

DBL™ CARBOPLATIN INJECTION

NAME OF MEDICINE

DBL™ Carboplatin Injection

PRESENTATION

DBL™ Carboplatin Injection (all presentations) is a sterile solution of carboplatin in Water for Injections BP. It is presented in vials containing 5, 15, 45 or 60 mL of 10 mg/mL carboplatin. The solution does not contain any preservatives. The pH of the injection ranges between 4.0 to 7.0

USES

ACTIONS

Carboplatin, an analogue of cisplatin, is an antineoplastic agent which interferes with DNA intrastrand and interstrand crosslinks in cells exposed to the drug. DNA reactivity has been correlated with cytotoxicity.

PHARMACOKINETICS

After a one-hour infusion of the drug (dose range 20 to 520 mg/m²) plasma levels of total platinum and ultrafilterable (free) platinum decay biphasically following first order kinetics. For ultrafilterable platinum reported values for the initial phases of the half life (t alpha ½) are about 90 minutes and in the later phase the half life (t beta ½) is about 6 hours. Total platinum elimination has a similar initial half life while in the later phase the half life of total platinum may be greater than 24 hours. Carboplatin is a stable molecule. All free platinum is in the form of carboplatin in the first 4 hours.

65% of the carboplatin dose is eliminated in the urine within 24 hours of administration with 32% of the dose being excreted as unchanged drug. Most of the drug is excreted in the first 6 hours.

Initially protein binding is low. During the first 4 hours after administration 0-29% of carboplatin is protein bound. By 24 hours 85-89% is protein bound. Excretion of carboplatin is by glomerular filtration. Patients with poor renal function have a higher Area Under Curve for total platinum and a reduction in dosage is recommended.

INDICATIONS

Carboplatin is indicated in the treatment of:

advanced stage ovarian cancer of epithelial origin
small cell lung carcinoma
carcinoma of the head and neck
carcinoma of the testis
paediatric cerebral tumours
soft tissue sarcoma
neuroblastoma

DOSAGE AND ADMINISTRATION

Adults: The recommended dose of carboplatin in previously untreated adults with normal renal function is 400 mg/m² given as a single intravenous infusion over 15 to 60 minutes. Therapy should not be repeated until four weeks after the previous carboplatin course.

It is recommended that according to clinical circumstances the initial dosage may require reduction by 20 to 25% in patients with risk factors such as previous myelosuppressive therapy and poor performance status.

Determination of haematologic nadir by weekly blood counts during initial courses is recommended for future dosage adjustment and scheduling of carboplatin.

Impaired Renal Function: In patients with initial impaired renal function reduction of dosage of carboplatin may be required. Haematological nadirs and renal function should be monitored in these circumstances.

A suggested dosage schedule in patients with impaired renal function based on creatinine clearance is as follows:

<u>Creatinine Clearance</u>	<u>Dose of Carboplatin</u>
>40 mL/min.	400 mg/m ²
20-39 mL/min.	250 mg/m ²
0-19 mL/min.	150 mg/m ²

Children: Sufficient usage of carboplatin in paediatrics has not occurred to allow specific dosage recommendations to be made. Physicians are advised to refer to recently published literature for information on the current dosing regimens for particular tumours.

CONTRAINDICATIONS

Carboplatin is contraindicated in patients with the following conditions:

Severe myelosuppression

Pre-existing severe renal impairment; dose adjustment may allow use in the presence of mild renal impairment (see "DOSAGE AND ADMINISTRATION")

History of severe allergic reactions to carboplatin, other platinum-containing compounds

Severe bleeding

Pregnancy or lactation.

WARNINGS AND PRECAUTIONS

Carboplatin should only be administered to patients under the supervision of a qualified physician who is experienced in the use of chemotherapeutic agents. Diagnostic and treatment facilities should be readily available for appropriate management of therapy and possible complications.

Peripheral blood counts and renal function should be monitored closely. Blood counts should be performed prior to commencement of carboplatin therapy and weekly thereafter. Aside from monitoring toxicity, this practice will help determine the nadir and recovery of the haematological parameters and assist in the subsequent dose adjustments. Lowest levels in white cells and platelets are generally seen between days 14 and 28, and days 14 and 21 respectively after initial therapy. A greater reduction in platelets is seen in patients who previously received extensive myelosuppressive chemotherapy than non-treated patients. White blood cells counts less than 2×10^9 cells/L (2,000 cells/mm³) or platelets less than 50×10^9 cells/L (50,000 cells/mm³) should cause consideration of postponement of carboplatin therapy until bone marrow recovery is evident, which is usually 5 to 6 weeks. Transfusions may be required.

Hypersensitivity and anaphylactic reactions to carboplatin have been reported. These allergic reactions have been similar in nature and severity to those reported with other platinum containing compounds. Symptoms include rash, urticaria, erythema, pruritus, bronchospasm and hypotension. Patients should be monitored for possible anaphylactoid reactions and appropriate equipment and medication should be readily available to treat such reactions (e.g. antihistamines, corticosteroids, epinephrine, oxygen) whenever carboplatin is administered.

Renal function should be assessed prior to and during therapy. Myelosuppression as a result of carboplatin treatment is closely related to the renal clearance of the drug. Therefore in patients who have abnormal renal function or who are receiving concomitant therapy with nephrotoxic drugs, myelosuppression, especially thrombocytopenia, may be more severe and prolonged.

The occurrence, severity and protraction of toxicity is likely to be greater in patients who have received extensive prior treatment for their disease, have poor performance status and who are more advanced in age.

Carboplatin courses should not, in general, be repeated more frequently than every four weeks in order to ensure that the nadir in blood counts has occurred and that there has been recovery to a satisfactory level.

Mutagenicity: carboplatin has been shown to be mutagenic in mammalian cells. Patients should be advised of its mutagenic potential and should use effective contraception for an adequate duration of time after ceasing therapy.

Renal toxicity is not usually dose-limiting. Pre-treatment and post-treatment hydration is not necessary. However, about 25% of patients show decreases in creatinine clearance and, less frequently, rises in serum creatinine and blood urea nitrogen may be seen. Impairment of renal function is more likely to be seen in patients who have previously experienced nephrotoxicity as a result of cisplatin therapy.

Neurotoxicity, such as paraesthesias and decreased deep tendon reflexes, and ototoxicity are more likely to be seen in patients who have received cisplatin previously. Neurological evaluations and an assessment of hearing should be performed on a regular basis.

Gastrointestinal, carboplatin can induce emesis. The incidence and severity of emesis may be reduced by pretreatment with antiemetics or by carboplatin administration as a continuous IV infusion over 24 hours, or as IV administration of divided doses over 5 consecutive days rather than a single infusion. Selective inhibitors of type 3 (5-HT₃), serotonergic receptors (e.g. ondansetron) or substituted benzamides (e.g. metoclopramide) may be particularly effective antiemetics and combination therapy may be considered for patients experiencing severe or refractory emetogenic effects.

Administration of live or live attenuated vaccines in patients immunocompromised by chemotherapeutic agents, including carboplatin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving carboplatin. Killed or inactivated vaccines may be administered; however the response to such vaccines may be diminished.

Aluminium-containing equipment should not be used (see "INTERACTIONS")

USE IN PREGNANCY

Category D. This category specifies drugs which have caused or may be expected to cause an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

Use in pregnancy is not recommended.

Women of child bearing potential should use adequate contraception.

USE IN LACTATION

It is not known whether carboplatin is excreted in breast milk. To avoid possible harmful effects in the infant, breast feeding is not advised during carboplatin therapy.

EFFECTS ON ABILITY TO DRIVE OR OPERATE MACHINERY

The effect of carboplatin on the ability to drive or use machinery has not been systematically evaluated.

ADVERSE EFFECTS

Myelosuppression is the dose-limiting toxicity of carboplatin. It is generally reversible and is not cumulative when carboplatin is used as single agent and at the recommended frequencies of administration.

Adverse reactions which have been observed in studies to date can be grouped under the following organ systems:-

Haematopoietic System: leucopenia (55%), thrombocytopenia (32%), anaemia (59%).

Transfusional support has been required in about one-fifth of patients.

Gastrointestinal System: nausea and vomiting (53%), nausea only (25%), diarrhoea (6%), constipation (3%). Nausea and vomiting generally are delayed 6 – 12 hours after administration of carboplatin and disappear within 24 hours. It is readily controlled (or may be prevented) with antiemetic medication.

Renal System: decrease in creatinine clearance (25%); increases in uric acid (25%), blood urea nitrogen (16%) and serum creatinine (7%). Acute renal failure has been reported rarely. Haemolytic uraemic syndrome. Mild and transient elevations of serum creatinine and of blood urea nitrogen concentrations may occur. Risk of carboplatin-induced nephrotoxicity (e.g. impaired creatinine clearance) becomes more prominent at relatively high dosages or in patients previously treated with Cisplatin.

Biochemistry: decreases in serum magnesium (37%), potassium (16%) and, rarely, calcium (5%). These changes have not been severe enough to cause clinical symptoms.

Neurotoxicity: peripheral neuropathy (6%) which was mild and dysgeusia (<1%). Peripheral neuropathies may occur, mainly in the form of paresthesias and decreased deep tendon reflexes. The effect, more common in patients over 65 years of age, appears to be cumulative, occurring mainly in patients receiving prolonged therapy and/or in those who have received prior cisplatin therapy. CNS effects may also occur. In some cases the neurotoxicity seen with carboplatin may be the result of a combination with some delayed effect of prior cisplatin therapy.

Ototoxicity: subclinical decrease in hearing acuity as determined by audiogram, in the high frequency (4,000 – 8,000Hz) range (15%); clinical ototoxicity, usually manifested as tinnitus (1%). In patients who developed hearing loss as a result of cisplatin therapy, the impairment may persist or worsen.

Hepatic System: Increases in liver enzymes have been transient in the majority of cases. Alkaline phosphatase (ALP) (30%), aspartate aminotransferase (AST) (15%), bilirubin (4%). Substantial abnormalities in liver function test have been reported in patients treated with carboplatin at high doses and autologous bone marrow transplantation.

Allergic Reactions: In less than 2% of patients reactions similar to those seen after cisplatin have been observed. Erythematous rash, fever, perioral tingling, urticaria, pruritus, bronchospasm,

hypotension, hypoxia and pyrexia have been observed. Anaphylaxis and anaphylactoid reactions have also occurred, while exfoliative dermatitis has been reported rarely. In a few cases, no cross-reactivity was present. The frequency of allergic reactions is higher in patients who receive carboplatin in conjunction with other antineoplastic agents. Hypersensitivity reactions may occur within a few minutes after IV administration of carboplatin

Eye Disorders: Visual abnormalities, such as transient sight loss (which can be complete for light and colours) or other disturbances may occur in patients treated with carboplatin. Improvement and/or total recovery of vision usually occurs within weeks after the drug is discontinued. Cortical blindness has been reported in patients with impaired renal function receiving high-dose carboplatin.

Neoplasms Benign, Malignant and Unspecified: There have been rare reports of acute myelogenous leukemias and myelodysplastic syndromes arising in patients who have been treated with carboplatin, mostly when given in combination with other potentially leukemogenic agents.

Cardiac Disorders: Cardiac failure; ischaemic coronary artery disorders (e.g. myocardial infarction, cardiac arrest, angina, myocardial ischaemia).

Vascular Disorders: Cerebrovascular events

Skin and Subcutaneous Tissue Disorders: Exfoliative dermatitis may rarely occur. Erythematous rash, pruritus, urticaria, and alopecia have also been reported in association with carboplatin.

Musculoskeletal and Connective Tissue Disorders: Myalgia/arthritis .

Metabolism and Nutrition Disorders: Electrolyte abnormalities (hypokalaemia, hypocalcaemia, hyponatraemia and/or hypomagnesaemia).

Others: alopecia (2%), flu-like syndrome (1%), reaction at injection site (<1%).

INTERACTIONS

Carboplatin may interact with aluminium to form a black precipitate. Needles, syringes, catheters or I.V administration sets that contain aluminium parts which may come in contact with carboplatin should not be used for preparation or administration of the drug.

Concurrent therapy with nephrotoxic drugs may increase or exacerbate toxicity due to carboplatin-induced changes in renal clearance.

Combination therapy with other myelosuppressive drugs may require modification of the dose or timing of carboplatin therapy to minimize additive myelosuppressive effects.

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

An increased incidence of emesis has been reported when carboplatin and other emetogenic drugs are given concurrently or carboplatin is administered to patients who previously received emetogenic therapy.

OVERDOSAGE

No overdosage occurred during clinical trials. Should it occur, the patient may need to be sustained through complications relating to myelosuppression, renal impairment and hepatic impairment. From reports in which doses up to 1600 mg/m² were used, patients were said to feel extremely unwell and developed diarrhoea and alopecia.

PHARMACEUTICAL PRECAUTIONS**STORAGE**

DBL™ Carboplatin Injection (glass vials) should be stored below 25°C. Do not freeze. Protect from light.

Carboplatin has been found to be stable for 24 hours when mixed within 5% glucose in water.

These products contain no antimicrobial agent. However in order to reduce microbiological contamination hazard, infusion should be commenced as soon as practicable after preparation. Infusion should be completed within 24 hours of preparation and any residue discarded.

MEDICINE CLASSIFICATION

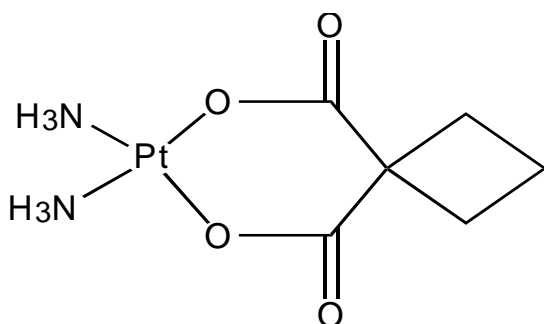
Prescription Medicine

PACKAGE QUANTITIES

<u>Code</u>	<u>Strength</u>	<u>Packs</u>
1665A	50 mg/5mL	1 x 5 mL glass vial
1675A	150 mg/15mL	1 x 20 mL glass vial
1685A	450 mg/45mL	1 x 50 mL glass vial
1710A	600 mg/60 mL	1 x 100 mL glass vial

FURTHER INFORMATION

The chemical structure of carboplatin is shown below:

**Preparation of Carboplatin Solution**

Equipment containing aluminium components should be avoided (See 'INTERACTIONS'). DBL™ Carboplatin Injection is a ready to use solution containing 10 mg/mL carboplatin in Water for Injections B.P.

The injections may be further diluted in 5% Glucose Intravenous Infusion B.P.

Handling Guidelines:

1. Carboplatin should be prepared for administration only by professionals who have been trained in the safe use of the preparation.
2. Operations such as transfer to syringes should be carried out only in the designated area.
3. The personnel carrying out these procedures should be adequately protected with clothing, gloves and eye shield.

4. Pregnant personnel are advised not to handle chemotherapeutic agents.

Contamination:

- (a) In the event of contact with the skin or eyes, the affected area should be washed with copious amounts of water or normal saline. A bland cream may be used to treat transient stinging of the skin. Medical advice should be sought if the eyes are affected.
- (b) In the event of spillage, operators should put on gloves and mop up the spilled material with a sponge kept in the area for that purpose. Rinse the area twice with water. Put all solutions and sponges into a plastic bag and then seal it. The bag should be prominently labelled with the words “Cytotoxic Waste” or similar.

Disposal

Syringes, containers, absorbent materials, solution and any other material which has come into contact with carboplatin should be placed in a thick plastic bag or other impervious container and incinerated at 1000°C or more.

NAME AND ADDRESS

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