SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT:

CABOO

Carboplatin Injection BP

Strength:

10 mg/ml – 15 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Sr. No.	Particulars	Grade	Qty./ml	Function
1.	Carboplatin	BP	10 mg	Active

For the list of full excipient see section 6.1.

3. PHARMACEUTICAL FORM:

Solution for Infusion

A clear, colourless to slight yellow solution.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

Initial Treatment of Advanced Ovarian Carcinoma:

Carboplatin Injection is indicated for the initial treatment of advanced ovarian carcinoma in established combination with other approved chemotherapeutic agents.

Secondary Treatment of Advanced Ovarian Carcinoma:

Carboplatin Injection 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.

Use as a Single Agent for Secondary Treatment of Advanced Ovarian Cancer:

With reference to literature data used in patients with advanced ovarian cancer previously treated with chemotherapy, Carboplatin Injection. The duration of these responses ranged from 45 to 71 + weeks.

4.2 Posology and method of administration:

Route of administration: For I.V. / I.V. Infusion after dilution.

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 injection.

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/m2 IV on day 1 every 4 weeks (alternatively). 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/m2 IV on day 1 every 4 weeks for 6 cycles.
Cyclophosphamide - 600 mg/m2 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.

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	125.00%
50 to 100,000	500 to 2,000	No Adjustment
< 50,000	< 500	75.00%
*Percentages apply to carboplatin injection as a single agent or to both carboplatin 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.		
Carboplatin injection 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 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 to 59 ml/min	250 mg/m^2
16 to 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 injection is the use of mathematical formulae, which are based on a patient's 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 under-dosing (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 injection target

area under the concentration versus time curve (AUC in mg/mL/min), has been proposed by Calvert. In these studies, GFR was measured by 51Cr-EDTA clearance.

CALVERT FORMULA FOR CARBOPLATIN DOSING

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

Note: With the Calvert formula, the total dose of carboplatin is calculated in mg, not mg/m2.

Geriatric Dosing

Because renal function is often decreased in elderly patients, formula dosing of carboplatin injection based on estimates of GFR should be used in elderly patients to provide predictable plasma carboplatin injection AUCs and thereby minimize the risk of toxicity.

4.3 Contraindications:

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

4.4 Special warnings and precautions for use:

Carboplatin should be administered only by a qualified physician experienced in the use of chemotherapeutic agents. Close monitoring for toxicity is mandatory, particularly in the case of administration of high drug dosages. Carboplatin is a highly toxic drug with a narrow therapeutic index and a therapeutic effect is unlikely to occur without some evidence of toxicity.

Bone Marrow Function

Bone marrow suppression (leucopenia, neutropenia and thrombocytopenia) is dose dependent and is the dose-limiting toxicity of carboplatin. Peripheral blood cell counts should be performed at frequent intervals (before start of therapy and weekly thereafter) in patients receiving carboplatin. Although at the recommended drug doses the haematologic toxicity of carboplatin is usually moderate and reversible, severe myelosuppression (especially thrombocytopenia) may occur in patients with renal impairment and in patients who are concurrently receiving (or have received) other myelosuppressive drugs or radiation therapy. Dose adjustment criteria for patients who experience myelosuppression following a dose of carboplatin are provided under Dosage and Administration. As an alternative to dosage reduction, administration of the full therapeutic dose of the drug may be delayed until recovery of neutrophil and platelet counts (values $\geq$ 2000/mm3 and 100,000/mm3 respectively). Treatment of severe haematologic toxicity may consist of supportive care, anti-infective agents for complicating infections, transfusions of blood products, autologous bone marrow rescue, peripheral stem cell transplantation and haematopoietic agents (colony-stimulating factors).

Renal Function

Carboplatin is excreted primarily in the urine and renal function must be monitored in patients receiving the medicine. Creatinine clearance appears to be the most sensitive measure of kidney function in patients receiving carboplatin. Dose adjustment criteria for patients with impaired renal function are provided under Dosage and Administration. Unlike cisplatin, pre- and post-treatment hydration is not necessary

with carboplatin as the drug has a relatively low nephrotoxic potential, however, previous therapy with cisplatin or concomitant administration of other nephrotoxic drugs (e.g. aminoglycoside antibiotics) may increase the risk of nephrotoxicity.

CNS/Hearing Functions

Routine neurologic examination is advisable during carboplatin therapy, particularly in patients previously treated with cisplatin and in patients over 65 years of age. Carboplatin may produce cumulative ototoxicity. Audiograms should be performed prior to initiating therapy and during treatment or when auditory symptoms occur. Clinically important deterioration of auditory function may require dosage modifications or discontinuation of therapy.

Gastrointestinal Effects

Carboplatin can induce emesis. The incidence and severity of emesis may be reduced by pretreatment with antiemetics or by carboplatin administration as a continuous IV infusion over 24 hours, or as IV administration of divided doses over 5 consecutive days rather than as a single infusion. Selective inhibitors of type 3 (5-HT3), serotonergic receptors (e.g. ondansetron) or substituted benzamides (e.g. metoclopramide) may be particularly effective antiemetics, and combination therapy may be considered for patients experiencing severe or refractory emetogenic effects.

Hypersensitivity Reactions

As in the case of other platinum complexed compounds, allergic reactions to carboplatin have been reported. Patients should be monitored for possible anaphylactoid reactions and appropriate equipment and medication should be readily available to treat such reactions (e.g. antihistamines, corticosteroids, epinephrine, oxygen) whenever carboplatin is administered.

Immunosuppressant Effects / Increased Susceptibility to Infections

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including carboplatin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving carboplatin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Carcinogenicity and Mutagenicity

Secondary malignancies are potential delayed effects of many antineoplastic agents although it is not clear whether the effect is related to their mutagenic or immunosuppressive action. The effect of dose and duration of therapy is also unknown although risk seems to increase with long-term use. Although information is limited, available data seems to indicate that the carcinogenic risk is greatest with the alkylating agents. Both in vitro and in vivo studies have shown carboplatin to be mutagenic.

Warning: Cytotoxic. To be supplied against demand from Cancer Hospitals, Institutions and against prescription of a Cancer Specialist only.

Caution: It is dangerous to take this preparation except under Medical Supervision.

4.5 Interaction with other medicinal products and other forms of interaction:

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

Due to the increase of thrombotic risk in cases of tumoral diseases, the use of anticoagulative treatment is frequent. The high intra-individual variability of the coagulabilty during diseases, and the possibility of interaction between oral anticoagulants and anticancer chemotherapy, may require an increase in frequency of INR monitoring if a patient is treated with oral anticoagulants.

Concomitant use contraindicated
Yellow fever vaccine: risk of generalized disease mortal.

Concomitant use not recommended
- Live attenuated vaccines (except yellow fever): Risk of systemic, possible fatal disease. This risk is increased in subjects who are already immunosuppressed by their underlying disease. Use an inactivated vaccine where this exist (poliomyelitis).
- Phenytoin, fosphenytoin: Risk of exacerbation of convulsions (resulting from the decrease of phenytoin digestive absorption by the cytotoxic drug), risk of toxicity enhancement or loss of efficacy of the cytotoxic drug (due to increased hepatic metabolism by phenytoin).

Concomitant use to take into consideration
- Ciclosporin (and by extrapolation tacrolimus and sirolimus): Excessive immunosuppression with risk of lymph proliferation.
- Concurrent therapy with nephrotoxic or ototoxic drugs such as aminoglycosides, vancomycin, capreomycin and diuretics, may increase or exacerbate toxicity, particularly in renal failure patients, due to carboplatin induced changes in renal clearance.
- Loop diuretics: The concomitant use of carboplatin with loop diuretic should be approached with caution due to the cumulative nephrotoxicity and ototoxicity.
Combination therapy with other myelosuppressive agents may require dose changes or rescheduling of doses in order to minimize the additive myelosuppressive effects.

4.6 Fertility, pregnancy and lactation:

Use in Pregnancy Category D
Carboplatin has been shown to be embryo-toxic and mutagenic, and its use in pregnant women is not recommended. Women of child-bearing potential should use adequate contraception and carboplatin should only be used in women of child-bearing potential if the expected benefits outweigh the risks of such therapy. If the patient becomes pregnant whilst receiving the drug she should be advised of the potential hazard to the foetus.

Use in Lactation
It is not clearly established whether carboplatin or its platinum-containing metabolites are distributed into human milk. However, because of the potential for serious adverse reactions in infants should the drug pass into the milk, nursing should be discontinued during therapy.

4.7 Effects on ability to drive and use machines:

The effect of carboplatin on the ability to drive or use machinery has not been systematically evaluated.

4.8 Undesirable effects:

Hematologic Toxicity: Bone marrow suppression is the dose-limiting toxicity of carboplatin. Thrombocytopenia with platelet counts below 50,000/mm3 (pretreated ovarian cancer patients); neutropenia with granulocyte counts below 1,000/mm3 occurs (pretreated ovarian cancer patients); leukopenia with WBC counts below 2,000/mm3 (pretreated ovarian cancer patients). The nadir usually occurs in patients receiving single agent therapy. 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 leukopenia and thrombocytopenia. Anemia with hemoglobin less than 11 g/dL has been observed in patients who started therapy with a baseline above that value. The incidence of anemia increases with increasing exposure to carboplatin. Bone marrow depression may be more severe when carboplatin is combined with other bone marrow suppressing drugs or with radiotherapy.

Gastrointestinal Toxicity: Vomiting, Carboplatin, as a single agent or in combination, is significantly less emetogenic than cisplatin; however, patients previously treated with emetogenic agents, especially cisplatin, appear to be more prone to vomiting. Both nausea and vomiting usually cease within 24 hours of treatment and are often responsive to antiemetic measures. Other gastrointestinal effects observed frequently were pain, diarrhea.

Neurologic Toxicity: Peripheral neuropathies have been observed in patients receiving carboplatin (pretreated ovarian cancer patients) with mild paresthesias occurring most frequently. Carboplatin therapy produces significantly fewer and less severe neurologic side effects than does therapy with cisplatin. Patients older than 65 years and/or previously treated with cisplatin appear to have an increased risk for peripheral neuropathies patients with pre-existing cisplatin-induced peripheral neurotoxicity there was no worsening of symptoms during therapy with carboplatin.

Nephrotoxicity

Development of abnormal renal function test results is uncommon, despite the fact that carboplatin, unlike cisplatin, has usually been administered without high-volume fluid hydration and/or forced diuresis. 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

In a limited series of patients receiving very high dosages of carboplatin and autologous bone marrow transplantation, severe abnormalities of liver function tests were reported.

Electrolyte Changes

Electrolyte supplementation was not routinely administered concomitantly with carboplatin, and these electrolyte abnormalities were rarely associated with symptoms.

Allergic Reactions

Hypersensitivity allergic reactions associated with carboplatin are similar in nature and severity to those reported with other platinum-containing compounds, i.e., rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Carboplatin is a second generation platinum compound that may be classified as a non-classical alkylating agent and is cell-cycle nonspecific. It is a cytotoxic platinum complex that reacts with nucleophilic sites of DNA. This causes inter-strand and intra-stand cross links and DNA protein cross links, which inhibit DNA, RNA and protein synthesis.

5.2 Pharmacokinetic properties:

Following administration of Carboplatin, the majority of the dose is rapidly cleared from the blood and largely excreted in urine within 6 hours. The remaining drug is eliminated in a biphasic manner, with mean half life of 2.5 hours and about 5 days. The rate of binding to plasma protein is significantly lower accounting for the greater proportion of 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 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 24hour 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 60 ml/min, the total body and renal clearances of carboplatin decrease as the creatinine clearance decreases and, therefore, reduced renal function increase the serum half life of carboplatin and results in increased myeiotoxicity. Carboplatin dosages should, therefore, be reduced in these patients since carboplatin is eliminated almost completely by glomerular filtration, there is little concentration of carboplatin at the renal tubular level which may account for its diminished nephrotoxic potential as compared to cisplatin.

5.3 Pre-clinical Safety Data:

No further relevant information other than that mentioned above.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of Excipients:

Water for Injections BP

6.2 Incompatibilities:

No further relevant information other than that mentioned above.

6.3 Shelf – life:

24 Months

6.4 Special precautions for storage:

Store below 25°C., protected from light and free from contact with metal.

6.5 Nature and contents of container:

20 ml amber colour USP-I vial, 20 mm GBBRS 20 mm F/O lacquered peach coloured plain alu. seal.

6.6 Special Precautions for Handling and Disposal:

The usual precautions for handling and preparing cytotoxic drugs should be observed when administering carboplatin: Personnel should be trained in good technique for handling. Pregnant staff should be excluded from working with carboplatin. Preparation should be performed in a designated area ideally in a vertical laminar flow hood, with the work surface covered with disposable plastic-backed absorbent paper. Care should be taken to prevent inhaling particles and exposing the skin to carboplatin.

Adequate protective clothing should be worn, such as PVC gloves, safety glasses, disposable gowns and masks. It is recommended that lock fittings are used in the assembly of syringes and giving sets to avoid leakage. In the event of contact with the eyes, wash with water or saline. If the skin comes into contact with the drug wash thoroughly with water and in both cases seek medical advice. Seek immediate medical attention if the drug is ingested or inhaled. All used material, needles, syringes, vials and other items which have come into contact with cytotoxic drugs should be

incinerated. Excreta should be similarly treated. Contaminated surfaces should be washed with copious amounts of water.
Solution with precipitate to be discarded.
Discard unused portion.

7. MARKETING AUTHORIZATION HOLDER:

M/s. NEON LABORATORIES LIMITED
140, Damji Shamji Industrial Complex,
28, Mahal Indl. Estate, Mahakali Caves Road,
Andheri (East), Mumbai - 400 093

8. MARKETING AUTHORIZATION NUMBER:

08340/08597/REN/2022

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORISATION:

Date of first authorization: 03-01-2023

10. DATE OF REVISION OF THE TEXT: JULY 2023

11. REFERENCE

- Carboplatin 10 mg/ml Intravenous Infusion - Summary of Product Characteristics (SmPC) print friendly - (emc) (medicines.org.uk)
- Carboplatin 10 mg/ml Intravenous Infusion - https://dailymed.nlm.nih.gov/dailymed/