

PRODUCT MONOGRAPH

^{Pr}CARBOPLATIN INJECTION

**Omega Standard
(Carboplatin)**

10 mg/mL

Antineoplastic

Omega Laboratories, Ltd.
11 177, Hamon
Montréal, Canada
H3M 3E4

Control No. 135287

Preparation date:
March 24, 2011

^{Pr}**CARBOPLATIN INJECTION**
10 mg/mL
Omega Standard

THERAPEUTIC CLASSIFICATION

Antineoplastic

CAUTION: CARBOPLATIN IS A POTENT DRUG AND SHOULD BE USED ONLY BY PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPEUTIC DRUGS (SEE WARNINGS AND PRECAUTIONS). BLOOD COUNTS AS WELL AS RENAL AND HEPATIC FUNCTION TESTS MUST BE DONE REGULARLY. DISCONTINUE THE DRUG IF ABNORMAL DEPRESSION OF BONE MARROW OR ABNORMAL RENAL OR HEPATIC FUNCTION IS SEEN.

ACTION

Carboplatin is a synthetic analogue of cisplatin. Like cisplatin, carboplatin interferes with DNA intrastrand and interstrand crosslinks in cells exposed to the drug. DNA reactivity has been correlated with cytotoxicity.

Following administration of carboplatin in man, linear relationships exist between dose and plasma concentrations of total and free ultrafilterable platinum.

The area under the plasma concentration versus time curve for total platinum also shows a linear relationship with the dose.

Repeated dosing during four consecutive days did not produce an accumulation of platinum in plasma.

Following administration of carboplatin, reported values for the terminal elimination half-lives of free ultrafilterable platinum and carboplatin in man were approximately 6 hours and 1.5 hours, respectively. During the initial phase, most of the free ultrafilterable platinum is present as carboplatin. The terminal half-life for total plasma platinum is 24 hours. Approximately 87% of the plasma platinum is protein bound within 24 hours following administration. Carboplatin is excreted primarily in the urine with recovery of approximately 70% of the administered platinum within 24 hours. Most of the drug is excreted in the first 6 hours.

Excretion of carboplatin is by glomerular filtration. Patients with poor renal function have a higher area under curve (AUC) for total platinum and a reduction in dosage is recommended (see **DOSAGE AND ADMINISTRATION**).

INDICATIONS

Carboplatin Injection is indicated for the treatment of ovarian cancer of epithelial origin in first line therapy, and in second line therapy after other treatments have failed.

CONTRAINDICATIONS

Carboplatin Injection is contraindicated in the following conditions:

1. Severe myelosuppression.
2. Pre-existing severe renal impairment. Dosage adjustment may allow use in the presence of mild renal impairment (see **DOSAGE AND ADMINISTRATION**).
3. History of severe allergic reactions to carboplatin, or other platinum-containing compounds. Patients allergic to mannitol may be given Carboplatin Injection.

WARNINGS

Myelosuppression as a result of carboplatin treatment is closely related to the renal clearance of the drug. Therefore in patients who have abnormal renal function or who are receiving concomitant therapy with nephrotoxic drugs, myelosuppression especially thrombocytopenia, may be more severe and prolonged.

The occurrence, severity and protraction of toxicity is likely to be greater in patients who have received extensive prior treatment for their disease, have poor performance status and who are more than 65 years of age.

Renal function parameters should be assessed prior to, during and after therapy. Peripheral blood counts (including platelets, white blood cells and hemoglobin) should be followed during and after therapy. Combination therapy with other myelosuppressive drugs may require modification of dosage and/or frequency of administration in order to minimize additive effects. Supportive transfusional therapy may be required in patients who suffer severe myelosuppression.

Carboplatin courses should not be repeated more frequently than monthly in most circumstances, in order to ensure that the nadir in blood counts has occurred and that there has been recovery to a satisfactory level.

PRECAUTIONS

General:

Carboplatin Injection should only be administered to patients under the supervision of a qualified physician who is experienced in the use of chemotherapeutic agents. Diagnostic and treatment facilities should be readily available for appropriate management of therapy and possible complications.

Peripheral blood counts and renal function should be monitored closely. Blood counts should be performed prior to commencement of carboplatin therapy and weekly to assess hematologic nadir for subsequent dose adjustments. Lowest levels in white cells and platelets are seen between days 14 and 28, and days 14 and 21 respectively after initial therapy. A greater reduction in platelets is seen in patients who have received extensive myelosuppressive chemotherapy than in untreated patients. White blood cell counts less than 2,000 cells/mm³ or platelets less than 50,000 cells/mm³ may necessitate postponement of carboplatin therapy until bone marrow recovery is evident, usually within 5 to 6 weeks.

Dosage reduction or discontinuation may be necessary in the case of severe alteration of renal function tests. Renal toxicity is not usually dose-limiting. Pre-treatment and post-treatment hydration is not necessary. However, about 25% of patients show decreases in creatinine clearance below 60 mL/min. and, less frequently, rises in serum creatinine and blood urea nitrogen may be seen in patients who have previously experienced nephrotoxicity as a result of cisplatin therapy.

Neurotoxicity, such as paresthesias and decreased deep tendon reflexes, and ototoxicity are more likely to be seen in patients who have received cisplatin previously. Neurological evaluations and an assessment of hearing should be performed on a regular basis.

Conception control: Carboplatin is mutagenic in *in-vitro* tests. It is recommended that patients with child bearing or conceiving potential who are receiving carboplatin, exercise adequate conception control.

Use in pregnancy: Carboplatin produces embryotoxicity and teratogenicity in rats. Safe use of carboplatin in human pregnancy has not been established and its use in pregnancy is not recommended.

Use in lactation: It is not known whether carboplatin is excreted in breast milk. To avoid possible harmful effects in the infant, breast feeding is not advised during carboplatin therapy.

Use in elderly: For patients aged 65 and over, dosage adjustment, initially or subsequently, may be necessary, depending on the patient's physical status.

Use in patients with impaired renal function: The optimal use of carboplatin in patients presenting with impaired renal function requires adequate dosage adjustments and frequent monitoring of both hematological nadirs and renal function.

Use in children: Sufficient use of carboplatin in pediatrics has not occurred to allow specific dosage recommendations to be made.

Interactions:

Needles, syringes, catheters or IV administration sets that contain aluminium parts which may come in contact with carboplatin should not be used for preparation or administration of Carboplatin Injection. Carboplatin may interact with aluminium to form a black precipitate.

Concurrent therapy with nephrotoxic drugs may increase or exacerbate toxicity due to carboplatin-induced changes in renal clearance.

Combination therapy with other myelosuppressive drugs may necessitate changes in the dose or frequency of administration of carboplatin in order to minimize additive myelosuppressive effects.

ADVERSE REACTIONS

Myelosuppression is the dose-limiting toxicity of Carboplatin Injection. It is usually reversible and is not cumulative when carboplatin is used as a single agent and at the recommended dosage regimens. Adverse reactions which have been observed include:

Hematologic system: Leucopenia 55%, thrombocytopenia 32%, anemia 59%, bleeding 6%. Transfusional support has been required in about one-fifth of patients.

Gastrointestinal system: Nausea and vomiting 53%, nausea only 25%, diarrhea 6%, constipation 3%. Nausea and vomiting usually occur 6 – 12 hours after administration of carboplatin and disappear within 24 hours. It is readily controlled (or may be prevented) by antiemetic medication.

Renal system: Decrease in creatinine clearance 25%, increases in uric acid 25%, blood urea nitrogen 16% and serum creatinine 7%.

Serum electrolytes: Decreases in serum magnesium 37%, potassium 16% and calcium 5%. These changes have not caused clinical symptoms.

Neurological system: Peripheral neuropathy 6%, dysgeusia <1%. Parasthesias present prior to treatment, especially if caused by cisplatin, may persist or worsen during carboplatin therapy (see **PRECAUTIONS**).

Special senses: Subclinical decrease in hearing acuity as determined by audiogram in the high frequency (4,000 – 8,000 Hz) range 15%, clinical ototoxicity usually manifested as tinnitus 1%. In patients who developed hearing loss as a result of cisplatin therapy, the impairment may persist or worsen.

Hepatic system: Increases in alkaline phosphatase 36%, SGOT 15%, SGPT 16%, total bilirubin 4%. Increases in liver enzymes have been transient in the majority of cases.

Allergic reactions: In less than 2% of patients, reactions similar to those seen after cisplatin have been observed, erythematous rash, fever and pruritus. However no cross-reactivity between cisplatin and carboplatin was seen.

Other: Alopecia 2%, influenza-like syndrome 1%, reaction at injection site <1%.

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free to 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789

- Mail to: Canada Vigilance Program
 Health Canada
 Postal Locator 0701D
 Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide advice.

SYMPTOMS AND TREATMENT OF OVERDOSE

**For management of a suspected drug overdose,
contact your regional Poison Control Centre Immediately.**

No cases of overdosage of carboplatin are known. Should it occur, the patient may need to be sustained through complications relating to myelosuppression, renal and hepatic impairment. From reports in which doses up to 1600 mg/m² were used, patients were said to feel extremely unwell and developed diarrhea and alopecia.

DOSAGE AND ADMINISTRATION

Adult dosage:

The recommended dose of carboplatin in previously untreated adults with normal renal function is 400 mg/m² given as a single intravenous infusion over 15-60 minutes. Therapy should not be repeated until four weeks after the previous carboplatin course.

Initial dosage should be reduced 20-25% in patients with risk factors such as previous myelosuppressive therapy and poor performance status. Initial and subsequent dose reduction may be required in elderly patients, depending upon their physical status.

Determination of hematologic nadir by weekly blood counts during initial courses is recommended for future dosage adjustment and scheduling of carboplatin.

Dosage in patients with impaired renal function:

Hematological nadir and renal function should be closely monitored.

A suggested dosage schedule based on creatinine clearance is:

CREATININE CLEARANCE	DOSE OF CARBOPLATIN
>40 mL/min.	400 mg/m ²
20-39 mL/min.	250 mg/m ²
0-19 mL/min.	150 mg/m ²

Pediatric dosage: Specific dosage recommendations cannot be made due to insufficient use in pediatrics.

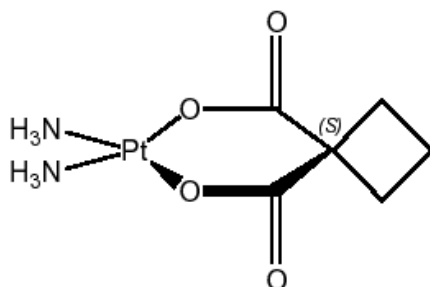
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Carboplatin

Chemical names: (1) Platinum, diammine[1,1-cyclobutanedicarboxylato(2-)-O,O']-,(SP-4-2).
(2) cis-Diammine(1,1-cyclobutanedicarboxylato)platinum.

Structure:



Molecular formula: C₆H₁₂N₂O₄Pt

Molecular weight: 371.25 g/mol

Description: Carboplatin USP is a white to off-white solid. Solubility in water is 14 mg/mL with slow decomposition over time. It is also soluble in organic solvents such as dimethylacetamide and dimethylformamide, but only very slightly soluble in acetone and alcohols. The pH value of an aqueous solution of 10 mg/mL is in the range of 5.0 – 7.5.

Composition: Carboplatin Injection is supplied as a 10 mg/mL solution of carboplatin in Sterile Water for Injection. **Contains no preservatives.**

Stability and storage recommendations:

Carboplatin Injection should be stored between 15°C and 25°C, protected from light.

Dilution for IV Infusion:

Vials of Carboplatin Injection may be further diluted with 5% Dextrose Injection or 0.9% Sodium Chloride Injection to give solutions containing approximately 0.3, 0.5 and 2.0 mg/mL carboplatin.

Diluted solutions of Carboplatin Injection are stable for 24 hours in glass or plastic containers, in light and dark storage conditions. Discard unused portion after 24 hours.

Dilutions prepared as directed with 5% Dextrose Injection or 0.9% Sodium Chloride Injection are stable for 48 hours under refrigeration from the time of initial dilution, after which time the unused portion should be discarded.

SPECIAL INSTRUCTIONS FOR HANDLING AND DISPOSAL

Carboplatin should be prepared for administration by professionals who have been trained in the safe use of cytotoxic drugs.

The personnel carrying out these procedures should be adequately protected with clothing, gloves, masks and eye protection.

Personnel regularly involved in the preparation and handling of carboplatin should have bi-annual blood examinations.

In the event of contact with the skin or eyes, the affected area should be washed with copious amounts of water or normal saline.

A bland cream may be used to treat the transient stinging of skin. Medical advice should be sought if the eyes are affected.

In the event of spillage, personnel wearing protective clothing should sponge up the spilled material. The area should be rinsed twice with water, and all solutions and contaminated clothing and sponges put into a plastic bag and sealed. The bag should be disposed of as below.

Syringes, containers, absorbent materials, solution and any other material which has come into contact with carboplatin should be placed in a thick plastic bag or other impervious container and incinerated at 1000°C. Tightly sealed containers may explode.

AVAILABILITY OF DOSAGE FORMS

Carboplatin Injection 10 mg/mL, is supplied in single use vials, as 50 mg in 5 mL, 150 mg in 15 mL, 450 mg in 45 mL and 600 mg in 60 mL, in sterile aqueous solution.

PHARMACOLOGY

In vitro, carboplatin has demonstrated slight cytotoxic activity against C26 colorectal, M109 lung, RCA colorectal and to a lesser degree against B16-F10 melanoma, Moser colorectal and KB nasopharyngeal cell lines. When carboplatin was tested against human and hamster pancreatic adenocarcinoma cell lines, it was found to be active against COLO 357, WD Pa Ca and PD Pa Ca. It was also active against Novikoff hepatoma cells. Carboplatin has shown activity, upon prolonged exposure, against a cisplatin-sensitive human ovarian cancer cell line (NCI-H2780).

In vivo, carboplatin demonstrated antitumour activity against the following tumours: B16 melanoma, C26 colon carcinoma, C38 colon carcinoma, M5076 reticulum cell sarcoma, Lewis lung carcinoma, L1210/CDDP, P388 murine leukemia, P388 murine leukemia/CDDP, ADJ/PC6A plasmacytoma, Yoshida ascites sarcoma, CD8F, mammary and Xeno mammary MX1.

TOXICOLOGY

Acute and subacute toxicity:

The LD₁₀, LD₅₀ and LD₉₀ were determined in rodents (Table 1).

Table 1. Toxicity of carboplatin in rats and mice.

Lethality	Mice, CDF1 (M&F)				Rats, F344 (M)		Rats, Sprague-Dawley (M&F)	
	Single Dose		5 Daily Doses		Single Dose		Single Dose	
	mg/kg	(mg/m ²)	mg/kg	(mg/m ² /day)	mg/kg	(mg/m ²)	mg/kg	(mg/m ²)
LD ₁₀	122.9	(369)	37.7	(113)	52.5	(313)	83.6	(502)
LD ₅₀	149.5	(448)	46.3	(139)	60.9	(365)	102.0	(613)
LD ₉₀	181.7	(545)	56.9	(171)	70.9	(425)	124.8	(749)

The toxicity studies in mice showed carboplatin to have a narrow margin of safety, as is common with many cancer therapeutic agents. Carboplatin exerted its toxic effect mainly on the rapidly dividing, quickly turned over cells in the immune, digestive, hematopoietic, and reproductive systems (in order of frequency). Mucous membrane necrosis of the colon correlated with clinical signs of gastrointestinal distress, which included anorexia, adipsia, loss of body weight, and bloody diarrhea. Hematopoietic hyperplasia of the bone marrow was reflected in the hematological changes of decreased reticulocyte and possibly lymphocyte counts. At doses up to 200 mg/kg/day IV as a single dose and as five consecutive daily doses, the clinical signs observed were reversible, as were most of the hematologic changes and pathologic lesions at the end of 29 (single dose study) and 33 days (five daily dose study).

Single doses of carboplatin to rats within the IV dose range of 40-80 mg/kg increased BUN values slightly on day 10, but, unlike cisplatin, produced no other indications of renal toxicity. The drug produced reductions in hematocrit and WBC counts with pronounced anemia, dose-related neutropenia and marked elevations of myeloid:erythroid (M:E) ratio. Unlike cisplatin, carboplatin produced no gastro-intestinal toxicity nor destruction of lymphocytes.

The lowest single IV dose of carboplatin causing emesis in dogs was 624 mg/m² (31.2 mg/kg). Both the leukocyte and platelet counts were constantly decreased in dogs given carboplatin at doses equivalent to one-half the lowest emetic dose. These hematologic changes were corroborated by the mild to marked hypocellularity of the bone marrows taken from these dogs.

Carboplatin caused renal lesions at doses equivalent to 75% of its lowest emetic dose. Female dogs showed a mild decrease in hematocrit, hemoglobin and erythrocytes, an apparently sex-linked response.

Dogs given five daily IV doses up to 12.0 mg/kg/day of carboplatin showed emesis, anorexia and diarrhea or loose feces, and leukopenia at 1.5 mg/kg/day. At 3.0 mg/kg/day, reticulopenia, thrombocytopenia, and mild decreases in hematocrit, hemoglobin and erythrocytes were also observed. At 6.0 and 12 mg/kg/day, additional diarrhea, blood, bile or mucous in the feces, anorexia and loss of body weight, moderate periportal hepatocellular vacuolization and mild to moderate renal tubular necrosis occurred. Gastrointestinal lesions included degeneration of crypt epithelial cells, lymphoid depletion of Peyer's patches and to lesser extent ulceration and mucosal erosion. Bone marrow hypocellularity and elevated M:E ratios were observed. Centrilobular congestion, marked ovarian atrophy, and significant increases in BUN and SGPT were seen in females.