CARBOplatin

SYNONYM(S): CBDCA; JM-8

COMMON TRADE NAME(S): Paraplatin AQ® (Brand Discontinued)

**Absorption**
- Oral: low (4-12%)
- 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
- Cross blood brain barrier? Yes
- Volume of distribution 16L
- PPB 87% within 24 h (platinum-containing products)

**Metabolism**
- Carboplatin is hydrolyzed to aquated and hydroxylated compounds
### Active metabolites

<table>
<thead>
<tr>
<th>Platinum complexes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive metabolites</td>
</tr>
</tbody>
</table>

### 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

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

## D - Adverse Effects

**Emetogenic Potential:** Moderate

**Extravasation Potential:** None

<table>
<thead>
<tr>
<th>ORGAN SITE</th>
<th>SIDE EFFECT* (%)</th>
<th>ONSET**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auditory</td>
<td>Hearing impaired (15%)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Tinnitus (1%)</td>
<td>E</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Arterial thromboembolism</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Venous thromboembolism</td>
<td>E</td>
</tr>
<tr>
<td>Dermatological</td>
<td>Alopecia (2%)</td>
<td>E</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Anorexia</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Constipation (3%)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Diarrhea (6%)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Nausea, vomiting (53%)</td>
<td>I</td>
</tr>
<tr>
<td>General</td>
<td>Flu-like symptoms (1%)</td>
<td>E</td>
</tr>
<tr>
<td>Hematological</td>
<td>Hemolytic uremic syndrome (rare)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Myelosuppression ± infection, bleeding (55%)</td>
<td>E</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>↑ LFTs (36%) (transient)</td>
<td>L</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Allergic reaction (&lt;2%)</td>
<td>I</td>
</tr>
<tr>
<td>Injection site</td>
<td>Injection site reaction (&lt;1%)</td>
<td>I</td>
</tr>
<tr>
<td>Metabolic / Endocrine</td>
<td>Abnormal electrolyte(s) (decrease in Na, K, Ca, Mg: 37%)</td>
<td>E</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Secondary malignancy</td>
<td>L</td>
</tr>
<tr>
<td>Nervous System</td>
<td>Dysgeusia (&lt;1%)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Other (5%) (CNS symptoms, including visual changes)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy (6%)</td>
<td>E</td>
</tr>
</tbody>
</table>
Renal 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. Dose-limiting side effects are underlined.

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

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

**Renal toxicity** is not usually dose-limiting and does not require hydration or forced diuresis. Decreases in serum electrolytes including magnesium (37%), potassium (16%) and calcium (5%), have not been reported to be severe enough to cause clinical signs or symptoms, nor require routine supplementation. **Nephrotoxicity** may be exacerbated in patients receiving concomitant aminoglycosides.

**Neurotoxicity** is usually limited to paresthesia and decreased deep tendon reflexes, although visual changes and ototoxicity may occur. The 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.

**Allergic reactions** have been reported with increasing incidence with prolonged exposure, and vary from mild to severe reactions. Cross sensitivity with other “platins” may not be complete. Desensitization and or antihistamine/steroid prophylaxis may allow retreatment.

**Secondary malignancies** have been reported when used in combination regimens.

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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.

**Adults:**
Carboplatin dosing by BSA is not recommended as it does not take into account of the patient’s renal function and/or desired platelet nadir, which may result in overdosing (i.e. patients with poor renal function) or underdosing (i.e. with above average renal function). Several methods have been proposed for calculating carboplatin doses, considering the area under the curve (AUC) and its subsequent hematologic toxicity, and also the direct relationship between glomerular filtration and carboplatin clearance.

**Calvert Formula:** (Most commonly used method)

Dose (mg) = Target AUC (mg/mL per min) x [CrCl† (mL/min) + 25]
(See "References - Appendix" section)

†Note: Older laboratory methods of measuring creatinine overestimated low levels of creatinine. Serum creatinine measured by the Isotope Diluted Mass Spectrometry (IDMS) method accurately measures creatinine, producing potentially lower levels than would have been reported with older methods; thus the lower limits of normal are significantly lower than the limits in the past. Using the IDMS method, if the creatinine levels are low, the calculated creatinine clearance (CrCl) and the estimated GFR may be substantially higher than the normal GFR when formally measured using radioisotopic methods. The Calvert formula was developed using the older methodology for creatinine measurement, and using it uncapped may result in certain patients with low serum creatinine levels appearing to have a very high GFR, and thus receiving very high and inappropriate carboplatin doses with resulting toxicity.

To avoid toxicity, FDA recommends capping the carboplatin dose for a desired AUC. The maximum dose is based on a GFR estimate that is capped 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)
(See FDA communication on carboplatin dosing)

**Egorin Formula:** Takes into account of BSA, creatinine clearance, desired platelet nadir and pretreatment platelet count. (See "References - Appendix" section)

**Chatelut Formula:**

Dose (mg) = Target AUC (mg/mL per min) x Carboplatin clearance (mL/min)
(See "References - Appendix" section)
The Chatelut formula should not be used in pediatric or hemodialysis patients.

**Dosage with Toxicity:**

(suggested)

Also refer to Appendix 6: "Dosage Modification for Hematologic and Non-Hematologic Toxicities".
### Toxicity / Counts x 10⁹/L

<table>
<thead>
<tr>
<th>Toxicity / Counts x 10⁹/L</th>
<th>Dose Modification (% previous dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile Neutropenia</td>
<td>Or Grade 4 ANC ≥ 5-7 d, Grade 4 platelets</td>
</tr>
<tr>
<td></td>
<td>75%*/#</td>
</tr>
<tr>
<td>Grade 3 related organ / non-hematologic</td>
<td>75%#</td>
</tr>
<tr>
<td>Grade 4 related organ / non-hematologic</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

* Use Egorin formula if isolated thrombocytopenia (See Appendix section).
# Do not retreat unless platelets ≥ 100 x 10⁹/L, ANC ≥ 1.5 x 10⁹/L and toxicities have recovered to ≤ grade 2.

### Dosage with Hepatic Impairment:

No adjustment required.

### Dosage with Renal Impairment:

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min)</th>
<th>Carboplatin (% previous dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 - 50</td>
<td>Use Calvert or Chatelut formula</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

### Dosage in the elderly:

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

### Children:

Safety and efficacy have not been systematically studied.
F - Administration Guidelines

- Mix in 100mL to 250mL bag (5% Dextrose or Normal Saline); infuse IV over 15 to 60 minutes.
- Incompatible with sets, needles or syringes containing aluminum – leads to precipitation and loss of potency.
- Protect from light.

G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or other platinum-containing compounds
- Patients with severe renal impairment, 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

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.
- Excretion into breast milk: Probable
  Breastfeeding is not recommended.
- Fertility effects: Unknown
### H - Interactions

<table>
<thead>
<tr>
<th>AGENT</th>
<th>EFFECT</th>
<th>MECHANISM</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>exacerbates nephro- and ototoxicity</td>
<td>Additive</td>
<td>Monitor</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>↓ serum phenytoin level</td>
<td>possibly ↓ absorption or increased metabolism of phenytoin</td>
<td>Monitor serum phenytoin level; ↑ dose of phenytoin if necessary</td>
</tr>
<tr>
<td>Other nephrotoxic drugs</td>
<td>↑ incidence of renal dysfunction</td>
<td>Additive</td>
<td>Monitor closely</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Risk of ↑ INR or bleeding</td>
<td>Unknown</td>
<td>Monitor INR and adjust warfarin dose accordingly</td>
</tr>
</tbody>
</table>

### 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**

<table>
<thead>
<tr>
<th>Monitor Type</th>
<th>Monitor Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal function tests</td>
<td>Baseline and regular including electrolytes</td>
</tr>
<tr>
<td>CBC</td>
<td>Baseline and regular</td>
</tr>
<tr>
<td>Clinical toxicity assessment for neurotoxicity, ototoxicity, hypersensitivity, bleeding, infection, nausea and vomiting</td>
<td>At each visit</td>
</tr>
</tbody>
</table>

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

**Suggested Clinical Monitoring**

<table>
<thead>
<tr>
<th>Monitor Type</th>
<th>Monitor Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver function tests</td>
<td>Baseline and regular</td>
</tr>
</tbody>
</table>
**K - References**


Micromedex 2.0. Truven Health Analytics Inc, 2014.


**Appendix:**

**Calvert Formula:**

Dose \( (\text{mg}) \) = Target AUC \( (\text{mg/mL per min}) \times \{\text{CrCl (mL/min)}+25\}\)

Formula for CrCl calculation (see Appendix 5)

Target AUC for: previously untreated patients = 6 - 8 mg/mL per min (single agent)

previously treated patients = 4 - 6 mg/mL per min (single agent)


**Egorin Formula:**

Previously Untreated Patients -
Dose (mg/m²) = 317 x \{(pre - nadir/ pre) x 100 - 82.1\} X (BSA / Cr Cl) + 447

Previously Treated Patients -

Dose (mg/m²) = 317 x \{(pre - nadir/ pre) x 100 - 92.4\} X (BSA / Cr Cl) + 447

- Pre = pretreatment platelet count
- Nadir = platelet nadir desired
- BSA = Body Surface Area
- Cr Cl = Creatinine Clearance


Chatelut Formula:

Dose (mg) = Target AUC (mg/mL per min) x Carboplatin clearance (Cl_{carboplatin} in mL/min)

where Cl_{carboplatin} equals to:

\[
\frac{\{218 \times wt \times (1 - \{0.00457 \times age\}) \} \times \{1 - (0.314 \times gender)\}}{(0.134 \times wt) + \frac{1}{\text{Serum creatinine (µmol/L)}}}
\]

- wt = Weight in kg
- Age (years)
- Gender (males = 0; females = 1)
- Serum Cr = Serum creatinine (µmol/L)


August 2016 edited other indications

L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public
funding information.

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