# PRODUCT INFORMATION – DBL™ CISPLATIN INJECTION (CISPLATIN)

## 1. NAME OF THE MEDICINE

Cisplatin

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of DBL Cisplatin Injection contains 1 mg cisplatin.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection.

DBL Cisplatin Injection is a clear, colourless to pale yellow sterile solution of cisplatin 1 mg/mL, mannitol 1 mg/mL and sodium chloride 9 mg/mL in water for injections. The solution does not contain any preservative.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

DBL Cisplatin Injection 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

**Dosage**

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

**Dosage adjustment**

***Hepatic impairment***

Human studies show a high uptake of cisplatin in the liver. An elevated serum glutamic oxaloacetic transaminase (SGOT) has been reported in some cases and the adult dosage should be used with caution.

***Renal impairment***

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) **Pre-treatment 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 pre-treatment hydration or after the hydration, 375 mL of 10% mannitol injection may be administered via a side-arm drip.

(b) **Preparation of cisplatin infusion:** DBL Cisplatin Injection should be added to 1 litre of sodium chloride IV infusion 0.9%.

(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.

## 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 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

Only individuals experienced in antineoplastic therapy should use cisplatin.

**Ototoxicity**

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.

As ototoxicity of cisplatin is cumulative, 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.

**Myelosuppression**

This may occur in patients treated with cisplatin. 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 $mg/m^2$. Anaemia (decrease of greater than 2 g% haemoglobin) occurs at approximately the same frequency but generally with a later onset than leucopenia and thrombocytopenia.

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 $4,000/mm^3$. A high incidence of severe anaemia requiring transfusion of packed red cells has been observed in patients receiving combination chemotherapy including cisplatin. Rarely, the drug has caused haemolytic anaemia; direct Coombs - positive results have been reported in a few of these cases.

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

**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 supportive equipment and medication should be available to treat such a complication.

**Cardiovascular toxicity**

Cisplatin has been found to be associated with cardiovascular toxicity (see section 4.8). 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).

**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**

Peripheral neuropathy, postural hypotension and seizures may occur with cisplatin administration. This appears to be more common after prolonged administration. The development of clinically significant symptoms should generally contraindicate further cisplatin usage.

**Others**

Neurological examinations should also be performed regularly.

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.

Extreme caution should be used where patients have recently been exposed to infections, particularly chicken pox and herpes zoster. Live virus vaccines should not be used in patients undergoing cisplatin therapy.

**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.

**Use in hepatic impairment**

Liver function should be monitored periodically.

**Use in renal impairment**

Measurements of Blood Urea Nitrogen (BUN), serum creatinine and creatinine clearance should be taken before initiating cisplatin therapy, and prior to subsequent doses, as toxicity is cumulative. Cisplatin is recommended to be given once every 3-4 weeks. Hydration is recommended to minimise nephrotoxicity.

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. Renal function must return to acceptable limits (serum creatinine below 0.14 mmol/L and/or blood urea below 9 mmol/L) before further doses are given.

**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

**Nephrotoxic drugs**

Potentially nephrotoxic medicines, e.g., aminoglycoside antibiotics and loop diuretics, may potentiate 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 medicines, e.g., aminoglycoside antibiotics and loop diuretics, may potentiate 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) 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). 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**[1]

In mice, cisplatin is teratogenic and embryotoxic. Cisplatin may be toxic to the fetal urogenital tract. Patients should be advised to avoid becoming pregnant.

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.

**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.

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

## 4.8 Adverse effects (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.

**Ear and labyrinth disorders**

Tinnitus and/or high frequency hearing loss has been observed in up to 31% of patients treated with cisplatin. Ototoxicity may be more severe in children and more frequent and severe with repeated doses.

**Eye disorders**

Vision blurred, color blindness acquired, blindness cortical, optic neuritis, papilloedema, retinal pigmentation

**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 (haemolytic uremic syndrome), bone marrow failure, neutropenia, thrombocytopenia, leukopenia, anaemia, Coombs positive hemolytic anaemia.

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.

**Immune system disorders**

Anaphylactic-like reactions, consisting principally of facial oedema, wheezing, tachycardia and hypotension have been reported in patients previously exposed to cisplatin. The reactions may be controlled by IV adrenaline, corticosteroids and/or antihistamines.

Other adverse effects to cisplatin which have been reported infrequently include cardiac abnormalities, elevated SGOT and liver damage. Secondary malignancies and acute leukaemia have been known to develop. Extravasation may result from infusion of solutions greater than 0.5 mg/mL cisplatin.

**Endocrine disorders**

Inappropriate antidiuretic hormone secretion has been known to develop.

**Metabolism and nutritional disorders**

Cisplatin may cause the following in patients: Hyponatraemia, hypomagnesaemia, dehydration, hypokalaemia, hypophosphataemia, hyperuricaemia, hypocalcaemia, tetany.

**Nervous system disorders**

Convulsion, neuropathy peripheral, leukoencephalopathy, reversible posterior leukoencephalopathy syndrome, cerebrovascular accident, haemorrhagic stroke, ischaemic stroke, ageusia, cerebral arteritis, Lhermitte's sign, myelopathy, autonomic neuropathy

**Cardiac disorders**

Arrhythmia, bradycardia, tachycardia, myocardial infarction, cardiac arrest, cardiac disorder

**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

**Gastrointestinal disorders**

Stomatitis, vomiting, nausea, anorexia, hiccups, diarrhoea

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

**Skin and subcutaneous tissue disorders**

Rash, alopecia

**Musculoskeletal and connective tissue disorders**

Muscle spasms

**Renal and urinary disorders**

Renal failure acute, renal failure, renal tubular disorder

**Reproductive system and breast disorders**

Impairment of spermatogenesis and azoospermia have been reported.

**General disorders and administration site conditions**

Pyrexia, asthenia, malaise, injection site extravasation (extravasation may result in local soft tissue toxicity including tissue cellulitis, fibrosis, and necrosis, pain, oedema, erythema)

Neurotoxicity, characterised by peripheral neuropathies, both sensory and motor, have occurred in some patients.

Myelosuppression may occur in patients treated with cisplatin.

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 used to reduce serum uric acid levels.

Hypomagnesaemia and hypocalcaemia may develop during cisplatin therapy or following discontinuance of the drug. Hypomagnesaemia and/or hypocalcaemia may be manifested by muscle irritability or cramps, clonus, tremor, carpopedal spasm and/or tetany. Regular monitoring of serum electrolyte levels and replacement where necessary are advisable.

## 4.9 Overdose

In the event of overdosage or toxic reactions, symptomatic or supportive measures should be taken. Patients should be monitored for 3 to 4 weeks in case of delayed toxicity.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

**Mechanism of action**

Cisplatin is an antineoplastic agent with 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.

**Clinical trials**

No data available.

## 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.

**Excretion**

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.

## 5.3 Preclinical safety data

**Genotoxicity**

Cisplatin is mutagenic in bacteria 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

Mannitol
Sodium chloride
Water for injections

## 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

Refer to outer carton for expiration date.

## 6.4 Special precautions for storage

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

**Stability**

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.

## 6.5 Nature and contents of container

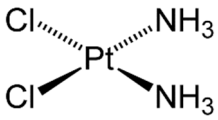
DBL Cisplatin Injection is available as followed.

| **Strength** | **Pack Size** |
|---|---|
| 50 mg/50 mL | 1 x 50 mL vial |
| 100 mg/100 mL | 1 x 100 mL vial |

Not all presentations may be available locally.

## 6.6 Physicochemical properties

**Chemical structure**




**CAS number**

15663-27-1

## 7. MANUFACTURER

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CISH-SIN-0420/0
Date of last revision: April 2020