should not be repeated until leukocyte, neutrophil, and platelet counts have recovered. Since anemia is cumulative, transfusions may be needed during treatment with carboplatin particularly in patients receiving prolonged therapy. Bone marrow suppression is increased in patients who have received prior therapy, especially in regimens including cisplatin. Marrow suppression is also increased in patients with impaired kidney function. Myelosuppression is generally reversible and not cumulative when carboplatin is used as a single agent at recommended frequencies of administration.

Carboplatin has limited nephrotoxic potential, but concomitant treatment with aminoglycosides has been seen to result in increased renal and or audiologic toxicity and caution must be exercised when a patient receives both drugs.

Carboplatin can induce emesis; the incidence and intensity of emesis have been reduced by premedication with anti-emetics.

Pheripheral neurotoxicity is infrequent but higher incidence has been seen in patients older than 65 years and in patients previously treated with cisplatin.

Loss of vision which can be complete for light and colors has been reported after the use of carboplatin with doses higher than recommended in the package insert; however the vision appears to recover totally or to a significant extent within weeks of stopping these high doses.

Allergic reactions as in the case of other platinum coordination compounds are also commonly seen with carboplatin; these may occur within minutes of administration and should be managed with appropriate supportive therapy. Rarely anaphylaxis and anaphylactic like reactions have been reported, including tachycardia, bronchospasm, dyspnoea, hypotension, wheezing, urticaria, facial oedema and facial flushing.

High doses of carboplatin (more than 4 times the recommended dose) have been reported to have resulted in severe abnormalities of liver function tests.

Carboplatin may cause fetal harm when administered to pregnant women; carboplatin has been reported to be embryotoxic and teratogenic in rats, however there are no adequate and well controlled studies in women.

Pulmonary fibrosis manifested by tightness of the chest and dyspnoea has been reported very rarely.

Transient increases in liver enzymes have been reported in some patients; alkaline phosphatase increased in few patients, while aspartate aminotransferase and elevated serum bilirubin occur less frequently.

PRECAUTIONS

Peripheral blood counts and renal function tests should be monitored closely. Neurological and hearing evaluation should be performed on a regular basis.

OVERDOSAGES

There is no known antidote for carboplatin overdosage; the anticipated overdosage complications would be secondary to myelosuppression, and or renal and hepatic impairment.

STORAGE

Store unopened vials at a temperature not exceeding 25 °C, with excursion permitted from 15-30 °C (59-86 °F) do not freeze. Protect from light. Single dose vials maintain microbial, chemical and physical stability for up to 14 days at 25 °C following multiple needle entries.

Vials should be inspected visually for particulate matter and discoloration prior to administration. Solutions diluted for infusion should be discarded within 8 hours of preparation

PRESENTATION

CARBOWEL™ (Carboplatin) is available in vials containing 150 mg and 450 mg of carboplatin as sterile injection.

CARBOWEL™ 150 mg/15 ml

CARBOWEL™ 450 mg/45 ml

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of cytotoxic medicinal products should be followed. However there is no general agreement that all of the recommended procedures are necessary or appropriate.

Marketed by:
Getwell Oncology Pvt. Ltd.
(A unit of Getwell)
464, Udyog Vihar, Phase-V, Gurgaon - 122016, Haryana, India

Manufactured by:
Getwell Pharmaceuticals
474, Udyog Vihar, Phase-V, Gurgaon - 122016, Haryana, India

0700DCN

GETWELL

For the use of Registered Medical Practitioner or Hospital or a Laboratory only.

Carboplatin Injection BP

CARBOWEL™

Rx only

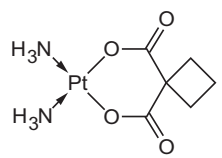
WARNING

Carboplatin injection should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate treatment facilities are readily available. Bone marrow suppression is dose related and may be severe, resulting in infection and/or bleeding. Anemia may be cumulative and may require transfusion support. Vomiting is another frequent drug related side effect. Anaphylactic like reactions to carboplatin have been reported and may occur within minutes of carboplatin administration. Epinephrine, corticosteroids, and antihistamines may be employed to alleviate symptoms.

DESCRIPTION

Carboplatin injection is supplied as a sterile, pyrogen free, 10 mg/ml aqueous solution of carboplatin. Carboplatin is a platinum coordination compound that is used as a cancer chemotherapeutic agent. Carboplatin injection is a premixed aqueous solution of 10 mg/ml carboplatin. Carboplatin injection can be further diluted to concentrations as low as 0.5 mg/ml with 5 % Dextrose in water or 0.9 % Sodium Chloride injection. When prepared as directed, carboplatin injection is stable for 8 hours at room temperature (25 °C); since no anti-bacterial preservative is incorporated in the formulation, it is recommended that carboplatin injection be discarded 8 hours after dilution.

CHEMICAL STRUCTURE



Molecular weight : 371.25

Molecular formulae : $C_6H_{12}N_2O_4Pt$

Chemically carboplatin is 1, 1 cyclobutanedicarboxylic acid platinum complex commonly written as CBDCA.

Carboplatin is a white crystalline powder; soluble in water at a rate of approximately 14 mg/ml, and the pH of 1 % solution is between 5 & 7. Carboplatin is soluble in normal saline but virtually insoluble in ethanol, acetone and dimethylacetamide. Carboplatin is stable in nature but incompatible with strong oxidizing agents. Carboplatin melts at 200 °C with decomposition.

COMPOSITION

Each ml contains	
Carboplatin BP	10 mg
Water for injection IP	q.s

CONTAINS NO ANTIMICROBIAL PRESERVATIVE

Carboplatin is available as 150 mg/15 ml and 450 mg/45 ml single dose vials.

CLINICAL PHARMACOLOGY

Mode of Action

Carboplatin is an antineoplastic medication which interferes with the growth of cancer cells, slows their growth and spread in the body. Carboplatin predominantly produces inter-strand DNA cross-links rather than DNA protein cross links. This effect is apparently cell cycle nonspecific. Two theories exist to explain the molecular mechanism of action of carboplatin with DNA:

Aquation, or the like-cisplatin hypothesis.

Activation, or the unlike-cisplatin hypothesis.

The former mechanism is more accepted owing to the similarity of the leaving groups with its predecessor cisplatin, while the latter hypothesis envisages a biological activation mechanism to release the active Pt^{2+} species. Apparently carboplatin and cisplatin induce

equal numbers of drug DNA cross links, causing equivalent lesions and biological effects. The differences in potencies for carboplatin and cisplatin appear to be directly related to the difference in aquation rates.

PHARMACOKINETICS & PHARMACODYNAMICS

Studies reveal that initial plasma half-life of carboplatin found to be 1.1 - 2 hours and the post distribution plasma half life was found to be 2.6 - 5.9 hours The total body clearance, apparent volume of distribution and mean residence time for carboplatin are 4.4 L/hour, 16 L and 3.5 hours respectively. C_{max} value and the area under plasma concentration vs time curve from 0 to infinity (AUC_{inf}) increases linearly with dose; however the increase was seen to be slightly more than dose proportional. It has been seen that carboplatin exhibits linear pharmacokinetics over the dosing range 300 - 500 mg/m^2. Carboplatin is not bound to plasma proteins; platinum from carboplatin becomes irreversibly bound to plasma proteins and is slowly eliminated with a minimum half-life of 5 days. Following 1 hour infusion (20 - 520 mg/m^2), plasma levels of total platinum and free (ultra filterable) platinum decay's bi-phasically following first order kinetics. Carboplatin is excreted primarily by glomerular filtration in urine and it has been seen that in patients with creatinine clearance of approximately 60 ml/min or greater excrete 65 % of the dose in the urine within 12 hours and 71 % of the dose within 24 hours. All of the platinum in the 24 hour urine is present as carboplatin. Only 3 - 5 % of the administered platinum is excreted in the urine between 24 and 96 hours; however there is insufficient data to determine the occurrence of biliary excretion.

DOSAGE AND ADMINISTRATION

Note: Aluminum reacts with carboplatin causing precipitate formation and loss of potency, therefore needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

As a single agent therapy the recommended dose of carboplatin in the chemotherapy of advanced ovarian cancer has been shown to be effective in patients with recurrent ovarian carcinoma at a dosage of 360 mg/m^2 IV on day 1 every 4 weeks; however single intermittent courses of carboplatin should not be repeated until the neutrophil count is at least 2000 and the platelet count is at least 100,000.

In combination therapy with cyclophosphamide for the chemotherapy of advanced ovarian cancer for previously untreated patients consists of Carboplatin injection - 300 mg/m^2 IV on day 1 every 4 weeks for 6 cycles and Cyclophosphamide - 600 mg/m^2 IV on day 1 every 4 weeks for 6 cycles. Intermittent courses of carboplatin injection in combination with cyclophosphamide should not be repeated until the neutrophil count is at least 2000 and the platelet count is at least 100,000. Pretreatment platelet count and performance status are important prognostic factors for severity of myelosupression in previously treated

An approach for determining the initial dose of carboplatin injection is the use of mathematical formulae, which is based on patients pre-existing renal function or renal function and desired platelet nadir. The use of dosing formulae as compared to empirical dose calculation based on body surface area, allows compensation for patient variations in pretreatment renal function that might otherwise resulting either underdosing or overdosing. A simple formula for calculating dosage based upon a patients glomerular filtration rate (GFR in ml/min) and carboplatin injection target area under the concentration versus time curve (AUC in mg/ml.min) has been proposed by Calvert. The Calvert formula used to determine dosage:

Dose (mg) = target AUC (mg/ml x min) x [GFR ml/min + 25]

Target AUC	Planned chemotherapy	Patient treatment status
5 - 7 mg/ml. min	single agent Carbowel	previously untreated
4 - 6 mg/ml. min	single agent Carbowel	previously treated
4 - 6 mg/ml. min	Carbowel plus cyclophosphamide	previously untreated

Note: Using the Calvert formula, the total dose of carboplatin is calculated in mg and not mg/m^2. Therapy should not be repeated until 4 weeks after the previous carboplatin course and or until the neutrophil count is at least 2000 cells/mm^3 and the platelet count is at least 100,000 cells/mm^3. Initial dosage should be reduced by 20 - 25 % in patients with risk factors such as previous myelosuppressive therapy and or poor performance status.

Impaired renal function: In patients with impaired renal function, dosage of carboplatin should be reduced (refer Calvert's formulae) while haematological nadirs and renal function are monitored.

Combination Therapy: The optimal use of carboplatin in combination with other myelosuppressive agents requires dosage adjustments according to the regimen and schedule adopted.

Elderly: Dosage adjustment may be necessary in elderly patients based on estimates of GFR to provide predictable plasma carboplatin AUC's and there by minimize the risk of toxicity.

Pediatrics patients: There is insufficient information to support a dosage recommendation in the pediatrics population.

Use in Pregnancy and Lactation: Safe use of carboplatin in pregnancy has not been established. Both men and women receiving carboplatin should be informed of the potential risk of adverse effects on reproduction. Women of childbearing potential should be fully informed of the potential hazard to the foetus should they become pregnant during carboplatin therapy. Carboplatin should not be used in pregnant women or women of childbearing potential who might become pregnant unless the potential benefits to the mother outweigh the possible risks to the foetus. 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.

INDICATIONS

Initial Treatment of Advanced Ovarian Carcinoma: Carboplatin is indicated for the initial treatment of advanced ovarian carcinoma in established combination with other approved chemotherapeutic agents. One established combination regimen consists of carboplatin and cyclophosphamide.

Secondary Treatment of Advanced Ovarian Carcinoma: Carboplatin is indicated for the palliative treatment of patients with ovarian carcinoma recurrent after prior chemotherapy, including patients who have been previously treated with cisplatin. Within the group of patients previously treated with cisplatin, those who have developed progressive disease while receiving cisplatin therapy may have a decreased response rate.

CONTRAINDICATIONS

Carboplatin is contraindicated in patients with severe myelosuppression, pre-existing severe renal impairment (with creatinine clearance of less than 20 ml per minute) and a history of severe allergic reaction to carboplatin or other platinum containing compounds. Dosage adjustment may allow use in the presence of mild renal impairment.

ADVERSE REACTIONS

Adverse reaction to carboplatin administration includes hematologic, gastrointestinal, neurologic, nephrology, hepatic toxicity in addition to electrolyte changes, allergic reactions, and injection site reactions.

Hematologic toxicity: bone marrow suppression is the dose limiting toxicity of carboplatin, is usually more severe in patients with impaired kidney function; although usually reversible, may result in infectious or hemorrhagic complications. Thrombocytopenia with platelet counts below 50000/mm^3, neutropenia with granulocyte counts below 1000/mm^3, leucopenia with WBC counts below 2000/mm^3 may be seen in pretreated ovarian cancer patients. Bone marrow depression may be more severe when carboplatin is combined with other bone marrow suppressing drugs or with radiotherapy.

Gastrointestinal toxicity: vomiting may be seen 65 % of pre-treated ovarian cancer patients however carboplatin is less emetogenic than cisplatin. Pain, diarrhea and constipation may also been seen in patients.

Neurologic toxicity: peripheral neuropathy may be observed in patients receiving carboplatin with frequently occurring mild paresthesias, however overall incidence of neurologic side effects is low but prolonged treatment particularly in cisplatin pre-treated patients may result in cumulative neurotoxicity.

Nephrotoxicity: carboplatin administration without high volume fluid hydration and or forced diuresis may result in not so common abnormal renal function tests. Creatinine clearance, one of the most sensitive measures of kidney function which is useful for correlating drug clearance and marrow suppression, may be reduced during carboplatin therapy.

Hepatotoxicity: incidence of abnormal liver function test (total bilirubin - 5 %, SGOT - 19 % and alkaline phosphatase - 37 %) are usually mild and reversible. Electrolyte levels may be abnormally decreased (sodium - 29 %, potassium - 20 %, calcium - 22 % and magnesium - 29 %) in patients on carboplatin therapy; these rates are further reduced in cisplatin pre-treated ovarian cancer patients (sodium - 47 %, potassium - 28 %, calcium - 31 % and magnesium - 43 %).

Allergic reactions to carboplatin include rash, urticaria, erythema, pruritus, bronchospasm, and hypotension. Injection site reactions include redness, swelling, pain and necrosis associated with extravasation. Asthenia, alopecia, hemolytic uremic syndrome, malaise, anorexia and hypertension has been reported in few patients.

WARNINGS

Myelosuppression is the dose limiting toxic reaction of carboplatin. Peripheral blood counts should be frequently monitored during carboplatin treatment and when appropriate until recovery is achieved. Median nadir occurs at day 21 in patients receiving single agent carboplatin. In general, single intermittent courses of carboplatin