least 100,000.

Combination therapy with Cyclophosphamide: In the chemotherapy of advanced ovarian cancer, carboplatin is given in doses of 300mg./m^2 I.V. on day 1 every 4 weeks for 6 cycles **(**alternatively see **Formula Dosing)** in combination with cyclophosphamide (600mg./m^2) I.V. on day 1 every 4 weeks for 6 cycles.

Intermitted courses of carboplatin in combination with cyclophosphamide should not be repeated until the neutrphil count is at least 2000 and the platelet count is at least 100,000.

Dose Adjustment Recommendations: Pretreatment platelet count and performance status are important diagnostic factors for severity of myelosuppression in previously treated patients.

Hematologic: Dosage adjustments in single agent combination therapy are based on the lowest post treatment platelet and neutrophil counts-

Platelets greater than100,000/neutrophil's greater than 2,000 adjusted dose is 125% from prior course.

Platelets between 50-100,000/neutrophil's between 500-2,000 no adjustment is required.

Platelets less than 50,000/neutrophil's less than 500 adjusted dose is 75% from prior course.

Renal impairment: Patients with creatinine clearance values below 60 ml/min are at increased risk of severe bone marrow suppression.

For the initial course of therapy-

CrCl 41-59mL/min give 250mg/m^2 .

CrCl 16-40mL/min give 200mg/m^2 .

Subsequent doses should be adjusted according to the patient's tolerance based on the degree of bone marrow suppression

Formula Dosing: The use of dosing formula, as compared to empirical dose calculation based on body surface area, allows compensation for patient variations in pretreatment renal function that might otherwise result in either under dosing or overdosing.

A simple formula for calculating dosage, based upon a patient's glomerular filtration rate (GFR in mL/min) and carboplating target area under the concentration versus time curve (AUC in mg/mL min). has been proposed by Calvert.

Total Dose (mg.)=target(AUC)x(GFR+25)

The target AUC of 4-6 mg/mL min using single agent carboplatin appears to provide the most appropriate dose range in previously treated patients.

PREPARATION OF INTRAVENOUS SOLUTION:

Carboplatin aqueous solution Injection is a premixed aqueous solution of 10mg/mL carboplatin. Carboplatin aqueous solution can be further diluted to concentrations as low as 0.5mg/mL with 5% Dextrose in Water (D_5 W) or 0.9% Sodium Chloride Injection, IP. When prepared as directed. carboplatin aqueous solutions are stable for 8 hours at room temperature (25°C). Since no antibacterial preservative is contained in the formulation. It is recommended that carboplatin aqueous solutions be discarded 8 hours after dilution.

OVERDOSAGE:

There is no known antidote for Carboplatin overdosage. The anticipated complications of overdosage would be secondary to bone marrow suppression and/or hepatic toxicity.

STORAGE:

Store below 25ºC and protected from light.

PRESENTATION:

Carboplatin Injection IP is available in vials containing 150mg/15 ml of Carboplatin in water for Injections IP.

Carboplatin Injection IP is available in vials containing 450mg/45 ml of Carboplatin in water for Injections IP.

HANDLING AND DISPOSAL:

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Use of 5% sodium hypochlorite solution is recommended as neutralizing agent in cases of Spills or leak of this solution.

REFERENCES:

1. Swenerton K, Jeffery J, Stuart G et al; J Cin Oncol, 1992 May;10(5):718-26.
2. Hannigan EV, Green S, Alberts DS et al; Oncology, 1993 Nov; 50 Suppl 2:2-9.
3. Thomson Micromedex-carboplatin Drug Summary Information, Micromedex Healthcare Series, Vol.121,2004.
4. Bristol Myers Squibb, Paraplatin Prescribing Information, Princeton, January2004.

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

℞ Carboplatin Injection IP
150mg/15ml , 450mg/45ml

Cytocarb

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. Anaemia 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 have been employed to alleviate symptoms.**

DESCRIPTION :

Carboplatin is a platinum coordination compound that is used as a cancer chemotherapeutic agent.

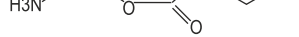
COMPOSITION :

Each ml contains :

Carboplatin	**IP**	**10 mg**
Water for Injections	**IP**	**qs**

CHEMICAL STRUCTURE :

Chemically carboplatin is platinum, diammine [1,1-cyclobutane-dicarboxylate (2)-0-0]-[SP-4-2]. It has a molecular formula of $C_6H_{12}N_2O_4$ Pt and molecular weight is 371.25. The structural formula of carboplatin is depicted below:



PHARMACOLOGY :

Mechanism of action:

Carboplatin, like cisplatin, produces predominantly interstrand DNA cros-links rather than DNA-protein cross-links. This effect is apparently cell-cycle nonspecific. The aquation of carboplatin, which is thought to produce the active species, occurs at a slower rate than in the case of cisplatin. Despite this difference, it appears that both carboplatin and cisplatin induce equal numbers of drug-DNA cross-link, causing equivalent lesions and biological effects. The differences in potencies for carboplatin and cisplatin appear to be directly related to the aquation rates.

Pharmacokinetics :

Following administration of carboplatin, the majority of the dose is rapidly cleared from the blood and largely excreted in urine within 6 hours. The carboplatin is eliminated in a biphasic manner, with initial half life (alpha) of 1.1 to 2 hours and the post distribution half life (beta) was found to be 2.6 to 5.9 hours. The rate of binding to plasma protein is signifacantly lower accounting for a greater proportion of the free drug available for rapid excretion. The degree of urinary excretion indicates less organ retention of the drug. The major route of elimination of carboplatin is renal excretion. Patients with creatinine clearance of approximately 60ml/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% to 5% of the administered platinum is excreted in the urine between 24 and 96 hours. In patients with creatinine clearances below 60ml/min. The total body and renal clearances of carboplatin decreases as the creatinine clearance decreases and therefore, reduced renal function increase the serum half life of carboplatin and result in increased mayelotoxioity. Carboplatin dosages should, therefore, be reduced in these patients since carboplatin is elminated almost completely by glomerrular filtration, there is little concentration of carboplatin at the renal tubular level which may account for its diminished nephrotoxic potential as compared to cisplatin.

CLINICAL STUDIES :

Use with cyclophosphamide for initial treatment of ovarian cancer : in two prospectively randomized, controlled studies conducted by National Cancer Institute of Canada, Clinical Trials Group (NCIC) and the Southwest Oncology Group (SWOG), 789 chemotherapy naive patients with Advanced ovarian cancer were treated with carboplatin or cisplatin, both in combination with

cyclophosphamide every 28 days for 6 courses before surgical reevaluation..

As reported by Swenerton K etal, in NCIC study, 447 patients were randomized to receive standard regimen of cisplatin-cyclophosphamide (300 mg/m^2 and 600 mg/m^2, respectively). Cisplatin treated patients were more likely to develop neuropathy and nephropathy, and carboplatin patients experienced myelosuppression, particularly thrombocytopenia. Efficacy was similar with no significant differences for the cisplatin and carboplatin arms in clinical response rate (57% V 59% in those with measurable disease), pathologic response rate (52% v 54% in those suitable for relaparotomy), time to progression (median, 56 v 58 weeks), or overall survival (median, 100 weeks v 100 weeks)

As reported by Hannigan EV, in SWOG study, 342 patients with stage III(suboptimal disease) and stage IV ovarian cancer were randomly assigned to treatment with cisplatin 100 mg/m^2 plus cyclophosphamide 600mg/m^2 carboplatin 300 mg/m^2 plus cyclophosphamide 600 mg/m^2. The median survival for the cisplatin arm was 17.4 month, for the carboplatin arm, median survival was 20.0 months. The null hypothesis of a 30% survival superiority with the cisplatin arm was rejected at the p= 0.02 level. Clinical response rates were 52% for the cisplatin arm and 61% for the carboplatin arm. There was less thrombocytopenia in the cisplatin arm (p<0.001) however, there was less nausea and emesis (p<0.001 for courses one to five) renal toxicity (p<0.001) hearing loss (p<0.001) and neuromuscular toxicity (p<0.001), anemia (p<0.001), hearing loss (p<0.001) and neuromuscular toxicity (p<0.001) in the carboplatin arm.[2]

Use as a single Agent for Secondary Treatment of Advanced Ovarian Cancer: In two prospective, randomized controlled studies in patients with advanced ovarian cancer previously treated with chemotherapy carboplatin achieved six clinical complete responses in 47 patients. The duration of these responses ranged from 45 to 71+ weeks.

INDICATIONS :

Carboplatin is used as initial chemotherapy of advanced ovarian carcinoma in combination with other approved chemotherapeutic agents. Carboplatin is used as palliative treatment of patients with ovarian carcinoma recurrent after prior chemotherapy including patients who have been previously treated with cisplatin.

CONTRAINDICATIONS:

1. Carboplatin is contraindicated in patients with a history of severe allergic reactions to Cisplatin or other platinum containing compounds.

2. Carboplatin should not be employed in patients with severe bone marrow depression or significant bleeding.

ADVERSE REACTIONS:

Hematologic Toxicity: Bone marrow suppression is the dose limiting toxicity of carboplatin. Thrombocytopenia with platelet counts below 50,000/mm occurs in 25% of the patients, neutropenia with granulocyte counts below 1,000/mm occurs in 15% of the patients. The nadir usually occurs about day 21 in patients receiving single agent therapy. By day 28.90% of patients have platelet counts above 100,00/mm, 74% have neutrophil counts above 2,000/mm, 67% have leukocyte counts above 4,000/mm.

Bone marrow suppression is usually more severe in patients with impaired kidney function. Patients with poor performance status has also experienced a higher incidence of severe leucopenia and thrombocytopenia. Anemia with hemoglobin less than 11g/dl occurs in majority of the patients who start therapy with a baseline above that value. The incidence of anemia increases with increasing exposure to carboplatin. Transfusions may be required in some patients treated with carboplatin. Bone marrow depression may be more severe when carboplatin is combined with other bone marrow suppressing drugs or with radiotherapy.

Gastrointestinal Toxicity: Vomiting occurs in about 65% of patients and in about one third of these patients. It is severe nausea alone occurs in an additional 10-15% of patients. Both nausea and vomiting usually cease within 24 Hrs. of treatment and often responsive to antimetic measures. Emesis was increased when carboplatin used in combination with other emetogenic compound. Other gastrointestinal effects observed frequently were pain, in 17% of the patients; diarrhoea in 6% and constipation, also in 6%.

Neurologic Toxicity: Peripheral neuropathies have been observed in small number of patients receiving carboplatin with mild parethesias occurring most frequently. Patients older than 65yrs. have an incresed risk for peripheral neuropathies. Clinical ototoxicity and other sensory abnormalities such as visualdisturbances and change in taste occur rarely. Central nervous system symptoms have been reported in fewer patients and appear to be most often related to the use of antiemetics. Although the overall incidence of peripheral neurologic side effects induced by carboplatin is low, prolonged treatment may result in cumulative neurotoxicity.

Nephrotoxicity: Development of abnormal renal function test results is uncommon with carboplatin. Creatinine clearance has proven to be the most sensitive measure of kidney function in patients receiving carboplatin and it appears to be the most useful test for correlating drug clearance and bone marrow suppression.

Hepatic Toxicity: Abnormal liver function tests in patients may be found with normal baseline value. These abnormalities (e.g. SGOT, total bilirubin and alkaline phosphatase) have generally been mild and reversible in about one-half of the cases, although the role of metastatic tumour in the liver may complicate the assessment in many patients.

Electrolyte Changes: The abnormally decreased serum electrolyte values may be found in some patients. Electrolyte supplementation is not routinely administered concomitantly with carboplatin, and these electrolyte abnormalities are rarely associated with symptoms.

Allergic Reactions: Hypersenstivity to carboplatin develops only in a small number of patients and consists of rash, urticaria erythema, pruritus and rarely bronchospasm and hypotension. These reactions are successfully managed with standard epinephrine, corticosteroid and antihistamine therapy.

Others: Pain and asthenia occur most frequently. Injection site reaction, alopecia, cardiovascular, respiratory genitourinary and mucosal side effects occur only in small number of patients.

WARNING & PRECAUTIONS:

1. Carboplatin 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 diagnostic and treatment facilities are readily available.

2. Bone marrow suppression (leucopenia, neutropenia, thrombocytopenia) is dose related and may be severe, resulting in infection and or bleeding. Peripheral blood count should be frequently monitored during carboplatin treatment and when appropriate, until recovery is achieved. Bone marrow suppression is increased in patients who have received prior therapy, especially regimens including cisplatin. Marrow suppression is also increased in patients with impaired kidney function. Initial carboplatin dosages in these patients should be appropriately reduced and blood counts should be carefully monitored between courses. anemia may be cumulative and may require transfusion support.

3. Carboplatin can induce emesis. The incidence and intensity of emesis can be reduced by using pre medication with anti emetics.

4. Anaphylactic- like reactions to carboplatin have been reported and may occur with in minutes of carboplatin administration. Epinephrine corticosteroids and antihistamines have been employed to alleviate symptoms.

5. Carboplatin has limited nephrotoxic potential but concomitant treatment with aminoglycosides has resulted in increased renal and/or audiologic toxicity and caution must be exercised when a patient receives both drugs.

6. Peripheral neurotoxicity is infrequent its incidence increases in patients older than 65yrs. and in patients previously treated with cisplatin.

7. Loss of vision, which can be complete for light and colour may occur after the use of carboplatin with doses higher than that recommended. Vision appears to recover totality or to a significant extent with in weeks of stopping these high doses.

8. Carboplatin may cause fetal harm when administered to a pregnant woman and is embryotoxic and teratogenic in rats. If this drug is used during pregnancy, the patients should be apprised of the potential hazard to the foetus. Woman of child bearing potential should be advised to avoid becoming pregnant.

9. Paediatric Use: Safety and effectiveness in paediatric patients have not been established.

10. Geriatric Use: of the 789 patients in initial treatment combination therapy studies (NCIC & SWOG). 395 patients were treated with carboplatin in combination with cyclophosphamide. Of these, 141 were over 65 yrs. of age and 22 were 75 yrs. or older. In these trials, age was not a prognostic factor for survival. In terms of safety, elderly patients treated with carboplatin were more likely to develop severe thrombocytopenia than youger patients. In a combined database of 1942 patients (414 were $\geq$ 65 years of age) that received single-agent carboplatin for different tumor types a similar incidence of adverse events was seen in patients 65 yrs. and older and in patients less than 65. other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Because renal fuction is often decreased in the elderly, renal function should be considered in the selection of carboplatin dosage.

11. Needles or intravenous administration sets containing aluminium parts that may come in contact with carboplatin should not be used for the preparation or the administration of the drug. Aluminium can react with carboplatin causing precipitate formation and loss of potency.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

The Carcinogenic potential of carboplatin has not been studied, but compounds with similar mechanisms of action and mutagenicity profiles have been reported to be carcinogenic. Carboplatin has been shown to be mutagenic both *in vitro and in vivo*. It has also been shown to be embryotoxic and teratogenic in rats receiving the drug during organogenesis. Secondary malignancies have been reported in association with multi-drug therapy.

Pregnancy:

Pregnancy category D

If this drug is used during pregnancy or if the patient becomes pregnant while receiving carboplatin, the patients should be appraised of the potential hazard to the foetus. Women of child bearing potential should be advised to avoid becoming pregnant.

Lactation:

It is not known whether carboplatin is excreted in human milk. Because there is a possibility of toxicity in nursing infants secondary to carboplatin treatment of the mother, it is recommended that breast feeding be discontinued if the mother is being treated with carboplatin.

DOSAGE & ADMINISTRATION:

Note: Needles or intravenous administration sets containing, aluminium parts that may come in contact with carboplatin should not be used for the preparation or the administration of the drug. Aluminium can react with carboplatin causing precipitate formation and loss of potency.

Single agent Therapy: Carboplatin Injection is given in doses of 360mg/m^2 I.V. on day 1 every & weeks (alternatively see **Formula Dosing**) In general however single intermittent courses of carboplatin should not be repeated until the neutrophil counts at least 2000 and the platelet count is at