PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]CARBOplatin Injection BP

Solution for Injection, 10 mg of carboplatin / mL, Intravenous injection only

Sterile solution

Antineoplastic Agent

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, Neurologic	12/2022
8 Adverse Reactions, 8.5 Post-Market Adverse Reactions	12/2022
7 Warnings and Precautions, Cardiovascular	02/2024
7 Warnings and Precautions, 7.1.2 Breast-feeding	02/2024

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Carboplatin Injection BP 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.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

- Severe myelosuppression.
- Pre-existing severe renal impairment. Dosage adjustment may allow use in the presence of mild renal impairment (see 4 DOSAGE AND ADMINISTRATION).
- History of severe allergic reactions to carboplatin, other platinum-containing compounds, or to any ingredients in the formulation, including any non-medicinal ingredients, or component of the container (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING). Patients allergic to mannitol may be given Carboplatin Injection BP.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Carboplatin Injection BP is a highly toxic drug with a narrow therapeutic index and a therapeutic effect is unlikely to occur without some evidence of toxicity.**
- **Serious and fatal infections following administration of live or live-attenuated vaccines in patients treated with carboplatin (see 7 WARNINGS AND PRECAUTIONS)**
- **Hypersensitivity reactions, sometimes fatal, have been reported and may occur within minutes of Carboplatin Injection BP administration (see 8 ADVERSE REACTIONS)**
- **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 (see 7 WARNINGS AND PRECAUTIONS).**
- **Fatal veno-occlusive disease (see 7 WARNINGS AND PRECAUTIONS)**
- **Fatal hemolytic anemia (see 7 WARNINGS AND PRECAUTIONS)**
- **Fatal hemolytic-uremic syndrome (see 7 WARNINGS AND PRECAUTIONS)**

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Carboplatin Injection BP should only be administered to patients under the supervision of a qualified physician who is experienced in the use of chemotherapeutic agents.
- Dosage reduction or discontinuation may be necessary in the case of severe alteration of renal function tests.
- Patients presenting with impaired renal function requires adequate dosage adjustments and frequent monitoring of both hematological nadirs and renal function.
- Peripheral blood counts and renal function should be monitored closely.
- Audiograms should be performed prior to initiating therapy and during treatment or when auditory symptoms occur.

4.2 Recommended Dose and Dosage Adjustment

Adult Dosage

The recommended dose of carboplatin in previously untreated adults with normal renal function is 400 mg/m^2 given as a single intravenous infusion over 15 to 60 minutes. Therapy should not be repeated until four weeks after the previous carboplatin course.

Initial dosage should be reduced 20 to 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 (<18 years of age); therefore, Health Canada has not authorized an indication for pediatric use.

4.3 Reconstitution

Parenteral Products:

Dilution for Intravenous Infusion

Carboplatin Injection BP may be further diluted to concentrations as low as 0.5 mg/mL (500 mcg/mL) with 5% Dextrose in Water and 0.9% Sodium Chloride USP.

The reconstituted solution must be used intravenously only and should be administered by short-term (15 to 60 minutes) intravenous infusion.

When reconstituted or diluted as directed, Carboplatin Injection BP solutions are stable for 8 hours at room temperature or twenty-four (24) hours under refrigeration (4°C). Since no antibacterial preservatives are contained in the present formulation, it is recommended that any Carboplatin Injection BP solution remaining after 8 hours from reconstitution be discarded.

4.4 Administration

- Carboplatin Injection BP 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.

4.5 Missed Dose

For a missed dose of Carboplatin Injection BP, the physician will decide when the patient should receive the next one.

5 OVERDOSAGE

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. Death may follow.

Signs and symptoms of overdosage should be managed with supportive measures including hemodialysis. From reports in which doses up to 1600 mg/m^2 were used, patients were said to feel extremely unwell and developed diarrhea and alopecia. Use of higher than recommended doses of carboplatin has been associated with loss of vision, especially in patients with impaired renal function (see 8 ADVERSE REACTIONS).

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous Infusion	Solution 10 mg/mL carboplatin	Sterile water for injection. Contains no preservatives.

Carboplatin Injection BP, 10 mg/mL is supplied in 5 mL, 15 mL, 45 mL and 60 mL amber glass sterile vials. Each mL contains 10 mg of carboplatin Ph. Eur. in sterile water for injection. Carboplatin Injection BP is preservative-free. The stopper is not made with natural rubber latex.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Carboplatin Injection BP 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.

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.

Carcinogenesis and Mutagenesis

Acute promyelocytic leukaemia (APL) and myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) have been reported years after therapy with carboplatin and other antineoplastic treatments.

Carboplatin is mutagenic in *in vitro* tests (see 16 NON-CLINICAL TOXICOLOGY).

Cardiovascular

There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (defined as acute allergic mediated coronary arteriospasm, including stent thrombosis, both of which can result in myocardial infarction, see 8.1 Adverse Reaction Overview – Cardiac Disorders). The clinical manifestations of this syndrome are associated with subclinical, clinical, acute or chronic allergic reactions accompanied by cardiac symptomatology. Kounis syndrome can develop in patients with and without cardiac risk factors and may be presented with a

combination of cardiac and/or allergic symptoms (such as cutaneous rash, urticaria, asthma, etc.) and should be promptly investigated and appropriate treatment should be initiated.

Ear/Nose/Throat

Carboplatin may produce cumulative ototoxicity. Audiograms should be performed prior to initiating therapy and during treatment or when auditory symptoms occur. Clinically important deterioration of auditive function may require dosage modifications or discontinuation of therapy. The risk of ototoxicity may be increased by concomitant administration of other ototoxic drugs (e.g., aminoglycosides and cisplatin).

Delayed onset hearing loss has been reported in pediatric patients. Ototoxicity may be more pronounced in younger children. Long-term audiometric follow-up in the pediatric population is recommended.

Endocrine and Metabolism

Patients at high risk of Tumour Lysis Syndrome (TLS) such as patients with high proliferative rate, high tumor burden and high sensitivity to cytotoxic agents should be monitored closely and appropriate precaution taken.

Gastrointestinal

Carboplatin induces emesis. The incidence and severity of emesis may be reduced by pretreatment with antiemetics.

Hematologic

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. Treatment of severe hematologic toxicity may consist of supportive care, anti-infective agents for complicating infections, transfusions of blood products, autologous bone marrow rescue, peripheral stem cell transplantation and hematopoietic agents (colony-stimulating factors).

Hemolytic anemia, with the presence of serologic, drug-induced antibodies, has been reported in patients treated with carboplatin. This event can be fatal. In case of unexplained hemolysis the specialized serologic testing and treatment discontinuation should be considered.

The occurrence, severity and protraction of toxicity are 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.

Hepatic/Biliary/Pancreatic

Cases of veno-occlusive disease, including hepatic veno-occlusive disease (sinusoidal obstructive syndrome) have been reported. Some of them were fatal. Patients should be monitored for signs and symptoms of vascular occlusion and thromboembolism.

Immune

Patients with a history of allergic reaction to platinum compounds should be monitored for allergic symptoms. In case of an anaphylactic-like reaction to carboplatin, the infusion should be immediately discontinued and appropriate symptomatic treatment initiated.

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including carboplatin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving carboplatin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Monitoring and Laboratory Tests

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.

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 2000 cells/mm^3 or platelets less than 50 000 cells/mm^3 may necessitate postponement of carboplatin therapy until bone marrow recovery is evident, usually within 5 to 6 weeks.

Audiograms should be performed prior to initiating therapy and during treatment or when auditory symptoms occur.

Patients should be monitored for signs and symptoms of vascular occlusion and thromboembolism.

Neurologic

Cases of encephalopathy have been reported in patients who have received extensive prior treatment for their disease. Patients should be observed for altered mental state and other neurological signs and symptoms.

Post-market cases of posterior reversible encephalopathy syndrome (PRES, also known as RPLS, reversible posterior leukoencephalopathy syndrome) have been reported in patients receiving carboplatin in combination chemotherapy. Signs and symptoms of PRES could be headache, altered mental functioning, seizures, abnormal vision from blurriness to blindness, hypertension (see 8.5 Post-Market Adverse Reactions). Diagnosis of PRES is based upon confirmation by brain imaging.

Neurotoxicity, such as parasthesias and decreased deep tendon reflexes, and ototoxicity are more likely to be seen in patients who have received cisplatin previously. Routine neurologic examination is advisable during carboplatin therapy, particularly in patients previously treated with cisplatin and in patients over 65 years of age.

Renal

Hemolytic-uremic syndrome (HUS) is a potentially life-threatening side effect. Carboplatin Injection BP should be discontinued at the first sign of any evidence of microangiopathic hemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or lactate dehydrogenase (LDH). Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.

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.

The optimal use of Carboplatin Injection BP in patients presenting with impaired renal function requires adequate dosage adjustments and frequent monitoring of both hematological nadirs and renal function.

Reproductive Health: Female and Male Potential

Women of childbearing potential should be advised to avoid becoming pregnant while receiving carboplatin and to use effective contraception during treatment with carboplatin and for at least 7 months after the last dose (see 7.1.1 Pregnant Women).

Men with female partners of childbearing potential should be advised to use effective contraception during treatment with carboplatin and for at least 4 months after the last dose.

- **Fertility**

Gonadal suppression resulting in amenorrhea or azoospermia may occur in patients receiving antineoplastic therapy. These effects appear to be related to dose and length of therapy and may be irreversible. Prediction of the degree of testicular or ovarian functional impairment is complicated by the common use of combinations of several antineoplastics, which makes it difficult to assess the effects of individual agents.

Male and female fertility may be impacted by treatment with carboplatin (see 16 NON-CLINICAL TOXICOLOGY). Both men and women should seek advice for fertility preservation before treatment with Carboplatin Injection BP.

7.1 Special Populations

7.1.1 Pregnant Women

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.

If the drug is administered during pregnancy or if the patient becomes pregnant while receiving Carboplatin Injection BP, the patient should be informed of the potential hazard to the fetus. Women of childbearing potential are advised to avoid becoming pregnant while on carboplatin therapy.

7.1.2 Breast-feeding

Carboplatin Injection BP and its active metabolites have been identified in human milk of treated mothers. Because of the potential for serious adverse reactions in infants, breast-feeding should be discontinued during therapy and for 1 month following last dose of treatment or treatment should be discontinued, taking into account the importance of the drug to the mother.

7.1.3 Pediatrics

Sufficient use of carboplatin in pediatrics (<18 years of age) has not occurred to allow specific dosage recommendations to be made; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

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

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Myelosuppression is the dose-limiting toxicity of Carboplatin Injection BP. 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:

Allergic reactions and immune system disorders: In less than 2% of patients, reactions similar to those seen after cisplatin have been observed: erythematous rash, fever, pruritus, hypotension and bronchospasm. However, no cross-reactivity between cisplatin and carboplatin was observed. Hypersensitivity reactions, sometimes fatal, may occur within a few minutes after intravenous administration of carboplatin.

Cardiac disorders: Isolated cases of cardiovascular incidents (cardiac insufficiency, embolism) as well as isolated cases of cerebrovascular accidents have been reported and were fatal in less than 1% of patients. Kounis syndrome has also been reported.

Gastrointestinal system: Nausea and vomiting 53%, nausea only 25%, diarrhea 6%, constipation 3%. Nausea and vomiting usually occur 6 to 12 hours after administration of carboplatin and disappear within 24 hours. It is readily controlled (or may be prevented) by antiemetic medication. Other gastrointestinal effects, such as abdominal pain (sometimes fatal) and stomatitis have been reported.

General disorders and administration site conditions: Alopecia 2%, influenza-like syndrome 1%, reaction at injection site < 1%. Mucosal inflammation has been reported. Asthenia has also been reported, sometimes fatal.

Hematologic system: Leucopenia 55%, thrombocytopenia 32%, anemia 59%, bleeding 6%. Hemolytic anemia (sometimes fatal), with the presence of serologic, drug-induced antibodies, has been reported in patients treated with carboplatin (see 7 WARNINGS AND PRECAUTIONS). Transfusional support has been required in about one-fifth of patients. Neutropenia has also been reported, sometimes fatal. Hemolytic uremic syndrome (HUS) has also been reported.

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.

Musculoskeletal and connective tissue disorders: Myalgia/arthralgia has been reported, sometimes fatal.

Neoplasms benign, malignant and unspecified: There have been rare reports of acute myelogenous leukemias and myelodysplastic syndromes, sometimes fatal, arising in patients who have been treated with carboplatin, mostly when given in combination with other potentially leukemogenic agents.

Neurological system: Peripheral neuropathy 6%, dysgeusia <1%. Paresthesias present prior to treatment, especially if caused by cisplatin, may persist or worsen during carboplatin therapy (see 7 WARNINGS AND PRECAUTIONS). Encephalopathy has also been reported (see 7 WARNINGS AND PRECAUTIONS).

Renal and urinary disorders: 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. Hyponatremia has also been reported, sometimes fatal.

Skin and subcutaneous tissue disorders: Exfoliative dermatitis may rarely occur. Urticaria has also been reported, sometimes fatal, in association with carboplatin. Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and erythema multiforme (EM) have also been reported.

Special Senses: Subclinical decrease in hearing acuity as determined by audiogram in the high frequency (4000 to 8000 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. Visual abnormalities, such as transient sight loss (which can be complete for light and colors) or other disturbances may occur in patients treated with carboplatin. Improvement and/or total recovery of vision usually occurs within weeks after the drug is discontinued. Cortical blindness has been reported in patients with impaired renal function receiving high-dose carboplatin.

Vascular: Cases of veno-occlusive disease, including hepatic veno-occlusive disease have been reported. Some of them were fatal (see 7 WARNINGS AND PRECAUTIONS).

8.5 Post-Market Adverse Reactions

Post-market cases of posterior reversible encephalopathy syndrome (PRES, also known as RPLS, reversible posterior leukoencephalopathy syndrome) have been reported infrequently in patients receiving carboplatin in combination chemotherapy (see 7 WARNINGS AND PRECAUTIONS).

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

Concomitant administration of carboplatin and aminoglycosides results in an increased risk of nephrotoxicity and/or ototoxicity, and the drugs should be used concurrently with caution. The use of other nephrotoxic drugs results in a potentiation of renal effects by carboplatin.

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.

A decrease in phenytoin serum levels has been observed with concurrent administration of carboplatin and phenytoin/fosphenytoin. This may lead to exacerbation of seizures.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of 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.

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).

No clinical trial data on which the original indication was authorized, however, *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.

10.3 Pharmacokinetics

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.

Distribution:

Carboplatin is not bound to plasma proteins. However, 87% of the platinum from carboplatin becomes irreversibly bound to plasma proteins within 24 hours following administration.

Elimination

Carboplatin is excreted primarily in the urine with recovery of approximately 70% of the administered platinum within 24 hours. Following administration of carboplatin, half-lives of free ultrafilterable platinum and carboplatin in man were approximately 6 hours and 1.5 hours, respectively. Plasma bound platinum from carboplatin is slowly eliminated with a minimum half-life of 5 days.

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 4 DOSAGE AND ADMINISTRATION).

11 STORAGE, STABILITY AND DISPOSAL

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

The product is available in an amber glass vial. It is recommended that the vial remains in the carton until time of use.

The Carboplatin Injection BP vial should be inspected for damage and visible signs of leaks before use. If there are signs of breakage or leakage from the vial, do not use. Incinerate the unopened package.

Parenteral drug products should be inspected visually for clarity, particulate matter, precipitation, and discolouration prior to administration, whenever possible. Vials with visible particulate matter should not be used.

12 SPECIAL HANDLING INSTRUCTIONS

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

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

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.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

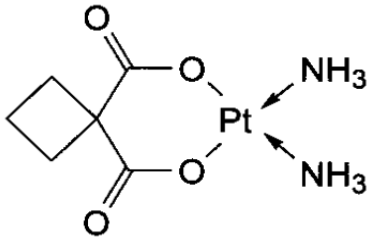
Drug Substance

Proper name: Carboplatin

Chemical name: (l,l-cyclobutane-dicarboxylato) platinum

Molecular formula and molecular mass: $C_6H_{12}N_2O_4Pt$, 371.25 g/mol

Structural formula:



Physicochemical properties: Carboplatin Ph. Eur. is a colourless crystalline powder which is soluble in water at concentrations below 15 mg/mL. It is virtually insoluble in ethanol, acetonitrile, acetone, and dimethylacetamide.

pH: Between 5.0 to 7.0

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Acute and Subacute Toxicity

The LD_{10}, LD_{50} and LD_{90} were determined in rodents (Table 1).

Table 1. Toxicity of Carboplatin in Rats and Mice

Lethality	Mice, CDF_1 (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 intravenously 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 intravenous dose range of 40 to 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 gastrointestinal toxicity or destruction of lymphocytes.

The lowest single intravenous dose of carboplatin causing emesis in dogs was 624 mg/m^2 (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 intravenous doses up to 12.0 mg/kg/day of carboplatin showed emesis, anorexia and diarrhea or loose feces, and leucopenia 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 Payer'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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PrPARAPLATIN - AQ (carboplatin for injection; Solution; 10 mg / mL), submission control 094707, Product Monograph, Bristol-Myers Squibb Canada (October 25, 2004).
2. PrCARBOPLATIN INJECTION BP solution, 10 mg/mL, submission control 274117, Product Monograph, Pfizer Canada ULC. (AUG 23, 2023).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] CARBOplatin Injection BP

Carboplatin injection

Read this carefully before you start taking **Carboplatin Injection BP** and each time you get an infusion. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Carboplatin Injection BP**.

Serious Warnings and Precautions

Carboplatin is a very toxic drug. It is unlikely for this medicine to work without some side effects.

Carboplatin Injection BP can cause serious and possibly fatal side effects including:

- **Serious** and fatal **infections** after receiving some vaccines.
- **Allergic reactions** that may happen within minutes of receiving Carboplatin Injection BP.
- **Myelosupression:** This is when your blood counts are low. It can affect red blood cells (**anemia**), white blood cells (**neutropenia**) or platelets (**thrombocytopenia**). Myelosuppression can be severe and may increase your risk for infection or bleeding. It may be worse as the number of doses you receive increases. You many need blood transfusions.
- **Vomiting**
- **Fatal hemolytic anemia:** This happens when red blood cells are broken down faster than the body can make new ones.
- **Fatal hemolytic uraemic syndrome:** This happens when there is abnormal breakdown of blood cells which clogs the kidney.
- **Fatal veno-occlusive disease:** This is when the blood vessels leading to and inside the liver are blocked.

What is Carboplatin Injection BP used for?

Carboplatin Injection BP is used to treat adult women with some types of ovarian cancer. It may be given when other treatments have not worked.

How does Carboplatin Injection BP work?

Carboplatin is an anti-cancer medicine, sometimes called chemotherapy. Carboplatin works by preventing the growth of cancer cells and eventually destroying them. Carboplatin can be used alone or in combination with other anti-cancer drugs.

What are the ingredients in Carboplatin Injection BP?

Medicinal ingredients: carboplatin

Non-medicinal ingredients: sterile water for injection

Carboplatin Injection BP comes in the following dosage forms:

Solution: 10 mg / mL

Do not use Carboplatin Injection BP if:

- you are allergic to carboplatin, to any other ingredients in this medicine or to any other medicines that contain platinum;
- you have myelosuppression;
- you have severe kidney disease.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Carboplatin Injection BP. Talk about any health conditions or problems you may have, including if you:

- have recently had or are planning on receiving any vaccinations
- have kidney disease or are taking medications that can damage the kidney. Your doctor will want to monitor you more regularly.
- have been treated with cisplatin or similar anti-cancer medicines in the past. This is because side effects affecting the nervous system are more likely in patients who have received cisplatin previously.
- are over 65 years old.

Other warnings you should know about:

- Carboplatin Injection BP should only be administered to you under the supervision of a qualified physician who is experienced in the use of chemotherapy drugs.
- Carboplatin can cause damage in the ear leading to loss of hearing. You will need to have hearing tests before and during your treatment. These will be repeated if you show signs of hearing loss.
- Tumour lysis syndrome (TLS) is a potentially life-threatening complication. It is caused by chemical disturbances in the blood when cancer cells breakdown and release their contents. If you are higher risk of TLS, your healthcare professional may follow you more closely.
- **Female patients – Pregnancy and breastfeeding:**
    - If you are pregnant, able to get pregnant or think you are pregnant, there are specific risks you should discuss with your healthcare professional.
    - Avoid becoming pregnant while you are using Carboplatin Injection BP. It could harm your unborn baby.

- Use effective birth control each time you have sex during your treatment and for at least 7 months after your last dose.
- If you do get pregnant during your treatment, tell your healthcare professional right away.
- Carboplatin passes into breastmilk. Avoid breastfeeding during your treatment and 1 month after the end of your treatment.

- **Male patients – Pregnancy:** Use effective birth control each time you have sex with a woman who could get pregnant. You should use this birth control during your treatment and for at least 4 months after your last dose.
- **Fertility – male and female patients:** Treatment with Carboplatin Injection BP may affect your ability to have a child in the future. Talk to your healthcare professional if you have questions about this.
- **Tests:** During your treatment with Carboplatin Injection BP, you will have regular blood and urine tests. The results of these tests will tell your healthcare professional how the treatment is affecting your blood, liver and kidneys. Your healthcare professional will also check you for blood clots, nerve damage and hearing loss.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Carboplatin Injection BP:

- Medicines used to treat bacterial infections called aminoglycosides
- Medicines which can reduce the number of cells in your blood
- Medicines that can affect or damage your kidneys
- Medicines used to treat convulsions and seizures called phenytoin and fosphenytoin

How to take Carboplatin Injection BP:

Carboplatin Injection BP will be given to you by a healthcare professional. It will be given by infusion (drip) over 15 to 60 minutes. This means Carboplatin Injection BP will be given through a tube placed into one of your veins.

Usual dose:

Your healthcare professional will work out the correct dose of Carboplatin Injection BP for you. It will depend on your medical condition, your height and weight and how well your kidneys are working. Your healthcare professional will also tell you how often you will receive Carboplatin Injection BP. There will be about 4 weeks between each dose.

Your healthcare professional may change your dose of Carboplatin Injection BP or stop your treatment completely. This can happen if you experience certain side effects.

Overdose:

This medicine will be given to you in a hospital, under the supervision of a doctor. It is unlikely that you will be given too much or too little, however, tell your doctor or nurse if you have any concerns. Too much Carboplatin Injection BP may affect your blood count, kidneys, or liver. Tell your healthcare professional if you have extreme fatigue, diarrhea, hair loss or abnormal vision.

If you think you, or a person you are caring for, have taken too much Carboplatin Injection BP, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed dose:

If you miss a dose, your healthcare professional will decide when you should receive the next one.

What are possible side effects from using Carboplatin Injection BP?

These are not all the possible side effects you may have when taking Carboplatin Injection BP. If you experience any side effects not listed here, tell your healthcare professional.

- nausea
- flu-like symptoms
- tingling or numbness in your hands, feet, arms or legs
- burning or prickling sensation
- decreased tendon reflex
- taste disturbance or loss of taste
- ringing in the ears or changes in your hearing
- diarrhea or constipation
- sore lips or mouth ulcers
- hair loss
- rash and/or itchy skin
- pain or discomfort in your bones, joints, muscles, or surrounding structures
- skin disorders such as hives, rash, skin redness, and itching
- swelling or soreness where the injection was given

Carboplatin Injection BP can cause abnormal blood test results. Your healthcare professional will do regular blood tests and will interpret the results. The results of these tests will tell your healthcare professional how Carboplatin Injection BP is affecting your blood, kidneys and liver. The results may also tell them if you have gout.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Get immediate medical help**
	Only if severe	**In all cases**	
Unknown frequency			
Severe allergic reaction (anaphylaxis / anaphylactic reactions): sudden itchy rash (hives), swelling of the hands, feet, ankles, face, lips, mouth or throat, difficulty swallowing or breathing, tightness of the chest or wheezing, feeling faint, death			**X**
Myelosuppression including: **Anemia** (low red blood cells): fatigue, loss of energy, pale skin, shortness of breath, weakness **neutropenia** (low white blood cells): signs of infection such as a sore throat and high temperature **thrombocytopenia** (low platelets): abnormal bruising, bleeding		**X**	
Hemolytic-uraemic syndrome (when blood vessels in the kidney are damaged or inflamed): decreased or no urine, blood in the urine, diarrhea, abdominal pain, vomiting and fever, death			**X**
Tumour lysis syndrome (the sudden, rapid death of cancer cells due to the treatment): muscle cramping, muscle weakness, confusion, visual loss or disturbances, irregular heartbeat, kidney failure or abnormal blood test results		**X**	
Hepatic veno-occlusive disease (blocked blood vessels leading to and inside the liver): enlarged liver, swelling and pain in the upper right abdomen, weight gain, yellowing of the skin and whites of eyes (jaundice), death		**X**	
Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), or erythema multiforme (EM) (severe skin rashes that may become life threatening): reddish target-like spots			**X**

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Get immediate medical help**
	Only if severe	**In all cases**	
or circular patches, blisters or peeling of the skin, blisters in the mouth, red and swollen eyes. The skin changes happen quickly and may follow fever, tiredness, headache, and cough			
Hemolytic anemia (decrease number of red blood cells): fatigue, loss of energy, pale skin, shortness of breath, weakness		**X**	
Serious and fatal infections: sore throat and high temperature		**X**	
Vision problems: temporary worsening of eyesight or changes to your vision, temporary loss of sight		**X**	
Liver problems: yellowing of the skin and eyeballs, pain in your abdomen, abdominal swelling, nausea, vomiting, feeling unwell, confusion, sleepiness		**X**	
Kidney problems: decreased urine output, swelling of legs, ankles or feet, shortness of breath, fatigue, confusion, nausea, weakness, irregular heartbeat		**X**	
Secondary blood malignancies (new cancers that affect the blood); fatigue, shortness of breath, paleness, bruising or bleeding, red spots under the skin, frequent infections, fever, bone pain, loss of appetite, nausea, night sweats, swollen lymph nodes, weight loss		**X**	
Posterior Reversible Encephalopathy Syndrome (PRES; swelling of some parts of the brain): headache, confusion, seizures, and visual disturbances (blurred vision, loss of sight), changes in mental function		**X**	
Stroke (lack of blood flow to the brain)**:** sudden loss of speech or numbness of part or all of the body, loss of vision or blurred vision, unexplained dizziness and/or sudden falls		**X**	
Heart Failure (heart does not pump blood as well as it should): feeling dizzy,		**X**	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Get immediate medical help**
	Only if severe	**In all cases**	
fatigue and weakness, lightheaded, shortness of breath, feeling like your heart is pounding, racing, beating irregularly, fluid retention, lack of appetite, nausea, swelling in the ankles, legs and feet			
Embolism (when the flow of blood is blocked within a blood vessel): chest pain, shortness of breath, dizziness, fainting, nausea, irregular heartbeat, palpitations, coughing, sweating		**X**	
Encephalopathy (mental changes): symptoms may include changes in memory, difficulty focusing, change in personality, fatigue, progressive loss of consciousness		**X**	
Pain in abdomen (sometimes fatal)	**X**		
Asthenia: extreme tiredness or weakness (sometimes fatal)	**X**		
Vomiting	**X**		
Kounis syndrome: acute coronary syndrome (chest pain with radiation to the next or left arm, pale skin, sweating, shortness of breath) caused by a severe allergic reaction (see Severe allergic reaction side effect above in this table, for symptoms).		**X**	

If you experience any side effects not listed here, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Your healthcare professional will store Carboplatin Injection BP vials between 15 and 25°C, protected from light.

If you want more information about Carboplatin Injection BP:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.accordhealth.ca, or by calling 1-866-296-0354.

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