Data Sheet

CARBOPLATIN INJECTION

NAME OF MEDICINE

Carboplatin Injection, 50 mg/5 mL, 150 mg/15 mL and 450 mg/45 mL.

PRESENTATION

Carboplatin is a sterile, hypotonic, preservative-free solution of carboplatin 10 mg/mL in Water for Injections.

USES

Actions

Carboplatin is an antineoplastic agent. It is an analogue of cisplatin, but it seems to be less toxic. Like cisplatin, it appears to form intra- and inter-strand crosslinks in cells which modifies DNA structure and inhibits DNA synthesis. It does not appear to be phase-specific in the cell cycle.

Pharmacokinetics

Elimination and Excretion: After intravenous infusion of single doses over one hour, plasma concentrations of total platinum and free platinum decline biphasically following first order kinetics. For free platinum, reported values for the initial phase of the half-life (talpha 1/2) are about 90 minutes and in the later phase the half-life (tbeta 1/2) 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. All free platinum is in the form of carboplatin in the first four hours.

The kidney is the major route of excretion. Most excretion occurs within the first 6 hours after administration with 50% to 70% excreted within 24 hours. 32% of the dose is excreted as unchanged medicine. A reduction in dosage is recommended for patients with poor renal function.

Protein Binding: Protein binding is less than with cisplatin, initially protein binding is low with up to 29% of carboplatin bound during the first 4 hours. However, platinum from carboplatin is irreversibly bound to plasma proteins (by 24 hours 85-89% is bound) and is slowly eliminated with a minimum half-life of 5 days.

Indications

For the treatment of advanced ovarian carcinoma of epithelial origin.

DOSAGE AND ADMINISTRATION

The recommended dosage for previously untreated adults (normal renal function) is 400mg/m² as a single intravenous infusion over 15-60 minutes.

Therapy should not be repeated again until four weeks have elapsed. In patients with risk factors such as previous myelosuppressive therapy or in the aged, the initial dosage may need to be reduced to 20-25%.

Determination of the haematological nadir by weekly blood counts is recommended for adjusting future doses and scheduling of carboplatin.

Patients with Impaired Renal Function

As carboplatin is excreted by the kidney and is nephrotoxic the optimum dosage should be determined by frequent monitoring of the haematological nadir and renal function.

The suggested dosage schedule for patients with impaired renal function based on creatinine clearance is:

Creatinine Clearance	Carboplatin Dose
> 40 mL/min	400 mg/m²
20-39 mL/min	250 mg/m²
0-19 mL/min	150 mg/m²

Paediatric Dose

Insufficient information is available to make specific recommendations.

Combination Therapy

Carboplatin may be used in combination with other anti-neoplastic agents and hence the dosage will vary according to the protocol used.

The optimal use of carboplatin in combination with other myelosuppressive drugs will require dosage adjustments and frequent haematological monitoring.

Carboplatin 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 carboplatin should not be used for preparation or administration of the medicine.

Aluminium reacts with carboplatin causing precipitate formation and loss of potency, therefore aluminium-containing equipment should not be used for preparation or administration of carboplatin.

Prior to administration, carboplatin solutions should be inspected visually for particulate matter and discoloration. Use the solution as soon as possible after preparation; infusion should be completed within 24 hours of preparation and any residue discarded.

CONTRAINDICATIONS

Treatment with carboplatin is contraindicated in the following conditions:

- in patients with a history of hypersensitivity reactions to carboplatin or other platinum-containing compounds (e.g. cisplatin)
- in the presence of severe renal impairment
- in the presence of severe bone marrow depression
- in the presence of substantial bleeding
- in pregnancy and lactation.

WARNINGS AND PRECAUTIONS

Carboplatin should be administered only by a qualified physician experienced in the use of chemotherapeutic agents. Close monitoring for toxicity is mandatory, particularly in the case of administration of high drug dosages.

Carboplatin is a highly toxic drug with a narrow therapeutic index and a therapeutic effect is unlikely to occur without some evidence of toxicity.

Bone Marrow Function

Bone marrow suppression (leucopenia, neutropenia and thrombocytopenia) is dose-dependent and is the dose-limiting toxicity of carboplatin. Peripheral blood cell counts should be performed at frequent intervals (before start of therapy and weekly thereafter) in patients receiving carboplatin. Although at the recommended drug doses the haematologic toxicity of carboplatin is usually moderate and reversible, severe myelosuppression (especially thrombocytopenia) may occur in patients with renal impairment and in patients who are concurrently receiving (or have received) other myelosuppressive drugs or radiation therapy. Dose adjustment criteria for patients who experience myelosuppression following a dose of carboplatin are provided under Dosage and Administration. As an alternative to dosage reduction, administration of the full therapeutic dose of the drug may be delayed until recovery of neutrophil and platelet counts (values $\geq$ 2000/mm3 and 100,000/mm3 respectively). Treatment of severe haematologic toxicity may consist of supportive care, anti-infective agents for complicating infections, transfusions of blood products, autologous bone marrow rescue, peripheral stem cell transplantation and haematopoietic agents (colony-stimulating factors).

Renal Function

Carboplatin is excreted primarily in the urine and renal function must be monitored in patients receiving the medicine. Creatinine clearance appears to be the most sensitive measure of kidney function in patients receiving carboplatin. Dose adjustment criteria for patients with impaired renal function are provided under Dosage and Administration. Unlike cisplatin, pre- and post-treatment hydration is not necessary with carboplatin as the drug has a relatively low nephrotoxic potential, however, previous therapy with cisplatin or concomitant administration of other nephrotoxic drugs (e.g. aminoglycoside antibiotics) may increase the risk of nephrotoxicity (see also Interactions).

CNS/Hearing Functions

Routine neurologic examination is advisable during carboplatin therapy, particularly in patients previously treated with cisplatin and in patients over 65 years of age. Carboplatin may produce cumulative ototoxicity. Audiograms should be performed prior to initiating therapy and during treatment or when auditory symptoms occur. Clinically important deterioration of auditory function may require dosage modifications or discontinuation of therapy.

Gastrointestinal Effects

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 as 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.

Hypersensitivity Reactions

As in the case of other platinum complexed compounds, allergic reactions to carboplatin have been reported. 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.

Immunosuppressant Effects / Increased Susceptibility to Infections

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.

Use in Pregnancy Category D

Carboplatin has been shown to be embryo-toxic and mutagenic, and its use in pregnant women is not recommended. Women of child-bearing potential should use adequate contraception and carboplatin should only be used in women of child-bearing potential if the expected benefits outweigh the risks of such therapy. If the patient becomes pregnant whilst receiving the drug she should be advised of the potential hazard to the foetus.

Use in Lactation

It is not clearly established whether carboplatin or its platinum-containing metabolites are distributed into human milk. However, because of the potential for serious adverse reactions in infants should the drug pass into the milk, nursing should be discontinued during therapy.

Effects on ability to drive and use machines

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

Carcinogenicity and Mutagenicity

Secondary malignancies are potential delayed effects of many antineoplastic agents although it is not clear whether the effect is related to their mutagenic or immunosuppressive action. The effect of dose and duration of therapy is also unknown although risk seems to increase with long-term use. Although information is limited, available data seems to indicate that the carcinogenic risk is greatest with the alkylating agents.

Both in vitro and in vivo studies have shown carboplatin to be mutagenic.

ADVERSE EFFECTS

Many side effects of carboplatin therapy are unavoidable due to the pharmacological actions of the drug. However, the adverse effects are generally reversible if detected early.

Adverse reactions as reported for the various organ systems are as follows:

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

Blood and lymphatic system disorders

The major and dose-limiting toxicity of carboplatin is bone marrow suppression, which is manifested by thrombocytopenia, leucopenia, neutropenia and/or anaemia. Myelosuppression is dose-related. Platelet and leucocyte/granulocyte nadirs usually occur two to three weeks from drug administration. Recovery is generally adequate to allow the administration of the subsequent carboplatin dose four weeks after a previous administration. Anaemia (haemoglobin less than 11 g/dL), which may be symptomatic, occurs in a substantial proportion of patients. This effect may be cumulative and transfusions may be needed particularly in patients receiving prolonged therapy (e.g. more than 6 cycles). Clinical sequelae of bone marrow/haematologic toxicity such as fever, infections, sepsis/septic shock and haemorrhage may be expected.

Metabolism and nutrition disorders

Electrolyte abnormalities (hypokalaemia, hypocalcaemia, hyponatraemia and/or hypomagnesaemia).

Gastrointestinal disorders

Nausea and/or vomiting, which generally are mild to moderate in severity, may occur within 6-12 hrs after carboplatin administration and may persist up to 24 hrs or longer. Other GI effects such as mucositis, diarrhoea, constipation and abdominal pain have also been reported.

Nervous system disorders

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.

Ear and labyrinth disorders

Tinnitus and hearing loss has been reported in patients receiving carboplatin. The risk of ototoxicity may be increased by concomitant administration of other ototoxic drugs (e.g. aminoglycosides).

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.

Cardiac disorders

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

Vascular disorders

Cerebrovascular events

Renal and urinary disorders

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.

Hepatobiliary disorders

Mild and usually transient elevations of serum alkaline phosphatase, aspartate aminotransferase or bilirubin concentrations may occur. Substantial abnormalities in liver function test have been reported in patients treated with carboplatin at high doses and autologous bone marrow transplantation.

Immune system disorders

Allergic reactions to carboplatin have been reported. These include anaphylaxis/anaphylactoid reactions, hypotension, bronchospasm, and pyrexia. Hypersensitivity reactions may occur within a few minutes after IV administration of carboplatin.

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/arthralgia .

General disorders and administration site conditions

Asthenia, flu-like symptoms, reactions at injection site.

INTERACTIONS

Carboplatin is mostly used in combination with antineoplastic drugs having similar cytotoxic effects. In these circumstances additive toxicity is likely to occur. Concomitant use of carboplatin and other myelosuppressive agents or radiation therapy may potentiate the hematologic toxicity.

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.

Concomitant administration of carboplatin and aminoglycosides results in an increased risk of nephrotoxicity and/or ototoxicity and the drugs should be used concurrently with caution. The use of other nephrotoxic drugs results in a potentiation of renal effects by carboplatin.

Carboplatin interacts with aluminium to form a black precipitate of platinum and loss of potency. Aluminium-containing IV sets, needles, catheters and syringes should not be used for administration.

OVERDOSAGE

There are no known antidotes for carboplatin overdosage; thus every possible measure should be taken to avoid an overdose including full awareness of the potential danger of an overdose, careful calculation of the dose to be administered and availability of adequate diagnostic and treatment facilities. Acute overdosage with carboplatin may result in an enhancement of its expected toxic effects (e.g. severe myelosuppression, intractable nausea and vomiting, severe neurosensorial toxicities, liver failure, kidney failure, etc). Death may follow. 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.

PHARMACEUTICAL PRECAUTIONS

Store below 25ºC. Protect from light. Use immediately upon opening. Discard any unused portion.

Instructions For Use/Handling

The usual precautions for handling and preparing cytotoxic drugs should be observed when administering carboplatin:

Personnel should be trained in good technique for handling. Pregnant staff should be excluded from working with carboplatin.

Preparation should be performed in a designated area ideally in a vertical laminar flow hood, with the work surface covered with disposable plastic-backed absorbent paper.

Care should be taken to prevent inhaling particles and exposing the skin to carboplatin.

Adequate protective clothing should be worn, such as PVC gloves, safety glasses, disposable gowns and masks.

It is recommended that lock fittings are used in the assembly of syringes and giving sets to avoid leakage.

In the event of contact with the eyes, wash with water or saline. If the skin comes into contact with the drug wash thoroughly with water and in both cases seek medical advice. Seek immediate medical attention if the drug is ingested or inhaled.

All used material, needles, syringes, vials and other items which have come into contact with cytotoxic drugs should be incinerated. Excreta should be similarly treated. Contaminated surfaces should be washed with copious amounts of water.

MEDICINE CLASSIFICATION

Prescription Medicine.

PACKAGE QUANTITIES

50 mg/5 mL, 150 mg/15 mL, 450 mg/45 mL: 1's.

FURTHER INFORMATION

Nil.

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