SUMMARY OF PRODUCT CHARACTERISTICS WOMASTIN
CARBOPLATIN INJECTION BP 450 mg / 45 mL
CARBOPLATIN INJECTION BP 150 mg / 15 mL

1. Name of the Finished Pharmaceutical Product

Carboplatin Injection BP 10mg/ml

2. Qualitative and Quantitative Composition Each ml contains:

Carboplatin BP 10 mg

Detailed list of excipient is enclosed in section 6.1

3. Pharmaceutical Form Liquid Injection

4. Clinical Particulars

4.1 Indications

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

4.2 Posology and method of administration

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 to be used for the preparation or administration of WOMASTIN.

Single Agent Therapy:

WOMASTIN 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. In general, however single intermittent courses of WOMASTIN 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: WOMASTIN 300 mg/m2 I.V. on day 1 every 4 weeks for six cycles. (Alternatively see formula dosing)

Cyclophosphamide - 600mg/m2 I.V. on day 1 every 4 weeks for 6 cycles. Intermittent courses of WOMASTIN 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 adjustment 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	75%

*Percentages apply to carboplatin as a single agent or 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.

WOMASTIN 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 WOMASTIN therapy, the incidence of sever leucopenia, 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/m²
16–40 mL/min	200 mg/m²

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

Note: with the Calvert formulae, the total dose of carboplatin is calculated in mg, not mg/m2

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 administration:

Carboplatin Injection is a premixed aqueous solution of 10 mg/mL carboplatin. It can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose injection or 0.9% Sodium Chloride Injection.

Method of administration

Carboplatin injection should be used by the intravenous route only.

4.3 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.

4.4 Warning &Precautions Bone marrow suppression:

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

Since anemia is cumulative, transfusions may be needed during treatment with carboplatin 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 carboplatin dosages in these patients should be appropriately reduced and blood counts should be carefully monitored between courses. The use of Carboplatin in combination with other bone marrow suppressing therapies must be carefully managed with respect to dosage and timing in order to minimize additive effects.

Toxicity:

Carboplatin has limited nephrotoxic potential, but concomitant treatment with aminoglycosides has resulted in increased renaI and/or audiologic toxicity, and caution mustbe exercised when a patient receives both drugs. Clinically significant hearing loss has been reported to occur in pediatric patients when carboplatin was administered at higher than recommended doses in combination with other ototoxic agents.

Emesis:

Carboplatin 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 pre-medication with antiemetics, Although no conclusive efficacy data exist with the following schedules of carboplatin, 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.

Peripheral neurotoxicity:

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 carboplatin as secondary treatment.

Ophthalmic:

Loss of vision, which can be complete for light and colors, has been reported after the use of carboplatin 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.

Allergic reactions:

As in the case of other platinum-coordination compounds, allergic reactions to carboplatin have been reported. These may occur within minutes of administration and should be managed with appropriate supportive therapy. There is increased risk of allergic reactions including anaphylaxis in patients previously exposed to platinum therapy.

4.5 Interaction with other medicinal products and other forms of interactions The renal effects of nephrotoxic compounds may be potentiated by Carboplatin.

4.6 Pregnancy and lactation Pregnancy

Pregnancy Category D

Carboplatin Injection may cause fetal harm when administered to a pregnant woman. There is 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 fetus. Women of childbearing 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 treated with carboplatin injection.

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established.

4.7 Effects on ability to drive and use machine Not known.

4.8 Adverse effects Hematologic 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 1000/mm3 occurs in 16% of the patients; leucopenia with WBC counts below 2000/mm3 occurs in 15% of the patients. The nadir usually occurs about day 21 in patients receiving single agent therapy. By day 26, 90% of patients have platelet counts above 100,000/mm3, 74% have neutrophil counts above 2000/mm3; 67% have leukocyte counts above 4000/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. Anemia with hemoglobin 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 65% of the patients and in about one-third of these patients it is severe. Nausea alone occurs in an additional 10% to 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 compounds. Other gastrointestinal effects observed frequently were pain, in 17%of the patients; diarrhea in 6%; and constipation in 6%.

Neurologic Toxicity:

Peripheral neuropathies have been observed in 4% of the patients receiving carboplatin with mild paresthesias occurring most frequently. Patients older than 65 years appear to 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 inpatients receiving carboplatin, and it appears to be the most useful test for correlating drug clearance and bone marrow suppression.

Hepatic Toxicity:

The incidences of abnormal liver function tests in patients with normal baseline values were reported as follows: total bilirubin, 5%; SGOT, 15%; and alkaline phosphatase, 24%. These abnormalities have generally been mild and reversible in about one-half of the cases. 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:

Abnormally decreased serum electrolyte values may be found in some patients. Electrolyte supplementation was not routinely administered concomitantly with carboplatin, and these electrolyte abnormalities were rarely associated with symptoms.

Allergic Reactions:

Hypersensitivity to carboplatin develops only in a small number of patients. These allergic reactions have been similar in nature and severity to those reported with other platinum-containing compounds, i.e. rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. These reactions are successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy.

Other events:

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

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

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

Pharmacotherapeutic group: Cytostatic - anti-neoplastic and immuno-suppresive agent, platinum compounds,

ATC Code: L01XA 02

Clinical Pharmacology:

Carboplatin is an antineoplastic agent. Its activity has been demonstrated against several murine and human cell lines.

Carboplatin exhibited comparable activity to cisplatin against a wide range of tumours regardless of implant site.

Alkaline elution techniques and DNA binding studies have demonstrated qualitatively similar modes of action of carboplatin and cisplatin. Carboplatin, like cisplatin, induces changes in the superhelical conformation of DNA which is consistent with a "DNA shortening effect."

5.2 Pharmacokinetic Properties

Carboplatin has biochemical properties similar to that of cisplatin, thus producing predominantly interstrand and intrastrand DNA crosslinks. Following administration of carboplatin in man, linear relationships exist between dose and plasma concentrations of total and free ultra filterable platinum. The area under the plasma concentration versus time curve for total platinum also shows a linear relationship with the dose when creatinine clearance 60ml/min.

Repeated dosing during four consecutive days did not produce an accumulation of platinum in plasma. Following the administration of carboplatin reported values for the terminal elimination of half-lives of free ultra filterable platinum and carboplatin in man are approximately 6 hours and 1.5 hours respectively. During the initial phase, most of the free ultra filterable platinum is present as carboplatin. The terminal half-life for total plasma platinum is 24 hours. Approximately 87% of plasma platinum is protein bound within 24 hours following administration. Carboplatin is excreted primarily in the urine, with recovery of approximately 70% of the administered platinum within 24 hours. Most of the drug is excreted in the first 6 hours. Total body and renal clearances of free ultra filterable platinum correlate with the rate of glomerular filtration but not tubular secretion.

5.3 Preclinical safety data ---

6. Pharmaceutical Particulars

6.1 List of Excipients Water for Injections

6.2 Incompatibilities None

6.3 Shelf life

The shelf life of the medicinal product as package for sale 24 months

The shelf life after dilution or reconstitution according to direction

The shelf life after first opening the container.

6.4 Special precautions for storage

Store below 300C. Protect from light. Do not freeze.

6.5 Nature and contents of container Womastin 150mg/15ml

20 ml amber moulded glass vial Type I closed with 20 mm Grey bromobutyl rubber (RFS) stopper, sealed with red aluminium flip off seal and packed in a printed carton

along with pack insert.

Womastin 450mg/45ml

50 ml amber moulded glass vial Type I closed with 20 mm Grey bromobutyl rubber (RFS) stopper, sealed with red aluminium flip off seal and packed in a printed carton along with pack insert.

Pack containing 1 vial.

6.6 Special precautions for disposal and other handling

No special requirement.

7. Marketing Authorization Holder and Manufacturing site address Khandelwal Laboratories Pvt. Ltd.

B-1, Wagle Industrial Estate, Thane - 400 604, India

Telephone: 00 91 22 25821793 / 0794 Fax: 00 91 22 25823837

8. Marketing Authorization Numbers

KD-349

9. Date of first authorization / renewal of the authorization Date of first authorization: 14.03.2006

Date of latest renewal: 13.12.2021

10. Date of revision of the text

17.06.2026