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 hours of treatment and are often responsive to antiemetic measures. Emesis was increased when carboplatin was 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 parsesthesias occurring most frequently. Patients older than 65 years have an increased risk for peripheral neuropathies. Clinical ototoxicity and other sensory abnormalities such as visual disturbances and change in taste occurs 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 (eg 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: 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: Hypersensitivity to Carboplatin develops only in a small number of patients and consists of rash of urticaria, erythema, pruritus and rarely bronchospasm and hypotension. These reactions are successfully managed with standard epinephrine, corticosteroid and antihistamine therapy.

Others: Pain and asthenia occurs most frequently. Alopecia, cardiovascular, respiratory genitourinary and mucosal side effects occur only in small number of patients.

Overdosage

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

STORAGE

Store below 25°C. Protect from light.
Do not freeze.

Presentation

CYTOCARB - Single dose vials of 15 ml and 45 ml

Cipla

043J E
IY 1

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

Carboplatin Injection

CYTOCARB

Composition
Each ml contains
Carboplatin USP ..... 10 mg
Water for Injection I.P. ..... q.s.
Contains no antimicrobial preservative

Description:
CYTOCARB (Carboplatin) is a platinum coordination compound that is used as a cancer chemotherapeutic agent.

Indications:
Carboplatin is used in the initial treatment of advanced ovarian cancer and as secondary treatment of advanced ovarian cancer.

Dosage and Administration:

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

Single Agent Therapy:

CYTOCARB as a single agent has been shown to be effective in patients with recurrent ovarian carcinoma at a dosage of 360 mg/m² I.V on day 1 every 4 weeks (alternatively see formula dosing). In general, however single intermittent courses of **CYTOCARB** should not be repeated until the neutrophil count is at least 2,000 and the platelet count is at least 100,000.

Combination therapy with cyclophosphamide:
In the chemotherapy of advanced ovarian cancer, an effective combination for previously untreated patients consists of;

CYTOCARB - 300 mg/m² I.V on day 1 every 4 weeks for six cycles (alternatively see formula dosing)

Cyclophosphamide- 600 mg/m² I.V on day 1 every 4 weeks for six cycles.

Intermittent courses of **CYTOCARB** in combination with cyclophosphamide should not be repeated until the neutrophil count is at least 2,000 and the platelet count is atleast 100,000.

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

The suggested dose adjustments for single agent or combination therapy shown in the table below are modified from controlled trials in previously treated and untreated patients with ovarian carcinoma. Blood counts were done weekly, and the recommendations are based on the lowest post-treatment platelet or neutrophil value.

PLATELETS	NEUTROPHILS	ADJUSTED DOSE * (From Prior Course)
> 100,000	> 2,000	125%
50-100,000	500-2,000	No Adjustment
< 50,000	< 500 to > 500	75%

*Percentages apply to CYTOCARB (carboplatin for injection) as a single agent or both CYTOCARB and cyclophosphamide in combination. In the controlled studies, dosages were also adjusted at a lower level (50 to 60%) for severe myelosuppression. Escalations above 125% were not recommended for these studies.

CYTOCARB is usually administered by an infusion lasting 15 minutes or longer. No pre- or post-treatment hydration or forced diuresis is required.

Patients with Impaired Kidney Function: Patients with creatinine clearance values below 60 mL/min are at increased risk of severe bone marrow suppression. In renally-impaired patients who received single agent **CYTOCARB** therapy, the incidence of severe leukopenia, neutropenia, or thrombocytopenia has been about 25% when the dosage modifications in the table below have been used.

Baseline Creatinine Clearance	Recommended Dose on Day 1
41-59 mL/min	250 mg/m 2
16-40 mL/min	200 mg/m 2

The data available for patients with severely impaired kidney function (creatinine clearance below 15 mL/min) are too limited to permit a recommendation for treatment.

These dosing recommendations apply to the initial course of treatment. Subsequent dosages should be adjusted according to the patient' tolerance based on the degree of bone marrow suppression.

Formula Dosing: Another approach for determining the initial dose of **CYTOCARB** is the use of mathematical formulae, which are based on a patient' pre-existing renal function or renal function and desired platelet nadir. Renal excretion is the major route of elimination for carboplatin. 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 result in either underdosing (in patients with above average renal function) or overdosing (in patients with impaired renal function).

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

CALVERT FORMULA FOR CARBOPLATIN DOSING
Total Dose (mg)=(target AUC) × (GFR + 25)
Note: With the Calvert formula, the total dose of CYTOCARB is calculated in mg, not mg/m².

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

Contraindications:

1. Carboplatin is contraindicated in patients with a history of severe allergic reactions to Cisplastin or other platinum containing compounds.
2. Carboplatin should not be employed in patients with severe bone marrow depression or significant bleeding.

Warnings and Precautions

Bone marrow suppression (leukopenia, neutropenia, and thrombocytopenia) is dose-dependent and is also the dose-limiting toxicity. Peripheral blood counts should be frequently monitored during **CYTOCARB** treatment and, when appropriate, until recovery is achieved. Median nadir occurs at day 21 in patients receiving single-agent **CYTOCARB**. In general, single intermittent courses of **CYTOCARB** should not be repeated until leukocyte, neutrophil, and platelet counts have recovered.

Since anemia is cumulative, transfusions may be needed during treatment with **CYTOCARB**, particularly in patients receiving prolonged therapy.

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 **CYTOCARB** dosages in these patients should be appropriately reduced (see " DOSAGE AND ADMINISTRATION " section) and blood counts should be carefully monitored between courses. The use of **CYTOCARB** in combination with other bone marrow suppressing therapies must be carefully managed with respect to dosage and timing in order to minimize additive effects.

CYTOCARB 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.

Clinically significant hearing loss has been reported to occur in pediatric patients when **CYTOCARB** was administered at higher than recommended doses in combination with other ototoxic agents.

CYTOCARB can induce emesis, which can be more severe in patients previously receiving emetogenic therapy. The incidence and intensity of emesis have been reduced by using premedication with antiemetics. Although no conclusive efficacy data exist with the following schedules of **CYTOCARB**, lengthening the duration of single intravenous administration to 24 hours or dividing the total dose over five consecutive daily pulse doses has resulted in reduced emesis.

Although peripheral neurotoxicity is infrequent, its incidence is increased in patients older than 65 years and in patients previously treated with cisplatin. Pre-existing cisplatin-induced neurotoxicity does not worsen in about 70% of the patients receiving **CYTOCARB** as secondary treatment.

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

As in the case of other platinum coordination compounds, allergic reactions to **CYTOCARB** have been reported. These may occur within minutes of administration and should be managed with appropriate supportive therapy.

High dosages of **CYTOCARB** (more than four times the recommended dose) have resulted in severe abnormalities of liver function tests.

CYTOCARB may cause foetal harm when administered to a pregnant woman.

DRUG INTERACTIONS

The effects of nephrotoxic compounds may be potentiated by **CYTOCARB**

PREGNANCY

Carboplatin may cause foetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving carboplatin, the patient should be apprised of the potential hazard to the foetus. Women of child bearing potential should be advised to avoid becoming pregnant.

NURSING MOTHERS

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.

PEDIATRIC USE

Safety and efficacy in pediatric patients have not been established

SIDE EFFECTS

Haematologic toxicity: Bone marrow suppression is the dose limiting toxicity of Carboplatin.Thrombocytopenia with platelet counts below 50,000/mm³ occurs in 25% of the patients; neutropenia with granulocyte counts below 1,000/mm³ occurs in 16% of the patients; leucopenia with WBC counts below 2,000/mm³ 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 100,000/ mm³, 74% have neutrophil counts above 2,000/ mm³; 67% have leukocyte counts above 4,000/ mm³. marrow suppression is usually more severe in patients with impaired kidney function. Patients with poor performance status have also experienced a higher incidence of severe leucopenia and thrombocytopenia. Anaemia with haemoglobin less than 11g.dl occurs in majority of the patients who start therapy with a baseline above the value. The incidence of anaemia 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 with radiotherapy.

Gastrointestinal toxicity: Vomiting occurs in about 65% of the patients and