CARBOPLATINO KEMEX
CARBOPLATIN 50, 150 and 450 mg
LYOPHILIZED POWDER FOR INJECTION – FOR INTRAVENOUS USE

ARGENTINE INDUSTRY PRESCRIPTION ONLY

Each vial contains
CARBOPLATINO KEMEX 50 mg
Carboplatin..... 50.00 mg
Mannitol..... 50.00 mg

CARBOPLATINO KEMEX 150 mg
Carboplatin..... 150.00 mg
Mannitol..... 150.00 mg

CARBOPLATINO KEMEX 450 mg
Carboplatin..... 450.00 mg
Mannitol..... 450.00 mg

THERAPEUTIC ACTION
Cytostatic.

THERAPEUTIC INDICATIONS
Initial treatment of ovarian carcinoma:
CARBOPLATIN is indicated for the palliative treatment of ovarian refractory carcinoma for standard chemotherapy that does not include cisplatin.
Initial treatment of advanced ovarian carcinoma:
CARBOPLATIN is indicated for the initial treatment of advanced carcinoma, in combination with other approved therapeutic chemical agents. As an alrady established combined regimen, there is the combination of CARBOPLATIN and cyclophosphamide.
Two randomized studies conducted in the USA with Carboplatin versus Cisplatin, both in combination with Cyclophosphamide, demonstrated overall increased survival in both groups.
There is a limited compilation of statistical data to demonstrate overall pathological equivalence which includes prolonged and complete survival response (3 years), due to the small number of patients who achieved these results. Even considering a tumor smaller than 2 cm after initial surgery, the possibility to obtain statistical data able to demonstrate equivalence in this subgroup is limited .
Secondary treatment of advanced ovarian carcinoma:
CARBOPLATIN is indicated for palliative treatment of patients with recurrent ovarian carcinoma, after a prior chemotherapy, including patients who have been treated with Cisplatin before. In this group previously treated with Cisplatin, who have developed progression of the disease while receiving Cisplatin, could significate that they may have a reduced response to the treatment.

CLINICAL PHARMACOLOGY
Carboplatin, as cisplatin, interferes with DNA intra-stand and extra-strand crosslinks in cells exposed to the drug, causing biological effects and equivalent lesions. In patients with creatinine clearance greater than 60 ml/min, plasma levels of carboplatin decline biphasically after a 30-minute intravenous infusion of 300 to 500 mg/ml of Carboplatin. It was found that the initial plasma half-life (alpha) is 1.1 to 2.0 hours (N=6), and the post-distribution plasma half-life (beta) was found to be 2.6 to 5.9 hours (N=6). The total body clearance, apparent volume of distribution and average permanence time for carboplatin are 4.4 l/hour, 16 l, and 3.5 hours, respectively. Cmax values and areas under the plasma concentration vs time from 0 to infinite (AUC inf) curve increase linearly with dosage, although the increase was slightly greater rather than proportional to dose. Therefore, Carboplatin exhibits linear pharmacokinetics in the dosification range studied (300-500 mg/m²).
Carboplatin is not protein-bound in plasma. There are no significant amounts of species containing ultra-filterable-protein-free platinum in plasma. However, carboplatin platinum becomes irreversibly protien-bound in plasma and is slowly eliminated with a minimum half-life of 5 days.
The major route of carboplatin elimination is renal excretion. Patients with creatinine clearance greater than 60 ml/min excrete 65% of the dose by urine within 12 hours and 71% of the dose within 24 hours. All platinum in a 24-hour urine cycle is present as carboplatin. Only 3% to 5% of the administered platinum is excreted by urine between 24 and 96 hours. There is insufficient data to determine if biliary excretion occurs.
In patients with creatinine clearance below 60 ml/min, total body and renal clearances of carboplatin decrease as creatinine clearance decreases. Therefore, Carboplatin posology should be adjusted in these patients.

POSOLOGY AND METHOD OF ADMINISTRATION
NOTE: Aluminum reacts with carboplatin causing a precipitate and loss of drug potency, therefore, needles or intravenous equipment containing aluminum parts that may have contact with the drug should not be used for the administration or preparation of Carboplatin for Injection.

Simple agent therapy:
Usual posology for adults
Ovarian carcinoma
Advanced initial treatment: Intravenous administration of 300 mg of carboplatin/m² of body surface, once every 4 weeks (day 1), for 6 cycles, in combination with intravenous administration of 600 mg of cyclophosphamide/m2 of body surface intravenously once every 4 weeks (day 1) for 6 cycles(Refractory to other IV chemotherapy; dosage of 360 mg/m² at day 1 every 4 weeks). However, simple 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.
Recommendations for dosage adjustment: Pretreatment platelet count and Performance condition are important prognostic factors of myelosuppression severity in previously treated patients. The suggested dose adjustments for single agent or combination therapy shown in the table below are modified by controlled trials in previously treated and untreated patients with ovarian carcinoma. Blood counts were done weekly, and recommendations are based on the lowest level of neutrophils or post-treatment platelet.

Adjusted dosage*		
Platelets count	**Neutrophil count**	**(From pre-treatment)**
> 100,000	> 2,000	125%
50-100,000	500-2,000	No adjustment
< 50,000	< 500	75%

* Percentages referring to Carboplatin as a simple agent or to both Carboplatin and cyclophosphamide in combination. In controlled studies, dosages were also adjusted to a lower level (50 to 60%) due to myelosuppression. Readjustments above 125% were not recommended for these studies.

Carboplatin lyophilized powder for injection is usually administered by a 15 minutes (o r longer)infusion . No forced diuresis or pre or post-treatment hydration is required.

Patients with impaired kidney function: Patients with creatinine clearance values below 60 ml/min have an increased risk of severe bone marrow suppression. In renally impaired patients receiving single agent therapy with Carboplatin, the incidence of severe leukopenia, neutropenia, or thrombocytopenia has been up to 25% when modifications of the dosage has been performed, described in the table below:

Creatinine Clearance baseline	Recommended dosage at 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 enable a treatment recommendation. These dosage recommendations are reflected in the initial treatment development. Subsequent dosages should be adjusted according to the patient's tolerance based on the level of bone marrow suppression.
Dosage Formula: Another approach to establish the initial dose of Carboplatin Lyophilized powder for Injection is the use of formulas based on the patient's pre-existing renal function or desired renal function and lowest platelet count. Renal excretion is the major route of elimination of Carboplatin. The use of dosage formulas, compared to empirical dose calculation based on body surface area, allows compensation for patient variations in pretreatment renal function that may otherwise result in underdose (in patients with above-average renal function) or overdose (in patients with impaired renal function).

CALVERT FORMULA FOR CARBOPLATIN LYOPHILIZED POWDER FOR INJECTION
Total Dose (mg) = (AUC target) x (GFR + 25)

Note: With the Calvert formula, the total dose of Carboplatin Lyophilized powder for Injection is calculated in mg, not mg/m².

% of Current Toxicity in Previously Treated Patients		
AUC	Gr3oGr4	Gr3oGr4
(mg/ml.min)	Trombocytopenia	Leucopenia
4 to 5	16%	13%
6 to 7	33%	34%

PREPARATION OF INTRAVENOUS SOLUTIONS
Initially before use, the content of each vial should be reconstituted with sterile water for injection, USP, or dextrose 5% in water (D5A), 0.9% sodium chloride for injection, USP, for the lyophilized powder according to the following program:

Vial	Volume of diluent
50mg	5 ml
150mg	15 ml
450mg	45 ml

All the resultant solutions of Carboplatin has a concentration of 10 mg/ml. Carboplatin powder for injection can also be diluted to concentrations of 0.5 mg/ml with 5% dextrose in water (D5A) or 0.9% sodium chloride for USP injection.

CONTRAINDICATIONS
CARBOPLATIN is contraindicated in patients with a history of severe allergic reactions to cisplatin or other compounds containing platinum or mannitol. Carboplatin Lyophilized powder for Injection should not be used in patients with severe bone marrow depression or significant bleeding.
Comparative toxicity
The toxicity pattern showed by the regimen containing Carboplatin lyophilized powder for Injection was significantly different from the combined cisplatin regimens. The differences between the two studies can be explained by different dosifications of cisplatin and by different supportive care.
The regimen containing Carboplatin lyophilized powder for Injection induced significantly more thrombocytopenia and, in one study, significantly more leukopenia and an increased need for blood transfusion. The regimen containing cisplatin produced significantly more anemia in one study. However, there were no significant differences in the incidences of infections and bleeding episodes.
Non-hematological toxicities (emesis, neurotoxicity, ototoxicity, renal toxicity, hypomagnesemia, and alopecia) were significantly more frequent in the cisplatin-containing branches.

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER NCIC STUDY

	Carboplatin Branch %*	Cisplatin branch %*	P Value**
Bone Narrow			
Thrombocytopenia, <100000/mm³	70	29	<0.001
<50000/mm³	41	6	0.001
Neutropenia <2000 cells/mm³	97	96	n.s.
<1000 cells/mm³	81	79	n.s
Leukopenia, <4000 cells/mm³	98	97	n.s
<2000 cells//mm³	68	52	0.001
Anemia, < 11g/dl	91	91	n.s
<8g/dl	18	12	n.s
Infections	14	12	n.s
Hemorrhage	10	4	n.s
Blood transfusion	42	31	0.018
Gastrointestinal			
Nausea or vomits	93	98	0.010
Vomits	84	97	<0.001
Other gastrointestinal side effects	50	62	0.013
Neurological			
Peripheral neuropathy	16	42	<0.001
Ototoxicity	13	33	<0.001
Other sensorial side effects	6	10	As.
Central neurotoxicity	28	40	0.009
Renal			
Plasma creatinine value increased	5	13	0.006
Plasma ureal value increased	17	31	<0.001
Hepatic			
Bilirubin value increased	5	3	n.s.
SGOT value increased	17	13	n.s.
Alkaline phosphatase value increased	-	-	-
Electrolyte values decreased			
Sodium	10	20	0.005
Potassium	16	22	n.s.
Calcium	16	19	n.s.
Magnesium	63	88	<0.001
Other side effects			
Pain	36	37	n.s.
Asthenia	40	33	n.s.
Cardiovascular	15	19	n.s.
Respiratory	8	9	n.s.
Allergic	12	9	n.s.
Genitourinary	10	10	n.s.
Alopecia+	50	62	0.017
Mucus	10	9	n.s.

* The values are in percentage of evaluable patients.
** n.s. = no significant, p > 0.05
+May have been affected by dosing of cyclophosphamide delivered.

Use as a simple agent for the secondary treatment of advanced ovarian cancer.

WARNINGS
Carboplatin lyophilized powder for injection should be administered under the supervision of a qualified physician experienced in the use of chemotherapeutic agents for cancer. Appropriate management of therapy and complications are possible only when appropriate treatment facilities are readily available.
Bone marrow suppression is dose-relative and can be severe, resulting in infection and/or bleeding. Anemia may be cumulative and may require blood transfusion support. Vomiting is another dose-related adverse side effect.
Anaphylactic-like reactions to Carboplatin have been reported and may occur within minutes of Carboplatin administration. Epinephrine, corticosteroids, and antihistamines have been used to relieve symptoms.

PRECAUTIONS
Bone marrow suppression (leukopenia, neutropenia and thrombocytopenia) is dose-dependent and is also dose-limiting toxicity. Peripheral blood counts should be monitored frequently during treatment with Carboplatin lyophilized powder for Injection and when appropriate, until full recovery. Mean nadir occurs during day 21 in patients receiving simple agent Carboplatin lyophilized powder for Injection. In general, simple intermittent courses of Carboplatin lyophilized

powder for Injection should not be repeated until leukocyte, platelet and neutrophil counts have been recovered.
Since anemia is cumulative, blood transfusion may be necessary during treatment with Carboplatin lyophilized powder for Injection, particularly in patients receiving prolonged therapy.
Bone marrow suppression increases in patients who have received previous therapy, especially regimens including cisplatin therapy. Bone marrow suppression is also increased in patients with impaired renal function. Initial dosages of Carboplatin lyophilized powder for Injection in these patients should be appropriately adjusted and blood cell count should be carefully monitored between courses. The use of Carboplatin lyophilized powder for Injection in combination with other bone marrow suppressor therapies should be carefully managed with respect to dosing, and regulated to minimize additive effects. Carboplatin lyophilized powder for Injection has potential limited nephrotoxicity, but concomitant treatment with aminoglycosides resulted in audiological and/or renal increased toxicity and should be carefully managed when a patient receives both drugs.
Carboplatin powder for injection may induce emesis, which may be more severe in patients previously receiving emetogenic therapy. The incidence and intensity of emesis has been reduced with the use of antiemetics. There are no conclusive efficacy data regarding the programs of Carboplatin lyophilized powder for Injection, the duration of simple intravenous administration can be extended to 24 hours.
Although peripheral neurotoxicity is uncommon, the incidence is increased in patients over 65 years old and in patients previously treated with cisplatin. Pre-existing cisplatin-induced neurotoxicity did not produce worsening in about 70% of patients receiving Carboplatin lyophilized powder for Injection as secondary treatment.
Loss of vision, which may be complete for light colors, has been reported after the use of Carboplatin lyophilized powder for Injection for grater doses than recommended in leaflet. Vision appears to recover fully or within a significant range within weeks from interruption of higher doses.
As in the case of other platinum coordination compounds, allergic reactions to Carboplatin have been reported. These can occur within minutes of administration and should be managed with appropriate supportive therapy.
High dosages of Carboplatin (more than four times the recommended dose) had resulted in severe abnormalities on liver function tests.
Carboplatin can cause fetal damage when it is administrated to pregnant women. It has been demonstrated that Carboplatin is 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 informed about the potential risk to the fetus.

General Precautions: Intravenous needles or equipment containing aluminum parts that may come into contact with Carboplatin should not be used for the administration or preparation of the drug. Aluminum can react with carboplatin causing precipitated formation and loss ondrug potency.
Drug Interactions: The renal effects of nephrotoxic compounds can be potentiated by Carboplatin.
Carcinogenesis, mutagenesis, impaired fertility: The carcinogenic potential of carboplatin has not been studied, but compounds with mutagenicity profiles and similar mechanisms of action have been reported to be carcinogenic. It has been demonstrated that Carboplatin is mutagenic both in vitro and in vivo. It has also been demonstrated to be embryotoxic and teratogenic in rats receiving the drug during organogenesis.
Pregnancy: Pregnancy Category "D"(see WARNINGS).
Breastfeeding mothers: It is unknown whether carboplatin is excreted in breast milk. As there is a possibility of toxicity in infants secondary to mother's treatment with Carboplatin, it is recommended breast feeding to be stopped if the mother is treated with Carboplatin.

ADVERSE REACTIONS
For a comparison of toxicities when carboplatin or cisplatin were given in combination with cyclophosphamide.

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER

	First line Therapy combination %*	Second line therapy simple agent %**
Bone Narrow		
Thrombocytopenia, <100000/mm3	66	62
<50000/mm3	33	35
Neutropenia <2000 cells/mm3	96	67
<1000 cells/mm3	82	21
Leukopenia, <4000 cells/mm3	97	85
<2000 cells//mm3	71	26
Anemia, < 11g/dl	90	90
<8g/dl	14	21
Infections	16	5
Hemorrhage	8	5
Blood transfusion	35	44
Gastrointestinal		
Nausea or vomits	93	92
Vomits	83	81
Other gastrointestinal side effects	46	21
Neurological		
Peripheral neuropathy	15	6
Ototoxicity	12	1
Other sensorial side effects	5	1
Central neurotoxicity	26	5
Renal		
Plasma creatinine value increased	6	10
Plasma ureal value increased	17	22
Hepatic		
Bilirubin value increased	5	5
SGOT value increased	20	19
Alkaline phosphatase value increased	29	37

* Use with cyclophosphamide for initial treatment of ovarian cancer: Data are based on the experience of 393 ovarian cancer patients (regardless of baseline status) who received initial combination therapy with Carboplatin and cyclophosphamide in two randomized controlled studies conducted by SWOG and NCIC. The combination with cyclophosphamide as well as the duration of treatment may be responsible for the differences that can be noted in the table of adverse experiences.
** Use of simple agent for the secondary treatment of ovarian cancer Hematological toxicity: Bone marrow suppression is the dose-limiting toxicity of Carboplatin. Thrombocytopenia with platelet counts below 50,000/mm³ occurs in 25% of patients (35% of pretreated ovarian cancer patients); neutropenia with granulocyte counts below 1,000/mm3 occurs in 16% of patients (21% of pretreated ovarian cancer patients); leukopenia with WBC counts below 2,000/mm³ occurs in 15% of patients (26% of patients pretreated for ovarian cancer). Nadir usually occurs around day 21 in patients receiving single-agent therapy. At day 28, 90% of patients have platelet counts above 100,000/mm³; 74% have neutrophil counts above 2,000/mm³; 67% have leukocyte counts above 4,000/mm³.

Bone marrow suppression is usually more severe in patients with impaired kidney function.
Hematological effects, are usually reversible, also have resulted in infectious or haemorrhagic complications in 5% of patients treated with Carboplatin, and drug-related death occurring in less than 1% of patients. Fever has also been reported in patients with neutropenia. Anemia with haemoglobin less than 11 g/dl has been observed in 71% of patients who started therapy with a baseline above this 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 suppressor drugs or with radiation therapy.
Gastrointestinal toxicity: Vomiting occurs in 65% of patients (81% of patients previously treated for ovarian cancer) and about a-third of these patients are severe. 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. Nausea alone occurs in an additional 10-15% of patients. Both nausea and vomiting usually cease within 24 hours of treatment and are often sensitive to antiemetic measures. While there are no conclusive data on the efficacy of the programmes, prolonged administration of Carboplatin, either by continuous infusion of 24 hours or in a daily dose administered for 5 consecutive days, were associated with less severe vomiting than the intermittent single-dose schedule. Emesis increased when Carboplatin was used in combination with other emetogenic compounds. Other frequently observed gastrointestinal effects were pain, in 17% of patients; diarrhea, in 6%; and constipation, also at 6%.
Neurological toxicity: Peripheral neuropathies have been observed in 4% of patients receiving Carboplatin (6% of patients pretreated for ovarian cancer) with mild paresthesias occurring more frequently. Carboplatin therapy produces significantly fever and less severe neurological side effects than cisplatin therapy. However, patients older than 65 years old and/or previously treated with cisplatin appear to have an increased risk (10%) of peripheral neuropathies. In 70% of patients with pre-existing cisplatin-induced peripheral neurotoxicity, there was no worsening of symptoms during Carboplatin therapy.
Clinical ototoxicity and other sensory abnormalities such as visual disturbances and change in taste have been reported in only 1% of patients. Symptoms about the central nervous system have been reported in 5% of patients and appear to be often related to the use of antiemetics. While the total incidence of peripheral neurological side effects induced by Carboplatin is low, prolonged treatment, particularly in patients pretreated with cisplatin, may result in cumulative neurotoxicity.
Nephrotoxicity: The development of abnormal kidney function test results is uncommon, even though carboplatin, unlike cisplatin, has usually been administered without high volume fluid hydration and/or forced diuresis. The reported incidences of abnormal renal function tests are 6% for serum creatinine and 14% for blood [urea nitrogen] (10% and 22%, respectively, for pretreated ovarian cancer patients). Most of these abnormalities reported have been mild and half of them were reversible.
It has been demonstrated that Creatinine clearance is the most sensitive measure of kidney function in patients receiving Carboplatin, and appears to be the most useful test for correlating drug clearance and bone marrow suppression. Twenty-seven percent of patients who had a baseline value equal or greater than 60 mL/min demonstrated a reduction in this value during Carboplatin therapy.
Liver toxicity: 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%; 5%, 19%, and 37%, respectively, in pretreated ovarian cancer patients. These abnormalities have generally been mild and reversible in about half of cases, although the role of metastatic tumor in the liver may complicate assessment in many patients. In limited series of patients receivingvery high doses of Carboplatin and autologous bone marrow transfusion, severe liver function test abnormalities were reported.
Electrolyte changes: The incidences of abnormally decreased serum electrolyte values were reported as follows: sodium 29%; potassium 20%; calcium 22% and magnesium 29%; 47%, 28%, 31%, and 43%, respectively, in pretreated ovarian cancer patients. Electrolyte supplementation was not routinely administered concomitantly with Carboplatin, and these electrolyte abnormalities were rarely associated with symptoms.
Allergic reactions: Hypersensitivity to Carboplatin has been reported in 2% of patients. These allergic reactions have been similar in nature and severity to those reported with other platinum-containing compounds, e.g., rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. These reactions have been successfully managed with epinephrine, corticosteroids and antihistamine therapy.
Other events: Pain and asthenia were the most frequently reported miscellaneous adverse effects, their relationship to tumor and anemia was likely. Alopecia was reported (3%).
Cardiovascular, respiratory, genitourinary and mucosal adverse effects have occurred in 6% or fewer of patients.
Cardiovascular events (heart failure, embolism, stroke) were fatal in less than 1% of patients and do not appear to be related to chemotherapy. Cancer-associated hemolytic uremic syndrome has been reported rarely.

OVERDOSE
There is no known antidote for overdosage with Carboplatin. Anticipated complications ofoverdosing would be secondary to bone marrow suppression and/or liver toxicity. In the event of an overdose, go to the nearest hospital or contact the Poison Control Centers.
In Argentina:

Dial 011 if you reside in the interior of the country
(011)-4962-2247 from (011)-4962-6666
Ricardo Gutierrez Children's Hospital
Sánchez de Bustamante 1399 Capital Federal
Specialized Healthcare for adults:
(011)-4801-5555 Fernandez Hospital
Cervino 3356 Federal Capital
Hospital Posadas:(011)-4654-6648/4658-7777

PRESENTATIONS
CARBOPLATINO KEMEX Lyophilized Powder for Injection 50 mg: containers with 1 vial ampoule and 25, 50 and 100 containers for hospital use only.
CARBOPLATINO KEMEX Lyophilized Powder for Injection 150 mg: containers with 1 vial and 25, 50 and 100 containers for hospital use only.
CARBOPLATINO KEMEX Lyophilized Powder for Injection 450 mg: containers with vial and 25, 50 and 100 containers for hospital use only.

CONSERVATION
CARBOPLATINO KEMEX Lyophilized Powder for Injection: Keep non-opened ampoule bottles at controlled room temperature 15°-30°C. Protect unopened blisters from light. Infusion solutions should be discarded 8 hours after preparation.

STABILITY
The unopened ampoules of Carboplatin Lyophilized Powder for Injection are stable during the shelf-life indicated on the package when stored at a controlled room temperature of 15°-30°C, protected from light.
When prepared as directed, Carboplatin Solutions for Injection are stable for 8 hours at room temperature (25°C).

This medicine must be used exclusively under prescription and medical supervision and cannot be repeated without a new prescription.

KEEP THIS PRODUCT OUT OF REACH OF CHILDREN
MEDICINAL SPECIALTY AUTHORIZED BY THE MINISTRY OF HEALTH (ARGENTINA)
CERTIFICATE No. 55,613

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kemex laboratorio