SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Womastin (Carboplatin Injection BP 450mg/45ml)

2. Pharmaceutical Form

Pharmaceutical Dosage form of the product: Liquid Injection

Strength: 1mg/ml

Route(s) of administration: Intravenous route of administration

3. Qualitative and Quantitative Composition

Womastin
(Carboplatin Injection BP 450mg/45ml)

Composition
Label claim:
Each ml contains:
Carboplatin BP..... 10 mg
Water for Injection BP .....qs

Composition:

Sr. No.	Ingredients	Qty in mg/ml	Function
1.	Carboplatin BP (with 2.5% overages)	10.25 mg	Antineoplastic
2.	Water for Injection BP	1.0 ml	Solvent

4. Clinical Particulars

4.1 Therapeutic indications

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

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/m^2 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/m^2 I.V. on day 1 every 4 weeks for six cycles. (Alternatively see formula dosing)
Cyclophosphamide - 600mg/m^2 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/m^2
16-40ml/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 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 ^{51}Cr-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/m^2

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 INTRAVENOUS INFUSION

Carbplatin 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 in Water or 0.9% Sodium Chloride Injection. Since no antibacterial preservative is contained in the formulation, it is recommended that diluted Carboplatin solutions be discarded 8 hours after dilution.

4.3 Method of administration

Intravenous Route of Administration

4.4 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.

4.5 Special warning & precautions for use

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.

Carboplatin has limited nephrotoxic potential, but concomitant treatment with aminoglycosides has resulted in increased renaI 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 carboplatin was administered at higher than recommended doses in combination with other ototoxic agents. Carboplatin can induce emesis; 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.
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.
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.
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.
Pregnancy: Pregnancy Category D - Carboplatin Injection 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 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

4.6 Interaction with other medicinal prodcuts and other forms of interactions

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

4.7 Pregnancy and lactation

Pregnancy: Pregnancy Category D - Carboplatin Injection 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 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

4.8 Effects on ability to drive and use machine

Not known.

4.9 Undesirable effects

Hematologic 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 1000/mm^3 occurs in 16% of the patients; leucopenia with WBC counts below 2000/mm^3 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/mm^3, 74% have neutrophil counts above 2000/mm^3; 67% have leukocyte counts above 4000/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 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 in patients 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 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 have occurred only in small number of patients.

4.10 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

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 the 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 ultrafilterable 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 ultrafilterable platinum and carboplatin in man are approximately 6 hours and 1.5 hours respectively. During the initial phase, most of the free ultrafilterable 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 ultrafilterable platinum correlate with the rate of glomerular filtration but not tubular secretion.

5.3 Preclinical safety data

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6. Pharmaceutical Particulars

6.1 List of Excipients
Water for injection BP

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 directions
Not Applicable.

The shelf life after first opening the container
Not Applicable

6.4 Special precaution for storage

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

6.5 Nature and contents of container
UNIT PACK: 50 ml amber coloured moulded Glass Type I vial sealed with 20 mm slotted GBBR stopper and sealed with red aluminium flip off seal packed in a printed carton along with pack insert.

7. Marketing Authorization Holder and Manufacturing site address

Name of Marketing Authorization Holder:
Khandelwal Laboratories Pvt. Ltd.

Address of manufacturing site:
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

14.03.2006

10. Date of revision of the text
