

**DRUG NAME: Cisplatin****SYNONYM:** CDDP,<sup>1</sup> cis-Diamminedichloroplatinum,<sup>2</sup> cis-dichlorodiammineplatinum(II),<sup>3</sup> cis-Patinum II,<sup>2</sup> DDP,<sup>4</sup>**COMMON TRADE NAME:** PLATINOL®; PLATINOL-AQ®, generic available**CLASSIFICATION:** Platinum compound,<sup>5</sup> cytotoxic<sup>6</sup>*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

Cisplatin is similar to the bifunctional alkylating agents. It covalently binds to DNA and disrupts DNA function.<sup>7</sup> After cisplatin enters the cells, the chloride ligands are replaced by water molecules.<sup>8,9</sup> This reaction results in the formation of positively charged platinum complexes that react with the nucleophilic sites on DNA.<sup>2</sup> These platinum complexes covalently bind to DNA bases using intra-strand and inter-strand cross-links creating cisplatin-DNA adducts thus preventing DNA, RNA and protein synthesis.<sup>7</sup> This action is cell cycle phase-nonspecific.<sup>10</sup> Cisplatin also has immunosuppressive, radiosensitizing, and antimicrobial properties.<sup>2</sup>

**PHARMACOKINETICS:**

Interpatient variability	systemic clearance resulting in variable blood platinum concentrations or AUCs <sup>11</sup>	
Oral Absorption	not absorbed <sup>12</sup>	
Distribution	rapidly diffuses into tissues <sup>13</sup> highest concentrations found in the liver, prostate and kidney; rapidly distributed into pleural effusions and ascitic fluid	
	cross blood brain barrier?	not readily <sup>10</sup>
	volume of distribution <sup>14</sup>	ultrafilterable platinum*: 41 L/m <sup>2</sup>
	plasma protein binding	>90% <sup>5,11,13</sup>
Metabolism	undergoes non-enzymatic conversion to several inactive metabolites which are highly bound to plasma proteins <sup>12</sup>	
	active metabolite	yes
	inactive metabolite	yes <sup>10</sup>
Excretion	primarily in the urine <sup>8</sup> urinary excretion of ultrafilterable platinum* was substantially greater after a 6-hour infusion than after a 15-minute injection <sup>15</sup>	
	urine	> 90% <sup>8</sup> ; 25% excreted during the first 24 h <sup>7</sup>
	feces	insignificant
	terminal half life of ultrafilterable platinum* <sup>8,11,16,17</sup>	20-45 min
	terminal half life of total platinum* <sup>8</sup>	5 days or longer
	clearance	6.3 mL/min/kg
Gender	no clinically important differences found	
Elderly	no clinically important differences found	
Children	terminal half life of ultrafilterable platinum* < 1 h <sup>12</sup> terminal half life of total platinum* 24-72 h <sup>12</sup>	
Ethnicity	no clinically important differences found	

Adapted from standard reference<sup>17</sup> unless specified otherwise.

\*Ultrafilterable platinum consists of non-protein-bound intact drug and metabolites, total platinum consists of all platinum species, both protein-bound or –unbound.<sup>8</sup> Note that it is the platinum that is usually measured.

## USES:

### **Primary uses:**

\* Bladder cancer  
Brain cancer  
Cervical cancer  
Esophageal cancer  
Gastric cancer  
Germ cell tumours  
Gestational trophoblastic neoplasia  
Head and neck cancer  
Lung cancer, non-small cell  
Lung cancer, small cell  
Lymphoma, Hodgkin's disease  
Lymphoma, non-Hodgkin's  
Mesothelioma  
Nasopharyngeal cancer  
Osteosarcoma  
\* Ovarian cancer  
Prostate cancer  
\*Testicular cancer

\*Health Canada approved indication

### **Other uses:**

Adrenal carcinoma<sup>2</sup>  
Anal cancer<sup>2</sup>  
Breast cancer<sup>2</sup>  
Choriocarcinoma<sup>2</sup>  
Endometrial cancer<sup>2</sup>  
Kidney cancer<sup>2</sup>  
Liver cancer<sup>2</sup>  
Lymphomas<sup>2</sup>  
Melanoma<sup>2</sup>  
Penile cancer<sup>2</sup>  
Sarcoma<sup>2</sup>  
Thyroid cancer<sup>2</sup>

## SPECIAL PRECAUTIONS:

**Administer with caution** to individuals with pre-existing renal impairment, myelosuppression or hearing impairment.<sup>14</sup>

**Breastfeeding** is not recommended as cisplatin is excreted in human milk.<sup>10</sup>

**Carcinogenicity:** found to have a carcinogenic effect in laboratory animals.<sup>17</sup>

**Contraindicated:** in patients who have a history of a hypersensitivity reaction to cisplatin<sup>17</sup> or other platinum-containing compounds.

**Fertility:** Cisplatin therapy is associated with at least temporary infertility in the majority of patients.<sup>18</sup> Among males receiving cisplatin for testicular cancer, almost all became azospermic within the first two cycles of therapy, but recovery of normal sperm morphology, motility, and sperm count occurred in 40% within 1.5-2 years.

**Hydration** is required to minimize nephrotoxicity.<sup>14</sup> The manufacturer recommends pre-treatment hydration with 1 or 2 L of fluid infused 8-12 hours prior to a cisplatin dose.<sup>17</sup> Hydration with NS, hypertonic saline infusion, and mannitol, or furosemide-induced diuresis is used to effectively decrease cisplatin-induced nephrotoxicity.<sup>8</sup> Lower doses of cisplatin are given with less intensive hydration. For example, patients receiving doses of 35 mg/m<sup>2</sup> have been pre-treated with 500 mL NS over 1 hour, with no post-hydration. Patients receiving doses of 25 mg/m<sup>2</sup> have been pre-treated with vigorous oral hydration (e.g., 600-900 mL) the morning of treatment and 8 glasses (e.g., 2000 mL/day) daily for a few days following treatment. **Please refer to the "Nephrotoxicity" paragraph, found below the Side Effects table for a suggested hydration guideline.**

**Inadvertent substitution** of cisplatin for carboplatin can result in a potentially fatal overdose.<sup>2</sup> Precautions should be taken to avoid overdosing such as writing the cisplatin dose as a daily dose, not as a total cisplatin dose used in one course of therapy. The manufacturer recommends that an alerting mechanism be instituted to verify any order for cisplatin >100 mg/m<sup>2</sup> per course every 3-4 weeks.

**Mutagenicity:** shown to be a mild to moderate mutagen in the Ames test.<sup>17</sup>

**Pregnancy:** FDA Pregnancy Category D.<sup>10</sup> There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

## 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.<sup>19</sup>

ORGAN SITE	SIDE EFFECT	ONSET			
Clinically important side effects are in <b>bold, italics</b> I = immediate [onset in hours to days]; E = early [days to weeks]; D = delayed [weeks to months] L = late [months to years]					
allergy/immunology	hypersensitivity (rare)	I			
auditory/hearing	<b>ototoxicity (31%)</b>		E		
	<b>audiogram abnormalities (24%)</b>		E		
	<b>tinnitus (9%)</b>		E		
	vestibular toxicity (rare)		E		
blood/bone marrow/ febrile neutropenia	<b>myelosuppression (25-30%) WBC nadir 18-23 days (range 7.5-45), platelet nadir 18-23 days (range 7.5-45), recovery 39 days (range 13-62)</b>	I			
	<b>anemia (25-30)%</b>	I			
cardiovascular (arrhythmia)	arrhythmias <sup>13</sup>		E		
cardiovascular (general)	bradycardia (rare)		E		
	<b>vascular toxicities may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy or cerebral arteritis</b>		E		
constitutional symptoms	hiccoughs	I			
dermatology/skin	<i>extravasation hazard: irritant</i> <sup>20</sup>				
	alopecia (uncommon)		E		
	rash (uncommon)		E		
	local soft tissue toxicity (rare)		E		
endocrine	glucose intolerance <sup>13</sup>				
gastrointestinal	<i>emetogenic potential: high</i> <sup>21</sup>				
	<b>nausea and vomiting (&gt; 90%)</b>	I			
	<b>delayed nausea and vomiting</b>	I			
	diarrhea		E		
	loss of taste		E		

ORGAN SITE	SIDE EFFECT	ONSET			
Clinically important side effects are in <b>bold, italics</b> I = immediate [onset in hours to days]; E = early [days to weeks]; D = delayed [weeks to months] L = late [months to years]					
	pancreatitis <sup>13</sup>		E		
	stomatitis <sup>10</sup>		E		
hepatic	transient elevation of hepatic enzymes and bilirubin	I			
metabolic/laboratory	elevated serum amylase	I			
	<b>electrolyte disturbances<sup>2</sup></b>	I			
	hyperuricemia		E		
musculoskeletal	muscle cramps		E		
neurology	autonomic neuropathy		E		
	dorsal column myelopathy		E		
	Lhermitte's sign		E		
	<b>neurotoxicity, usually peripheral neuropathies</b>		E		
	seizures (rare) <sup>7</sup>		E		
ocular/visual	visual impairment (rare)		E		
	altered colour perception		E		
	blurred vision		E		
	cerebral blindness (infrequent)		E		
	optic neuritis		E		
	papilledema		E		
renal/genitourinary	<b>nephrotoxicity (28-36%)</b>		E		
secondary malignancy	acute leukemia (rare) <sup>10</sup>				L
syndromes	inappropriate antidiuretic hormone syndrome		E		

Adapted from standard references<sup>2,16,17</sup> unless specified otherwise.

**Anemia** observed with cisplatin use may be caused by a decrease in erythropoietin or erythroid stem cells.<sup>2</sup>

Cisplatin has been shown to sensitize red blood cells, sometimes resulting in a direct Coombs' positive hemolytic anemia.<sup>17</sup>

**Electrolyte disturbances** can be serious and mainly includes hypomagnesemia, hypocalcemia and hypokalemia. Hypophosphatemia and hyponatremia have occurred in some patients receiving cisplatin combination regimens.<sup>2</sup> These effects are due to renal tubular damage. Cisplatin greatly increases the urinary excretion of magnesium and calcium; increased excretion of potassium, zinc, copper and amino acids also occurs. Hypomagnesemia and/or hypocalcemia may become symptomatic, with muscle irritability or cramps, clonus, tremor, carpopedal spasm and/or tetany. Children may be at greater risk for developing hypomagnesemia.

**Emetogenic effects** are common with cisplatin therapy and may be serotonin-mediated.<sup>11</sup> **Acute** nausea and vomiting may occur within 1-6 (usually 2-3) hours after administration of cisplatin.<sup>2</sup> This early period is the most severe and usually lasts 8 hours, but can last up to 24 hours. Various levels of nausea, vomiting and anorexia may persist for up to 5-10 days. **Delayed** nausea and vomiting can occur 24 hours or longer following chemotherapy when complete emetic control had been attained on the day of cisplatin therapy. The incidence and severity of cisplatin-induced nausea and vomiting appear to be increased in: females, the young, high doses, rapid infusion and combinations with other emetogenic drugs. Incidence and severity may be decreased in patients with a history of chronic alcohol use. **Acute** nausea and vomiting can be prevented by pre-treatment with a 5-HT<sub>3</sub> antagonist (e.g.,

granisetron, ondansetron) plus a corticosteroid; this can be continued for the first 24 hours following chemotherapy. **Delayed** nausea and vomiting should not routinely be treated with 5-HT<sub>3</sub> antagonists; although there is anecdotal evidence that some patients can benefit from 5-HT<sub>3</sub> antagonists<sup>19</sup>, generally these agents are ineffective more than 24 hours after chemotherapy.<sup>21</sup> Corticosteroids are the cornerstone of the treatment for delayed nausea, although other combinations are widely used.<sup>13</sup> **Please refer to the BC Cancer Agency SCNAUSEA Protocol for more in-depth information.**

**Nephrotoxicity** is a major concern when prescribing cisplatin. Renal dysfunction due to cisplatin may manifest as renal insufficiency, hypokalemia and hypomagnesemia. The risk for these adverse effects is related to the dose and interval of cisplatin and may be minimized by adequate hydration. Geriatric patients may also be at increased risk.

- The manufacturer recommends pre-treatment hydration with 1 or 2 L of fluid infused 8-12 hours prior to a cisplatin dose.<sup>17</sup> Others suggest hydration with NS, hypertonic saline infusion, and mannitol, or furosemide-induced diuresis to effectively decrease cisplatin-induced nephrotoxicity.<sup>8</sup>

Refer to protocol by which patient is being treated. Numerous hydration regimens exist. Hydration regimens should take into account the following conditions for the patient; adequate renal function, clinically euvolemic prior to administration of cisplatin, no contraindication to saline loading (e.g., uncompensated cardiac conditions, anasarca), and ability to comply with recommended oral hydration protocol, or expectation that volume status can be maintained (e.g., with fluids via enteral feeding tube or IV). Below is one suggested hydration regimen for adults.<sup>22</sup>

Cisplatin (mg/m <sup>2</sup> )	Hydration	Electrolyte Additives*	Comments
> 80	4000 mL* NS over 4 h	KCl 20 mEq MgSO <sub>4</sub> 1 g Mannitol 30 g	inpatient or medical daycare unit admission to monitor urine output
60-80	2000 mL* NS over 2 h	KCl 20 mEq MgSO <sub>4</sub> 1 g Mannitol 30 g	
40-60	1000 mL* NS over 1 h	KCl 10 mEq MgSO <sub>4</sub> 0.5 g	includes regimens with cisplatin administered over multiple days
<40	500 mL* NS over 30 min	none	includes regimens with cisplatin administered over multiple days

\*Volume may include hydration associated with the administration of other drugs (e.g., other chemotherapy agents, supportive IV medications). The volumes and durations are minimum administration standards to accommodate the wide variation in clinical practice in delivery of cisplatin. They should be individualized based on the clinical situation, which may affect the hydration regimen and addition of electrolytes.

In children, for moderate to high-dose cisplatin give pre-hydration at 125mL/m<sup>2</sup>/h for a minimum of 2 hours to increase urine output to >100 mL/m<sup>2</sup>/h (> 3 mL/kg/h).<sup>23</sup> The hydration fluid most commonly used is D51/2NS + 10mEq/L KCL. In post-hydration maintain urine output at 65-100 mL/m<sup>2</sup>/h with oral/IV fluids.<sup>23</sup> D51/2NS + 20 mEq/L KCL + 20 mEq MgSO<sub>4</sub> + mannitol 20 g/L is commonly used for IV post-hydration.<sup>23</sup>

**Nervous system effects** are usually peripheral neuropathies and sensory in nature (e.g., paresthesias of the upper and lower extremities).<sup>2</sup> They can also include motor difficulties (especially gait); reduced or absent deep-tendon reflexes and leg weakness may also occur. Peripheral neuropathy is cumulative and usually reversible, although recovery is often slow.<sup>13</sup> Geriatric patients may be at greater risk for these cisplatin-induced neuropathies. Muscle cramps have been reported, and usually occurred in patients with symptomatic peripheral neuropathy who received relatively high cumulative doses of cisplatin. Lhermitte's sign (a sensation during neck flexion resembling electric shock) often is present with cisplatin-induced neuropathy. The occurrence of Lhermitte's sign may coincide with the onset of peripheral neuropathies, and can last for 2-8 months. When signs of neuropathy occur, cisplatin should be discontinued.

**Otic effects** include tinnitus, with or without clinical hearing loss, and occasional deafness.<sup>2</sup> Ototoxicity is cumulative and irreversible and results from damage to the inner ear.<sup>13</sup> These effects may be more severe in children than in adults.<sup>10</sup> The manufacturer recommends that audiograms be performed prior to initiating therapy and prior to each subsequent dose of drug.<sup>17</sup> Initially, there is loss of high frequency acuity (4000 to 8000 Hz). When acuity is affected in the range of speech, cisplatin should be discontinued under most circumstances and carboplatin substituted where appropriate. Ototoxicity appears to be dose related. Higher cumulative doses, higher individual doses and administration by IV bolus resulted in more severe ototoxicity,<sup>24</sup> corresponding with higher plasma levels of ultrafilterable platinum.<sup>15</sup> Ototoxicity may be enhanced in patients with prior or simultaneous cranial irradiation. Vestibular ototoxicity may increase with increasing cumulative dosage and may be more likely to occur in patients with pre-existing vestibular dysfunction.

**Sensitivity reactions** can include anaphylactoid reactions consisting of facial edema, flushing, wheezing or respiratory difficulties, tachycardia, and hypotension.<sup>17</sup> These reactions can occur within a few minutes after IV administration of cisplatin; diaphoresis, nasal stuffiness, rhinorrhea, conjunctivitis, generalized erythema, apprehension, and sensation of chest constriction may also occur. Cisplatin-induced anaphylactoid reactions usually have occurred after multiple cycles of cisplatin (e.g., at least 5 doses), but also can occur after the first dose.<sup>2</sup> There is a case report of a patient who experienced an anaphylaxis to cisplatin following nine previous uncomplicated cycles.<sup>25</sup> Some reactions may also be due to the mannitol that is given with cisplatin to prevent nephrotoxicity.<sup>26</sup> Occasionally, patients who experienced anaphylactoid reactions have been safely retreated with cisplatin following pre-treatment with corticosteroids and/or antihistamines; however, such prophylaxis is not uniformly effective in preventing recurrence.

#### INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
etoposide	synergistic antineoplastic activity against testicular, small cell lung and, non-small cell lung cancers	possible impaired elimination of etoposide in patients previously treated with cisplatin	some protocols are designed to take advantage of this effect; monitor toxicity closely
nephrotoxic drugs such as aminoglycoside antibiotics and amphotericin	increased risk of nephrotoxicity	cumulative nephrotoxicity	use with extreme caution during or shortly after cisplatin
ototoxic drugs such as aminoglycoside antibiotics or loop diuretics (e.g., ethacrynic acid, furosemide)	increased risk of ototoxicity	cumulative ototoxicity	carefully monitor for signs of ototoxicity
phenytoin	decreased phenytoin serum levels	decreased absorption and/or increased metabolism of phenytoin	monitor serum levels of phenytoin
pyridoxine <sup>27</sup>	decrease in cisplatin activity	further investigation required	avoid concomitant use of pyridoxine with cisplatin
renally excreted drugs	increase the serum levels of renally excreted drugs	reduced renal function caused by cisplatin	monitor toxicity

Adapted from standard references<sup>2</sup> unless specified otherwise.

#### SUPPLY AND STORAGE:

**Injection:** Cisplatin is available as sterile, unpreserved; single-dose vials (10 mg/10 mL, 50 mg/50 mL and 100 mg/100 mL) at a concentration of 1 mg/mL.<sup>17</sup> Unopened vials are stored at room temperature. Do not refrigerate or freeze cisplatin solutions as a precipitate will form. Protect from light.

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

## SOLUTION PREPARATION AND COMPATIBILITY:

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

Do not use IV needles, syringes or sets that have aluminum components in the preparation or administration of cisplatin.<sup>17</sup> An interaction between aluminum and platinum will occur resulting in the formation of a black precipitate, accompanied with a loss of potency.

**Diluted solution for infusion:** Dilute the prepared cisplatin injection in 2 L of D51/2S or 0.3%NS, containing 37.5 g of mannitol.<sup>17</sup> The solution is not preserved and should be used within 24 hours. Any unused portion should be discarded. In children, the administration volume of cisplatin should be maintained at >125 mL/m<sup>2</sup>/hr, and contain mannitol 15 g/m<sup>2</sup> and MgSo4 20 mEq/L.<sup>23</sup> Urine output should be maintained at > 90 mL/m<sup>2</sup>/hr during administration.<sup>23</sup>

**Compatibility<sup>28</sup>:** The following are compatible with cisplatin via Y-site injection: allopurinol, aztreonam, bleomycin, chlorpromazine, cimetidine, cladribine, cyclophosphamide, dexamethasone, diphenhydramine, doxorubicin, doxorubicin liposome, droperidol, famotidine, filgrastim, fludarabine, fluorouracil, furosemide, ganciclovir, gatifloxacin, gemcitabine, granisetron, heparin, hydromorphone, leucovorin, linezolid, lorazepam, melphalan, methotrexate, methylprednisolone, metoclopramide, mitomycin, morphine, ondansetron, paclitaxel, prochlorperazine, promethazine, propofol, ranitidine, sargramostim, teniposide, topotecan, vinblastine, vincristine, vinorelbine.

The following are compatible with cisplatin in the same syringe in certain concentrations: bleomycin, cyclophosphamide, doxapram, doxorubicin, droperidol, fluorouracil, furosemide, heparin, leucovorin, methotrexate, metoclopramide, mitomycin, vinblastine, and vincristine.

The following are compatible with cisplatin in the same infusion bag in certain concentrations and diluents: carboplatin, cyclophosphamide with etoposide, etoposide, etoposide with floxuridine, etoposide with mannitol and KCL, floxuridine, floxuridine with leucovorin, hydroxyzine, ifosfamide, and ifosfamide with etoposide, leucovorin, magnesium, mannitol, ondansetron and paclitaxel.

The following solutions are compatible with cisplatin at the stated concentrations: cisplatin 50 mg, 500 mg, 300 mg in D51/2NS 1L; cisplatin 50 mg, 300 mg, 500 mg in D5NS 1L; cisplatin 50 mg, 100 mg, 200 mg in D51/2NS with mannitol 1.875%; cisplatin 300 mg in D5W 1L; cisplatin 50 mg, 100 mg, 167 mg, 200 mg, 300 mg, 500 mg, 600 mg, 900 mg in NS 1L; cisplatin 50 mg, 100 mg, 200 mg in 1/2NS.

**Incompatibility<sup>28</sup>:** The following are incompatible with cisplatin via Y-site injection: amifostine, amphotericin, cefepime, piperacillin-tazobactam and thiotepa.

The following are incompatible with cisplatin in the same infusion solution at the stated concentrations: cisplatin 200 mg with etoposide 400 mg, mannitol 1.875%, KCl 20 mEq in NS 1L; cisplatin 200 mg with fluorouracil 1 g in NS 1L; cisplatin 500 mg with fluorouracil 10 g in 1L NS; cisplatin 67 mg with mesna 3.33 g in NS 1L; cisplatin 67 mg with mesna 110 mg in NS 1L; cisplatin 200 mg with paclitaxel 1.2 g in NS 1L; cisplatin 200 mg with thiotepa 1 g in NS 1L.

The following solutions are incompatible with cisplatin at the stated concentrations: cisplatin 100 mg/L in D5W 5%; cisplatin 75 mg/L in D5W; cisplatin 50 mg/L in Sodium bicarbonate 5%; cisplatin 500 mg/L in Sodium bicarbonate 5%.

## PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in **bold, italics**

BCCA administration guideline noted in ***bold, italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	not to be administered by the direct IV route
<b><i>Intermittent infusion</i></b>	50-100 mL of compatible IV solution, over 15-30 minutes
<b><i>Continuous infusion</i></b>	in 1-2 L of compatible IV solution, over 6-24 hours (administration over 24 hours may decrease nausea, vomiting and nephrotoxicity)
Intraperitoneal	has been used <sup>16</sup>
Intrapleural	has been used <sup>5</sup>
Intrathecal	no information found
Intra-arterial	has been used <sup>16</sup>
Intravesical	has been used <sup>29</sup>

**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. Dosage may be reduced, delayed or discontinued in patients with bone marrow suppression due to cytotoxic/radiation therapy or with other toxicities.

**Adults:**BCCA usual dose noted in ***bold, italics***

	Cycle Length:	
<i>Intravenous:</i>	1 week <sup>30,31</sup> :	<b><i>25-40 mg/m<sup>2</sup> IV on day 1</i></b> (total dose per cycle 25-40 mg/m <sup>2</sup> )
	2 weeks <sup>32</sup> :	<b><i>30 mg/m<sup>2</sup> IV for one dose on days 1-3</i></b> (total dose per cycle 90 mg/m <sup>2</sup> )
	3 weeks <sup>33-38</sup> :	<b><i>20-100 mg/m<sup>2</sup> IV on day 1</i></b> (total dose per cycle 20-100 mg/m <sup>2</sup> )
	3 weeks <sup>39</sup> :	<b><i>60 mg/m<sup>2</sup> IV once daily for 2 consecutive days starting on day 1</i></b> (total dose per cycle 120 mg/m <sup>2</sup> )
	3 weeks <sup>40</sup> :	<b><i>20 mg/m<sup>2</sup> IV for one dose on days 1 and 5</i></b> (total dose per cycle 40 mg/m <sup>2</sup> )
	3 weeks <sup>37</sup> :	<b><i>30 mg/m<sup>2</sup> IV for one dose on days 1 and 8</i></b> (total dose per cycle 60 mg/m <sup>2</sup> )
	3 weeks <sup>41-46</sup> :	<b><i>25 mg/m<sup>2</sup> IV for one dose on days 1-3</i></b> (total dose per cycle 75 mg/m <sup>2</sup> )
	3 weeks <sup>47-50</sup> :	<b><i>20 mg/m<sup>2</sup> IV for one dose on days 1-5</i></b> (total dose per cycle 100 mg/m <sup>2</sup> )
	4 weeks <sup>51,52</sup> :	<b><i>70-100 mg/m<sup>2</sup> IV on day 1</i></b>

BCCA usual dose noted in ***bold, italics***

Cycle Length:	(total dose per cycle 70-100 mg/m <sup>2</sup> )
4 weeks <sup>53,54</sup> :	<b><i>25-30 mg/m<sup>2</sup> IV once daily for 3 consecutive days starting on day 1</i></b> (total dose per cycle 75-90 mg/m <sup>2</sup> )
6 weeks <sup>55</sup> :	<b><i>75 mg/m<sup>2</sup> IV for one dose on day 1</i></b> (total dose per cycle 75 mg/m <sup>2</sup> )
<i>Concurrent radiation:</i>	
1 week <sup>56</sup> :	<b><i>40 mg/m<sup>2</sup> IV for one dose on day 1</i></b> (total dose per cycle 40 mg/m <sup>2</sup> )
2 weeks <sup>50</sup> :	<b><i>100 mg/m<sup>2</sup> IV for one dose on day 1</i></b> (total dose per cycle 100 mg/m <sup>2</sup> )
3 weeks <sup>57</sup> :	<b><i>100 mg/m<sup>2</sup> IV for one dose on day 1</i></b> (total dose per cycle 100 mg/m <sup>2</sup> )
4 weeks <sup>58</sup> :	<b><i>25 mg/m<sup>2</sup> IV for 3 consecutive days starting on day 1</i></b> (total dose per cycle 75 mg/m <sup>2</sup> )

*Dosage in myelosuppression:* modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"

*Dosage in renal failure:*

Suggested dose modifications:

Creatinine clearance mL/min <sup>59</sup>	Cisplatin dose
≥ 60	100%
45 - 59	75% cisplatin or go to carboplatin option (if available)
< 45	hold cisplatin or delay with additional IV fluids or go to carboplatin option (if available)

$$\text{Calculated creatinine clearance} = \frac{N * (140 - \text{Age}) * \text{weight}}{\text{Serum Creatinine in } \mu\text{mol/L}}$$

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

*Dosage in hepatic failure:* no adjustment required

*Dosage in dialysis:* removable by dialysis, but only within 3 h of administration<sup>10</sup>

### **Children<sup>2</sup>:**

<i>Intravenous:</i>	Cycle Length:
	1 week: 30 mg/m <sup>2</sup> IV one dose on day 1
	3 weeks: 90 mg/m <sup>2</sup> IV one dose on day 1
	3-4 weeks: 60 mg/m <sup>2</sup> IV one dose on day 1 and day 2

### **REFERENCES:**

1. Matsusaka S, Nagareda T, Yamasaki H. Does cisplatin (CDDP) function as a modulator of 5-fluorouracil (5-FU) antitumor action? A study based on a clinical trial. *Cancer Chemotherapy Pharmacology* 2005;55:387-392.
2. McEvoy GK, editor. AHFS 2004 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc.; 2004. p. 929-945.
3. Meyer KB, Madias NE. Cisplatin nephrotoxicity. *Mineral & Electrolyte Metabolism*. 1994;20(4):201-13.
4. Farris FF, Dedrick RL, King FG. Cisplatin pharmacokinetics: applications of a physiological model. *Toxicology Letters* 1988;43(1-3):117-37.
5. Pizzo P, Poplack D. Principles and Practice of Pediatric Oncology. Fourth ed. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 256-259.
6. National Institute for Occupational Safety and Health (NIOSH). Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. Cincinnati, Ohio: NIOSH - Publications Dissemination; 25 March 2004. p. 71-83.
7. Chabner BA, Longo DL. Cancer chemotherapy and biotherapy. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001. p. 453-459.
8. Go R, Adjei A. Review of the comparative pharmacology and clinical activity of cisplatin and carboplatin. *J Clin Oncol* 1999;17(1):409-422.
9. Nieto Y. DNA-binding agents. *Cancer Chemotherapy & Biological Response Modifiers* 2003;Annual 21:Chapter 8.
10. Cisplatin. USP DI. Volume 1. Drug information for the health care professional. 20th ed. Englewood, Colorado: Micromedex, Inc.; 2002.
11. Murry DJ. Comparative clinical pharmacology of cisplatin and carboplatin. *Pharmacotherapy* 1997;17(5 Pt 2):140S-145S.
12. Crom WR, Glynn-Barnhart AM, Rodman JH, et al. Pharmacokinetics of Anticancer Drugs in Children. *Clinical Pharmacokinetics* 1987;12:179-182.
13. O'Dwyer P, Stevenson J, Johnson S. Clinical Pharmacokinetics and Administration of Established Platinum Drugs. *Drugs* 2000 2000;59 Suppl. 4:19-27.
14. Repchinsky C. Compendium of Pharmaceuticals and Specialties. Ottawa, Ontario: Canadian Pharmacists Association; 2004. p. 431-432.
15. Belt RJ, Himmelstein KJ, Patton TF, et al. Pharmacokinetics of Non-Protein-Bound Platinum Species Following Administration of cis-Dichlorodiammineplatinum(II). *Cancer Treatment Reports* 1979;63(No. 9-10):1515-1521.
16. McEvoy GK, editor. AHFS 1989 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc.; 1989. p. 929-945.
17. Mayne Pharma (Canada) Inc. Cisplatin product monograph. Montreal, Quebec; 2003.
18. Perry M, M.D. FACP. The Chemotherapy Source Book. Baltimore, Maryland: Williams & Wilkins; 1992. p. 405-409.
19. Christopher Lee MD. Personal Communication. Medical Oncologist, BC Cancer Agency, Fraser Valley Cancer Centre; 2005.
20. B.C. Cancer Agency Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer Agency; 1 February 2004.
21. B.C. Cancer Agency. SCNAUSEA Protocol Summary. Vancouver, British Columbia: BC Cancer Agency; May 1999.
22. BC Cancer Agency Genitourinary Tumour Systemic Policy Group. Administration of cisplatin in the outpatient setting. BC Cancer Agency; 8 June 2000.
23. Arthur R. Supportive care of children with cancer. 2nd ed. Baltimore: John Hopkins University Press; 1997.
24. Balis FM, Holcenberg JS, Bleyer WA. Clinical Pharmacokinetics of Commonly Used Anticancer Drugs. *Clinical Pharmacokinetics* 1983;8:202-232.
25. Basu R, Rajkumar A, Datta RN. Anaphylaxis to cisplatin following nine previous uncomplicated cycles. *Int J Clin Oncol* 2002;7:365-367.
26. Ackland SP, Hillcoat BL. Immediate hypersensitivity to mannitol: a potential cause of apparent hypersensitivity to cisplatin [letter]. *Canc Treat Rep* 1985;69(5):562-3.
27. Wiernik P, Yeap B, Vogl S, et al. Hexamethylmelamine and low or moderate dose cisplatin with or without pyridoxine for treatment of advanced ovarian carcinoma: a study of the Eastern Cooperative Oncology Group. *Cancer Investigation* 1992;10(1):1-9.
28. Trissel L. Handbook on Injectable Drugs. 12th ed. Bethesda MD: American Society of Health-System Pharmacists; 2003.
29. Dorr RT, Von-Hoff DD. Drug monographs. Cancer chemotherapy handbook. 2nd ed. Norwalk, Connecticut: Appleton and Lange; 1994. p. 286-293.
30. BC Cancer Agency Gastrointestinal Tumour Group. BCCA Protocol summary for palliative chemotherapy for upper gastrointestinal tract cancer (gastric, esophageal, gall bladder carcinoma and cholangiocarcinoma) using infusional fluorouracil and cisplatin. (GIFUC). Vancouver: BC Cancer Agency; 2001.
31. BC Cancer Agency Head and Neck Tumour Group. BCCA Protocol summary for recurrent and metastatic nasopharyngeal cancer using cisplatin and etoposide (HNDE). Vancouver: BC Cancer Agency; 2004.
32. BC Cancer Agency Gynecology Tumour Group. BCCA Protocol summary for treatment of high risk gestational trophoblastic cancer (GOTDHR). Vancouver: BC Cancer Agency; 2005.
33. BC Cancer Agency Genitourinary Tumour Group. BCCA Protocol summary for palliative therapy for urothelial carcinoma using cisplatin and gemcitabine (GUAVPG). Vancouver: BC Cancer Agency; 2002.
34. BC Cancer Agency Genitourinary Tumour Group. BCCA protocol summary for neo-adjuvant therapy for urothelial carcinoma using cisplatin and gemcitabine (UGUNAJPJG). Vancouver: BC Cancer Agency; 2005.
35. BC Cancer Agency Genitourinary Tumour Group. BCCA Protocol summary for nonseminoma consolidation/salvage protocol using etoposide, cisplatin, ifosfamide, mesna (GUVIP2). Vancouver: BC Cancer Agency; 2005.
36. BC Cancer Agency Lung Tumour Group. BCCA protocol summary for adjuvant cisplatin and etoposide following resection of stage I, II and IIIA non-small cell lung cancer (LUAJEP). Vancouver: BC Cancer Agency; 2001.

37. BC Cancer Agency Lung Tumour Group. BCCA protocol summary for treatment of advanced non-small cell lung cancer with platinum and gemcitabine (LUAVPG). Vancouver: BC Cancer Agency; 2005.
38. BC Cancer Agency Lung Tumour Group. BCCA protocol summary for first-time treatment of advanced non-small cell lung cancer with cisplatin and docetaxel (LUCISDOC). Vancouver: BC Cancer Agency; 2005.
39. BC Cancer Agency Gynecology Tumour Group. BCCA protocol summary for treatment of small cell carcinoma of cervix using paclitaxel, cisplatin, etoposide and carboplatin with radiation (GOSMCC2). Vancouver: BC Cancer Agency; 2002.
40. BC Cancer Agency Genitourinary Tumour Group. BCCA protocol summary for consolidation/salvage treatment for germ cell carcinoma using vinblastine, cisplatin, ifosfamide and mesna (GUVEIP). Vancouver: BC Cancer Agency; 2003.
41. BC Cancer Agency Genitourinary Tumour Group. BCCA protocol summary for therapy of genitourinary small cell tumours with a platin and etoposide (GUSCPE). Vancouver: BC Cancer Agency; 2003.
42. BC Cancer Agency Head and Neck Tumour Group. BCCA Protocol summary for advanced head and neck cancer using cisplatin and fluorouracil (HNFUP). Vancouver: BC Cancer Agency; 2005.
43. BC Cancer Agency Head and Neck Tumour Group. Cisplatin and etoposide for recurrent and metastatic nasopharyngeal cancer. (HNDE). Vancouver: BC Cancer Agency; 1999.
44. BC Cancer Agency Lung Tumour Group. BCCA protocol summary for treatment of limited stage small cell lung cancer alternating cyclophosphamide, doxorubicin and vincristine with etoposide and cisplatin plus early thoracic irradiation (LUALTL). Vancouver: BC Cancer Agency; 2002.
45. BC Cancer Agency Lung Tumour Group. BCCA protocol summary for palliative therapy of selected solid tumours using cisplatin and etoposide (LUPE). Vancouver: BC Cancer Agency; 2004.
46. BC Cancer Agency Lung Tumour Group. BCCA protocol summary for treatment of limited stage small-cell lung cancer with etoposide and cisplatin and early thoracic irradiation (LUPESL). Vancouver: BC Cancer Agency; 2004.
47. BC Cancer Agency Gynecology Tumour Group. BCCA Protocol summary for non-dysgerminomatous ovarian germ cell cancer using bleomycin, etoposide and cisplatin. Vancouver: BC Cancer Agency; 2001.
48. BC Cancer Agency Gynecology Tumour Group. BCCA Protocol summary for therapy of dysgerminomatous ovarian germ cell cancer using cisplatin and etoposide. Vancouver: BC Cancer Agency; 2001.
49. BC Cancer Agency Genitourinary Tumour Group. BCCA Protocol Summary for Bleomycin, Etoposide, Cisplatin for Nonseminoma Germ Cell Cancers (GUBEP). Vancouver: BC Cancer Agency; 2002.
50. BC Cancer Agency Genitourinary Tumour Group. BCCA protocol summary for therapy for etoposide - cisplatin protocol for germ cell cancers (GUBP). Vancouver: BC Cancer Agency; 2005.
51. BC Cancer Agency Genitourinary Tumour Group. BCCA protocol summary for therapy for transitional cell cancers of the urothelium using methotrexate, vinblastine, doxorubicin and cisplatin (GUMVAC). Vancouver: BC Cancer Agency; 2003.
52. BC Cancer Agency Lung Tumour Group. BCCA protocol summary for combined chemotherapy and radiation treatment for stage 3 non-small cell lung cancer (LUCMT-1). Vancouver: BC Cancer Agency; 2005.
53. BC Cancer Agency Gynecology Tumour Group. BCCA Protocol Summary for Treatment of Advanced/Recurrent Non-Small Cell Cancer of the Cervix with Cisplatin and Etoposide (GOCXADV). Vancouver: BC Cancer Agency; 2000.
54. BC Cancer Agency Genitourinary Tumour Group. BCCA protocol summary for combined modality therapy for squamous cell cancer of the genitourinary system using fluorouracil and cisplatin (GUFUP). Vancouver: BC Cancer Agency; 2005.
55. BC Cancer Agency Neuro-Oncology Tumour group. BCCA Protocol Summary for adjuvant lomustine, cisplatin and vincristine in adult high-risk medulloblastoma or other primitive neuro-ectodermal tumour (PNET) - CNCCV. Vancouver: BC Cancer Agency; 2002.
56. BC Cancer Agency Gynecology Tumour Group. BCCA Protocol summary for treatment of high risk squamous cell carcinoma of cervix with concurrent cisplatin and radiation. (GOCXRADC). Vancouver: BC Cancer Agency; 2002.
57. BC Cancer Agency Head and Neck Tumour Group. BCCA Protocol summary for combined chemotherapy and radiation treatment for locally advanced squamous cell carcinoma of the head and neck (HNCMT2). Vancouver: BC Cancer Agency; 2004.
58. BC Cancer Agency Gastrointestinal Tumour Group. BCCA Protocol Summary for combined modality therapy for locally advanced esophageal cancer using cisplatin, infusional fluorouracil and radiation therapy. (GIEFUP). Vancouver: BC Cancer Agency; 2000.
59. International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *New England Journal of Medicine* 2004;325(4):351-60.