing at the recommended storage condition until a clear solution is obtained.

### 6.5 NATURE AND CONTENTS OF CONTAINER

Cisplatin Accord is available in four strengths: 10 mg/10 mL, 25 mg/25 mL, 50 mg/50 mL and 100 mg/100 mL, in Type I amber glass vials in packs of 1.

Not all presentations may be marketed.

### 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Cisplatin 0.15 mg/mL in sodium chloride IV infusion 0.9% is chemically stable for 24 hours when stored at room temperature and protected from light. The solution does not contain any antimicrobial preservatives and to avoid microbial contamination hazards, infusion should be commenced as soon as practicable after preparation. Infusion should be completed within 24 hours of preparation and any residue discarded.

Chemical and physical in-use stability after dilution with sodium chloride IV infusion 0.9%, stored in PE bags, has further been demonstrated for the below concentrations and storage conditions:

Concentration after dilution	Temperature conditions	Other conditions	*Stability demonstrated for
0.01 mg/mL	2 to 8°C	Unprotected from light	21 days
	25°C	Unprotected from light	21 days
0.1 mg/mL	2 to 8°C	Unprotected from light	21 days
	25°C	Unprotected from light	21 days
0.4 mg/mL	25°C	Unprotected from light	21 days

\*based on physico-chemical stability of the drug product after dilution

**Syringe study:** the undiluted solution is stable for 14 days at room temperature protected from light when stored in a syringe.

No microbiological claims are made in relation to the data above, and from the microbiological point of view the product should be used immediately. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user and would not normally exceed 24 hours, unless dilution has taken place in controlled and validated aseptic conditions.

## **7 MEDICINE SCHEDULE**

Prescription Only Medicine

## **8 SPONSOR**

Pharmacy Retailing (NZ) Limited Trading as Healthcare Logistics  
58 Richard Pearse Drive  
Airport Oaks  
Auckland 2022  
New Zealand  
  
Phone 0800 004 375

## **9 DATE OF FIRST APPROVAL**

08 July 2010

## **10 DATE OF REVISION OF TEXT**

04 December 2024

Version 3.0

### **Summary table of changes**

<b>Section changed</b>	<b>Summary of new information</b>
4.6	Additional information included regarding the effects of cisplatin in rats and mice. Update to animal embryotoxicity information. Update to contraception duration for males and females. Removal of washout period information for patients with end-stage renal disease. Include lactation advice. Additional statement regarding use in pregnancy. Category D definition.
5.2	Update information on elimination half life.
5.3	Update to information on genotoxicity and carcinogenicity.