Drug Monograph

A - Drug Name

CISplatin

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B - Mechanism of Action and Pharmacokinetics

Cisplatin is biochemically similar to bifunctional alkylating agents as it inhibits DNA synthesis through covalent binding leading to intrastrand, interstrand, and protein cross-linking causing apoptosis. It is cell cycle phase-nonspecific and based on animal studies, may increase the host immune response.

Distribution	Well distributed with highest levels in kidney, liver and prostate. Accumulation of free (ultrafilterable) platinum in plasma can potentially occur when cisplatin is administered on a daily basis. Platinum has been detected in many tissues for up to 6 months after the last dose.	
	Cross blood brain barrier?	Not readily
	PPB	Cisplatin: not significantly Platinum: >90%
Metabolism	Non-enzymatically transformed to multiple metabolites.	
	Active metabolites	Yes
	Inactive metabolites	Yes
Elimination	Renal clearance is non-linear and depends on dose, urine flow rate, individual variations in tubular secretion and reabsorption.	

Urine	>90%; 10-40% (platinum) in 24 hours
Half-life	Cisplatin: 20-30 minutes Platinum: ≥ 5 days

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C - Indications and Status

Health Canada Approvals:

- Bladder cancer
- Ovarian cancer
- Testicular cancer

Refer to the product monograph for a full list and details of approved indications

Other Uses:

- Gynecological cancers (cervical, endometrial, uterine sarcoma, gestational trophoblastic disease)
- Penile cancer
- Head and neck cancer
- Lung cancer (small cell; non-small cell; mesothelioma)
- GI cancers (anal, esophageal, gastric, biliary cancers)
- Adrenocortical cancer
- Neuroendocrine tumours
- Thymoma
- Bladder (combination chemotherapy)
- Non-Hodgkin's or Hodgkin's lymphoma
- Breast cancer
- Skin cancer
- Small cell carcinoma
- Osteogenic sarcoma
- Soft tissue sarcoma
- Merkel cell cancer
- CNS cancer
- Unknown primary

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D - Adverse Effects

Emetogenic Potential: Moderate (< 70 mg/m2)
High (≥ 70 mg/m2)

Extravasation Potential: Irritant

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Auditory	Hearing impaired (31%) (may be severe)	D
Cardiovascular	Arrhythmia (<10%)	I E
	Arterial thromboembolism (rare)	E
	Venous thromboembolism (<10%)	E
Dermatological	Alopecia (<1%)	E
	Rash (infrequent)	I E
Gastrointestinal	Anorexia (≥10%)	E
	Diarrhea (≥10%)	E
	Mucositis (rare)	E
	Nausea, vomiting (100%) (early and delayed)	I E
General	Fatigue	E
Hematological	Hemolysis (Coombs positive) (rare)	E
	Hemolytic uremic syndrome (rare)	E
	Myelosuppression ± infection, bleeding (30%) (may be severe; including anemia)	E
	Thrombotic microangiopathy (rare)	E
Hepatobiliary	↑ Amylase (<1%)	E
	↑ LFTs (transient) (<10%)	E
Hypersensitivity	Hypersensitivity (including anaphylaxis - rare)	I
Injection site	Injection site reaction (<10%)	I
	Other - Soft tissue toxicity (if extravasated) (rare)	I E
Metabolic / Endocrine	Abnormal electrolyte(s) (↓ Mg (40-90%), Na (up to 43%), K, Ca, PO4)	E
	Hyperuricemia	I E
	SIADH (rare)	D
Musculoskeletal	Musculoskeletal pain	E
Neoplastic	Secondary malignancy (rare, including leukemia)	L
Nervous System	Dysgeusia (rare)	E

	Leukoencephalopathy (rare)	E D
	Neurotoxicity (peripheral - approximately 50%, autonomic, myelopathy, vestibular toxicity, slurred speech, memory loss)	D
	Optic neuritis (rare)	E
	Posterior reversible encephalopathy syndrome (PRES) (rare)	E
	Seizure (rare)	D
Ophthalmic	Eye disorders (including papilledema, blurred vision, cerebral blindness, altered colour perception - rare)	D
Renal	Nephrotoxicity (36%)	I E
Reproductive and breast disorders	Infertility	L
Respiratory	Hiccups (infrequent)	E
	Other - Pulmonary toxicity (in combination with bleomycin or 5-fluorouracil)	E
Vascular	Peripheral ischemia (Raynaud's syndrome - rare, with bleomycin, vinblastine ± cisplatin)	D
	Vasculitis (cerebral arteritis- rare)	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 cisplatin include nausea, vomiting, abnormal electrolytes (Mg, Na), nephrotoxicity, hearing impaired and myelosuppression ± infection.

Anaphylactic reactions consisting of facial edema, wheezing, flushing, tachycardia, or hypotension, and may be severe. These usually occur in patients with prior exposure to cisplatin (e.g. at least 5 doses), but can also occur after the first dose within a few minutes of drug administration.

Aortic thrombosis has been reported and may be fatal. Some cases were identified after the last dose of cisplatin. Possible confounding factors in the Canadian reported cases included a higher coagulation state associated with the malignancy, and other known risk factors such as smoking, obesity and previous history of vascular disease (e.g. TIA). Some of these cases stabilized or resolved after starting anticoagulation or thrombectomy.

The relative risk of **venous thromboembolism** (VTE) was 1.67-fold higher in advanced solid tumour patients treated with cisplatin-based therapies versus those treated with non-cisplatin therapies (Seng 2012). Patients receiving an equivalent weekly dose greater than 30 mg/m^2 were at higher risk.

Hyperuricemia has been reported with cisplatin and more pronounced at doses greater ≥ 50 mg/m^2. Peak levels of uric acid generally occur between 3-5 days after the dose.

Severe **myelosuppression** including fatalities due to infection (secondary to myelosuppression) have been reported. Nadirs in circulating platelets and leukocytes occur after about 2 weeks with levels returning to pre-treatment values in most patients within 4 weeks. Leukopenia and thrombocytopenia are dose-related and may become clinically relevant in patients receiving high doses of cisplatin or in patients who have received prior myelosuppressive treatments. Anemia (hemoglobin ↓ of 20 g/L) occurred at approximately the same frequency and timing as leukopenia and thrombocytopenia.

The major dose-limiting toxicity of cisplatin is cumulative **nephrotoxicity**. Tubular necrosis or degeneration of both proximal and distal renal tubules may occur. Although reversible, effects are cumulative. They occur in 28-36% of patients treated with a single dose of 50mg/m^2. Renal toxicity may be permanent with high doses or prolonged treatment. Nephrotoxicity can be minimized or prevented by IV hydration.

Renal tubular abnormality such as acidosis, hypomagnesemia, hypocalcemia, hypophosphatemia, hyponatremia or hypokalemia may be present with normal glomerular function. **Hypomagnesemia** may become severe enough to cause tetany; it usually develops within 3-4 weeks after starting treatment and appears to increase in severity with subsequent treatment courses. Hypomagnesemia may persist for greater than one year following treatment. Children are particularly at risk.

Cisplatin produces moderate to severe **nausea and vomiting** in virtually all patients. Nausea and vomiting may start within one hour and may persist for more than 24 hours after chemotherapy. Tolerance may improve with 5-day continuous infusion as compared to rapid, intermittent IV administration. Various degrees of nausea and anorexia may persist for up to 1 week, even with well-controlled acute nausea and vomiting. The use of prophylactic and continuing antiemetic medication is recommended.

Neurotoxicity consists of peripheral neuropathy, which is sensory in nature in a stocking-glove distribution, but can also include motor effects, reduced deep-tendon reflexes, loss of proprioception and vibratory sensation. Symptoms usually occur after prolonged therapy (4-7 months) or high dose treatment and may be irreversible in some patients. Symptoms usually develop during treatment but rarely may begin after the last dose of cisplatin. Seizures, altered taste, slurred speech, and memory loss have occurred rarely. Sudden onset of muscle cramps have been reported, and are usually observed in patients with a high cumulative cisplatin dose and with relatively severe peripheral neuropathy.

Optic neuritis, papilledema and cerebral blindness are infrequent at standard cisplatin doses; they usually recover after cisplatin discontinuation. Blurred vision and altered colour perception have occurred at higher cisplatin doses or at greater dose frequencies than recommended.

Ototoxicity usually results in hearing loss in the high frequency range, but at late stages may affect the normal hearing range. Hearing loss can be unilateral or bilateral. Ototoxicity is cumulative and dose-related; it is unclear if the ototoxicity is reversible. Ototoxicity appears to be related to peak levels of cisplatin, as significant hearing loss has been reported with single high doses. Cranial

irradiation may lower the cumulative dose at which cisplatin will cause hearing loss. Vestibular ototoxicity is rare, but the risk may increase with cumulative dosage.

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

All patients should receive adequate hydration and premedication for emesis, according to local guidelines.

Adults:

Doses greater than 100 mg/m^2/cycle once every 3 to 4 weeks are rarely used.

Frequency	Schedule	Dose
Q3-4 weekly	Day 1	50-75* mg/m^2
	Day 1-5	15-20 mg/m^2

* A higher dose has been used for some curative regimens.

Dosage with Toxicity:

Worst Toxicity in Previous Cycle	Dose for Next Cycle*
Grade 4 platelets, grade 4 ANC ≥ 5 days, thrombocytopenic bleeding or febrile neutropenia	↓ 25%
Grade 2 neurotoxicity /ototoxicity	↓ 25% or discontinue depending on risk-benefit
Grade 3 or 4 neurotoxicity/ototoxicity	Discontinue
Other grade 3 non-hematologic/organ toxicity	↓ 25%

Other grade 4 non-hematologic/organ toxicity	Discontinue
Hemolysis, optic neuritis, arterial or venous thromboembolism, grade 3 or 4 ↑ LFTs, PRES, leukoencephalopathy	Discontinue
* Do not retreat until platelets ≥100 x 10^9/L, ANC ≥ 1.5 x 10^9/L, toxicity has recovered to ≤ grade 2 (grade 1 for neurotoxicity) and creatinine ≤ ULN.	

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.	• 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 adjustment required.

Dosage with Renal Impairment:

Refer to specific protocol.

A repeat course of Cisplatin should not be given until creatinine is ≤ ULN. If continued treatment is considered to be mandatory, the following dose modifications could be considered at the physician's discretion (Kintzel 1995).

Creatinine Clearance (mL/min)	% Previous Dose
46-60	75%
30-45	50%*
<30	Discontinue

* if clinically appropriate, consider discontinuing or using alternative (i.e. carboplatin).

Dosage in the elderly:

Geriatric patients may be at higher risk of developing nephrotoxicity, ototoxicity/neurotoxicity or hematologic adverse effects with cisplatin.

Children:

Refer to protocol by which patient is being treated. May be at higher risk of ototoxicity (including delayed-onset cases).

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F - Administration Guidelines

- Cisplatin is physically incompatible with any IV set, needle or syringe containing aluminum.
- Drug dilution and infusion durations vary according to the regimen. Some centres dilute cisplatin in 500 to 1000 mL of NS, depending on the dose.
- All patients should receive adequate hydration and premedication for emesis, according to local guidelines.
- Additional hydration may be ordered for hypovolemic patients.
- Hydration and diuresis for patients with pre-existing renal, cardiac, or diabetic history at discretion of physician.
- Adequate hydration and urinary output must be maintained for 24 hours following cisplatin treatment.
- Oral hydration with 8 glasses of fluid per day is strongly encouraged on treatment day and for 1-2 days after cisplatin; if nausea and vomiting prevent oral hydration, the patient may need to return for more IV hydration.
- Store unopened vials between 15°C to 25°C and protect from light. Do not refrigerate or freeze since precipitation will occur.

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 are hypersensitive to this drug, other platinum-containing compounds, or any component of the formulation
- Patients who are myelosuppressed
- Patients with pre-existing renal impairment and hearing impairment, unless the possible benefits of treatment outweigh the risks

Other Warnings/Precautions:

- Administration of cisplatin prior to an infusion with paclitaxel may increase exposure to paclitaxel by 33% and may intensify neutropenia and neurotoxicity.

Other Drug Properties:

- Carcinogenicity: Yes

Pregnancy and Lactation:

- Mutagenicity: Yes
- Embryotoxicity: Documented in animals
- Fetotoxicity: Documented in humans
- Teratogenicity: Documented in animals
- Crosses placental barrier: Yes
- Pregnancy:
  Cisplatin is not recommended for use in pregnancy.
  - Adequate contraception should be used by patients who can become pregnant and their partners during treatment, and for at least **29 weeks (7 months)** after the last dose.
  - Adequate contraception should be used by patients who produce sperm and their partners during treatment, and for at least **17 weeks (4 months)** after the last dose.
- Excretion into breast milk: Documented in humans
- Breastfeeding:
  Breastfeeding is not recommended during treatment and for **1 month** after the last dose.
- Fertility effects: Yes
  Observed in humans. Consider fertility preservation counselling prior to starting treatment.
  Do not donate sperm while using cisplatin and up to **2 years** after the last dose.

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H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Renally excreted drugs (especially high dose methotrexate, bleomycin)	↓ renal clearance and increased t½; toxicities of these drugs may be enhanced	↓ renal function caused by cisplatin	ascertain renal function prior to giving potentially toxic renally-excreted drugs (such as other chemotherapy) and modify doses as necessary
Nephrotoxic drugs (e.g. aminoglycosides amphotericin)	↑ nephrotoxicity	Additive	Avoid or use with extreme caution during or shortly after cisplatin therapy (for 1-2 weeks)
Pyridoxine (high dose > 300mg/m2)	↓ efficacy when given with cisplatin and altretamine	Unknown	Avoid concomitant use with the combination of cisplatin and altretamine
Ototoxic drugs (e.g. furosemide, ethacrynic acid)	↑ ototoxicity	Additive, especially in the presence of renal impairment	Avoid concomitant use; use furosemide if a diuretic is essential (may be less ototoxic than ethacrynic acid)
Ifosfamide	↑ ototoxicity, ↓ renal clearance and ↑ toxicity	Possibly additive (ototoxicity); ↓ renal function caused by cisplatin	Caution and monitor; ascertain renal function prior to administration
Paclitaxel (given after cisplatin)	↑ toxicity (may ↑ paclitaxel exposure by 33% and ↓ efficacy)	↑ neutropenia and neurotoxicity; ↓ efficacy because of reduced cycling of cells	give paclitaxel prior to cisplatin when used in combination
Anticonvulsant agents (phenytoin, carbamazepine, valproate sodium)	↓ anticonvulsant serum levels	decreased absorption and/or increased metabolism of anticonvulsant agent	monitor serum levels; increase dose if necessary
Lithium	↓ lithium serum levels (observed with cisplatin, bleomycin, and etoposide combination)	Unknown	Monitor lithium levels

Warfarin	↑ INR has been reported	Unknown	Monitor INR
Topotecan	↑ topotecan toxicity	Unknown. Appears to be sequence dependent. Higher hematologic toxicity was observed even when topotecan was given 8 days after carboplatin	Consider giving platinum after topotecan (e.g. day 5 platinum in a 5 day regimen). Lower topotecan doses are recommended when platinum is given before topotecan. Monitor for myelosuppression.

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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.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Liver function tests	Baseline and as clinically indicated
CBC	Baseline and at each cycle
Renal function tests	Baseline and at each cycle
Electrolytes, including magnesium, sodium, potassium, phosphate and calcium.	Baseline and at each cycle
Audiogram	Baseline and as clinically indicated
Clinical toxicity assessment of injection site reactions, infection, bleeding, nausea/vomiting, neurotoxicity, ototoxicity, ocular toxicity, arterial and venous thromboembolism	At each cycle

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

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K - References

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November 2024 Modified Adverse effects, Contraindications, Warnings/Precautions, and Pregnancy/lactation sections.

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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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