LACHMAN CONSULTANT SERVICES, INC.
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES

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September 26, 2005

OVERNIGHT COURIER 09/26/05

Division of Dockets Management
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Citizen Petition

Dear Sir or Madam:

The undersigned submits this petition, in quadruplicate, pursuant to Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act, and in accordance with 21 CFR 10.30 on behalf of a client requesting the Commissioner of the Food and Drug Administration to declare that the drug product, Carboplatin Injection, 10 mg / mL in a 1000 mg / 100 mL multiple-dose vial, is suitable for consideration in an abbreviated new drug application (ANDA).

A. Action Requested

The petitioner requests that the Commissioner of the Food and Drug Administration declare that Carboplatin Injection 10 mg / mL in a 1000 mg / 100 mL multiple-dose vial is suitable for submission as an ANDA. The reference-listed drug product (RLD), upon which this petition is based, is Paraplatin® (carboplatin) Injection 600 mg / 60 mL (10 mg / mL) by Bristol Myers Squibb (BMS) (as listed in the electronic Orange Book). The applicant is requesting that the total drug content for this injectable product be increased from 600 mg / 60 mL to 1000 mg / 100 mL, however, the concentration of the solution will remain unchanged (i.e., 10 mg / mL).

B. Statement of Grounds

The Federal Food, Drug and Cosmetic Act provides for the submission of an Abbreviated New Drug Application for a drug product that differs in strength (or in the case of a parenteral product, total drug content) from that of the reference-listed drug provided the FDA has approved a petition that proposed filing such an application.

The RLD, Paraplatin® Injection by BMS, is an aqueous injection product containing 600 mg / 60 mL (10 mg / mL) of carboplatin. See listing from the electronic version of the Orange Book, *Approved Drug Products with Therapeutic Equivalence Evaluations*, (accessed September 26, 2005) (Attachment 1). The proposed drug product also represents an aqueous injectable dosage form at a concentration of 10 mg / mL, but containing a total drug content in the multiple-dose vial of 1000 mg in 100 mL. Historically, the FDA has required a firm to submit and obtain approval of an ANDA suitability petition prior to permitting a change in the total drug content in a parenteral product (i.e., amount in a single container, e.g., vial), even though the

concentration of the product remains exactly the same. The Agency has indicated that they consider this tantamount to a change in strength, and that is the intent and purpose of this petition. The petition is thus seeking a change in strength (total drug content) from 600 mg / 60 mL to 1000 mg / 100 mL, from that of the RLD. Please note that the proposed change in total drug content does not represent a change in concentration of the product as mentioned above.

Paraplatin® is currently available and approved in multiple-dose containers of 50 mg / 5 mL, 150 mg / 15 mL, 450 mg / 45 mL and 600 mg / 60 mL.

The acceptability of the proposed 1000 mg / 100 mL strength (total drug content) is clearly contemplated in the approved labeling of the 600 mg / 60 mL RLD product. The current dosing instructions in the approved labeling of the Paraplatin® RLD labeling provides for dosing of carboplatin up to 360 mg/m^2. Thus, a single, currently approved multiple-dose container could contain two or fewer doses for certain patients. The availability of a larger 100 mL size multiple-dose vial would permit hospitals, oncology centers and home infusion centers the option of a more convenient packaging configuration that might permit less waste and permit stocking of fewer vials at potentially reduced cost to the patient. It is also possible that fewer manual manipulations would be required to withdraw an appropriate dose for a patient from a single container, rather than perhaps requiring entry of multiple containers to withdraw the required dose.

The labeling of the approved RLD thus clearly contemplates a multiple-dose vial containing a total drug content of 1000 mg / 100 mL.

There are no proposed changes in labeling with the exception of the obvious changes in strength (total drug content) sought in this petition. The uses, indications, warnings and directions for use will remain the same as that of the RLD with the obvious exception as would be required by the change in the strength proposed in the petition. Draft labeling for the proposed product is included in Attachment 2. The RLD's approved labeling is provided in Attachment 3.

Therefore, the petitioner's request for the Commissioner to find that a change in strength (total drug content from 600 mg / 60 mL of Carboplatin to 1000 mg / 100 mL of Carboplatin) should raise no questions of safety or effectiveness, and the Agency should approve the petition.

C. Environmental Impact

The petitioner claims a categorical exclusion under 21 CFR 25.31.

D. Economic Impact

The petitioner does not believe that this is applicable in this case, but will agree to provide such an analysis, if requested by the Agency.

E. Certification

The undersigned certifies, that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,

Robert Pollock

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Senior Vice President
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RWP/pk

Attachments:
1. Approved Drug Products with Therapeutic Equivalence Evaluations (Electronic Orange Book) accessed 4/6/05
2. Draft Insert Labeling Proposed for Carboplatin Injection 1000 mg / 100 mL
3. Labeling for the RLD, Paraplatin® Injection

cc: Arianne Camphire (OGD)

F02P5269

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Westbury, NY 11590

ATTACHMENT 1

Proprietary Name Search Results from "OB_Rx" table for query on "paraplatin."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
019880	AP	Yes	CARBOPLATIN	INJECTABLE; INJECTION	150MG/VIAL	PARAPLATIN	BRISTOL MYERS SQUIBB
019880	AP	Yes	CARBOPLATIN	INJECTABLE; INJECTION	450MG/VIAL	PARAPLATIN	BRISTOL MYERS SQUIBB
019880	AP	Yes	CARBOPLATIN	INJECTABLE; INJECTION	50MG/VIAL	PARAPLATIN	BRISTOL MYERS SQUIBB
020452	AP	Yes	CARBOPLATIN	INJECTABLE; IV (INFUSION)	EQ 150MG /15ML (10MG/ML)	PARAPLATIN	BRISTOL MYERS SQUIBB
020452	AP	Yes	CARBOPLATIN	INJECTABLE; IV (INFUSION)	EQ 450MG /45ML (10MG/ML)	PARAPLATIN	BRISTOL MYERS SQUIBB
020452	AP	Yes	CARBOPLATIN	INJECTABLE; IV (INFUSION)	EQ 50MG /5ML (10MG/ML)	PARAPLATIN	BRISTOL MYERS SQUIBB
020452	AP	Yes	CARBOPLATIN	INJECTABLE; IV (INFUSION)	EQ 600MG /60ML (10MG/ML)	PARAPLATIN	BRISTOL MYERS SQUIBB

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through August, 2005
Patent and Generic Drug Product Data Last Updated: September 23, 2005

Search results from the "OB_Rx" table for query on "020452."

Active Ingredient:	CARBOPLATIN
Dosage Form;Route:	INJECTABLE; IV (INFUSION)
Proprietary Name:	PARAPLATIN
Applicant:	BRISTOL MYERS SQUIBB
Strength:	EQ 50MG /5ML(10MG/ML)
Application Number:	020452
Product Number:	001
Approval Date:	Jul 14, 2003
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AP**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	CARBOPLATIN
Dosage Form;Route:	INJECTABLE; IV (INFUSION)
Proprietary Name:	PARAPLATIN
Applicant:	BRISTOL MYERS SQUIBB
Strength:	EQ 150MG /15ML(10MG/ML)
Application Number:	020452
Product Number:	002
Approval Date:	Jul 14, 2003
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AP**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	CARBOPLATIN
Dosage Form;Route:	INJECTABLE; IV (INFUSION)
Proprietary Name:	PARAPLATIN
Applicant:	BRISTOL MYERS SQUIBB
Strength:	EQ 450MG /45ML(10MG/ML)
Application Number:	020452
Product Number:	003
Approval Date:	Jul 14, 2003
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AP**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	CARBOPLATIN
Dosage Form;Route:	INJECTABLE; IV (INFUSION)
Proprietary Name:	PARAPLATIN
Applicant:	BRISTOL MYERS SQUIBB
Strength:	EQ 600MG /60ML(10MG/ML)

Application Number:	020452
Product Number:	004
Approval Date:	Jan 15, 2004
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AP**
Patent and Exclusivity Info for this product:	View

Return to Electronic Orange Book Home Page

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ATTACHMENT 2

Carboplatin Injection
*Rx*only

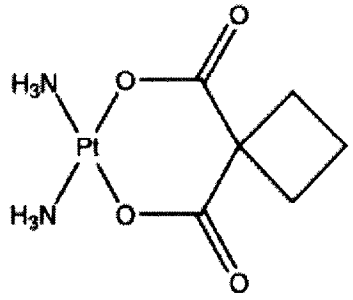
WARNING
Carboplatin Injection should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate treatment facilities are readily available.

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.

DESCRIPTION
Carboplatin Injection is supplied as a sterile, aqueous solution available in 50 mg/5 mL, 150 mg/15 mL, 450 mg/45 mL, 600 mg/60 mL or 1000 mg/100 mL multi-dose vials containing 10 mg/mL of carboplatin for administration by intravenous infusion. Each mL contains 10 mg 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 $C_6H_{12}N_2O_4Pt$ and a molecular weight of 371.25. It is soluble in water at a rate of approximately 14 mg/mL, and the pH of a 1% solution is 5-7. It is virtually insoluble in ethanol, acetone, and dimethylacetamide.

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 60 mL/min or greater, plasma levels of intact carboplatin decay in a biphasic manner after a 30-minute intravenous infusion of 300 to 500 mg/m^2 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, 16 L and 3.5 hours, respectively. The C_{max} 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/m^2).

Carboplatin is not bound to plasma proteins. No significant quantities of protein-free, ultrafilterable platinum-containing species other than carboplatin are present in plasma. However, platinum from carboplatin becomes irreversibly bound to plasma proteins and is slowly eliminated with a minimum halflife of 5 days.

The major route of elimination of carboplatin is renal excretion. Patients with creatinine clearances of approximately 60 mL/min or greater excrete 65% of the dose in the urine within 12 hours and 71% of the dose within 24 hours. All of the platinum in the 24-hour urine is present as carboplatin. Only 3% to 5% of the 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 60 mL/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.

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 naive patients with advanced 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

	NCIC	SWOG
Number of patients randomized	447	342
Median age (years)	60	62
Dose of cisplatin	75 mg/m^2	100 mg/m^2
Dose of carboplatin	300 mg/m^2	300 mg/m^2
Dose of cyclophosphamide	600 mg/m^2	600 mg/m^2
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)	(-13.9%, 18.6%)	(-2.3%, 31.1%)

Pathologic Complete Response*

	NCIC	SWOG
Carboplatin (number of patients)	11% (24/224)	10% (17/171)
Cisplatin (number of patients)	15% (33/223)	10% (17/171)
95% C.I. of difference (Carboplatin – Cisplatin)	(-10.7%, 2.5%)	(-6.9%, 6.9%)

*114 Carboplatin and 109 Cisplatin patients did not undergo second look surgery in NCIC study. 90 Carboplatin and 106 Cisplatin patients did not undergo second look surgery in SWOG study.

Progression-Free Survival (PFS)

	NCIC	SWOG
Median		
Carboplatin	59 weeks	49 weeks
Cisplatin	61 weeks	47 weeks
2-Year PFS*		
Carboplatin	31%	21%
Cisplatin	31%	21%
95% C.I. of difference (Carboplatin – Cisplatin)	(-9.3, 8.7)	(-9.0, 9.4)
3-Year PFS*		
Carboplatin	19%	8%
Cisplatin	23%	14%
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)

* 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.

Survival	NCIC	SWOG
Median		
Carboplatin	110 weeks	86 weeks
Cisplatin	99 weeks	79 weeks
2-Year Survival*		
Carboplatin	51.9%	40.2%
Cisplatin	48.4%	39.0%
95% C.I. of difference (Carboplatin – Cisplatin)	(-6.2, 13.2)	(-9.8, 12.2)
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)

* Kaplan-Meier Estimates

** Analysis adjusted for factors found to be of prognostic significance were consistent with unadjusted analysis.

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**
Bone Marrow				
Thrombocytopenia	<100,000/mm^3	70	29	<0.001
	<50,000/mm^3	41	6	<0.001
Neutropenia	<2000 cells/mm^3	97	96	n.s.
	<1000 cells/mm^3	81	79	n.s.
Leukopenia	<4000 cells/mm^3	98	97	n.s.
	<2000 cells/mm^3	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.
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.

* Values are in percent of evaluable patients

** n.s. = not significant, p>0.05

\+ May have been affected by cyclophosphamide dosage delivered

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER SWOG STUDY			
	Carboplatin Arm Percent*	Cisplatin Arm Percent*	P-Values**
Bone Marrow			
Thrombocytopenia <100,000/mm^3	59	35	<0.001

	<50,000/mm^3	22	11	0.006
Neutropenia	<2000 cells/mm^3	95	97	n.s.
	<1000 cells/mm^3	84	78	n.s.
Leukopenia	<4000 cells/mm^3	97	97	n.s.
	<2000 cells/mm^3	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	n.s.
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.

* Values are in percent of evaluable patients
** n.s. = not significant, p>0.05
+ May have been affected by cyclophosphamide dosage delivered

Use as a Single Agent for Secondary Treatment of Advanced Ovarian Cancer: In two prospective, randomized controlled studies in patients with advanced

ovarian cancer previously treated with chemotherapy, Carboplatin Injection achieved six 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 in established combination with other approved chemotherapeutic agents. One established combination regimen consists of Carboplatin Injection and cyclophosphamide. Two randomized controlled studies conducted by the NCIC and SWOG with carboplatin vs. cisplatin, both in combination with 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 <2 cm 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.

CONTRAINDICATIONS

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

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

WARNINGS

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 when 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 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. (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 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.

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.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility: The carcinogenic potential of carboplatin has not been studied, but compounds with similar mechanisms of action and mutagenicity profi les 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**).

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.

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 SWOG), 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 thrombocytopenia 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 differences in responses between 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**).

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
Bone Marrow			
Thrombocytopenia	<100,000/mm^3	66	62
	<50,000/mm^3	33	35
Neutropenia	<2000 cells/mm^3	96	67
	<1000 cells/mm^3	82	21
Leukopenia	<4000 cells/mm^3	97	85
	<2000 cells/mm^3	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
Blood urea elevations	17	22
Hepatic		
Bilirubin elevations	5	5
SGOT elevations	20	19
Alkaline phosphatase elevations	29	37
Electrolytes loss		
Sodium	10	47
Potassium	16	28
Calcium	16	31
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

***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 SWOG 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.

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/mm^3 occurs in 25% of the patients (35% of pretreated ovarian cancer patients); neutropenia with granulocyte

counts below 1,000/mm^3 occurs in 16% of the patients (21% of pretreated ovarian cancer patients); leukopenia with WBC counts below 2,000/mm^3 occurs in 15% of the patients (26% 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/mm^3; 74% have neutrophil counts above 2,000/mm^3; 67% have leukocyte counts above 4,000/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 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 also 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 paresthesias occurring most frequently. Carboplatin therapy produces significantly fewer and less severe neurologic side effects than does therapy with cisplatin. However, patients older than 65 years and/or previously treated with cisplatin appear to have an increased risk (10%) for peripheral neuropathies. In 70% of the patients with pre-existing 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 60 mL/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, urticaria, 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: Injection site reactions, including redness, swelling, and pain, have been reported during postmarketing surveillance. Necrosis associated with extravasation has also been reported.

Other Events: Pain and asthenia were the most frequently reported miscellaneous adverse effects; their relationship to the tumor and to anemia was likely. Alopecia was reported (3%). Cardiovascular, respiratory, genitourinary, and mucosal side effects have occurred in 6% or less of the patients. 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 rarely.

Malaise, anorexia and hypertension have been reported as part of post marketing surveillance.

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.

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/m^2 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 advanced ovarian cancer, an effective combination for previously untreated patients consists of:

Carboplatin Injection - 300 mg/m^2 IV on day 1 every four weeks for six cycles (alternatively see **Formula Dosing**).

Cyclophosphamide - 600 mg/m^2 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 100,000.

Dose Adjustment Recommendations: Pretreatment platelet count and performance status are important prognostic factors for severity of myelosuppression in previously treated patients.

The suggested dose adjustments for single agent or combination therapy shown in the table below are modified from controlled trials in previously treated and untreated patients with ovarian carcinoma. Blood counts were done weekly, and the recommendations are based on the lowest post-treatment platelet or neutrophil value.

Platelets	Neutrophils	Adjusted Dose* (From Prior Course)
>100,000	>2000	125%
50-100,000	500-2000	No Adjustment
<50,000	<500	75%

*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.

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

Patients with Impaired Kidney Function: Patients with creatinine clearance values below 60 mL/min are at increased risk of severe bone marrow suppression. In renally-

impaired patients who received single-agent Carboplatin 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/m^2
16 - 40 mL/min	200 mg/m^2

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

These dosing recommendations apply to the initial course of treatment. Subsequent dosages should be adjusted according to the patient's tolerance based on the degree of bone marrow suppression.

Formula Dosing: Another approach for determining the initial dose of Carboplatin Injection is the use of mathematical formulae, which are based on a patient's preexisting renal function or renal function and desired platelet nadir. Renal excretion is the major route of elimination for carboplatin. (See **CLINICAL PHARMACOLOGY.**) 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 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/mL•min), has been proposed by Calvert. In these studies, GFR was measured by ^{51}Cr-EDTA clearance.

CALVERT 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, <u>not</u> mg/m^2.**

The target AUC of 4-6 mg/mL•min 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	
AUC (mg/mL•min)	Gr 3 or Gr 4 Thrombocytopenia	Gr 3 or Gr 4 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 10 mg/mL is supplied as a Ready To Use (RTU) sterile solution in 5 mL, 15 mL, 45 mL, 60 mL or 100 mL vials. Total content of carboplatin per vial is described in following table:

Vial Strength	Diluent Volume
50 mg	5 mL
150 mg	15 mL
450 mg	45 mL
600 mg	60 mL
1000 mg	100 mL

Carboplatin Injection can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water (D_5W) or 0.9% Sodium Chloride Injection, USP.

When further diluted, Carboplatin Injection solutions are stable for 8 hours at room temperature (25°C). 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.

HOW SUPPLIED

Carboplatin Injection 10 mg/mL sterile solution is available in the following presentations:
NDC XXXXX-XXX-XX 50 mg/5 mL vials, individually cartoned. (Blue flip-off seals)
NDC XXXXX-XXX-XX 150 mg/15 mL vials, individually cartoned. (Blue flip-off seals)
NDC XXXXX-XXX-XX 450 mg/45 mL vials, individually cartoned. (Blue flip-off seals)
NDC XXXXX-XXX-XX 600 mg/60 mL vials, individually cartoned. (Blue flip-off seals)
NDC XXXXX-XXX-XX 1000 mg/100 mL vials, individually cartoned. (Blue flip-off seals)

STORAGE

Unopened vials of Carboplatin Injection are stable for the life indicated on the package when stored at 25°C (77°F) [excursions permitted to 15°- 30°C (59°- 86°F) [see USP Controlled Room Temperature] and protected from light.

Carboplatin injection multidose vials maintain microbial, chemical, and physical stability for up to 15 days at 25°C following multiple needle entries.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published[1-7]. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.
2. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *JAMA* 1985; 253(11):1590-1592.

3. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc.D., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
4. Clinical Oncological Society of Australia. Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med J Australia* 1983; 1:426-428.
5. Jones RB, et al: Safe Handling of Chemotherapeutic Agents: A Report From the Mount Sinai Medical Center. *CA-A Cancer Journal for Clinicians* 1983; (Sept/Oct) 258-263.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm* 1990; 47:1033-1049.
7. Controlling Occupational Exposure to Hazardous Drugs. (OSHA WORK-PRACTICE GUIDELINES). *Am J Health-Syst Pharm* 1995; 52:1669-1685.

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Please Tear Here

Patient Information

Rx only

Read this entire leaflet carefully. Keep it for future reference.

Carboplatin Injection

This information will help you learn more about Carboplatin Injection. It cannot, however, cover all the possible warnings or side effects relating to Carboplatin Injection, and it does not list all of the benefits and risks of Carboplatin Injection. Your doctor should always be your first choice for detailed information about your medical condition and your treatment. Be sure to ask your doctor about any questions you may have.

What is cancer?

Under normal conditions, the cells in your body divide and grow in an orderly, controlled fashion. Cell division and growth are necessary for the human body to perform its functions and to repair itself. Cancer cells are different from normal cells because they are not able to control their own growth. The reasons for this abnormal growth are not yet fully understood.

A tumor is a mass of unhealthy cells that are dividing and growing fast and in an uncontrolled way. When a tumor invades surrounding healthy body tissue it is known as a malignant tumor. A malignant tumor can spread (metastasize) from its original location to other parts of the body.

What is Carboplatin Injection?

Carboplatin Injection is a medicine that is used to treat cancer of the ovaries. It acts by interfering with the division of rapidly multiplying cells, particularly cancer cells.

Who should not take Carboplatin Injection?

Treatment with Carboplatin Injection is not recommended if you:

- are allergic to Carboplatin Injection or other platinum-containing products;
- have a weakened blood-forming system (bone marrow depression) or significant bleeding;
- are pregnant, intend to become pregnant, or are breast-feeding a baby.

How is Carboplatin Injection used?

Only a professional experienced in the use of cancer drugs should give you this medication. Carboplatin Injection is given by dripping the medicine slowly and directly into a vein (intravenous infusion) for 15 minutes or longer. Your doctor will determine the dose of Carboplatin Injection for you based on your weight, height, and kidney function. Carboplatin Injection may be given alone or with other drugs. Treatment is usually repeated every four weeks for a number of cycles.

Before and after Carboplatin Injection treatment, your doctor may give you medication to lessen the nausea and vomiting associated with this cancer treatment.

What should you tell your doctor before starting treatment with Carboplatin Injection?

Discuss the benefits and risks of Carboplatin Injection with your doctor before beginning treatment.

Be sure to inform your doctor:

- If you are allergic to Carboplatin Injection or other platinum-containing products;
- If you are or intend to become pregnant, since Carboplatin Injection may harm the developing fetus. It is important to use effective birth control while you are being treated with Carboplatin Injection;
- If you are breast-feeding, since nursing infants may be exposed to Carboplatin Injection in this way;
- If you are taking other medicines, including all prescription and non-prescription (over-the-counter) drugs, since Carboplatin Injection may affect the action of other medicines;
- If you have any other medical problems, especially chicken pox (including recent exposure to adults or children with chicken pox), shingles, hearing problems, infection, or kidney disease, since treatment with Carboplatin Injection increases the risk and severity of these conditions.

What should I avoid while taking Carboplatin Injection?

If you are pregnant or think you might be pregnant, or if you are breast feeding, let your doctor know right away. Carboplatin Injection may harm your developing fetus or breast-

feeding baby. If you are a woman of childbearing age, you should use birth control to avoid getting pregnant while you are taking Carboplatin Injection.

You should avoid contact with adults and children who have infections, and tell your doctor right away if you show signs of infection such as cough, fever, and/or chills. Also, while you are being treated with Carboplatin Injection or after you stop treatment, first check with your doctor **before** getting any immunizations (vaccinations). Avoid contact with adults or children who have received oral polio vaccine since they can pass the polio virus to you.

What are the possible side effects of Carboplatin Injection?

Carboplatin Injection may cause unwanted effects, particularly because Carboplatin Injection interferes with the growth of normal cells as well as cancer cells. For example, the occurrence of another cancer (secondary malignancy) has been reported in patients receiving cancer chemotherapy with multiple drugs. It is not always possible to tell whether such effects are caused by Carboplatin Injection, another drug you may be taking, or your illness. Because some of these effects may be serious, you will need close medical supervision during treatment with Carboplatin Injection.

The most serious side effects of Carboplatin Injection are:

- **bleeding and reduced blood cells, including reduced red blood cells (anemia) and platelets (needed for propper blood clotting)**, which may be severe enough to require blood transfusion. You should tell your doctor right away if you notice any unusual bruising or bleeding, including black tarry stools or blood in the urine.
- **infection** – Carboplatin Injection can temporarily lower the number of white blood cells in your blood, increasing the risk of infection;
- **life-threatening allergic reaction** – during and after treatment the doctor or nurse will observe you carefully for signs of allergic reaction;
- **kidney and liver problems**;
- **loss of hearing or ringing in the ears**;

Contact your doctor right away if you experience any of these effects, or notice effects that worry you or are troublesome.

Of the less serious side effects associated with Carboplatin Injection treatment, the most common are nausea, vomiting, diarrhea, loss of appetite, hair loss and numbness, tingling, burning, or pain in the hands or feet.

This medicine was prescribed for your particular condition. It must be given under close medical supervision by a doctor trained in the use of drugs for the treatment of cancer.

This summary does not include everything there is to know about Carboplatin Injection. Medicines are sometimes prescribed for purposes other than those listed in patient leaflets. If you have questions or concerns, or want more information about Carboplatin

Injection, your physician and pharmacist have the complete prescribing information upon whish this information is based. You may want to read it and discuss it with your doctor. Remember, no written summary can replace careful discussion with your doctor.

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LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT 3

℞ ONLY

PARAPLATIN®

(carboplatin aqueous solution) INJECTION

WARNING

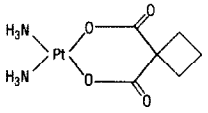
PARAPLATIN® (carboplatin aqueous solution) INJECTION should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents Appropriate management of therapy and complications is possible only when adequate treatment facilities are readily available.

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 have been reported and may occur within minutes of PARAPLATIN administration Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms

DESCRIPTION

PARAPLATIN® (carboplatin aqueous solution) INJECTION is supplied as a sterile, pyrogen-free, 10 mg/mL aqueous solution of carboplatin Carboplatin is a platinum coordination compound The chemical name for carboplatin is platinum, diammine [1,1-cyclobutane-dicarboxylato (2-)-0,0]-,(SP-4-2), and carboplatin has the following structural formula.



Carboplatin is a crystalline powder with the molecular formula of $C_6H_{12}N_2O_4Pt$ and a molecular weight of 371.25. It is soluble in water at a rate of approximately 14 mg/mL, and the pH of a 1% solution is 5-7 It is virtually insoluble in ethanol, acetone, and dimethylacetamide

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 60 mL/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. The initial plasma half-life (alpha) was found to be 1 1 to 2 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 mean residence time for carboplatin are 4 4 L/hour, 16 L and 3.5 hours, respectively The C_{max} 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 No significant quantities of protein-free, ultrafilterable platinum-containing species other than carboplatin are present in plasma However, platinum from carboplatin becomes irreversibly 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 60 mL/min or greater excrete 65% of the dose in the urine within 12 hours and 71% of the dose within 24 hours All of the platinum in the 24-hour urine is present as carboplatin. Only 3 to 5% of the 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 60 mL/min the total body and renal clearances of carboplatin decrease as the creatinine clearance decreases **PARAPLATIN dosages should therefore be reduced in these patients (see DOSAGE AND ADMINISTRATION).**

The primary determinant of PARAPLATIN 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 PARAPLATIN plasma AUCs should be used in elderly patients to minimize the risk of toxicity

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 naive patients with advanced ovarian cancer were treated with carboplatin 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

	NCIC	SWOG
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)	(-13 9%, 18 6%)	(2 3%, 31 1%)

Pathologic Complete Response*

	NCIC	SWOG
Carboplatin (number of patients)	11% (24/224)	10% (17/171)
Cisplatin (number of patients)	15% (33/223)	10% (17/171)
95% C I of difference (Carboplatin - Cisplatin)	(-10 7%, 2 5%)	(-6 9%, 6 9%)

* 114 Carboplatin and 109 Cisplatin patients did not undergo second look surgery in NCIC study.
90 Carboplatin and 106 Cisplatin patients did not undergo second look surgery in SWOG study

Progression-Free Survival (PFS)

	NCIC	SWOG
Median		
Carboplatin	59 weeks	49 weeks
Cisplatin	61 weeks	47 weeks
2-year PFS*		
Carboplatin	31%	21%
Cisplatin	31%	21%
95% C I of difference (Carboplatin-Cisplatin)	(-9 3, 8 7)	(-9 0, 9 4)
3-year PFS*		
Carboplatin	19%	8%
Cisplatin	23%	14%
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)

* 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

Survival

	NCIC	SWOG
Median		
Carboplatin	110 weeks	86 weeks
Cisplatin	99 weeks	79 weeks
2-year Survival*		
Carboplatin	51 9%	40 2%
Cisplatin	48 4%	39 0%
95% C I of difference (Carboplatin-Cisplatin)	(-6 2, 13 2)	(-9 8, 12 2)
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)

* Kaplan-Meier Estimates
** Analysis adjusted for factors found to be of prognostic significance were consistent with unadjusted analysis

Comparative Toxicity: The pattern of toxicity exerted by the carboplatin-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-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**
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

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER NCIC STUDY *(Continued)*

	Carboplatin Arm Percent*	Cisplatin Arm Percent*	P-Values**
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
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

* Values are in percent of evaluable patients
** n s = not significant, p > 0 05
\+ May have been affected by cyclophosphamide dosage delivered

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER SWOG STUDY

		Carboplatin Arm Percent*	Cisplatin Arm Percent*	P-Values**
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	n s
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

* Values are in percent of evaluable patients
** n s = not significant, p > 0 05
\+ May have been affected by cyclophosphamide dosage delivered

Use as a Single Agent for Secondary Treatment of Advanced Ovarian Cancer: In two prospective, randomized controlled studies in patients with advanced ovarian cancer previously treated with chemotherapy, carboplatin achieved six clinical complete responses in 47 patients The duration of these responses ranged from 45 to 71+ weeks

INDICATIONS

Initial Treatment of Advanced Ovarian Carcinoma: PARAPLATIN (carboplatin aqueous solution) INJECTION is indicated for the initial treatment of advanced ovarian carcinoma in established combination with other approved chemotherapeutic agents One established combination regimen consists of PARAPLATIN and cyclophosphamide Two randomized controlled studies conducted by the NCIC and SWOG with carboplatin vs cisplatin, both in combination with 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 < 2 cm after initial surgery also limits the statistical power to demonstrate equivalence in this subgroup

Secondary Treatment of Advanced Ovarian Carcinoma: PARAPLATIN 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

CONTRAINDICATIONS

PARAPLATIN INJECTION is contraindicated in patients with a history of severe allergic reactions to cisplatin or other platinum-containing compounds

PARAPLATIN should not be employed in patients with severe bone marrow depression or significant bleeding

WARNINGS

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 PARAPLATIN 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 PARAPLATIN should not be repeated until leukocyte, neutrophil, and platelet counts have recovered

Since anemia is cumulative, transfusions may be needed during treatment with PARAPLATIN, 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 PARAPLATIN dosages in these patients should be appropriately reduced (see **DOSAGE AND ADMINISTRATION**) and blood counts should be carefully monitored between courses The use of PARAPLATIN 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 when carboplatin was administered at higher than recommended doses in combination with other ototoxic agents

PARAPLATIN 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 PARAPLATIN, 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 (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.

PARAPLATIN (carboplatin aqueous solution) 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

PRECAUTIONS

General

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

Drug Interactions: The renal effects of nephrotoxic compounds may be potentiated by PARAPLATIN

Carcinogenesis, Mutagenesis, Impairment of Fertility: The carcinogenic potential of carboplatin has not been studied, but compounds with similar mechanisms 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**).

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 PARAPLATIN treatment of the mother, it is recommended that breast feeding be discontinued if the mother is treated with PARAPLATIN INJECTION

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 SWOG), 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 thrombocytopenia 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 differences in responses between 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 PARAPLATIN dosage (see **DOSAGE AND ADMINISTRATION**)

ADVERSE REACTIONS

For a comparison of toxicities when carboplatin or cisplatin was given in combination with cyclophosphamide, see **CLINICAL STUDIES:** *Comparative Toxicity*

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER

		First Line Combination Therapy* Percent	Second Line Single-Agent Therapy** Percent
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
Blood urea elevations		17	22
Hepatic			
Bilirubin elevations		5	5
SGOT elevations		20	19
Alkaline phosphatase elevations		29	37
Electrolytes loss			
Sodium		10	47
Potassium		16	28
Calcium		16	31
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

***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 SWOG 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

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 PARAPLATIN (carboplatin lyophilized powder) for INJECTION 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 1000/mm³ occurs in 16% of the patients (21% of pretreated ovarian cancer patients), leukopenia with WBC counts below 2000/mm³ occurs in 15% of the patients (26% 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 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 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 also 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 PARAPLATIN 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 PARAPLATIN 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 5 consecutive days, was associated with less severe vomiting than the singledose 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 paresthesias occurring most frequently Carboplatin therapy produces significantly fewer and less severe neurologic side effects than does therapy with cisplatin However, patients older than 65 years and/or previously treated with cisplatin appear to have an increased risk (10%) for peripheral neuropathies In 70% of the patients with pre-existing 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 60 mL/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, ie, rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension Anaphylactic reactions have been reported as part of postmarketing surveillance (see **WARNINGS**) These reactions have been successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy

Injection Site Reactions: Injection site reactions, including redness, swelling, and pain, have been reported during postmarketing surveillance Necrosis associated with extravasation has also been reported

Other Events: Pain and asthenia were the most frequently reported miscellaneous adverse effects, their relationship to the tumor and to anemia was likely. Alopecia was reported (3%) Cardiovascular, respiratory, genitourinary, and mucosal side effects have occurred in 6% or less of the patients 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 rarely

Malaise, anorexia, and hypertension have been reported as part of postmarketing surveillance

OVERDOSAGE

There is no known antidote for PARAPLATIN (carboplatin aqueous solution) INJECTION overdosage The anticipated complications of overdosage would be secondary to bone marrow suppression and/or hepatic toxicity

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 PARAPLATIN.

Single-Agent Therapy: PARAPLATIN (carboplatin aqueous solution) INJECTION, 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 (alternatively see **Formula Dosing**) In general, however, single intermittent courses of PARAPLATIN 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

PARAPLATIN—300 mg/m² I V on day 1 every four weeks for six cycles (alternatively see **Formula Dosing**)

Cyclophosphamide—600 mg/m² I V 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 PARAPLATIN in combination with cyclophosphamide should not be repeated until the neutrophil count is at least 2,000 and the platelet count is at least 100,000

Dose Adjustment Recommendations: Pretreatment platelet count and performance status are important prognostic factors for severity of myelosuppression in previously treated patients

The suggested dose adjustments for single agent or combination therapy shown in the table below are modified from controlled trials in previously treated and untreated patients with ovarian carcinoma Blood counts were done weekly, and the recommendations are based on the lowest post-treatment platelet or

Platelets	Neutrophils	Adjusted Dose* (From Prior Course)
> 100,000	> 2000	125%
50-100,000	500-2000	No Adjustment
< 50,000	< 500	75%

neutrophil value

*Percentages apply to PARAPLATIN INJECTION as a single agent or to both PARAPLATIN 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.

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

Patients with Impaired Kidney Function: Patients with creatinine clearance values below 60 mL/min are at increased risk of severe bone marrow suppression. In renally-impaired patients who received single-agent carboplatin therapy, the incidence of severe leukopenia, neutropenia, or thrombocytopenia has been about 25% when the dosage modifications in the table below have been used

Baseline Creatinine Clearance	Recommended Dose on Day 1
41-59 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 recommendations apply to the initial course of treatment Subsequent dosages should be adjusted according to the patient's tolerance based on the degree of bone marrow suppression

Formula Dosing: Another approach for determining the initial dose of PARAPLATIN is the use of mathematical formulae, which are based on a patient's pre-existing renal function or renal function and desired platelet nadir Renal excretion is the major route of elimination for carboplatin. (See **CLINICAL PHARMACOLOGY**) 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 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 PARAPLATIN 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 CARBOPLATIN DOSING
Total Dose (mg)=(target AUC) x (GFR + 25)
Note: With the Calvert formula, the total dose of PARAPLATIN 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 This study also showed a trend between the AUC of single-agent carboplatin administered to previously treated patients and the likelihood of developing toxicity

	% Actual Toxicity in Previously Treated Patients	
AUC (mg/mL•min)	Gr 3 or Gr 4 Thrombocytopenia	Gr 3 or Gr 4 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 PARAPLATIN based on estimates of GFR should be used in elderly patients to provide predictable plasma PARAPLATIN AUCs and thereby minimize the risk of toxicity

PREPARATION OF INTRAVENOUS SOLUTIONS

PARAPLATIN (carboplatin aqueous solution) INJECTION is a premixed aqueous solution of 10 mg/mL carboplatin

PARAPLATIN aqueous solution can be further diluted to concentrations as low as 0 5 mg/mL with 5% Dextrose in Water (D_5W) or 0 9% Sodium Chloride Injection, USP

When prepared as directed, PARAPLATIN aqueous solutions are stable for 8 hours at room temperature (25° C) Since no antibacterial preservative is contained in the formulation, it is recommended that PARAPLATIN aqueous solutions be discarded 8 hours after dilution

HOW SUPPLIED

PARAPLATIN® (carboplatin aqueous solution) INJECTION

NDC 0015-3210-30	**50 mg**/5 mL aqueous solution in multidose vials (with white flip-off seals), individually cartoned
NDC 0015-3211-30	**150 mg**/15 mL aqueous solution in multidose vials (with white flip-off seals), individually cartoned
NDC 0015-3212-30	**450 mg**/45 mL aqueous solution in multidose vials (with white flip-off seals), individually cartoned.
NDC 0015-3216-30	**600 mg**/60 mL aqueous solution in multidose vials (with white flip-off seals), individually cartoned

Storage

Unopened vials of PARAPLATIN (carboplatin aqueous solution) INJECTION are stable to the date indicated on the package when stored at 25° C (77° F); excursions permitted from 15°-30° C (59°-86° F) [see USP Controlled Room Temperature] Protect from light

PARAPLATIN (carboplatin aqueous solution) INJECTION multidose vials maintain microbial, chemical, and physical stability for up to 14 days at 25° C following multiple needle entries

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration Solutions for infusion should be discarded 8 hours after preparation

Handling and Disposal

Procedures for proper handling and disposal of anti-cancer drugs should be considered Several guidelines on this subject have been published[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate

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