Drug Monograph

A - Drug Name

oxaliplatin

back to top

B - Mechanism of Action and Pharmacokinetics

Oxaliplatin is a platinum alkylating agent, which contains platinum complexed to oxalate and diaminocyclohexane (DACH) complex. Platinum complexes are formed intracellularly and bind to DNA, forming cross-links which inhibit DNA replication and transcription, leading to cytotoxic and antitumor effects. Cytotoxicity is cell-cycle nonspecific.

Absorption	C_{max}: reached at the end of 2-hour infusion of oxaliplatin at 85 mg/m^2	
Distribution	At the end of a 2 hour infusion, approximately 15% of the administered platinum is present in the systemic circulation. The remaining 85% is rapidly distributed into tissues or eliminated in the urine.	
	Cross blood brain barrier?	No
	PPB	> 90 % (irreversible; also binds irreversibly to erythrocytes)
Metabolism	Rapid and extensive nonenzymatic (no cytochrome P450-mediated metabolism) biotransformation to reactive platinum complexes.	
	Active metabolites	Yes. Diaminocyclohexane (DACH) platinum complexes
	Inactive metabolites	Yes, including one associated with neurotoxicity

Elimination		
	Triphasic elimination	
	Half-life	391 hours (terminal)
	Urine	54 % within 5 days
	Feces	2% within 5 days

back to top

C - Indications and Status

Health Canada Approvals:

- Colorectal cancer

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

Other Uses:

- Pancreatic cancer
- Gastroesophageal cancer
- Biliary tract cancer
- GI neuroendocrine carcinoma
- Bladder cancer
- Testicular cancer
- Cancer of unknown primary origin
- Ovarian cancer
- Thyroid cancer
- Non-Hodgkin lymphoma
- T-cell lymphoma

back to top

D - Adverse Effects

Emetogenic Potential: Moderate

Extravasation Potential: Irritant

The following table lists adverse effects that occurred in ≥ 5% of patients who received adjuvant treatment in colorectal cancer, in a clinical study with oxaliplatin in combination with 5-FU/LV. Other adverse events, which may be severe, from other studies or post-marketing are also included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Auditory	Hearing impaired (rare)	E D
Cardiovascular	Arterial thromboembolism (rare)	E
	Hypertension (<5%)	I
	Hypotension (<5%)	I
	QT interval prolonged (rare)	E
	Venous thromboembolism (<10%)	E
Dermatological	Alopecia (30%) (mostly mild)	D
	Hand-foot syndrome (7%)	E
	Nail disorder (<5%)	E
	Rash (14%)	E
Gastrointestinal	Abdominal pain (18%)	E
	Anorexia (13%)	E
	Constipation (22%)	E
	Diarrhea (56%) (11% severe)	E
	Dyspepsia (8%)	E
	GI obstruction (5%)	E
	GI perforation (rare)	E
	GI ulcer (duodenal – rare)	E
	Mucositis (42%)	E
	Nausea, vomiting (74%) (5% severe)	I E
	Other - ischemia (rare; may be severe)	E
	Weight changes (10%)	E
General	Edema (15%)	E
	Fatigue (44%)	E
Hematological	Disseminated intravascular coagulation (rare)	E
	Hemolysis (immune hemolytic anemia; rare)	I E
	Hemolytic uremic syndrome / microangiopathic hemolytic anemia (rare)	E
	Immune thrombocytopenic purpura (rare)	E
	INR / prothrombin time increased (<5%)	E

	Myelosuppression ± infection, bleeding (77%) (2% severe)	E
Hepatobiliary	↑ LFTs (57%) (2% severe)	E
	Pancreatitis (rare)	E
	Veno-occlusive disease (rare)	D
Hypersensitivity	Hypersensitivity (10%) (3% severe)	I E
Injection site	Injection site reaction (11%)	I E
Metabolic / Endocrine	Abnormal electrolyte(s) (11%) (↓ Ca, K, Na)	E
	Hyperglycemia (14%)	E
Musculoskeletal	Musculoskeletal pain (14%)	E
	Rhabdomyolysis (rare)	
Nervous System	Ataxia (<5%)	I E
	Dizziness (<5%)	E
	Dysgeusia (12%)	E
	Guillain-Barre syndrome (rare)	E
	Headache (7%)	E
	Insomnia (<5%)	E
	Optic neuritis (rare)	E
	Pharyngolaryngeal dysesthesia (38%)	I
	Posterior reversible encephalopathy syndrome (PRES) (rare)	E
	Sensory neuropathy (92%) (including cranial neuropathy; 12% severe)	I E
Ophthalmic	Conjunctivitis (9%)	I
	Other (transient vision loss; rare)	E
	Watering eyes (<5%)	I
Renal	Nephrotoxicity (<5%) (<1% severe)	E
Respiratory	Cough, dyspnea (5%)	E
	Pneumonitis (<5%)	D
Urinary	Urinary symptoms (5%)	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 associated with the of combination oxaliplatin/5FU/LV include sensory neuropathy, myelosuppression ± infection, bleeding, nausea, vomiting, ↑ LFTs, diarrhea, fatigue, mucositis, pharyngolaryngeal dysesthesia, alopecia and constipation.

Two different types of **peripheral sensory neuropathy** are associated with oxaliplatin. The first type is an acute presentation (within hours or 1 to 2 days of dosing), reversible (usually resolves within 14 days), and primarily peripheral, sensory neuropathy that frequently recurs with further dosing. Symptoms include sensory dysesthesia, paresthesia and hypoesthesia of the limbs, mouth, throat and larynx. Jaw spasm, abnormal tongue sensation, dysarthria, eye pain, and a feeling of chest pressure have also been observed.

Pharyngolaryngeal dysesthesia is common, with severe symptoms in 1-2% of patients shortly after drug infusion. Symptoms usually resolve within hours of onset. The feeling of difficulty in breathing or swallowing may be distressing to the patient. As symptoms may be precipitated or exacerbated by exposure to cold temperatures or objects, cold avoidance should be exercised. The second type of neuropathy is a more persistent (>14 days) presentation, characterized by paresthesias, dysesthesias, hypoesthesias and altered proprioception. It can interfere with daily activities (e.g. buttoning clothing, holding objects, writing) and occurs in most patients receiving oxaliplatin with 5-FU/LV. Lhermittes sign and urinary retention are seen rarely. Persistent neuropathy can occur without prior acute neuropathy event. Symptoms may improve in some patients upon discontinuation of oxaliplatin. Calcium gluconate 1 g and magnesium sulphate 1 g infusions pre ± post-oxaliplatin did not appear to be effective neuroprotective agents in a randomized study.

Anaphylaxis has been reported, including severe events in 2-3% of patients, and can occur during any cycle, but incidence increases as cycle number increases (generally after 6 cycles). In the post-marketing experience, some cases of anaphylaxis have been fatal. Patients should not be re-challenged if possible. If re-challenge is clinically necessary (ie. benefits of treatment outweigh risks and no other treatment option available), a desensitization protocol should be used.

Pneumonitis, including fatal cases, has been reported rarely, and presents with cough, dyspnea, crackles and pulmonary infiltrates.

Hepatotoxicity, **transaminitis**, **VOD** and **nodular regenerative hyperplasia** have been reported.

back to top

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.

For adjuvant use, treatment is recommended for a total of 12 cycles.

Avoid mucositis prophylaxis with ice chip as cold temperatures can precipitate or exacerbate acute neurological symptoms.

Premedication (prophylaxis for infusion reactions):

- There is insufficient evidence that routine prophylaxis with pre-medications reduces IR rates.
- Consider corticosteroids and H1-receptor antagonists ± H2-receptor antagonists in high-risk patients (i.e. ≥ cycle 6, younger age, female gender, prior platinum exposure, platinum-free interval ≥ 3 years).

Adults:

In Combination with 5-Fluorouracil and Leucovorin: 85 mg/m^2 IV on day 1 every 2 weeks.

Dosage with Toxicity:

Modify according to protocol by which patient is being treated.

Consider dose reduction in subsequent cycles after recovery from Grade 3 or 4 hematological toxicities.

Neurotoxicity was graded based on the following scales from the adjuvant or metastatic colorectal cancer trials.

Neurotoxicity Grade	Adjuvant	Metastatic
1	No change or none	Resolved and did not interfere with functioning
2	Mild paresthesias, loss of deep tendon reflexes	Interfered with function but not daily activities

3	Mild or moderate objective sensory loss, moderate paresthesias	Pain or functional impairment that interfered with daily activities
4	Severe objective sensory loss or paresthesias that interfere with function	Persistent impairment that is disabling or life-threatening

Toxicity Grade	Combinations - Adjuvant^	Combinations - Palliative^
Persistent[1] Grade 2 Neurotoxicity	↓ from 85 → 75 mg/m^2	↓ from 85 → 65 mg/m^2
Transient[1] Grade 3 Neurotoxicity	↓ to 75mg/m2	↓ to 65mg/m2
Persistent[1] Grade 3 Neurotoxicity or grade 4	Discontinue	
≥ Grade 3 GI toxicity (after prophylaxis) OR ≥ Grade 3 Platelets OR ≥ Grade 3 Neutropenia (including febrile neutropenia)	↓ from 85 → 75 mg/m^2 Reduce 5FU by 20%	↓ from 85 → 65 mg/m^2 Reduce 5FU by 20%
Sepsis / septic shock	Discontinue	
Other ≥ grade 3 toxicity [3]	Consider dose ↓	
Pharyngolaryngeal dysesthesia	Hold; then increase duration of next infusion to 6 hours[4]	
Pneumonitis	Hold, investigate; discontinue if confirmed.	
Anaphylactic-like reaction	Discontinue	
RPLS		
Hemolytic uremic syndrome or any signs of microangiopathic hemolytic anemia		
Disseminated intravascular coagulation (DIC)		
QT prolongation		
Intestinal ischemia or duodenal ulcer		
Symptoms of rhabdomyolysis		

^Do not re-treat until the ANC ≥ 1.5 x 10^9/L and the platelets ≥ 75 x 10^9/L, GI and neurotoxicities have resolved and other non-hematologic toxicities ≤ grade 1.

[1] Transient = >7days - <1 cycle; persistent = ≥ 1 cycle

[3] For skin toxicity, reduce 5FU dose only.

[4] If oxygen saturation is normal, an anxiolytic agent may be given.

Management of Infusion-related reactions:

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

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 symptoms 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:

Hepatic Impairment	Oxaliplatin Dose
Mild to moderate	No adjustment required
Severe	No information found

Dosage with Renal Impairment:

Creatinine Clearance (mL/min)	Oxaliplatin (% previous dose)
50 - 80	No adjustment required
30 - <50	Caution
<30	Discontinue

Dosage in the elderly:

Patients ≥ 65 years had a higher incidence of GI toxicity, myelosuppression, syncope and fatigue. No dose adjustments were needed but caution should be exercised. Efficacy (on disease free survival benefit) in the adjuvant setting was not confirmed.

Dosage based on gender:

Women may be at higher risk of severe (grades 3-4) GI effects, fatigue or neutropenia in adjuvant treatment of colorectal cancer. In metastatic colorectal cancer, females were observed to have higher number of severe adverse effects than men across all treatment arms.

Children:

Safety and efficacy not established.

back to top

F - Administration Guidelines

- Oxaliplatin is administered by intravenous infusion.
- Oxaliplatin should always be administered before fluorouracil.
- May be mixed in 250-500 mL bag of D5W only. Do not mix with NS, chloride containing or alkaline solutions, or with fluorouracil.
- Administer by slow infusion. Concentration must be between 0.2 to 0.7 mg/mL
- Infuse IV over 2 hours. Increasing infusion time to 6 hours may decrease acute toxicity such as pharyngolaryngeal dysesthesia.
- Do not mix oxaliplatin with other drugs in the same infusion bag or infusion line.
- Infusion may be given at the same time as Leucovorin in separate D5W bags using a Y-site, providing trometamol is not used as an excipient. Do not administer concurrently with fluorouracil.
- If another drug is given before oxaliplatin, flush infusion line with D5W before giving oxaliplatin. Flush the line with D5W after oxaliplatin before giving a subsequent drug (e.g. fluorouracil).
- The compatibility of oxaliplatin solution for infusion has been tested with representative, PVC-based, administration sets.
- Do not use with injection equipment containing aluminum, as this can degrade platinum compounds.
- Unopened vials should be stored at 15-30°C; protect from light.

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

back to top

G - Special Precautions

Contraindications:

- Hypersensitivity to the drug or to other platinum agents (e.g. cisplatin, carboplatin) or to any component of the formulation.
- Pregnancy and breastfeeding.
- Severe renal impairment (CrCl < 30 mL/min).

Other Warnings/Precautions:

- Oxaliplatin may result in dizziness or visual disturbances (including transient vision loss) in some patients; patients should exercise caution in driving or operating machinery.
- Do not give oxaliplatin intraperitoneally.

Other Drug Properties:

- Carcinogenicity: Yes

Pregnancy and Lactation:

- Fetotoxicity: Yes
- Mutagenicity: Yes
- Clastogenicity: Yes
- Teratogenicity: Yes
- Genotoxicity: Yes
- Embryotoxicity: Yes
  Oxaliplatin is **contraindicated** in pregnancy.
  - Adequate contraception should be used by patients who can become pregnant and their partners during treatment, and for at least **9 months** after the last dose.
  - Adequate contraception should be used by patients who produce sperm and their partners during treatment, and for at least **6 months** after the last dose.
- Breastfeeding:
  Breastfeeding is **contraindicated** during treatment and for **3 months** after the last dose.
- Fertility effects: Yes
  Oxaliplatin may cause irreversible infertility. Men are advised to seek counseling on sperm storage before starting treatment.

back to top

H - Interactions

Drug interactions with CYP450 enzymes are unlikely.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Anticoagulants	Occasionally associated with hemorrhage (in patients who received oxaliplatin plus 5-FU/leucovorin)	Prolong INR and prothrombin time	Monitor INR closely
Fluorouracil	Possibly ↑ fluorouracil side effects with higher oxaliplatin dosage	↑ Fluorouracil exposure (approximately 20%) observed at oxaliplatin 130mg/m2 q3w	Caution; interaction unlikely at oxaliplatin 85mg/m2 q2w
Other nephrotoxic drugs	↑ Incidence of renal impairment	↓ Renal clearance	Monitor closely
Drugs that may prolong QT (i.e. amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, sunitinib, methadone, chloroquine, clarithromycin, haloperidol, fluconazole, moxifloxacin, domperidone, ondansetron, etc)	↑ QTc-prolonging effect	Additive	Monitor closely
Other drugs associated with rhabdomyolysis	↑ Risk of rhabdomyolysis	Additive	Monitor closely

back to top

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
CBC	Baseline and before each cycle
Liver function tests	Baseline and before each cycle
Renal function tests	Baseline and before each cycle
Electrolytes, including magnesium	Baseline and before each cycle
INR, if patient on anticoagulants	Baseline and as clinically indicated
Clinical assessment of GI effects, neurotoxicity, infection, bleeding, thromboembolism, hypersensitivity, local reactions, respiratory or ophthalmic effects	At each visit

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

back to top

K - References

Haller D., Tabernero J., Maroun J et al. Capecitabine Plus Oxaliplatin Compared With Fluorouracil and Folinic Acid As Adjuvant Therapy for Stage III Colon Cancer. Journal of Clinical Oncology 2011 29:11, 1465-1471

Loprinzi CL, Qin R, Dakhil SR, et al. Phase III randomized, placebo (PL)-controlled, double-blind study of intravenous calcium/magnesium (CaMg) to prevent oxaliplatin-induced sensory neurotoxicity (sNT), N08CB: An alliance for clinical trials in oncology study. J Clin Oncol 2013; 31 suppl; abstr 3501.

McEvoy GK, editor. AHFS Drug Information 2013. Bethesda: American Society of Health-System Pharmacists.

Product Monograph: Eloxatin® (oxaliplatin), Sanofi-Aventis Inc., January 8, 2015.

Product monograph: Oxaliplatin injection. Accord Healthcare Inc., November 27, 2018.

Product monograph: Oxaliplatin injection. Pfizer Canada ULC., May 2023.

October 2023 Modified Indications and Pregnancy/lactation sections

back to top

L - Disclaimer

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

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an “as-is” basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information’s quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary's content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person's use of the information in the Formulary.

back to top