

DRUG NAME: Carboplatin

SYNONYM(S): CBDCA, JM8, NSC 241240

COMMON TRADE NAME(S): PARAPLATIN®, PARAPLATIN-AQ®

CLASSIFICATION: Alkylating agent

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Carboplatin is an analog of cisplatin. Like cisplatin, it contains a platinum atom surrounded in a plane by two ammonia groups and two other ligands in the *cis* position. The other two ligands in carboplatin are present in a ring structure rather than as two chloride atoms in cisplatin. This difference makes carboplatin more stable and has less nephrotoxicity, neurotoxicity, ototoxicity and emetogenesis.^{1,2} The exact mechanism of action of carboplatin is not known. Carboplatin undergoes intracellular activation to form reactive platinum complexes which are believed to inhibit DNA synthesis by forming interstrand and intrastrand cross-linking of DNA molecules. Carboplatin is a radiation-sensitizing agent.^{3,4} It is cell cycle-phase nonspecific.²

PHARMACOKINETICS:

Interpatient variability	2- to 3-fold variability in AUC with BSA-based dosing. ^{5,6} Variability can be reduced with Calvert AUC-based dosing formula. ^{6,7}	
Oral Absorption	poorly absorbed; oral route not used clinically ⁸	
Intraperitoneal Absorption	peak plasma level within 2-4 h after intraperitoneal instillation with 65% of dose absorbed over 4 h of dwelling ^{2,9}	
Distribution	widely distributed, mostly in kidney, liver, skin, tumour tissue; also in erythrocytes	
	cross blood brain barrier?	yes
	volume of distribution ¹⁰	ultrafilterable platinum*: 17 ± 2 L/1.73 m ²
	plasma protein binding	carboplatin: minimal ^{2,11} platinum: 87%, ^{2,12}
Metabolism	undergoes intracellular hydrolysis to form reactive platinum complexes	
	active metabolite(s)	platinum complexes
	inactive metabolite(s)	no information found
Excretion	renal excretion via glomerular filtration; extensively removed by hemodialysis.	
	urine	71% within 24 h
	terminal half life	5.8 ± 1.6 days (total platinum*) ^{1,10} platinum elimination from erythrocytes: 12 days
	clearance	1.38 ± 0.36 L/h/1.73 m ² (total platinum*) ¹⁰
Gender	no information found	
Elderly	clearance may be reduced due to age-related renal function impairment ^{2,11}	
Children	similar to adults ^{6,13}	
Ethnicity	no information found	

Adapted from reference² unless specified otherwise.

*Ultrafilterable platinum consists of carboplatin and free carboplatin metabolites; total platinum consists of protein bound and free platinum. Pharmacokinetics of ultrafilterable platinum is clinically more useful as only free platinum species are cytotoxic.²

USES:

Primary uses:

Anal cancer¹⁴
Brain tumour¹⁴
Breast cancer¹⁴
Cervical cancer¹⁴
Endometrial cancer¹⁴
Esophageal cancer¹⁴
Gallbladder cancer¹⁴
Gastric cancer¹⁴
Germ cell tumour¹⁴
Head and neck cancer¹⁴
Lymphoma, non-Hodgkin¹⁴
Merkel cell carcinoma¹⁴
Lung cancer, non-small cell¹⁴
Lung cancer, small cell¹⁴
*Ovarian cancer
Testicular cancer¹⁴
Thymoma¹⁴
Urothelial cancer¹⁴

*Health Canada approved indication

Other uses:

Bladder cancer¹⁴
Ewing's sarcoma¹⁴
Lymphoma, Hodgkin¹⁴
Malignant mesothelioma¹⁴
Melanoma¹⁴
Osteosarcoma¹⁴
Neuroendocrine tumours¹⁴
Prostate cancer¹⁴
Retinoblastoma¹⁴
Thyroid malignancies¹⁴
Wilm's tumour¹⁴

SPECIAL PRECAUTIONS:

Contraindications:

- history of hypersensitivity reaction to carboplatin, other platinum agents (e.g., cisplatin) or mannitol¹² per manufacturer; however, rechallenging with carboplatin or switching to cisplatin with appropriate precautions has been tolerated by some patients with hypersensitivity reactions to carboplatin.^{2,15,16}

Caution:

- **prior exposure to cisplatin** increases the risk and severity of toxicities (e.g., myelosuppression, nausea, vomiting, peripheral neuropathy, ototoxicity).¹²

Special populations (Geriatrics): Incidence of peripheral neuropathy is increased and myelosuppression may be more severe in patients older than 65 years of age. In addition, elderly patients are more likely to have age-related renal function impairment, which may require dosage reduction and careful monitoring of blood counts.^{2,11}

Carcinogenicity: Acute promyelocytic leukemia and myelodysplastic syndrome/acute myeloid leukemia have been reported years after therapy with carboplatin.¹⁷

Mutagenicity: Carboplatin is mutagenic in *in vitro* studies.¹⁷

Fertility: Carboplatin may cause gonadal suppression (e.g., amenorrhea, azoospermia) in patients which has generally been related to dose and length of therapy and may be irreversible. **Marked ovarian atrophy was reported in animal studies. If applicable, fertility preservation should be considered prior to treatment.**¹⁷

Pregnancy: In animal studies, carboplatin produced embryotoxicity and teratogenicity. In female patients with reproductive potential, contraception is recommended during treatment and for at least 6 months after treatment has

ended. In male patients with female partners of reproductive potential, contraception is recommended during treatment and for at least 3 months after treatment has ended.¹⁷

Breastfeeding is not recommended due to the potential secretion into breast milk.¹¹

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
allergy/immunology	hypersensitivity (2-30%) ¹⁸⁻²⁰ ; see paragraph following Side Effects table
auditory/hearing	ototoxicity (tinnitus, visual and taste disturbances) (1%)
blood/bone marrow febrile neutropenia (see paragraph following Side Effects table)	anemia (71%)
	leukopenia (severe 14%); nadir 21 days, recovery 30 days ¹¹
	neutropenia (severe 18%); nadir 21-28 days, recovery 35 days ¹¹
	thrombocytopenia (severe 25%); nadir 21 days, recovery 30 days ¹¹
constitutional symptoms	asthenia (8%)
dermatology/skin	extravasation hazard: nonvesicant ²¹
	alopecia (3%)
gastrointestinal	emetogenic potential: moderate ²²
	constipation (6%)
	diarrhea (6%)
	nausea (15%); see paragraph following Side Effects table
	vomiting (64%); see paragraph following Side Effects table
hepatic	elevated alkaline phosphatase (24%)
	elevated AST (15%)
	elevated bilirubin (5%)
infection	infections (4%)
metabolic/laboratory	hypocalcemia (22%)
	hypomagnesemia (29%)
	hypokalemia (20%)
	hyponatremia (29%)
	increased BUN (14%)
	increased uric acid (5%)
neurology	CNS symptoms (5%) ²
	dysgeusia ¹⁷ (<1%)
	encephalopathy ¹⁷ (<1%); see paragraph following Side Effects table
	peripheral neuropathy (4-6%) ¹⁷ ; see paragraph following Side Effects table

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	posterior reversible encephalopathy syndrome (PRES) (<1%) ^{17,23} ; see paragraph following Side Effects table
ocular/visual	visual disturbances (<1%) ²
pain	abdominal pain (17%)
renal/genitourinary	acute renal failure (<1%) ² ; see paragraph following Side Effects table
	decreased creatinine clearance (27%)
	increased serum creatinine (6%)
syndromes	hemolytic-uremic syndrome (<1%)

Adapted from reference¹² unless specified otherwise.

Cases of **encephalopathy** and altered mental state have been reported in patients receiving carboplatin, particularly in patients who have received extensive treatment of their disease. Symptoms may include changes in memory, difficulty focusing, personality changes, progressive loss of consciousness, and fatigue. Cases of posterior reversible encephalopathy syndrome (PRES) have also been reported in patients receiving carboplatin in combination with other chemotherapy. PRES is a rare but serious event that may also be known by reversible posterior leukoencephalopathy (RPLS). In addition to altered mental functioning, symptoms of PRES may include headache, seizures, abnormal vision (blurriness to blindness), and hypertension. Diagnosis of PRES is confirmed by brain imaging. Monitor for altered mental state and neurologic signs and symptoms during treatment with carboplatin.^{17,23}

Hypersensitivity has been reported in 2% of patients receiving carboplatin alone and in 9-30% patients receiving carboplatin with other cytotoxic drugs.¹⁸⁻²⁰ Reactions are similar to those seen with other platinum agents (e.g., cisplatin) and include anaphylaxis and anaphylactoid reactions.² Symptoms may vary in severity and include pruritus, rash, palmar erythema, fever, chills, rigors, swelling (face, tongue, and infusion arm), GI upset, dyspnea, wheezing, tachycardia, and hypertension or hypotension.^{15,19} Reactions can develop during carboplatin administration or several hours to days after. The risk of reactions increases with repeated exposure to platinum agents,^{18,19} particularly after 7 courses of carboplatin or receiving the second course of carboplatin after prior platinum therapy.^{15,19} The hypersensitivity appears to be mainly an IgE-mediated type I immediate reaction but may also involve direct histamine release. Some reactions may also be due to the mannitol present in some carboplatin formulations.² Management includes prompt treatment of anaphylaxis (see BCCA Hypersensitivity Guidelines) and oral diphenhydramine 25-50 mg every 4-6 hours for minor delayed reactions.¹⁹ In some cases, carboplatin therapy may be continued with prophylactic corticosteroid and antihistamine and/or desensitization.^{16,19}

Myelosuppression is the dose-limiting toxicity, usually manifested as thrombocytopenia and less commonly as leukopenia, neutropenia and anemia. Risk factors include prior cytotoxic therapy (especially cisplatin), poor performance status, old age, impaired renal function and concurrent myelosuppressive therapy.^{2,12} Myelosuppression is dose dependent, closely related to the renal clearance of carboplatin, and minimized by using the Calvert AUC-based dosing formula.^{7,12} Anemia is more common with increased carboplatin exposure and blood transfusions may be needed during prolonged carboplatin therapy (e.g., more than 6 cycles).²

Nausea and vomiting usually begin within 6-12 hours after administration and may persist up to 24 hours or longer. Acute vomiting appears to be mediated by local GI and central serotonin mechanisms and is most common in patients with prior emetogenic cytotoxic therapy or receiving concurrent emetogenic agents. The incidence and severity of vomiting may be reduced by prophylactic antiemetics. There is some evidence that the incidence of nausea and vomiting is reduced when carboplatin is given as a 24-hour continuous IV infusion or in divided doses over 5 consecutive days.²

Neurotoxicity such as peripheral sensory neuropathy (e.g., paresthesia) is less frequent or severe than with cisplatin. Peripheral neuropathy is more common in patients over 65, receiving prolonged carboplatin therapy, or

with prior cisplatin therapy. [Paresthesias that are present prior to treatment, especially if caused by cisplatin, may persist or worsen during treatment with carboplatin.](#)¹⁷ Neurologic evaluations should be performed regularly.²⁴

Nephrotoxicity: is less common or severe than with cisplatin; concomitant IV hydration and diuresis generally are not needed with carboplatin.^{1,2} The risk and severity of nephrotoxicity are increased with high dose carboplatin regimen, especially when given concurrently with other nephrotoxic chemotherapy.^{25,26}

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
phenytoin ^{27,28}	decreased serum phenytoin level	possibly decreased absorption or increased metabolism of phenytoin	monitor serum phenytoin level carefully during and after carboplatin therapy; adjust phenytoin dose as needed
warfarin ^{28,29}	increased anticoagulant effect of warfarin	unknown; possibly decreased protein binding or decreased metabolism of warfarin	monitor INR carefully during and after carboplatin therapy; adjust warfarin dose as needed

SUPPLY AND STORAGE:

Injection:

Accord Healthcare Inc. supplies carboplatin as 50 mg, 150 mg, 450 mg, and 600 mg single use (preservative free) vials in a concentration of 10 mg/mL. Store at room temperature. Protect from light.¹⁷

Pfizer Canada ULC supplies carboplatin as 50 mg, 150 mg, 450 mg, and 600 mg single use (preservative free) vials in a concentration of 10 mg/mL. Store at room temperature. Protect from light.³⁰

Teva Canada Ltd supplies carboplatin as 50 mg, 150 mg, 450 mg, and 600 mg single use (preservative free) vials in a concentration of 10 mg/mL. Store at room temperature. Protect from light.³¹

For basic information on the current brand used at BC Cancer, see [Chemotherapy Preparation and Stability Chart](#) in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see [Chemotherapy Preparation and Stability Chart](#) in Appendix.

Additional information:

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold, italics***

Subcutaneous	no information found
Intramuscular	no information found

BC Cancer administration guideline noted in **bold, italics**

Direct intravenous	no information found
<i>Intermittent infusion</i> ^{2,12}	<i>over 30 min</i> ; can also be given over 15-60 min
Continuous infusion ²	<i>over 24 h</i>
<i>Intraperitoneal</i> ^{9,32,33}	<i>infuse into abdominal cavity as rapidly as possible by gravity</i>
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial ³⁴	investigational, 600 mg/m ² in NS 500 mL infused over 1 h
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BC Cancer usual dose noted in **bold, italics**

Intravenous: Cycle Length:
1-4 weeks³⁵⁻³⁹: ***AUC-based carboplatin dose IV for one dose on day 1***

Calculate carboplatin dose with Calvert formula:

$$\text{Dose (mg)} = \text{AUC} \times (\text{GFR} + 25)^{7,8,40}$$

Where AUC = 4-7, GFR obtained from nuclear renogram (preferred) or approximated by CrCl calculated from serum creatinine using the Cockcroft-Gault formula⁴¹:

$$\text{calculated creatinine clearance} = \frac{\text{N} \times (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$$

* For males N=1.23; for females N=1.04

Estimated GFR (reported by lab as eGFR) or calculated creatinine clearance (using Cockcroft Gault formula) should be **capped** at 125 mL/min when used to calculate the **initial** dose of carboplatin using the Calvert Formula (AUC(GFR+25)).⁴²

Note that the Cockcroft-Gault formula overpredicts CrCl in certain conditions (e.g., muscle wasting, obesity, ascites). Lean or ideal body weight may be used to correct for excess fat or fluid.⁴³ Repeat renogram to modify dose if >20% increase in serum creatinine during treatment.^{44,45}

Calvert AUC-based dosing formula is not recommended with GFR or CrCl <20 mL/min.^{2,7}

3-4 weeks^{1,17}: ***300 mg/m² (range 200-400 mg/m²) IV for one dose on day 1***

BC Cancer usual dose noted in **bold, italics**

Bone marrow transplant: Cycle Length: higher doses are used for tumour ablation prior to bone marrow transplant^{25,46,47}; (e.g., 266-666 mg/m²/day IV for 3 days; 200-500 mg/m²/day IV for 4 days; 175-400 mg/m²/day IV for 5 days)

Concurrent radiation: 1-3 weeks⁴⁸⁻⁵¹: **AUC-based carboplatin dose IV for one dose on day 1 given concurrently with radiation**

30 mg/m² IV once daily on days 1-5 in weeks 1-4 has been used as radiosensitizer³

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"

Dosage in renal failure: adjustment is required when BSA-based dosing (mg/m²) is used; the following guideline is suggested:^{28,41}

CrCl (mL/min)	Starting dose (mg/m ²)
>40	400
20-39	250
10-19	150
0-9	100

calculated creatinine clearance =
$$\frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$$

* For males N=1.23; for females N=1.04

adjust **subsequent dose** according to hematological toxicity to previous dose^{2,12,52}

Dosage in hepatic failure: no adjustment required

Dosage in dialysis: hemodialysis: • supplement with 50% of the dose after dialysis⁵³
In dialysis-dependent chronic renal failure, a fixed dose of 100 mg (previous platinum treatment) or 150 mg (no previous platinum treatment) may be used, with dialysis performed 24 h after carboplatin administration.⁵⁴

peritoneal dialysis⁵³: dose as per GFR <10 mL/min (25% of the dose)

continuous renal replacement therapy⁵³: 200 mg/m²

Children:

<i>Intravenous:</i>	Cycle length:	
	3-4 weeks:	400 mg/m ² IV for one dose daily for 2 consecutive days starting on day 1 (total dose per cycle 800 mg/m ²) ⁵⁵
	4 weeks ⁵ :	560 mg/m ² IV for one dose on day 1
	4 weeks:	80-216 mg/m ² IV for one dose daily for 5 consecutive days starting on day 1 (total dose per cycle 400-1080 mg/m ²) ^{5,56}

Some investigators calculate carboplatin dose with modified Calvert formula (GFR is obtained from nuclear renogram)^{55,57}

Dose (mg) = AUC x [(GFR x BSA)/1.73 + (15 x BSA)]
(where GFR in mL/min/1.73 and AUC^{55,57} = 6-7)

OR

Dose (mg) = AUC x {GFR + [0.36 x weight (kg)]}
(where AUC^{6,58} = 2-7)

Bone marrow transplant: higher doses are used for tumour ablation prior to bone marrow transplant⁵; (e.g., 100-800 mg/m²/day IV for 3 days; 250-300 mg/m²/day IV for 4 days; 250-350 mg/m²/day IV for 5 days)

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