Aricarb

Carboplatin USP

COMPOSITION

Aricarb 150 Injection: Each vial contains Carboplatin USP 150 mg, as sterile preservative free 15 ml concentrated solution for IV Infusion.

Aricarb 450 Injection: Each vial contains Carboplatin USP 450 mg, as sterile preservative free 45 ml concentrated solution for IV Infusion.

CLINICAL PHARMACOLOGY

Mechanism of action: Carboplatin is a platinum coordination compound, it produces interstrand DNA cross-links that cause changes in the conformation of the DNA and affect DNA replication. This DNA reactivity has been correlated with cytotoxicity.

Pharmacokinetics: Carboplatin is not bound to plasma proteins. No significant quantities of protein-free, ultrafilterable platinum-containing species other than Carboplatin are present in plasma. However, platinum from Carboplatin becomes irreversibly bound to plasma proteins and is slowly eliminated with a minimum half-life of 5 days. The major route of elimination of Carboplatin is renal excretion. Patients with creatinine clearances 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% to 5% of the administered platinum is excreted in the urine between 24 and 96 hours. There are insufficient data to determine whether biliary excretion occurs.

INDICATIONS

Carboplatin injection is indicated for-

- initial treatment of advanced ovarian carcinoma in established combination with other approved chemotherapeutic agents.
- palliative treatment of patients with ovarian carcinoma recurrent after prior chemotherapy, including patients who have been previously treated with Cisplatin.
- treatment of small cell lung cancer.

DOSAGE AND ADMINISTRATION

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

Single-Agent Therapy: Carboplatin injection, as a single agent, 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. In general, however, single intermittent courses of Carboplatin 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 Carboplatin 300 mg/m^2 IV on day 1 every 4 weeks for 6 cycles, Cyclophosphamide 600 mg/m^2 IV on day 1 every 4 weeks for 6 cycles. Intermittent courses of Carboplatin in combination with Cyclophosphamide should not be repeated until the neutrophil count is at least 2,000 and the platelet count is at least 100,000.

Formula Dosing is an alternative method, also used for dose calculation.

Dose Adjustment Recommendations: Pretreatment platelet count and performance status are important prognostic factors for severity of myelosuppression in previously treated patients. Based on the lowest post-treatment platelet or neutrophil value for weekly blood count, following is the suggested dose adjustments for single agent or combination therapy-

Platelets	**Neutrophils**	**Adjusted Dose** (From Prior Course)
>100,000	>2,000	125%
50-100,000	500-2,000	No Adjustment
<50,000	<500	75%

Patients with Impaired Kidney Function: Patients with creatinine clearance values below 60 ml/min are at increased risk of severe bone marrow suppression. In renal-impaired patients who received single-agent Carboplatin 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's tolerance based on the degree of bone marrow suppression.

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. Use of this 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). Calvert formula is used to calculate dosage which is 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). Studies measured GFR by 51Cr-EDTA clearance.

Calvert formula for Carboplatin dosing:

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

Note: Calvert formula calculates the total dose of Carboplatin in mg, not mg/m^2

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

Geriatric Dosing: As renal function is often decreased in elderly patients, formula dosing of Carboplatin based on estimates of GFR should be used in elderly patients to provide predictable plasma Carboplatin AUCs and thereby minimize the risk of toxicity.

Preparation for Administration: Carboplatin injection is supplied as aqueous solution of 10 mg/ml Carboplatin. Carboplatin 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, 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.

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.

Precautions during Handling: Caution should be exercised in handling the aqueous solution. Procedures for proper handling and disposal of anticancer drugs should be utilized. To minimize the risk of dermal exposure, always wear impervious gloves when handling vials and IV sets containing Carboplatin. If Carboplatin contacts the skin or mucosa, immediately and thoroughly wash the skin with soap and water and flush the mucosa with water.

CONTRAINDICATIONS

Carboplatin injection is contraindicated in patients with a history of severe allergic reactions to any platinum-containing compounds. Carboplatin should not be employed in patients with severe bone marrow depression or significant bleeding.

ADVERSE REACTIONS

Hematologic: Thrombocytopenia, Neutropenia, Leukopenia, Anemia, Infections, Bleeding. **Gastrointestinal:** Nausea, Vomiting. **Neurologic:** Peripheral neuropathies, Ototoxicity, Central neurotoxicity. **Renal:** Serum creatinine elevations, Blood urea elevations. **Hepatic:** Bilirubin elevations, SGOT elevations, Alkaline phosphatase elevations, **Electrolytes loss:** Loss of Sodium, Potassium, Calcium, Magnesium. **Other side effects:** Pain, Asthenia, Alopecia, Mucositis.

PRECAUTIONS

Pregnancy: Pregnancy category D. Carboplatin has been shown to be embryo toxic and teratogenic in animal, can causes fetal harm when administered to a pregnant woman.

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 treated with Carboplatin injection.

Pediatric use: Safety and effectiveness in pediatric patients have not been established.

Geriatric use: In terms of safety, elderly patients treated with Carboplatin are more likely to develop severe thrombocytopenia than younger patients. Clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As renal function is often decreased in the elderly, renal function should be considered in the selection of Carboplatin dosage.

DRUG INTERACTIONS

The renal effects of nephrotoxic compounds may be potentiated by Carboplatin.

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 in a dry place at temperature below 25°C. Protect from light and do not refrigerate. Keep out of the reach of children.

PRESENTATION

Aricarb 150 Injection: Each box contains a single dose glass vial of Carboplatin 150 mg.

Aricarb 450 Injection: Each box contains a single dose glass vial of Carboplatin 450 mg.

Manufactured for:
ARISTOPHARMA LTD.
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