Drug Monograph

A - Drug Name

CARBOplatin

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B - Mechanism of Action and Pharmacokinetics

Carboplatin is a cisplatin derivative and shares the same mechanism of action. Highly reactive platinum complexes are formed intracellularly. These complexes inhibit DNA synthesis through covalent binding of DNA molecules to form intrastrand and interstrand DNA crosslinks. Carboplatin is considered to be cell cycle phase-nonspecific, but recent studies have shown complex and variable effects on the cell cycle.

Absorption	Intraperitoneal: 65% after a 4-hour dwell period.	
Distribution	Widely distributed, highest concentration in liver, kidney and skin. Pharmacokinetics are dose proportional. No apparent accumulation with repeated daily dosing, after 4 days.	
	Cross blood brain barrier?	Yes; Low concentrations
	PPB	87% within 24 h (platinum-containing products)
Metabolism	Carboplatin is hydrolyzed to aquated and hydroxylated compounds	
	Active metabolites	Platinum complexes
	Inactive metabolites	No information found

Elimination		
	Primarily renal via glomerular filtration, clearance correlates with glomerular filtration rate.	
	Urine	70% as carboplatin
	Half-life	total plasma platinum: 24 hours
	Half-life	free plasma platinum: 6 hours
	Half-life	carboplatin: 1.5 hours
	Half-life	total platinum from erythrocytes: 12 days

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C - Indications and Status

Health Canada Approvals:

- For the treatment of ovarian cancer of epithelial origin in first-line therapy or second-line therapy after other treatments have failed.

Other Uses:

- Brain and CNS tumours
- Breast cancer
- Neuroendocrine Tumours
- Bladder cancer
- Gynecological cancers: endometrial, fallopian tube, cervical, vulvar, primary peritoneal, sarcoma
- Lung cancer: small cell, non-small cell
- Testicular cancer
- Anal cancer
- Colorectal cancer
- Gastroesophageal cancer
- Hepatobiliary cancer
- Pancreatic cancer
- Prostate cancer
- Head and Neck cancer
- Mesothelioma
- Thymoma
- Thyroid cancer

- Melanoma
- Merkel cell cancer
- Cancer of unknown primary origin
- Cutaneous squamous cell cancer
- Part of combination therapy for lymphomas

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D - Adverse Effects

Emetogenic Potential: Moderate + NK1 antagonist (Carboplatin AUC ≥ 5)
Moderate (Carboplatin AUC < 5)

Extravasation Potential: None

The following table contains adverse effects reported with single agent carboplatin in the product monograph. It also includes severe, life-threatening and post-marketing adverse effects from other sources.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Auditory	Hearing impaired (15%)	E
	Tinnitus (1%)	E
Cardiovascular	Arterial thromboembolism (rare)	E
	Venous thromboembolism (rare)	E
Dermatological	Alopecia (2%)	E
Gastrointestinal	Constipation (3%)	E
	Diarrhea (6%)	E
	Nausea, vomiting (53%)	I
General	Fatigue (11%) (may be severe)	E
	Flu-like symptoms (1%)	E
Hematological	Hemolytic anemia (rare)	E
	Hemolytic uremic syndrome (rare)	E
	Myelosuppression ± infection, bleeding (59%)	E
Hepatobiliary	↑ LFTs (16%) (AST; transient)	L
	Veno-occlusive disease (rare)	E
Hypersensitivity	Hypersensitivity (<2%)	I
Injection site	Injection site reaction (<1%)	I
Metabolic / Endocrine	Abnormal electrolyte(s) (≤37%) (↓Mg 37% ↓K 16%, ↓Ca 5%, ↓Na; may be severe)	E

	Tumor lysis syndrome (rare)	E
Neoplastic	Secondary malignancy (rare)	L
Nervous System	Dysgeusia (<1%)	E
	Encephalopathy (rare)	E
	Other (5%) (CNS symptoms)	E
	Peripheral neuropathy (6%)	E
Ophthalmic	Other (1%) Visual disturbances	E
Renal	↑ BUN (16%)	E
	Creatinine increased (7%)	E
	Nephrotoxicity (25%) (may be severe)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for CARBOplatin include myelosuppression ± infection, bleeding, nausea, vomiting, abnormal electrolyte(s), nephrotoxicity, ↑ LFTs, ↑ BUN, hearing impairment and fatigue.

Myelosuppression is dose-limiting, especially thrombocytopenia. Myelosuppression may be more pronounced than with cisplatin. Patients with renal dysfunction, receiving nephrotoxic drugs, with poor performance status, the elderly or with prior exposure to cisplatin may experience more prolonged and severe myelosuppression. Anemia may be cumulative and transfusions may be required.

Nausea and vomiting usually occur within 6 to 12 hours after administration and may persist for up to 24 hours or longer. Incidence and severity of vomiting may be reduced by prophylactic antiemetics.

Nephrotoxicity is not usually dose-limiting and does not usually require hydration or forced diuresis. Nephrotoxicity is less common and severe than that associated with cisplatin. Decreases in serum electrolytes including magnesium, potassium and calcium have not been reported to be severe enough to cause clinical signs or symptoms, nor require routine supplementation.

Neurotoxicity is usually limited to paresthesia and decreased deep tendon reflexes, although visual changes and ototoxicity may occur. The incidence and severity of neurotoxicity are less with carboplatin than with cisplatin but severity increases in patients on prolonged therapy, who were previously treated with cisplatin or other nephrotoxic drugs and in elderly patients. Visual disturbances including vision loss has been reported rarely; this is usually reversible when carboplatin is discontinued.

Infusion reactions have been reported in up to 2% of patients who recently started treatment and

are receiving carboplatin alone, in 10-12% when given with other agents, and in > 40% of patients who have received several lines of treatment. They vary from mild to severe and may occur within minutes after administration. Reactions are similar to other platinum agents and include rash, fever, pruritis and anaphylaxis. Risk of reaction is increased in patients with previous exposure to platinum therapy; however, exact cross sensitivity with other platinum agents is not known. With appropriate precautions (eg. desensitization and/or antihistamine/steroid prophylaxis etc.) patients with hypersensitivity to carboplatin may tolerate retreatment or switch to other platinum agents; however, recurrent reactions can still occur in some patients and may be severe.

Secondary malignancies: Acute promyelocytic leukemia (APL) and myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) have been reported years after use of combination treatment.

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E - Dosing

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 myelosuppression. Dosage may be reduced and/or delayed in patients with bone marrow depression due to cytotoxic/radiation therapy, in the elderly or in patients with poor performance status.

Pre-medications (prophylaxis for infusion reactions):

- There is insufficient evidence that routine prophylaxis with pre-medications reduce infusion reaction (IR) rates.
- Corticosteroids and H1-receptor antagonists ± H2-receptor antagonists **may** reduce IR rates for some patients (e.g. gynecological patients with a PFI >12 months or a history of drug allergy who are receiving carboplatin starting from the 7th cycle) but no optimal pre-medication regimen has been established.

Adults:

Carboplatin dosing by BSA does not take into account renal function, which may result in overdosing (i.e. in patients with poor renal function) or underdosing (i.e. in patients with above average renal function). Alternative methods that consider the area under the curve (AUC) and the direct relationship between glomerular filtration and carboplatin clearance are more commonly used to calculate carboplatin dose.

Calvert Formula:

Dose (**mg**) = Target AUC (mg/mL per min) x [CrCl† (mL/min) + 25]

(See "References - Appendix" section)

†Note: Serum creatinine measured by Isotope Diluted Mass Spectrometry (IDMS) is a standardized and more accurate measure of creatinine compared to older laboratory methods, which overestimated serum creatinine values when values were low. However, the IDMS method generally produces lower serum creatinine levels in patients with normal renal function, which could result in an overestimation of the calculated creatinine clearance (CrCl) and the estimated GFR, in these patients, compared to previous methods. A Calvert formula-calculated carboplatin dose, based on estimated GFR using IDMS serum creatinine, could be higher than desired and result in increased toxicity.

To avoid toxicity, FDA recommends capping the carboplatin dose for a desired AUC. The maximum dose is based on a capped GFR estimate at 125 mL/min for patients with normal renal function:

Maximum Carboplatin Dose (mg) = target AUC (mg/mL per min) x (125 mL/min + 25)

For a target AUC = 6, the maximum dose is 6 x 150 = 900 mg

For a target AUC = 5, the maximum dose is 5 x 150 = 750 mg

For a target AUC = 4, the maximum dose is 4 x 150 = 600 mg

(See FDA communication on carboplatin dosing)

Dosage with Toxicity:

Modify according to protocol by which patient is being treated.

Below are suggested dose modifications.

Toxicity / Counts (x 10^9/L)	Dose Modification
ANC < 1.5 but ≥ 0.5 and/or Platelets < 100 but ≥ 25	Hold#; may consider dose ↓ at restart
Febrile Neutropenia OR ANC < 0.5 for ≥ 5-7 days OR Platelets < 25	Hold# Restart by ↓ 25%
Grade 3 related organ / non-hematologic	Hold#

	Restart by ↓ 25%
Grade 4 related organ / non- hematologic	Discontinue

Do not retreat unless platelets ≥ 100 x 10^9/L, ANC ≥ 1.5 x 10^9/L and toxicities have recovered to ≤ grade 2.

Management of Infusion-related reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

There is insufficient evidence that routine prophylaxis with extended infusion reduces IR rates.

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • After symptom resolution, restart with pre-medications ± reduced infusion rate.	• There is evidence that re-challenging with **cisplatin** after carboplatin reaction can be a viable option. • **However**: exact cross reactivity between platinum agents is not known, but can be as high as 25%. • Consider pre-medications* and infusing at a reduced infusion rate prior to re-challenge • May consider adding oral montelukast ± oral acetylsalicylic acid
3 or 4	• Stop treatment. • Aggressively manage symptoms.	• Re-challenge is discouraged, especially if vital signs have been affected. • Consider desensitization if therapy is necessary.

* Up to 50% of patients can experience recurrent reactions during re-challenge **despite** using pre-medications (e.g. corticosteroid and H1/H2-receptor antagonist

Dosage with Hepatic Impairment:

No dose adjustment required.

Dosage with Renal Impairment:

Creatinine Clearance (ml/min)	Carboplatin (% previous dose)
20 - 50	Use Calvert formula
< 20	Discontinue

Dosage in the elderly:

Caution should be exercised and dose reduction considered as elderly patients may have reduced renal function, more severe myelosuppression and neuropathy.

Children:

Safety and efficacy have not been systematically studied.

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F - Administration Guidelines

- Mix in 100mL to 250mL bag (5% Dextrose or Normal Saline); infuse IV over 15 to 60 minutes.

- There is insufficient evidence that routine prophylaxis with extended infusion reduces IR rates.
- Incompatible with sets, needles or syringes containing aluminum – leads to precipitation and loss of potency.
- Protect from light.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

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G - Special Precautions

Contraindications:

- Patients who have a severe allergic reaction to this drug or other platinum-containing compounds
- Patients with pre-existing severe renal impairment
- Patients with severe myelosuppression or bleeding tumours

Other Warnings/Precautions:

- Patients with abnormal renal function or who are receiving concomitant nephrotoxic drugs
- Patients who have received extensive prior treatment, have poor performance status and those over 65 years of age
- Avoid live vaccines. Reduced immunogenicity may occur with the use of inactivated vaccines.

Other Drug Properties:

- Carcinogenicity: Yes

Pregnancy and Lactation:

- Embryotoxicity: Yes
- Teratogenicity: Yes
  Carboplatin is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 6 months after the last dose (general recommendation).
- Excretion into breast milk: Probable
  Breastfeeding is not recommended.
- Fertility effects: Unknown

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H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Aminoglycosides	Exacerbates nephro- and ototoxicity	Additive	Monitor
Phenytoin	↓ serum phenytoin level	possibly ↓ absorption or increased metabolism of phenytoin	Monitor serum phenytoin level; ↑ dose of phenytoin if necessary
Other nephrotoxic drugs	↑ incidence of renal dysfunction	Additive	Monitor closely
Warfarin	Risk of ↑ INR or bleeding	Unknown	Monitor INR and adjust warfarin dose accordingly

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Renal function tests, including electrolytes	Baseline and before each cycle
CBC	Baseline and before each cycle
Clinical toxicity assessment for neurotoxicity, ototoxicity, hypersensitivity, bleeding, infection, nausea and vomiting	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Liver function tests	Baseline and as clinically indicated
INR	Baseline and as clinically indicated

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K - References

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Lexicomp drug monograph: Carboplatin. Access January 18, 2019.

Product Monograph: Carboplatin Injection. Novopharm Limited., November 16, 2004

Drug Monograph: Carboplatin. BC Cancer Agency Cancer Drug Manual. Revised January 1, 2014.

Calvert AH. Dose optimisation of carboplatin in adults. Anticancer Res 1994; 14(6A): 2273-8.

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McEvoy GK, editor. AHFS Drug Information 2011. Bethesda: American Society of Health-System Pharmacists, p. 963-71.

Micromedex 2.0. Truven Health Analytics Inc, 2014.

Product Monograph: Carboplatin Injection. Hospira Healthcare Corp., July 17, 2014.

Sliesoraitis S, Chikhale PJ. Carboplatin hypersensitivity. Int J Gynecol Cancer 2005; 15: 13-8.

van der Vijgh WJ. Clinical pharmacokinetics of carboplatin. Clin Pharmacokinet 1991;21(4)242-61.

Appendix:

Calvert Formula:

Dose (**mg**) = Target AUC (mg/mL per min) x {CrCl (mL/min)+ 25}

Refer to regimen for target AUC.

(see Creatinine Clearance Calculation)

Calvert AH, Newell DR, Gumbrell LA, et al. Carboplatin dosage: prospective evaluation of a simple formula based on

renal function. J Clin Oncol 1989; 7: 1748-56.

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L - Disclaimer

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