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

Carboplatin Concentrate for Solution for Infusion
Kemocarb Concentrate for solution for infusion 10mg/ml

SAFETY WARNINGS:

- Carboplatin Injection BP 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 Injection administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms.

DESCRIPTION:

Kemocarb (Carboplatin) Injection is a clear, colourless to pale yellow solution. Free from visible particles. Carboplatin is a platinum coordination compound that is used as a cancer chemotherapeutic agent.

Dosage form: Concentrate for Solution for Infusion

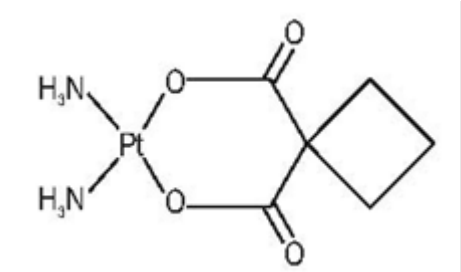
COMPOSITION:

Each ml contains

Carboplatin BP	10mg
Water for injections BP	q.s.

CHEMICAL STRUCTURE:

Chemically carboplatin is platinum, diammine [1,1-cyclobutane-dicarboxylate (2-)-0-0']-[SP-4-2]. It has a molecular formula of $C_6H_{12}N_2O_4Pt$ and molecular weight is 371.25. The structural formula of carboplatin is depicted below:



PHARMACOLOGY:

Pharmacodynamics:

Carboplatin is a second-generation platinum compound; non-classical alkylating agent and is cell-cycle-phase non-specific. It is a cytotoxic platinum complex that reacts with nucleophilic sites of DNA. This causes interstrand and intrastrand DNA cross links, which inhibit DNA, RNA and protein synthesis.

Pharmacokinetics:
After a 1 hour infusion (20-520mg/m^2) plasma levels of total platinum and free (ultrafilterable) platinum decay biphasically following first order kinetics. For free platinum the initial phase (t alpha) half-life is approximately 90 minutes, and the later phase (t beta) half-life approximately 6 hours. All free platinum is in the form of Carboplatin in the first 4 hours after administration.

Carboplatin is excreted primarily by glomerular filtration in urine, with recovery of 65% of a dose within 24 hours. Most of the drug is excreted within the first 6 hours. Approximately 32% of a given dose of carboplatin is excreted unchanged.

Protein binding of carboplatin reaches 85-89% within 24 hours of administration although during the first 4 hours only up to 29% of the dose is protein bound. Patients with poor renal function may require dosage adjustments due to altered pharmacokinetics of carboplatin.

INDICATIONS:
Carboplatin is indicated in the treatment of:

- Advanced ovarian cancer of epithelial origin
- Small cell and non-small cell carcinoma of the lung
- Squamous cell carcinoma of Head & neck
- Advanced transitional cell carcinoma of the bladder (in combination with other agents)
- Significant responses have been observed when carboplatin has been employed in the treatment of carcinoma of the cervix

CONTRAINDICATIONS:

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

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

Patients with pre-existing severe renal impairment.

ADVERSE EFFECTS:

Haematologic toxicity:
Bone marrow suppression is the dose limiting toxicity of Carboplatin. Thrombocytopenia with platelet counts below 50,000/mm^3 occurs in 25% of the patients; neutropenia with granulocyte counts below 1,000/mm^3 occurs in 16% of the patients, leucopenia with WBC counts below 2,000/ mm^3 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^3, 74% have neutrophil counts above 2,000/mm^3; 67% have leukocyte counts above 4,000/mm^3. 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. Anemia with haemoglobin less than 11 g/dl occurs in majority of the patients who start therapy with a baseline above the 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 the 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 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; diarrhea, in 6% and constipation, also in 6%.

Neurologic toxicity:
Peripheral neuropathies have been observed in small number of patients receiving carboplatin with mild paresthesia 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 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:
Abnormalities of liver function tests (usually mild to moderate) have been reported with carboplatin in about one-third of the patients with normal baseline values. The alkaline phosphatase level is increased more frequently than SGOT, SGPT or total bilirubin. The majority of these abnormalities regress spontaneously during the course of treatment.

Electrolyte changes:
Decreases in serum electrolytes (sodium, magnesium, potassium and calcium) have been reported after treatment with carboplatin but have not been reported to be severe enough to cause the appearance of clinical signs or symptoms. Cases of hyponatraemia have been reported. Haemolytic uraemic syndrome has been reported rarely.

Allergic reactions:
Hypersensitivity 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. Alopecia, cardiovascular, respiratory, genitourinary and mucosal side effects occur only in small number of patients. Use of higher than recommended dose of carboplatin has been associated with loss of vision.

WARNING & PRECAUTIONS:

Warnings:
Myelosuppression as a result of carboplatin treatment is closely related to the renal clearance of the drug. Therefore, in patients with 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 are advanced in years. Renal function parameters should be assessed prior to, during, and after carboplatin therapy.

Peripheral blood counts (including platelets, white blood cells and haemoglobin) should be followed during and after therapy. Combination therapy with other myelosuppressive drugs may require modification of dosage/timing of schedules in order to minimize additive effects.

Carboplatin courses should not, in general, be repeated more frequently than every 4 weeks in order to ensure that the nadir in blood counts has occurred and there has been recovery to a satisfactory level.

Infrequent allergic reactions to carboplatin have been reported, e.g. erythematous rash, fever with no apparent cause or pruritus. Rarely anaphylaxis, angioedema and anaphylactoid reactions including bronchospasm, urticaria and facial oedema have occurred. These reactions are similar to those observed after administration of other platinum containing compounds and may occur within minutes. The incidence of allergic reactions may increase with previous exposure to platinum therapy; however, allergic reactions have been observed upon initial exposure to carboplatin. Patients should be observed carefully for possible allergic reactions and managed with appropriate therapy, including antihistamines, adrenaline and/or glucocorticoids.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
Cases of RPLS have been reported in patients receiving carboplatin in combination chemotherapy. RPLS is a rare, reversible after treatment discontinuation, rapidly evolving neurological condition, which can include seizure, hypertension, headache, confusion, blindness, and other visual and neurological disturbances. Diagnosis of RPLS is based upon confirmation by brain imaging, preferably MRI.

Precautions
Carboplatin should only be administered 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 management of therapy and possible complications.

Peripheral blood counts and renal function tests should be monitored closely. Blood counts should be performed prior to commencement of carboplatin therapy, and at weekly intervals thereafter. This will monitor toxicity and help determine the nadir and recovery of haematological parameters and assist in subsequent dosage adjustments. Lowest levels of platelets are generally seen between days 14 and 21 of initial therapy. A greater reduction is seen in patients who previously received extensive myelosuppressive chemotherapy. Lowest levels of white cells occur generally between days 14 and 28 of initial therapy. If levels fall below 2000 cells/mm^3 or platelets less than 100,000 cells/mm^3 then postponement of carboplatin therapy until bone marrow recovery is evident, should be considered. This recovery usually takes 5 to 6 weeks. Transfusions may be necessary and dosage reductions recommended for subsequent treatment.

The incidence and severity of nephrotoxicity may increase in patients who have impaired kidney function before carboplatin treatment. It is not clear whether an appropriate hydration programme might overcome such an effect, but dosage reduction or discontinuation of therapy is required in the presence of severe alteration in renal function test. Impairment of renal function is more likely in

patients who have previously experienced nephrotoxicity as a result of cisplatin therapy. Neurological evaluation and an assessment of hearing should be performed on a regular basis. Neurotoxicity, such as paraesthesia, decreased deep tendon reflexes, and ototoxicity are more likely seen in patients previously treated with cisplatin.

Aluminium containing equipment should not be used during preparation and administration of carboplatin.

Carcinogenicity, Mutagenicity, 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.

Use in Special Population:

Pregnancy:
Pregnancy category D

Carboplatin may cause fetal harm when administered to a pregnant woman. Carboplatin has been shown to be embryotoxic and teratogenic in rats. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, 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.

DOSAGE & ADMINISTRATION :

Dosage & Dose Modifications :
Carboplatin should be used by intravenous route only. The recommended dose of carboplatin in previously untreated adults with normal renal function is 400mg/m^2 given as a single short-term intravenous infusion over 15 to 60 minutes. Alternatively see Formula dosing below.).

Therapy should not be repeated until 4 weeks after the previous carboplatin course and/or until the neutrophil count is at least 2,000 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.

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

Impaired Renal Function
Patients with creatine clearance values below 60ml/min are at increased risk of severe myelosuppression. The frequency of severe leucopenia, neutropenia, of thrombocytopenia has been maintained at about 25% with the following dosage recommendations:

Creatinine clearance (mL/min)	Starting dose(mg/m^2)
>60	No dose reduction
41-59	250
16-40	200

Insufficient data exists on the usage of carboplatin in patients with creatinine clearance of 15ml/min or less to permit a recommendation for treatment.

All the above dosing recommendations apply to the initial course of treatment. Subsequent dosages should be adjusted according to the patient's tolerance and to the acceptable level of myelosuppression.

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

Formula Dosing
Another approach for determining the initial dose of carboplatin is the use of mathematical formulae, which are based on a patient's pre-existing renal function or renal function and desired platelet nadir. The use of dosing formulae, as compared to empiric dose calculation based on body surface area allows for adjustment for patient variations in pretreatment renal function that might otherwise result in 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's glomerular filtration rate (GFR in ml/min) and carboplatin target area under the concentration versus time curve (AUC in mg/ml*min), as proposed by Calvert is:

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

Note: With the Calvert formula, the total dose of carboplatin is calculated in mg not mg/m^2.

Target AUC	**Planned Chemotherapy**	**Patient Treatment status**
5-7 mg/ml.min	single agent carboplatin	previously untreated
4-6 mg/ml.min	single agent carboplatin	previously treated
4-6 mg/ml.min	Carboplatin plus cyclophosphamide	previously untreated

An approach in heavily pretreated patients* receiving single agent carboplatin, when there is the desire to target a particular platelet nadir, is the use of the Egorin formula.

Dose (mg/m^2) = 0.091{Cr. Clearance (ml/min)/BSA (mg/m^2)} [{(Pretreatment platelet count-desired platelet nadir) x100/ Pretreatment platelet count}-17) + 86

*Patients are considered heavily pretreated if they have received any of the following: mitomycin-C, nitrosoureas, combination therapy with doxorubicin, cyclophosphamide and cisplatin; chemotherapy with 5 or

more different agents; or radiotherapy ≥ 4,500 rads to a single port 20x20 cm or more than one field of therapy.

INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION:

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

Concurrent therapy with nephrotoxic or ototoxic drugs such as aminoglycosides, vancomycin, capreomycin and diuretics may increase or exacerbate toxicity due to carboplatin induced changes in renal clearance.

Combination therapy with other myelosuppressive agents may require dose changes or rescheduling of doses in order to minimize the additive myelosuppressive effects.

INCOMPATIBILITIES:
It is important not to use needles or other equipment that contain aluminium while preparing or administering Kemocarb.

PREPARATION OF INTRAVENOUS SOLUTION:
KEMOCARB (Carboplatin aqueous solution) Injection is a premixed aqueous solution of 10mg/ml Carboplatin. KEMOCARB aqueous solution can be further diluted to concentrations as low as 0.5 mg/ml with 5% Dextrose in Water (D5W) or 0.9% Sodium Chloride Injection USP. When prepared as directed, KEMOCARB 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.

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

STORAGE:
Store below 30°C. Do not freeze. Protect from light.

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.

PRESENTATION:
KEMOCARB (Carboplatin Injection BP) is available in vials containing 150mg and 450mg of carboplatin, as sterile injection.

KEMOCARB 150mg/15ml and KEMOCARB 450mg/45ml
Not all presentations may be available locally.

REFERENCES:
Prescribing Information, Carboplatin Injection, Teva Parenteral Medicines, Inc., 01/2016

MANUFACTURER INFORMATION:

Manufactured in India by:
Fresenius Kabi Oncology Limited
Village- Kishanpura,
Tehsil – Nalagarh,
Distt. Solan [H.P.] - 174101

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