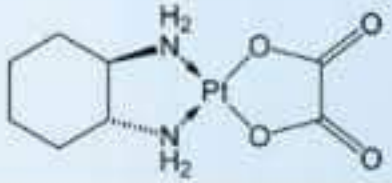

NDC 0781-3317-80
Oxaliplatin
Injection, USP
100 mg/20 mL
(5 mg/mL)
Caution: Cytotoxic Agent
FOR INTRAVENOUS USE ONLY
SINGLE USE VIAL ONLY
Sterile Aqueous Solution
Preservative Free
R only
SANDOZ
Oxaliplatin
Injection, USP

# Oxaliplatin



[(1*R*,2*R*)-cyclohexane-1,2-diamine]
(ethanedioato-*O*,*O*')platinum(II)

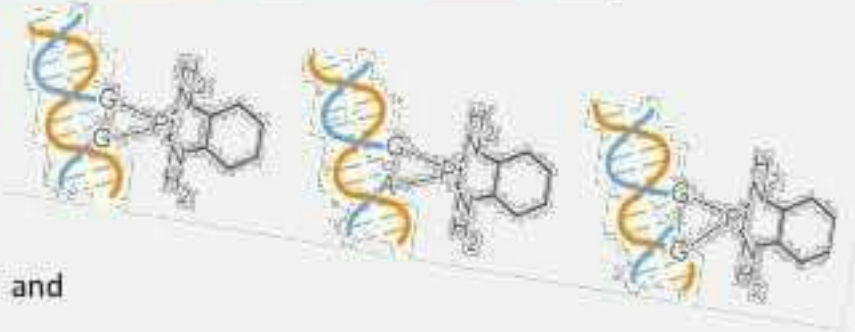
- **Pharmacological Properties**
  - Third-generation platinum derivative, an alkylating agent
  - Covalently binds to DNA forming cross-links which inhibit DNA replication and transcription, resulting in cell death
  - Cell-cycle nonspecific
- **Indication**

| FDA-labeled |
| --- |
| ***In combination with 5-FU/leucovorin*** <br> • **Stage III colon cancer, adjuvant** <br> • **Metastatic colorectal cancer, first-line** |
| **Unlabeled** |
| Esophageal cancer, gastric cancer, hepatobiliary cancer, non-hodgkin's lymphoma, ovarian cancer, pancreatic cancer, testicular cancer |

*Micromedex, Uptodate*
*Expert Opin Drug Saf. 2006 Sep;5(5):687-94.*

# FOLINIC ACID (LEUCOROVIN) + 5-FU + OXALIPLATIN

Mechanism of action of Oxaliplatin



- Adducts formation
- Arrest and Inhibition of mRNA synthesis
- Immunologic mechanisms – mediated by T-cells and dendritic cells
- Inhibition of thymidylate synthase
- Downregulation of dihydropyrimidine dehydrogenase

ADR: peripheral neuropathy, diarrhea

# Oxaliplatin

- Mechanism of Action:
  - Forms cross-linking-adducts, thus blocking DNA replication and transcription
- Combination with leucovorin + 5-FU significantly improves response rates
- Approved for both second-line and first-line treatment of colorectal cancer
- Adverse effects:
  - Sensitivity to cold
  - Numbness/tingling in hands and feet
  - Myelosuppression
  - Nausea/vomiting

# Mechanism of Action

- Cycle-phase nonspecific
- Binds to DNA forming cross-links, which inhibit DNA replication and transcription
- Synergistic antiproliferative activity of oxaliplatin and fluorouracil exhibited in vitro and in vivo

# OXALIPLATIN

- Platinum Analog
- Cell cycle non-specific
- MOA:- Inhibhits DNA synthesis
- Widely distirbuted in body

Toxicity

- Nausea/ vomiting 65% when used alone, 90% when used with 5FU/LV
- Dose limiting- Neurotoxicity

Acute toxicity 80-85% pts- peripheral sensory neuropathy, distal parasethesia within 1-3 days of therapy

Chronic toxicity- if cumulative dose >850 mg- impairment of proprioception

- Myelosupression
- Should be used with precaution in abnormal renal function

# Oxaliplatin

| Common Side Effects (>10%) | Clinical trials & post marketing experience |
|---|---|
| Hematologic | Anemia, thrombocytopenia, leukopenia, lymphopenia |
| Immunologic | **Allergic reaction (skin rash, conjunctivitis, rhinitis)** |
| Neurologic | **Peripheral neuropathy (dose limiting)**, dysgeusia, headache |
| Respiratory | Dyspnea, cough |
| Gastrointestinal | N/V, diarrhea, abdominal pain, constipation, anorexia, stomatitis |
| Musculoskeletal | Back pain |
| Other | Fatigue, fever, hepatic enzyme increase |

| Pharmacokinetics | |
|---|---|
| Distribution | $V_d$: 440 L<br>Protein binding: >90% (irreversible binding) |
| Metabolism | Nonenzymatic biotransformation, rapid and extensive |
| Excretion | Urine: 54%; feces: 2% |
| Elimination Half Life | $T_{1/2\alpha}$: 0.43 h, $T_{1/2\beta}$: 16.8 h, $T_{1/2\gamma}$: 391 h |

*Product Information: ELOXATIN®. Sanofi-Aventis U.S. LLC, Bridgewater, NJ, 2011*
*Drugs 2000; 60(4):895-924.*

Table 1

## Grading of Oxaliplatin-Induced Neurotoxicity[a]

| Scale | NCI CTC Grading for Neuropathy | Sanofi-aventis Oncology Classification of Neuropathy |
|---|---|---|
| Grade 1 | Asymptomatic, loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function | Paresthesia or dysesthesia not interfering with function |
| Grade 2 | Sensory alteration or paresthesia (including tingling) interfering with function but not ADL | Paresthesia or dysesthesia interfering with function but not ADL |
| Grade 3 | Sensory alteration or paresthesia interfering with ADL | Paresthesia or dysesthesia with pain or functional impairment that interferes with ADL |
| Grade 4 | Disabling | Persistent paresthesia or dysesthesia that is disabling or life-threatening |

[a] Source: Sanofi-aventis.[22]

ADL = activities of daily living; NCI CTC = National Cancer Institute Common Toxicity Criteria (version 3.0).

# Commonly used medications for colorectal cancer

| Chemotherapy |
| --- |
| 5-Fluorouracil |
| Oxaliplatin |
| Irinotecan |
| Cetuximab |
| Bevacizumab |
| Panitumumab |
| Capecitabine |
| Regorafenib |

## Commonly given combinations:

**FOLFOX** : 5-Fluorouracil + Leucovorin + Oxaliplatin

**FOLFIRI**: 5-Fluororuacil + Leucovorin + Irinotecan

**Capeox** = XELOX = Capecitabine and Oxaliplatin

**Capeiri** : Capecitabine and Irinotecan

# DRUG NAME: Oxaliplatin

**SYNONYM(S):** ACT-078, l-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,[8] 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[8] |
| | feces | minimal[9] |
| | terminal half life | ultrafilterable platinum*: 273 ± 19 h[6]<br>platinum elimination from erythrocytes: 48 days[1] |
| | clearance | ultrafilterable platinum*: 10.1 ± 3.07 L/h[6] |

Adapted from reference[1] unless specified otherwise.

*Ultrafilterable platinum consists of oxaliplatin and free oxaliplatin metabolites.





## USES:

***Primary uses:***
*Colorectal cancer[10-12]

***Other uses:***
Breast cancer[13]
Gastric cancer[14]
Germ cell cancer[15]
Head and neck cancer[16]
Lung cancer, non-small cell[17]
Lymphoma, non-Hodgkin's[18]
Mesothelioma[19,20]
Ovarian cancer[21,22]
Pancreatic cancer[23]
Prostate cancer[24]

*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]

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***Caution:***

- QT prolongation and torsades de pointes are reported; use caution in patients with history of QT prolongation or cardiac disease and those receiving concurrent therapy with other QT prolonging medications. Correct electrolyte disturbances prior to treatment and monitor periodically.[25,26]

***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. ***Incidence of adverse events*** is 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.[1,27]

| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| allergy/immunology | anaphylaxis (0.5-2%)[6,28,29] |
| blood/bone marrow<br>febrile neutropenia | anemia (64-83%, severe 4-5%) |
| | febrile neutropenia (< 2%) |
| | immune hemolytic anemia (rare)[30] |
| | 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*: irritant[31-36]; treat as vesicant[37]; see paragraph following **Side Effects** table |
| | alopecia (2%) |
| gastrointestinal | *emetogenic potential:* high moderate[38] |
| | diarrhea: single agent (41%, severe 5%); with fluorouracil and leucovorin (58%, severe 10%) |
| | 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%) |
| investigations | QT prolongation, torsades de pointes[25,26,39,40] |
| neurology | central neurotoxicity/reversible posterior leukoencephalopathy syndrome (<1%)[41-45]; see paragraph following **Side Effects** table |
| | ***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%) |
| vascular | thromboembolic events, including deep vein thrombosis[46] (1-10%)[46-48] |

Adapted from reference[6] 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).[1,38] 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] The use of calcium gluconate or magnesium sulfate infusions pre- and/or post oxaliplatin treatment do not appear to reduce or protect against oxaliplatin-induced neurotoxicity.[49-52]

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,[53] while carbamazepine does not appear to be effective.[54] 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.[55] 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]

***Reversible posterior leukoencephalopathy syndrome*** (RPLS; also known as PRES) has been associated with oxaliplatin,[41-45] which may cause endothelial dysfunction and lead to vasogenic edema.[42,43] Clinical presentation includes altered mental status, seizures, headache, and loss of vision with associated radiographic abnormality on MRI or CT.[42] Symptom onset may be delayed relative to treatment, with cases reported 8 to 12 days after the first infusion and as long as 6 weeks post treatment.[43,44,56] Management is usually supportive, with control of hypertension, electrolyte replacement, seizure management, and discontinuation of oxaliplatin.[42,43] Although usually reversible, permanent disability and fatalities have been reported.[42,43]

***Management of extravasation:*** Extravasation of oxaliplatin may sometimes cause severe local inflammation and potentially tissue necrosis.[31-36] The optimal non-pharmacological management of oxaliplatin extravasation is unclear. However, it has been suggested that warm compresses may be preferred over cool compresses[33,57,58] which may theoretically precipitate or worsen peripheral sensory neuropathy. For management of extravasation reactions, see BCCA Policy Number III-20 ***Prevention and Management of Extravasation of Chemotherapy***.

**INTERACTIONS:**

| AGENT | EFFECT | MECHANISM | MANAGEMENT |
|---|---|---|---|
| fluorouracil[59] | no influence on fluorouracil pharmacokinetics | | |
| irinotecan[60-62] | induction of irinotecan-related cholinergic syndrome | may potentiate irinotecan inhibition of acetylcholinesterase | give prophylactic atropine before irinotecan |
| topotecan[63] | no effects on topotecan pharmacokinetics | | |
| warfarin[64] | significantly higher incidence of INR elevation when administered with oxaliplatin/fluorouracil based regimens | unknown; possible synergy of anticoagulant effect of fluorouracil by oxaliplatin | for oxaliplatin/fluorouracil based regimens only: monitor INR regularly during and for one month following completion of treatment; adjust warfarin dose as needed |

Avoid concurrent use of QT/QTc-prolonging drugs if possible. Use caution with drugs that may disrupt electrolyte levels. Correct electrolytes as needed and monitor as applicable.[25]

## 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 h***[11]***;***<br>• in 250-500 mL D5W over 30 min[9], 3 h[68], or 6 h[12];<br>• administer before fluoropyrimidines (eg, fluorouracil)[6];<br>• 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 | ***hyperthermic intraperitoneal chemotherapy (HIPEC):*** pump solution into abdominal cavity and circulate as per protocol using hyperthermia pump; solutions and dwell time vary by protocol[69-71] |
| Intrapleural | no information found |
| Intrathecal | no information found |
| Intra-arterial | investigational, over 4 h[72] |
| 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 ***bold, italics***

| | Cycle Length: | |
|---|---|---|
| *Intravenous:* | 1 week[68]: | 35 mg/m² IV for one dose on day 1 |
| | 2 weeks[1,10,73]: | 85 mg/m² (range 80-100 mg/m²) IV for one dose on day 1 |
| | 3 weeks[1,3,73]: | 130 mg/m² (range 85-135 mg/m²) IV for one dose on day 1 |
| | | 30 mg/m²/day by continuous IV infusion for 5 consecutive days<br>(total dose per cycle 150 mg/m²)[74] |
| | | 35 mg/m²/day by chronomodulated IV infusion for 5 consecutive days<br>(total dose per cycle 175 mg/m²)[74] |

| | | |
|---|---|---|
| | 4 weeks: | 85 mg/m² IV for one dose on days 1 and 15 (total dose per cycle 170 mg/m²)[75] |
| | 50 days: | 50 mg/m² IV for one dose on days 1,8, 15, 22, 29, 36 (total dose per cycle 300 mg/m²)[76] |

*Concurrent radiation:* investigational, 130 mg/m² IV on days 1 and 29 concurrent with radiation[4]

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

*Dosage in neurotoxicity:*[6]

| ***Duration of Neurotoxicity*** | ***Severity*** | ***Dose*** |
|---|---|---|
| > 7 days[6,11] | troublesome | reduce dose from: 130 mg/m² to 100 mg/m²; or from 85 mg/m² to 65 mg/m²; or from 65 mg/m² to 50 mg/m² |
| persists until next cycle[6] | no functional impairment | reduce dose from 85 mg/m² to 65 mg/m² |
| > 7 days[11] | functional impairment | reduce dose from 85 mg/m² to 50 mg/m² |
| persists until next cycle[6,11] | functional impairment | discontinue* |

*if neurotoxicity improves following discontinuation, resumption of therapy may be considered[6,77]

*Dosage in renal failure:*

| ***CrCl (mL/min)*** | ***Dose*** |
|---|---|
| > 30 | 100%[78] |
| < 30 | no information found |

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

where N = 1.04 for females and 1.23 for males

*Dosage in hepatic failure:* no adjustment required for mild to moderate liver dysfunction[6]; no information found regarding severe hepatic insufficiency

*Dosage in dialysis:* no information found

***Children:*** has been used; effectiveness has not been established[45]