

DRUG NAME: Oxaliplatin**SYNONYM(S):** ACT-078, I-OHP, LOHP, oxalatoplatin, oxaliplatinum**COMMON TRADE NAME(S):** ELOXATIN®**CLASSIFICATION:** Alkylating agent*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

Oxaliplatin belongs to a new class of platinum agent. It contains a platinum atom complexed with oxalate and diaminocyclohexane (DACH). The bulky DACH is thought to contribute greater cytotoxicity than cisplatin and carboplatin.¹ The exact mechanism of action of oxaliplatin is not known. Oxaliplatin forms reactive platinum complexes which are believed to inhibit DNA synthesis by forming interstrand and intrastrand cross-linking of DNA molecules. Oxaliplatin is not generally cross-resistant to cisplatin or carboplatin, possibly due to the DACH group and resistance to DNA mismatch repair.^{1,2} Preclinical studies have shown oxaliplatin to be synergistic with fluorouracil and SN-38, the active metabolite of irinotecan.³ Oxaliplatin is a radiation-sensitizing agent.^{4,5} It is cell-cycle-phase nonspecific.⁶

PHARMACOKINETICS:

Interpatient variability	inter- and intra-subject variability is low ⁶	
Distribution	minimal in plasma; accumulation in erythrocytes does not diffuse into plasma or act as a drug reservoir	
	cross blood brain barrier?	no information found
	volume of distribution	ultrafilterable platinum*: 582 ± 261 L ⁶
	plasma protein binding	70-95%
Metabolism	rapid nonenzymatic biotransformation to reactive platinum complexes ⁷	
	active metabolite(s)	DACH platinum species ⁶
	inactive metabolite(s)	several conjugates, ⁶ including the 1,2-DACH-platinum dichloride (2%) associated with neurotoxicity ³
Excretion	platinum is mainly by renal excretion and tissue distribution, ⁸ while platinum metabolites are mainly by renal excretion ¹	
	urine	50% within 3 days ⁹
	feces	minimal ⁹
	terminal half life	ultrafilterable platinum*: 273 ± 19 h ⁶ platinum elimination from erythrocytes: 48 days ¹
	clearance	ultrafilterable platinum*: 10.1 ± 3.07 L/h ⁶

Adapted from reference¹ unless specified otherwise.

*Ultrafilterable platinum consists of oxaliplatin and free oxaliplatin metabolites.

USES:**Primary uses:***Colorectal cancer¹⁰⁻¹²**Other uses:**Breast cancer¹³Gastric cancer¹⁴Germ cell cancer¹⁵Head and neck cancer¹⁶Lung cancer, non-small cell¹⁷Lymphoma, non-Hodgkin's¹⁸Mesothelioma^{19,20}

Ovarian cancer^{21,22}
 Pancreatic cancer²³
 Prostate cancer²⁴

*Health Canada Therapeutic Products Programme approved indication

No pediatric indications.

SPECIAL PRECAUTIONS:

Contraindications:

- history of hypersensitivity reaction to oxaliplatin or other platinum agents (eg, cisplatin, carboplatin).⁶
- peripheral sensory neuropathy interfering with function or severe renal dysfunction (CrCl < 30 mL/min).⁶

Special populations:

- **Elderly patients** over 65 may be at higher risk of severe (grades 3-4) diarrhea.¹¹
- **Women** may be at higher risk of severe (grades 3-4) neutropenia.¹¹

Carcinogenicity: Oxaliplatin is considered a probable carcinogen, although carcinogenic studies have not been done.⁶

Mutagenicity: Mutagenic in mammalian *in vitro* mutation chromosome tests.⁶

Fertility: No information found.

Pregnancy: Oxaliplatin produced embryo-fetal toxicity in rats.⁶

Breastfeeding is not recommended due to the potential secretion into breast milk.⁶

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. **Incidences of adverse events** are generally similar when oxaliplatin is used as a single agent or in combination with fluorouracil and leucovorin, although severe (grades 3-4) diarrhea, nausea and vomiting, and neurotoxicity are more common with combination therapy.^{1,25}

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
allergy/immunology	anaphylaxis (0.5-2%) ^{6,26,27}
blood/bone marrow febrile neutropenia	anemia (64-83%, severe 4-5%)
	febrile neutropenia (< 2%)
	immune hemolytic anemia (rare) ²⁸
	neutropenia: single agent (15%, severe 3%); with fluorouracil and leucovorin (66%, severe 38%)
	thrombocytopenia: single agent (41%, severe 3%); with fluorouracil and leucovorin (76%, severe 4%)
constitutional symptoms	fever (36%)
dermatology/skin	extravasation hazard: irritant²⁹⁻³⁴ , see paragraph following Side Effects table
	alopecia (2%)
gastrointestinal	emetogenic potential: high moderate³⁵
	diarrhea: single agent (41%, severe 5%); with fluorouracil and leucovorin (58%, severe 10%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	mucositis: single agent (4%, severe 2%); with fluorouracil and leucovorin (42%, severe 8%)
	nausea, vomiting (69-71%, severe 12-14%)
hepatic	liver function abnormalities (46%, severe 12%)
infection	infection (23%)
neurology	central neurotoxicity (rare) ³⁶
	neuropathy, sensory (85-95%); see paragraph following Side Effects table
	pharyngolaryngeal dysesthesia (1-2%); see paragraph following Side Effects table
renal/genitourinary	renal dysfunction (3%, severe < 1%)

Adapted from reference⁶ unless otherwise specified.

Peripheral sensory neuropathy is cumulative, dose-related and usually reversible a few months after stopping treatment. Symptoms include sensory ataxia and dysesthesia of the limbs, mouth, throat and larynx, and may be exacerbated by exposure to cold (eg, touching cold surface, drinking cold liquid).^{1,35} The incidence of grade 2 neuropathy is 10% after 3 treatment cycles and 50% after 10 cycles. Grade 3 neuropathy occurs in 10% after 9 cycles and 50% after 14 cycles, is reversible in 74% of the cases, and begins to recover after 13 weeks. Paresthesia interfering with function (eg, buttoning clothing, holding objects, writing) is seen in 16% of patients after 4 months of treatment and rarely leads to oxaliplatin withdrawal.¹¹ Unlike cisplatin, oxaliplatin neuropathy is related to injury to small rather than large sensory fibres.¹⁷ To reduce the incidence and severity of peripheral neuropathy, patients should be considered to receive infusions of 1 g of calcium gluconate and 1 g of magnesium sulphate prior to and following oxaliplatin treatment for metastatic colorectal cancer, especially if peripheral neuropathy has developed while on oxaliplatin treatment. Calcium/magnesium infusions do not appear to reduce the efficacy of oxaliplatin-based chemotherapy.³⁷⁻³⁹ However, they are not recommended in patients with hypercalcemia or receiving digoxin or thiazide diuretics. Calcium can precipitate arrhythmias when given with digoxin and increase the risk of hypercalcemia with thiazide diuretics.⁴⁰

Gabapentin PO 100 mg twice daily, with increments of 100 mg PO daily as needed, may be effective in some patients to reduce oxaliplatin neuropathy,⁴¹ while carbamazepine does not appear to be effective.⁴² Other agents used with some success include alpha-lipoic acid IV 600 mg weekly for 3-5 weeks, then followed by oral 600 mg three times daily.⁴³ Oxaliplatin delivered according to 24-hour biologic rhythms (chronomodulated) appears to be associated with less peripheral neuropathy than fixed rate infusion.^{1,12}

Pharyngolaryngeal dysesthesia with sporadic reduced sensitivity of the larynx and pharynx is seen in 1-2% of patients shortly after drug infusion. Symptoms usually resolve within hours of onset but the feeling of difficulty in breathing or swallowing may be distressing to the patient. Treatment is usually not needed, although antihistamines and bronchodilators have been used. To prevent recurrence, infusion time should be extended to 6 hours with subsequent treatments.^{1,6}

Management of extravasation: Extravasation of oxaliplatin may sometimes cause severe local inflammation and potentially tissue necrosis.²⁹⁻³⁴ The optimal non-pharmacological management of oxaliplatin extravasation is unclear. However, it has been suggested that warm compresses may be preferred over cool compresses^{31,44,45} which may theoretically precipitate or worsen peripheral sensory neuropathy.

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
fluorouracil ⁴⁶	no influence on fluorouracil pharmacokinetics		

AGENT	EFFECT	MECHANISM	MANAGEMENT
irinotecan ⁴⁷⁻⁴⁹	induction of irinotecan-related cholinergic syndrome	may potentiate irinotecan inhibition of acetylcholinesterase	give prophylactic atropine before irinotecan
topotecan ⁵⁰	no effects on topotecan pharmacokinetics		
warfarin ⁵¹	possible increased effect and toxicity of warfarin	unknown; reported increase in effect and toxicity of warfarin may be attributable to fluorouracil; however, patients given fluorouracil and oxaliplatin are more likely to have abnormal INR's than patients given fluorouracil and other agents	check baseline INR; monitor weekly INR during, and for one month after, oxaliplatin and fluorouracil therapy; increase frequency and duration of monitoring if INR unstable; adjust warfarin dose as needed

SUPPLY AND STORAGE:

Injection: sanofi-aventis Canada Inc. supplies oxaliplatin as 50 mg and 100 mg single-use vials of sterile lyophilized powder and 50 mg, 100 mg, and 200 mg single-use vials of sterile preservative-free aqueous solution in a concentration of 5 mg/mL. Store at room temperature. Do not freeze. Protect from light for long-term storage.⁵²

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.

Additional information:

- Aluminum-containing IV needles, syringes or sets should not be used to prepare or administer oxaliplatin; aluminum reacts with platinum from oxaliplatin to form a precipitate, resulting in loss of potency.⁶
- Oxaliplatin can be co-administered with leucovorin infusion using a Y-line placed immediately before the site of injection; however, the drugs should not be combined in the same infusion bag.^{53,54}

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	no information found
Intermittent infusion	in 500 mL D5W over 2 h¹¹; in 250-500 mL D5W over 30 min ⁹ , 3 h ⁵⁵ , or 6 h ¹² ; administer before fluoropyrimidines (eg, fluorouracil) ⁶ ; do not piggyback or flush lines with sodium chloride solution ⁶
Continuous infusion	chronomodulated infusion over 5 days using programmable-in-time pump ¹²
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	investigational, over 4 h ⁵⁶
Intravesical	no information found

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 (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or in patients with other toxicities.

Adults:

		BCCA usual dose noted in <i>bold, italics</i>
<i>Intravenous:</i>	Cycle Length:	
	1 week ⁵⁵ :	35 mg/m ² IV for one dose on day 1
	2 weeks ^{1,10,57} :	85 mg/m ² (range 80-100 mg/m ²) IV for one dose on day 1
	3 weeks ^{1,3,57} :	130 mg/m ² (range 85-135 mg/m ²) IV for one dose on day 1
		30 mg/m ² /day by continuous IV infusion for 5 consecutive days (total dose per cycle 150 mg/m ²) ⁵⁸
		35 mg/m ² /day by chronomodulated IV infusion for 5 consecutive days (total dose per cycle 175 mg/m ²) ⁵⁸
	4 weeks:	85 mg/m ² IV for one dose on days 1 and 15 (total dose per cycle 170 mg/m ²) ⁵⁹
	50 days:	50 mg/m ² IV for one dose on days 1, 8, 15, 22, 29, 36 (total dose per cycle 300 mg/m ²) ⁶⁰
<i>Concurrent radiation:</i>		investigational, 130 mg/m ² IV on days 1 and 29 concurrent with radiation ⁴
<i>Dosage in myelosuppression:</i>		modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"
<i>Dosage in neurotoxicity:</i> ⁶		

<i>Duration of Neurotoxicity</i>	<i>Severity</i>	<i>Dose</i>
> 7 days ^{6,11}	troublesome	reduce dose from: 130 mg/m ² to 100 mg/m ² ; or from 85 mg/m ² to 65 mg/m ² ; or from 65 mg/m ² to 50 mg/m ²
persists until next cycle ⁶	no functional impairment	reduce dose from 85 mg/m ² to 65 mg/m ²
> 7 days ¹¹	functional impairment	reduce dose from 85 mg/m ² to 50 mg/m ²
persists until next cycle ^{6,11}	functional impairment	discontinue*

*if neurotoxicity improves following discontinuation, resumption of therapy may be considered^{6,61}

Dosage in renal failure:

CrCl (mL/min)	Dose
> 30	100% ⁶²
< 30	no information found

$$\text{CrCl (mL/min)} = \frac{N \times (140 - \text{Age}) \times \text{wt (kg)}}{\text{Serum Creatinine } (\mu\text{mol/L})}$$

where N = 1.04 for females and 1.23 for males

Dosage in hepatic failure:

No adjustment required for mild to moderate liver dysfunction⁶; no information found regarding severe hepatic insufficiency.

Dosage in dialysis:

no information found

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