Oxaliplatin

Oxalee®

50 mg & 100 mg
Lyophilized Powder for IV Infusion
Antineoplastic

FORMULATIONS
Each vial contains:
Oxaliplatin ..... 50 mg or 100 mg

PRODUCT DESCRIPTION
Powder: Well-formed white cake free from foreign particles
Solution: Limpid and colorless solution, free from foreign particles

PHARMACODYNAMICS / MECHANISM OF ACTION
Oxaliplatin is an organoplatinum complex in which the platinum atom is complexed with 1,2-diaminocyclohexane (DACH) and oxalate ligand. It undergoes non-enzymatic conversion in physiologic solutions to active derivatives via displacement of the labile oxalate ligand. Several transient reactive species are formed, including monoaquo and diaquo DACH platinum, which covalently bind with macromolecules. Both inter- and intrastrand Pt-DNA crosslinks are formed. These crosslinks inhibit DNA replication and transcription. Cytotoxicity is cell-cycle nonspecific.

Oxaliplatin has a synergistic action when used in combination with 5-fluorouracil (5-FU).

PHARMACOKINETICS
The reactive oxaliplatin derivatives are present as a fraction of the unbound platinum in plasma ultrafiltrate. The decline of ultrafilterable platinum levels following oxaliplatin administration is triphasic, characterized by two relatively short distribution phases ($t_{1/2\alpha}$, 0.43 hours and $t_{1/2\beta}$, 16.8 hours) and a long terminal elimination phase ($t_{1/2\gamma}$, 391 hours). After a single 2-hour IV infusion of oxaliplatin at a dose of 85 mg/m^2, peak plasma concentration (C_{max}) and volume of distribution of oxaliplatin expressed as ultrafilterable platinum were 0.814 mcg/mL and 440 L, respectively.

Interpatient and intrapatient variability in ultrafilterable platinum exposure (AUC_{0-48}) assessed over 3 cycles was moderate to low (23% and 6%, respectively).

After IV doses, oxaliplatin is widely distributed throughout the body. At the end of a 2-hour oxaliplatin infusion, approximately 15% of administered platinum is present in the systemic circulation. The remaining 85% is rapidly distributed into tissues or eliminated in the urine. Plasma protein binding of platinum, mainly to albumins and gamma-globulins, is irreversible and is greater than 90%. Platinum also binds irreversibly and accumulates (about 2-fold) in erythrocytes, which can prolong its half-life but appears to have no relevant activity. No platinum accumulation was observed in plasma ultrafiltrate following 85 mg/m^2 every two weeks.

Oxaliplatin undergoes rapid and extensive non-enzymatic biotransformation and is mainly excreted by the kidneys. There is no evidence of cytochrome P450-mediated metabolism. At five days after a single 2-hour infusion of oxaliplatin, urinary elimination accounted for about 54% of the platinum eliminated, with fecal excretion accounting for only about 2%. Platinum was cleared from plasma at 10 to 17 L/hour.

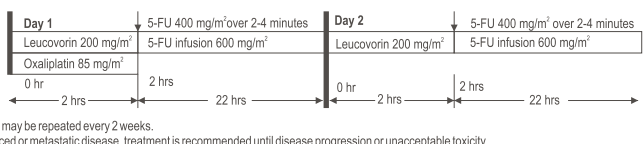
Patients with Renal Impairment
The AUC_{0-48} of platinum in the plasma ultrafiltrate increases as renal function decreases. The AUC_{0-48} of platinum in patients with mild (creatinine clearance Clcr 50 to 80 mL/min), moderate (Clcr 30 to < 50 mL/min) and severe (Clcr < 30 mL/min) renal impairment is increased by about 60, 140 and 190%, respectively, compared to patients with normal renal function (Clcr > 80 mL/min). Use with caution in patients with renal impairment.

INDICATIONS
Oxaliplatin, in combination with infusional 5-fluorouracil (5-FU) and leucovorin is indicated for:
- Treatment of advanced colorectal cancer.
- Adjuvant treatment of stage III colon cancer in patients who have undergone complete resection of the primary tumor.

DOSAGE AND ADMINISTRATION
General Dosing Instructions
- **Oxaliplatin should be reconstituted and diluted prior to IV infusion.**
- **Oxaliplatin should always be administered before fluoropyrimidines (i.e., 5-FU).**
- Use only the recommended diluents in preparing the solution.
  (See **Incompatibilities**)
- Oxaliplatin administration does not require prehydration.
- Antiemetics (5-HT$_3$ blockers with or without dexamethasone) should be given during pre- and post-therapy with oxaliplatin since oxaliplatin is highly emetogenic.

Treatment of patients with advanced colorectal cancer
Day 1: Oxaliplatin 85 mg/m^2 (as IV infusion diluted in 250 to 500 mL of 5% Dextrose Solution) and leucovorin 200 mg/m^2 IV infusion in 5% Dextrose Solution both given over 120 minutes (2 hours) at the same time in different bags using a Y-line, followed by 5-FU 400 mg/m^2 by IV bolus given over 2 to 4 minutes, followed by 5-FU 600 mg/m^2 diluted in 500 mL 5% Dextrose Solution as a 22-hour continuous IV infusion.

Day 2: Leucovorin 200 mg/m^2 in 5% Dextrose Solution by IV infusion over 120 minutes (2 hours), followed by 5-FU 400 mg/m^2 by IV bolus over 2 to 4 minutes, followed by 5-FU 600 mg/m^2 diluted in 500 mL 5% Dextrose Solution as a 22-hour continuous IV infusion.



- Treatment may be repeated every 2 weeks.
- For advanced or metastatic disease, treatment is recommended until disease progression or unacceptable toxicity.

Adjuvant treatment of patients with stage III (Duke's C) colon cancer who have undergone complete resection of primary tumor
Treatment is recommended for a total of 6 months (i.e., 12 cycles), given every 2 weeks, according to the dose schedule described above for the treatment of patients with advanced colorectal cancer.
Or, as prescribed by a physician.

Dose Modification Recommendations
Oxaliplatin dosage adjustment is recommended according to the duration and severity of toxicities. Prior to subsequent therapy cycles, patients should be evaluated for clinical toxicities and recommended laboratory tests. Prolongation of infusion time for oxaliplatin from 2 to 6 hours may mitigate acute toxicities. The infusion times for 5-FU and leucovorin do not need to be changed.

Toxicities	Oxaliplatin Dose	5-FU / Leucovorin Dose
Treatment of Advanced Colorectal Cancer Persistent grade 2 neurosensory events	65 mg/m^2	NO CHANGE
Persistent grade 3 neurosensory events	DISCONTINUE	NO CHANGE
After recovery from grade 3/4 gastrointestinal (despite prophylactic treatment) or grade 4 neutropenia or grade 3/4 thrombocytopenia	65 mg/m^2	Reduce 5-FU dose to 300 mg/m^2 bolus over 3 to 4 minutes and 500 mg/m^2 22-hour infusion
	Postpone next dose until hematological values return to acceptable levels (neutrophils ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L)	
Adjuvant Therapy of Stage III Colon Cancer Persistent grade 2 neurosensory events	75 mg/m^2	NO CHANGE
Persistent grade 3 neurosensory events	DISCONTINUE	NO CHANGE
After recovery from grade 3/4 gastrointestinal (despite prophylactic treatment) or grade 4 neutropenia or grade 3/4 thrombocytopenia	75 mg/m^2	Reduce 5-FU dose to 300 mg/m^2 bolus over 3 to 4 minutes and 500 mg/m^2 22-hour infusion
	Postpone next dose until hematological values return to acceptable levels (neutrophils ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L)	

For more information on 5-FU and leucovorin, see respective package inserts.

Laboratory Monitoring
- Hematological and neurological tests should be performed before initiation of treatment and periodically thereafter.
- Standard monitoring of white blood cell counts with differential, hemoglobin, platelet count, and blood chemistries (including alanine transaminase, aspartate aminotransferase, bilirubin, and creatinine) is recommended before each oxaliplatin cycle.
- There have been reports of prolonged prothrombin time and international normalized ratio (INR) occasionally associated with hemorrhage in patients who received oxaliplatin plus 5-FU/leucovorin while on anticoagulants. Patients receiving oxaliplatin plus 5-FU/leucovorin and requiring anticoagulants may require closer monitoring.

Preparation of Infusion Solution
- Recommended solvent is Water for Injection or 5% Dextrose Solution.
- Add 10 mL (for 50 mg oxaliplatin) or 20 mL (for 100 mg oxaliplatin) of solvent to obtain an oxaliplatin concentration of 5 mg/mL.
- The reconstituted solution is further diluted in an infusion solution of 250 mL to 500 mL of 5% Dextrose Solution prior to IV administration.

Stability
The reconstituted solution may be stored for up to 48 hours in its original vial under refrigeration (2 to 8°C). After final dilution with 250 mL to 500 mL of 5% Dextrose Solution, the infusion solution may be stored at temperatures 15 to 30°C for 24 hours.

Handling Precautions
- As with other potentially toxic antineoplastic agents, caution should be exercised in the preparation and handling of oxaliplatin. The use of gloves is recommended.
- If a solution of oxaliplatin gets in contact with the skin, wash the skin immediately and thoroughly with water. If oxaliplatin gets in contact with the mucous membrane, flush thoroughly with water.
- Precautions for preparing any antineoplastic agent apply to the handling and reconstitution of oxaliplatin.

Incompatibilities
- **RECONSTITUTION OR FINAL DILUTION MUST NEVER BE PERFORMED WITH A SODIUM CHLORIDE SOLUTION OR OTHER CHLORIDE-CONTAINING SOLUTIONS.**
- Needles or IV administration sets containing aluminum parts **should not be used.**
- Alkaline medicines or media may cause oxaliplatin degradation (especially 5-FU alkaline solution and trometamol). The infusion line should be flushed with 5% Dextrose Injection prior to administration of any concomitant medication.

CONTRAINDICATIONS
- Hypersensitivity to oxaliplatin, other platinum compounds (e.g., cisplatin, carboplatin) or any component in the product.
- Patients with peripheral sensory neuropathy with functional impairment prior to first course.
- Patients with severely impaired renal function (Clcr < 30 mL/min).
- Patients with myelosuppression prior to starting first course, with baseline neutrophils < 1.5 x 10^9/L and/or platelet count of < 75 x 10^9/L.
- Patients who are pregnant or breastfeeding.

WARNINGS and PRECAUTIONS
Anaphylactic reactions to oxaliplatin have been reported, and may occur within minutes of oxaliplatin administration. Epinephrine, corticosteroids and antihistamines have been employed to alleviate symptoms of anaphylaxis.

General
Patients receiving oxaliplatin should be under the supervision of a physician experienced in chemotherapy. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.
As oxaliplatin therapeutic regimen includes the use of 5-FU/leucovorin, the usual cautions, precautions, and contraindications of these drugs should be considered.

Allergic Reactions
Grade 3/4 hypersensitivity, including anaphylactic/anaphylactoid reactions to oxaliplatin, has been observed in 2 to 3% of colon cancer patients. These allergic reactions (e.g., rash, urticaria, erythema, pruritus, bronchospasm, and hypotension), which rarely may be fatal, can occur within minutes of administration and at any cycle, and were similar in nature and severity to those reported with other platinum-containing compounds. The symptoms associated with hypersensitivity reactions reported in previously untreated patients were urticaria, pruritus, flushing of the face, diarrhea, shortness of breath, bronchospasm, diaphoresis, chest pain, hypotension, disorientation and syncope. Drug-related deaths associated with anaphylaxis from platinum compounds have been reported. Rechallenge with oxaliplatin is contraindicated (see **Boxed Warning**).

Neuropathy
Oxaliplatin is associated with acute or persistent neuropathy, both of which are principally peripheral neuropathies. The duration and severity of peripheral neuropathy appear to increase with increasing cumulative dosage of oxaliplatin.

- **Acute Neuropathy: An acute, reversible, primarily peripheral, sensory neuropathy that is of early onset, occurring within hours or one to two days of dosing, that resolves within 14 days, and that frequently recurs with further dosing.**

Acute neurotoxicity, primarily peripheral sensory neuropathy, is common, reversible and generally not dose-limiting. Symptoms include transient paresthesia, dysesthesia, and hypoesthesia of the hands, feet, perioral area, or throat. In addition, jaw spasm, abnormal tongue sensation, dysarthria, eye pain, and chest pressure have been observed.
A sudden, self-limiting laryngopharyngeal dysesthesia, characterized by subjective sensations of dysphagia or dyspnea without laryngospasm or bronchospasm, and thought to result from decreased sensitivity of the larynx and pharynx, has been described in approximately 2%.
Patients should be advised to **AVOID COLD FOODS AND DRINKS AND COVER SKIN BEFORE COLD EXPOSURE** during or within 48 hours after oxaliplatin administration to avoid neurological effects.

- **Persistent Neuropathy: A persistent (>14 days), primarily peripheral, sensory neuropathy that is usually characterized by paresthesias, dysesthesias, hypoesthesias, but may also include deficits in proprioception that can interfere with daily activities (e.g., writing, buttoning, swallowing, and difficulty walking from impaired proprioception).** This form of neuropathy can occur without any prior acute neuropathy, and generally progresses with continued cycles. Symptoms may improve over time upon discontinuation of oxaliplatin.

Pulmonary Toxicity
Pulmonary fibrosis, which may be fatal, has been reported. Dyspnea and cough were reported more often in the oxaliplatin combination arm than in the infusional 5-FU/leucovorin alone arm in adjuvant colon cancer patients. Oxaliplatin should be discontinued in cases of unexplained respiratory symptoms (e.g., non-productive cough, dyspnea, crackles, or radiological pulmonary infiltrates) until further pulmonary investigation excludes interstitial lung disease or pulmonary fibrosis.

Hepatotoxicity
Hepatotoxicity as evidenced in a clinical study, by increase in transaminases (57%) and alkaline phosphatase (42%) was observed. Bilirubin was also increased. Changes noted on liver biopsies include: peliosis, nodular regenerative hyperplasia or sinusoidal fibrosis, and veno-occlusive lesions. Hepatic vascular disorders should be investigated in case of abnormal liver function test results or portal hypertension, which cannot be explained by liver metastases.

Effects on Ability to Drive or Use Machines
No studies have been performed. However, oxaliplatin treatment resulting in an increased risk of dizziness, nausea and vomiting, and other neurologic symptoms that affect gait and balance may lead to a minor or moderate influence on the ability to drive and use machines.
Vision abnormalities, particularly transient vision loss (reversible following therapy discontinuation), may affect patient's ability to drive and use machines. Therefore, patients should be warned of the potential effect of these events on the ability to drive and use machines.

CARCINOGENICITY, MUTAGENICITY, FERTILITY
Long-term animal studies have not been performed to evaluate the carcinogenic potential of oxaliplatin. oxaliplatin was not mutagenic to bacteria (Ames test) but was mutagenic to mammalian cells *in vitro*. oxaliplatin was clastogenic both *in vitro and in vivo*.
Administration of 2 mg/kg/day (less than one-seventh the recommended human dose on a body surface area basis) in female rats caused developmental mortality (e.g., increased early resorptions, decreased live fetuses, decreased live births) and delayed growth (e.g., decreased fetal weight) but did not affect pregnancy rate. Testicular damage, characterized by degeneration, hypoplasia, and atrophy, was observed in dogs administered oxaliplatin at 0.75 mg/kg/day for 5 days every 28 days for 3 cycles (approximately one-sixth of recommended human dose).
Genotoxic effects were observed with oxaliplatin in preclinical studies. **Therefore, contraception is also advised among men during treatment and for 6 months after treatment with oxaliplatin. Patients should seek advice on sperm conservation because oxaliplatin could have an irreversible anti-fertility effect.**

INTERACTIONS WITH OTHER MEDICAMENTS
- Pharmacokinetic interaction with 5-FU is unlikely when recommended dosages and administration schedule are used (see **Dosage and Administration**). Potential pharmacokinetic interaction (20% increase in plasma 5-FU concentrations) during concomitant use of 5-FU and 130 mg/m^2 of oxaliplatin every 3 weeks.
- Nephrotoxic drugs may decrease the clearance of platinum-containing compounds; however, this interaction has not been specifically studied.
- Interactions with other antineoplastic drugs (e.g., irinotecan, topotecan), protein-bound drugs (e.g., erythromycin, salicylate, sodium valproate, granisetron, Paclitaxel) and drugs affecting human cytochrome P450 enzymes.

HIGH RISK GROUPS

PREGNANCY
Pregnancy Category D
There are no adequate and well-controlled studies of oxaliplatin in pregnant women. However, based on direct interaction with DNA, oxaliplatin may cause fetal harm when administered to a pregnant woman. Reproductive toxicity studies in rats demonstrated adverse effects on fertility and embryo-fetal development at maternal doses that were below the recommended human dose. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant and use effective contraception while receiving treatment and for 4 months after treatment with oxaliplatin.

LACTATION
It is not known whether oxaliplatin or its derivatives are excreted in human milk. Because many drugs are excreted in human milk and there is a potential for serious adverse reactions from oxaliplatin in breastfed infants, breastfeeding is contraindicated during oxaliplatin therapy.

USE IN THE ELDERLY
No significant effect of age on the clearance of ultrafilterable platinum has been observed. However, the incidence of certain adverse effects (i.e., diarrhea, dehydration, hypokalemia, fatigue) was higher in geriatric patients (≥ 65 years old) than in younger adults. Patients ≥ 70 years old have shown a higher risk of thrombocytopenia and stomatitis in clinical studies.

USE IN CHILDREN
Oxaliplatin is not recommended for use in children. The safety and efficacy of oxaliplatin in children have not been established. Oxaliplatin has been tested in patients 7 months to 22 years old with solid tumors and no significant activity was observed.

RENAL IMPAIRMENT
Oxaliplatin is contraindicated in patients with severe renal impairment. In patients with moderate renal impairment, treatment may be initiated with caution at the normally recommended dose. Renal function should also be closely monitored and the dose should be adjusted according to toxicity. There is no need for dose adjustment in patients with mild renal dysfunction.

HEPATIC IMPAIRMENT
No specific dose adjustment is recommended.

UNDESIRABLE EFFECTS
Nervous System Effects: Neurological toxicity is the principal dose-limiting adverse effect of oxaliplatin. Peripheral sensory neuropathy, sensory disturbance, dysgeusia, headache, dizziness, motor neuritis, meninginism depression, insomnia, and nervousness are common. Dysarthria was rarely reported (see **Warnings and Precautions**).

Hematologic Effects: Anemia, leukopenia, neutropenia, thrombocytopenia, febrile neutropenia, lymphopenia, and hemorrhagic effects (e.g., gastrointestinal bleeding, hematuria, epistaxis) occurred more frequently in patients receiving oxaliplatin, 5-FU and leucovorin as compared with patients who received 5-FU and leucovorin only. Immune-mediated acute hemolysis with and without anemia and Evan's syndrome (immune-mediated thrombocytopenia and hemolytic anemia) have also been reported.

Gastrointestinal (GI) Effects: Nausea, vomiting, diarrhea, stomatitis, abdominal pain, constipation, anorexia, dyspepsia, taste perversion, mouth dryness, and mucositis were the adverse effects reported. Grade 3/4 nausea, vomiting, diarrhea, and stomatitis appear to be exacerbated by the addition of oxaliplatin to 5-FU and leucovorin. Gastroesophageal reflux, hiccup, flatulence, and colitis have also been reported. Dehydration, ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhea/emesis, particularly when combining oxaliplatin with 5-FU.

Dermatologic Reactions: The incidence of alopecia and rare hand-foot syndrome appears to be similar among patients receiving oxaliplatin, 5-FU and leucovorin and in those receiving 5-FU and leucovorin. Flushing, rash, dry skin, hyperhidrosis, and nail disorder have also been reported.

IV Site Reactions: Extravasation, in some cases including necrosis, has been reported. Injection site reaction, including redness, swelling, and pain have also been reported. In case of extravasation, the infusion must be stopped immediately and usual local symptomatic treatment should be initiated.

Hepatic Effects: Hepatotoxicity (defined as elevation of liver enzymes) appears to be related to oxaliplatin combination therapy. The development of ascites, portal hypertension, and hepatic lesions in a patient with colorectal cancer was considered to be due to oxaliplatin.

Renal Effects: About 5 to 10% of patients had some degree of serum creatinine elevation. Dysuria and abnormal micturition frequency were reported in some patients.

Respiratory Effects: Dyspnea, cough, rhinitis, upper respiratory tract infection, and pharyngitis. There have also been rare reports of interstitial lung disease and pulmonary fibrosis (see **Warnings and Precautions**).

Ocular Effects: Abnormal vision, lacrimation, conjunctivitis and visual disturbance. Reduction of visual acuity, visual field disturbances, optic neuritis, and transient vision loss were rarely reported.

Ear and Labyrinth Effects: Ototoxicity and deafness were uncommon.

Musculoskeletal: Fatigue, back pain, chest pain, rigors, myalgia, arthralgia, and bone pain were common adverse effects reported.

Metabolic Effects: Weight increase or decrease, increase in alkaline phosphatase, blood bilirubin increase, hyperglycemia, hypoalbuminemia, hypocalcemia, and hyponatremia.

Cardiovascular Effects: Thromboembolic effects occurred in 9% of patients receiving oxaliplatin, 5-FU and leucovorin compared with 4% of those who received 5-FU and leucovorin only. Hypotension and edema rarely occurred.

Other Adverse Effects: Fever and infection.

OVERDOSAGE AND TREATMENT
Exacerbation of known adverse effects may be expected in case of overdose. No known antidote is available for oxaliplatin overdose.
In such cases, hematological parameters should be monitored and symptomatic treatment of toxic manifestations should be performed.

AVAILABILITY
Oxaliplatin 50 mg Lyophilized Powder for IV Infusion in box of 1 vial.
Oxaliplatin 100 mg Lyophilized Powder for IV Infusion in box of 1 vial.

STORAGE CONDITIONS
Store at temperatures not exceeding 30°C in its original package.
Protect from light.

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

Manufactured by
Laboratorios Richmond S.A.C.I.F.
Street 3 N°519 Pilar Industrial Park
of the Province of Buenos Aires
Republica Argentina
Imported and Distributed by
UNILAB, Inc.
No. 66 United Street, Mandaluyong City
Metro Manila, Philippines

Date of Revision : January 2017 *Reg.POPHIL

Laboratorios RICHMOND

BIO154617IN01

041639-02