For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Carboplatin Injection

COMPOSITION:

Zucarb (15ml, 45ml)

Carboplatin Injection BP

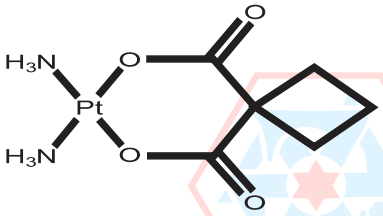
Each ml contains:

Carboplatin BP 10mg

DESCRIPTION

Carboplatin Injection is supplied as a sterile, aqueous solution available in 50mg/5ml, 150mg/15ml, 450mg/45ml or 600mg/60ml multi-dose vials containing 10mg/ml of carboplatin for administration by intravenous infusion. Each ml contains 10mg carboplatin and Water for Injection, USP.

Carboplatin is a platinum coordination compound that is used as a cancer chemotherapeutic agent. The chemical name for carboplatin is platinum, diammine [1, 1-cyclobutane-dicarboxylato (2-)-0, 0']-, (SP-4-2), and has the following structural formula:



Carboplatin is a crystalline powder with the molecular formula of C6H12N2O4Pt and a molecular weight of 371.25. it is soluble in water at a rate of approximately 14mg/ml, and the pH of a 1% solution is 5-7. It is virtually insoluble in ethanol, acetone, and dimethylacetamide.

MECHANISM OF ACTION / CLINICAL PHARMACOLOGY

Carboplatin, like cisplatin, produces predominantly interstrand DNA cross-links rather than DNA-protein cross-links. This effect is apparently cell-cycle nonspecific. The aquation of carboplatin, which is thought to produce the active species, occurs at a slower rate than in the case of cisplatin. Despite this difference, it appears that both carboplatin and cisplatin induce equal numbers of drug-DNA cross-links, causing equivalent lesions and biological effects. The differences in potencies for carboplatin and cisplatin appear to be directly related to the difference in aquation rates.

In patients with creatinine clearances of about 60ml/min or greater, plasma levels of intact carboplatin decay in a biphasic manner after a 30-minute intravenous infusion of 300 to 500 mg/m2 of Carboplatin Injection. The initial plasma half-life (alpha) was found to be 1.1 to 2 hours (N=6), and the postdistribution 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 mean residence time for carboplatin are 4.4 L/hour, 16L and 3.5 hours, respectively. The Cmax values and areas under the plasma concentration vs time curves from 0 to infinity (AUC inf) increase linearly with dose, although the increase was slightly more than dose proportional. Carboplatin, therefore, exhibits linear pharmacokinetics over the dosing range studied (300-500 mg/m2).

Carboplatin is not 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 60ml/min or greater excrete 65% of the dose in the urine within 12 hours and 71% of the dose administered platinum is excreted in the urine between 24 and 96 hours. There are insufficient data to determine whether biliary excretion occurs.

In patients with creatinine clearances below 60ml/min the total body and renal clearances of carboplatin decrease as the creatinine clearance decreases. Carboplatin Injection dosages should therefore be reduced in these patients (see DOSAGE AND ADMINISTRATION).

The primary determinant of Carboplatin Injection clearance is glomerular filtration rate (GFR) and this parameter of renal function is often decreased in elderly patients. Dosing formulas incorporating estimates of GFR (see DOSAGE AND ADMINISTRATION) to provide predictable Carboplatin Injection plasma AUCs should be used in elderly patients to minimize the risk of toxicity.

PHARMACOKINETICS / CLINICAL STUDIES

Use with Cyclophosphamide for Initial Treatment of Ovarian Cancer:

In two prospectively randomized, controlled studies conducted by the National Cancer Institute of Canada, Clinical Trials Group (NCIC) and the Southwest Oncology Group (SWOG), 789 chemotherapy naïve patients with advance ovarian cancer were treated with Carboplatin Injection or cisplatin, both in combination with cyclophosphamide every 28 days for six courses before surgical reevaluation. The following results were obtained from both studies:

Comparative Efficacy:		
Overview of Pivotal Trials		
*114 Carboplatin and 109 Cisplatin patient did not undergo second look surgery in NCIC study. 90 Carboplatin and 106 Cisplatin patients did not undergo second look surgery in SWOG study.		
Number of patients randomized	447	342
Median age (years)	60	62
Dose of cisplatin	75 mg/m2	100 mg/m2
Dose of carboplatin	300 mg/m2	300 mg/m2
Dose of cyclophosphamide	600 mg/m2	600 mg/m2
Residual tumor <2 cm (number of patients)	39% (174/447	14% (49/342)
Clinical Response in Measurable Disease Patients		
	NCIC	SWOG
Carboplatin (number of patients)	60% (48/80)	58% (48/83)
Cisplatin (number of patients)	58% (49/85)	43% (33/76)
95% C.I. of difference (Carboplatin – Cisplatin)	(-10.7%, 2.5%)	(-6.9%, 6.9%)
Progression-Free Survial (PFS)		
	NCIC	SWOG
*Kaplan-Meier Estimates – Unrelated deaths occurring in the absence of progression were counted as events (progression) in this analysis.		
**Analysis adjusted for factors found to be of prognostic significance were consistent with unadjusted analysis.		
Median		
Carboplatin	59 weeks	49 weeks
Cisplatin	61 weeks	47 weeks
95% C.I. of difference (Carboplatin – Cisplatin)	(-9.3, 8.7)	(-9.0, 9.4)
3-Years PFS*		
Carboplatin	19%	8%
Cisplatin	23%	14%
Progression-Free Survival (PFS)		
	NCIC	SWOG
95% C.I. of difference (Carboplatin – Cisplatin)	(-11.5, 4.5)	(-14.1, 0.3)
Hazard ratio**	1.10	1.02
95% C.I. (Carboplatin – Cisplatin)	(0.89, 1.35)	(0.81, 1.29)
Survival		
	NCIC	SWOG
*Kaplan-Meier Estimates		

**Analysis adjusted for factors found		
Median		
Carboplatin	110 weeks	86 weeks
Cisplatin	99 weeks	79 weeks
2 year Survival*		
Carboplatin	5.19%	40.2%
Cisplatin	4.84%	39.0%
3-Year Survival*		
Carboplatin	34.6%	18.3%
Cisplatin	33.1%	24.9%
95% C.I. of difference (Carboplatin – Cisplatin)	(-7.7, 10.7)	(-15.9, 2.7)
Hazard Ratio**	0.98	1.01
95% C.I. (Carboplatin-Cisplatin)	(0.78, 1.23)	(0.78, 1.30)

Comparative Toxicity:

The pattern of toxicity exerted by the Carboplatin Injection-containing regimen was significantly different from that of the cisplatin-containing combinations. Differences between the two studies may be explained by different cisplatin dosages and by different supportive care.

The Carboplatin Injection-containing regimen induced significantly more thrombocytopenia and, in one study, significantly more leukopenia and more need for transfusional support. The cisplatin-containing regimen produced significantly more anemia in one study. However, no significant differences occurred in incidences of infections and hemorrhagic episodes.

Non-hematologic toxicities (emesis, neurotoxicity, ototoxicity, renal toxicity, hypomagnesemia, and alopecia) were significantly more frequent in the cisplatin-containing arms.

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER NCIC STUDY				
		Carboplatin Arm Percent*	Cisplatin Arm Percent*	P-Values**
*Values are in percent of evaluable patients				
**n.s. = not significant, p>0.05				
+May have been affected by cyclophosphamide dosage delivered				
Bone Marrow				
Thrombocytopenia	<100,000/mm3	70	29	<0.001
	<50,000/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	<11 g/dl	91	91	n.s.
	<8 g/dl	18	12	n.s.
Infections		14	12	n.s.
Bleeding		10	4	n.s.
Transfusions		42	31	0.018
Gastrointestinal				
Nausea and vomiting		93	98	0.010
Vomiting		84	97	<0.001
Other GI side effects		50	62	0.013
Neurologic				
Peripheral neuropathies		16	42	<0.001
Ototoxicity		13	33	<0.001
Other sensory side effects		6	10	n.s.

Central neurotoxicity		28	40	0.009
Renal				
Serum creatinine elevations		5	13	0.006
Blood urea elevations		17	31	<0.001
Hepatic				
Bilirubin elevations		5	3	n.s.
SGOT elevations		17	13	n.s.
Alkaline phosphatase elevations		-	-	-
Electrolytes loss				
Sodium		10	20	0.005
Potassium		16	22	n.s.
Calcium		16	19	n.s.
ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER NCIC STUDY				
		Carboplatin Arm Percent*	Cisplatin Arm Percent*	P-Values**
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
Mucositis		10	9	n.s.

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER SWOG STUDY				
		Carboplatin Arm Percent*	Cisplatin Arm Percent*	P-Values**
*Values are in percent of evaluable patients				
**n.s. = not significant, p>0.05				
+May have been affected by cyclophosphamide dosage delivered				
Bone Marrow				
Thrombocytopenia	<100,000/mm3	59	35	<0.001
	<50,000/mm3	22	11	0.006
Neutropenia	<2000 cells/mm3	95	97	n.s.
	<1000 cells/mm3	84	78	n.s.
Leukopenia	<4000 cells/mm3	97	97	n.s.
	<2000 cells/mm3	76	67	n.s.
Anemia	<11 g/dl	88	87	n.s.
	<8 g/dl	8	24	<0.001
Infections		18	21	n.s.
Bleeding		6	4	n.s.
Transfusions		25	33	0.018
Gastrointestinal				
Nausea and vomiting		94	96	n.s.
Vomiting		82	91	0.007
Other GI side effects		40	48	n.s.
Neurologic				
Peripheral neuropathies		13	28	0.001
Ototoxicity		12	30	<0.001

Other sensory side effects		4	6	n.s.
Central neurotoxicity		23	29	n.s.
Renal				
Serum creatinine elevations		7	38	<0.001
Blood urea elevations		-	-	-
Hepatic				
Bilirubin elevations		5	3	n.s.
SGOT elevations		23	16	n.s.
Alkaline phosphatase elevations		29	20	n.s.
Electrolytes loss				
Sodium		-	-	-
Potassium		-	-	-
Calcium		-	-	-
Magnesium		58	77	<0.001
Other side effects				
Pain		54	52	n.s.
Asthenia		43	46	n.s.
Cardiovascular		23	30	n.s.
Respiratory		12	11	n.s.
Allergic		10	11	n.s.
Genitourinary		11	13	n.s.
Alopecia +		43	57	0.009
Mucositis		6	11	n.s.

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

In two prospective, randomized controlled studies in patients with advance ovarian cancer previously treated with chemotherapy, Carboplatin Injection achieved sex clinical complete responses in 47 patients. The duration of these responses ranged from 45 to 71 + weeks.

INDICATIONS AND USAGE

Initial Treatment of Advanced Ovarian Carcinoma:

Carboplatin Injection is indicated for the initial treatment of advanced ovarian carcinoma is established combination with other approved chemotherapeutic agents. One established combination regimen consists of Carboplatin Injection and cyclophosphamide, have demonstrated equivalent overall survival between the two groups (see CLINICAL STUDIES).

There is limited statistical power to demonstrate equivalence in overall pathologic complete response rates and long-term survival (≥ 3 years) because of the small number of patients with these outcomes : the small number of patients with residual tumor <2cm after initial surgery also limits the statistical power to demonstrate equivalence in this subgroup.

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.

Carboplatin Injection should not be employed in patients with severe bone marrow depression or significant bleeding.

DOSAGE AND 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 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 see Formula Dosing)/ in general, however, single intermittent courses of Carboplatin Injection should not be repeated until the neutrophil count is at least 2000 and the platelet count is at least 100,000.

Combination Therapy with Cyclophosphamide:

In the chemotherapy of advance ovarian cancer, an effective combination for previously untreated patients consists of:

Carboplatin Injection – 300 mg/m2 IV on day 1 every four weeks for six cycles (alternatively see Formula Dosing). Cyclophosphamide – 600mg/m2 IV on day 1 every four weeks for six cycles. For directions regarding the use and administration of cyclophosphamide please refer to its package insert. (See CLINICAL STUDIES). Intermittent courses of Carboplatin Injection in combination with cyclophosphamide should not be repeated until the neutrophil count is at least 2000 and the platelet count is at least 10,000.

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)
*Percentages apply to Carboplatin Injection as a single agent or to both Carboplatin Injection 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.		
>100,000	>2000	125%
50-100,000	500-2000	No Adjustment
<50,000	<500	75%

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

Patients with Impaired Kidney Function:

Patients with creatinine clearance values below 60mL/min are at increased risk of severe bone marrow suppression. In renally-impaired patients who received single-agent Carboplatin Injection 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/m2
16 – 40 mL/min	200 mg/m2

The data available for patients with severely impaired kidney function (creatinine clearance below 15mL/min) are too limited to permit a recommendation for treatment.

These dosing recommendations apply to the initial course of treatment. Subsequent dosages shluld 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 preexisting renal function or renal function and desired platelet nadir. Renal excretion is the major route of elimination for carboplatin. (See CLINICAL PHARMOCOLOGY). 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 result in either underdosing (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/mLmin), has been proposed by Calvert. In these studies, GFR was measured by 51 Cr-EDTA clearance.

GALVERT FORMULA FOR CARBOPLATIN DOSING
Total Dose (mg) = (target AUC) X (GFR +25)
Note: With the Calvert formula, the total dose of Carboplatin Injection is calculated in mg, not mg/m2.

The target AUC of 4-6 mg/mLmin using single agent Carboplatin Injection appears to provide the most appropriate dose range in previously treated patients. This study also showed a trend between the AUC of single agent Carboplatin Injection administered to previously treated patients and the likelihood of developing toxicity.

% Actual Toxicity in Previously Treated Patients		
	Gr 3 or Gr 4	Gr 3 or Gr 4
AUC (mg/mLmin)	Thrombocytopenia	Leukopenia
4 to 5	16%	13%
6 to 7	33	34%

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.

PREPARATION OF INTRAVENOUS SOLUTIONS

Carboplatin Injection 10mg/mL is supplied as a Ready To Use (RTU) sterile solution in 5ml, 15ml, 45ml or 60ml vials. Total content of carboplatin per vial is described in following tableL

Vial Strength	Diluent Volume
50 mg	5 ml
150 mg	15 ml
450 mg	45 ml
600 mg	60 ml

Carboplatin Injection 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 further diluted, Carboplatin Injection solutions are stable for 8hours at room temperature (25ºC). Since no antibacterial preservative is contained in the formulation, it is recommended that Carboplatin Injection solutions be discarded 8 hours after dilution.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

WARNNGS

Carboplatin Injection should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents appropriate management of therapy and complications is possible only when adequate treatment facilities are readily available Bone marrow suppression is dose related and may be severe, resulting in infection and/or bleeding. Anemia may be cumulative and may require transfusion support. Vomiting is another frequent drug-related side effect.

Anaphylactic-like reactions to Carboplatin Injection have been reported and may occur within minutes of Carboplatin Injection administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms.

Bone marrow suppression (leukopenia, 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 (see DOSAGE AND ADMINISTRATION) 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 renal 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 wen carboplatin was administered at higher than recommended doses in combination with other ototoxic agents.

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 premedication with antiemetics. Although no conclusive efficacy data exist with the following schedules of carboplatin, lengthening the duration of single intravenous administration to 24hours 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. 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. (See CONTRAINDICATIONS AND ADVERSE REACTIONS: Allergic Reactions.)

High dosages of carboplatin (more than four times the recommended dose) have resulted in severe abnormalities of liver function tests.

Carboplatin may cause fetal harm when administered to a pregnant woman. Carboplatin has been shown to be embryotoxic and teratogenic in rats. There are o 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.

PRECAUTIONS

General:

Needles or intravenous administration sets containing aluminum parts that may come in contact with carboplatin should not be used for the preparation or administration of the drug. Aluminum can react with carboplatin causing precipitate formation and loss of potency.

ADVERSE REACTIONS

For a comparison of toxicities when carboplatin or cisplatin was given in combination with cyclophosphamide, see the Comparative Toxicity subsection of the CLINICAL STUDIES section.

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER			
		First Line Combination Therapy* Percent	Second Line Single Agent Therapy** Percent
*Use with Cyclophosphamide for initial Treatment of Ovarian Cancer: Data are based on the experience of 393 patients with ovarian cancer (regardless of baseline status) who received initial combination therapy with carboplatin and cyclophosphamide in two randomized controlled studies conducted by SWAG and NCIC (see CLINICAL STUDIES). Combination with cyclophosphamide as well as duration of treatment may be responsible for the differences that can be noted in the adverse experience table.			
**Single Agent Use for the Secondary Treatment of Ovarian Cancer: Data are based on the experience of 553 patients with previously treated ovarian carcinoma (regardless of baseline status) who received single-agent carboplatin.			
Bone Marrow			
Thrombocytopenia	<100,000/mm3	66	62
	<50,000/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	<11 g/dl	90	90
	<8 g/dl	14	21
Infections		16	5
Bleeding		8	5
Transfusions	35	44	
Gastrointestinal			
Nausea and vomiting		93	92
Vomiting		83	81
Other GI side effects		46	21
Neurologic			
Peripheral neuropathies		15	6
Ototoxicity		12	1
Other sensory side effects		5	1
Central neurotoxicity		26	5
Renal			
Serum creatinine elevations		6	10
Hepatic			
Bilirubin elevations		5	5
SGOT elevations		20	19
Alkaline phosphatase elevations		29	37
Electrolytes loss			
Sodium		10	47
Potassium		16	28
Calcium		16	28
Magnesium		61	43
Other side effects			
Pain		44	23
Asthenia		41	11
Cardiovascular		19	6
Respiratory		10	6
Allergic		11	2
Genitourinary		10	2
Alopecia		49	2

Mucositis		8	1

In the narrative section that follows, the incidences of adverse events are based on data from 1893 patients with various types of tumors who received carboplatin as single-agent therapy.

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 (35% of pretreated ovarian cancer patients); neutropenia with granulocyte counts below 1,000/mm3 occurs in 16% of the patients (21% of pretreated ovarian cancer patients). The nadir usually occurs about day 21 in patients receiving single-agent therapy. By 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.

Marrow suppression is usually more severe in patients with impaired kidney function. Patients with poor performance status have also experience a higher incidence of severe leukopenia and thrombocytopenia.

The hematologic effects, although usually reversible, have resulted in infectious or hemorrhagic complications in 5% of the patients treated with carboplatin, with drug related death occurring in less than 1% of the patients. Fever has been reported in patients with neutropenia.

Anemia with hemoglobin less than 11 g/dL has been observed in 71% of the patients who started therapy with a baseline above that value. The incidence of anemia increases with increasing exposure to carboplatin. Transfusions have been administered to 26% of the patients treated with carboplatin (44% of previously treated ovarian cancer patients).

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 (81% of previously treated ovarian cancer patients) and in about one-third of these patients it is 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% to 15% of patients. Both nausea and vomiting usually cease within 24 hours of treatment and are often responsive to antiemetic measures. Although no conclusive efficacy data exist with the following schedules, prolonged administration of carboplatin, either by continuous 24-hour infusion or by daily pulse doses given for five consecutive days, was associated with less severe vomiting than the single dose intermittent schedule. 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, also in 6%.

Neurologic Toxicity:

Peripheral neuropathies have been observed in 4% of the patients receiving carboplatin (6% of pretreated ovarian cancer patients) with mild pareshesias occurring most frequently. Carboplatin therapy produces signigicantly gewer and less severe neurologic side effects than does thrapy with cisplatin. However, patients older than 65 years and/or previously treated with cisplatin-induced peripheral neurotoxicity, there was no worsening of symptoms during therapy with carboplatin. Clinical ototoxicity and other sensory abnormalities such as visual disturbances and change in taste have been reported in only 1% of the patients. Central nervous system symptoms have been reported in 5% of the 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 particularly in cisplatin pretreated patients, may result in cumulative neurotoxicity.

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. The incidences of abnormal renal function tests reported are 6% for serum creatinine and 14% for blood urea nitrogen (10% and 22%, respectively, in pretreated ovarian cancer patients). Most of these reported abnormalities have been mild and about one-half of them were reversible.

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. Twenty-seven percent of the patients who had a baseline value of 60mL/min or more demonstrated a reduction below this value during carboplatin therapy.

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%; (5%, 19% and 37% respectively, in pretreated ovarian cancer patients). These abnormalities have generally been mild and reversible in about one-half of the cases, although the role of metastatic tumor in the liver may complicate the assessment in many patients. 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:

The incidences of abnormally decreased serum electrolyte values reported were 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 the patients. These allergic reactions have been similar in nature and severity to those reported with other platinum-containing compounds, i.e., rash, urticarial, erythema, pruritus, and rarely bronchospasm and hypotension. Anaphylactic reactions have been reported as part of post-marketing surveillance (see WARNINGS). These reactions have been successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy.

Injection Site Reactions:

Pain and asthenia were the most frequently reported (3%). Cardiovascular events (cardiac failure, embolism, cerebrovascular accidents) were fatal in less than 1% of the patients and did not appear to be related to chemotherapy. Cancer-associated hemolytic uremic syndrome has been reported as part of post marketing surveillance.

Drug Interactions:

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

Carcinogenic, Mutagenesis, Impairment of Fertility:

The carcinogenic potential of carboplatin has not been studied, but compounds with similar mechanism of action and mutagenicity profiles have been reported to be carcinogenic. Carboplatin has been shown to be mutagenic both in vitro and in vivo. It has also been shown to be embryotoxic and teratogenic in rats receiving the drug during organogenesis. Secondary malignancies have been reported in association with multi-drug therapy.

Pregnancy:

Pregnancy “Category D” (see WARNINGS).

It is not known whether carboplatin treatment of the mother, it is recommended that breast feeding be discontinued if the mother is treated with carboplatin.

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established (see WARNINGS; “Audiologic Toxicity”).

Geriatric Use:

Of the 789 patients in initial treatment combination therapy studies (NCIC and SWAG), 395 patients were treated with carboplatin in combination with cyclophosphamide. Of these, 141 were over 65 years of age and 22 were 75 years or older. In these trials, age was not a prognostic factor for survival. In terms of safety, elderly patients treated with carboplatin were more likely to

develop severe thrombovytopenia than younger patients. In a combined database of 1942 patients (414 were ≥ 65 years of age) that received single agent carboplatin for different tumor types, a similar incidence of adverse events was seen in patients 65 years and older and in patients less than 65. Other reported clinical experience has not identified diffences in reponsesbetween elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Because renal function is often decreased in the elderly, renal function should be considered in the selection of carboplatin dosage (see DOSAGE AND ADMINISTRATION).

OVERDOSAGE

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.

CONTRAINDICATIONS

Carboplatin Injection is contraindicated in patients with a history of severe allergic reactions to cisplatin or other platinum-containing compounds.

STORAGE

Unopened vials of Carboplatin Injection are stable for the life indicated on the package when store in cool place and protected from light.

PRESENTATION

Carboplatin Injection 10mg/ml sterile solution is available in the following presentations:

150 mg/15ml vials, individually cartoned.

450 mg/45ml vials, individually cartooned

Manufactured in India by:

ZUVIUS LIFESCIENCES PVT. LTD.
A WHO-GMP CERTIFIED COMPANY
B/111, 112, 113, Kanara Business Centre,
Link Road, Ghatkopar (East), Mumbai 400075.
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