# Relbiplat™


RELIC
Biotechnology Pvt. Ltd.
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For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

# Oxaliplatin for Injection USP 50mg & 100mg

# Relbiplat™-50 & 100

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**$R_x$ Only**

**COMPOSITION**

Relbiplat™-50

Oxaliplatin for Injection USP 50mg
Each Lyophilized vial contains

| | |
|---|---|
| Oxaliplatin USP | 50mg |
| Lactose IP | 450mg |

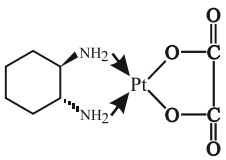
Relbiplat™-100

Oxaliplatin for Injection USP 100mg
Each Lyophilized vial contains

| | |
|---|---|
| Oxaliplatin USP | 100mg |
| Lactose IP | 900mg |

**DESCRIPTION**

Oxaliplatin for Injection is an antineoplastic agent with the molecular formula $C_8H_{14}N_2O_4Pt$ and the chemical name of cis-[(1 R,2 R)-1,2-cyclohexanediamine-N,N'] [oxalato(2-)-O,O'] platinum. Oxaliplatin is an organoplatinum complex in which the platinum atom is complexed with 1,2-diaminocyclohexane(DACH) and with an oxalate ligand as a leaving group.




The molecular weight is 397.3. Oxaliplatin is slightly soluble in water at 6mg/mL, very slightly soluble in methanol, and practically insoluble in ethanol and acetone.

Oxaliplatin for Injection is supplied in vials containing 50 mg or 100 mg of Oxaliplatin as a sterile, preservative-free lyophilized powder for reconstitution. Lactose monohydrate is present as an inactive ingredient at 450 mg and 900 mg in the 50 mg and 100 mg dosage strengths, respectively.

**CLINICAL PHARMACOLOGY**

**Mechanism of action**

Oxaliplatin undergoes nonenzymatic 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. Crosslinks are formed between the N7 positions of two adjacent guanines (GG), adjacent adenine-guanines (AG), and guanines separated by an intervening nucleotide (GNG). These crosslinks inhibit DNA replication and transcription. Cytotoxicity is cell-cycle nonspecific.

**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 (t1/2α; 0.43 hours and t1/2β; 16.8 hours) and a long terminal elimination phase (t1/2γ; 391 hours). Pharmacokinetic parameters obtained after a single 2-hour intravenous infusion of Oxaliplatin for injection at a dose of 85 mg/m$^2$ expressed as ultrafilterable platinum were Cmax of 0.814 mcg/mL and volume of distribution of 440 L. Inter patient and intra patient variability in ultra filterable platinum exposure (AUC0-48hr) assessed over 3 cycles was moderate to low (23% and 6%, respectively). A pharmacodynamic relationship between platinum ultra filtrate levels and clinical safety and effectiveness has not been established.

Distribution At the end of a 2-hour infusion of Oxaliplatin for Injection, 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. In patients, plasma protein binding of platinum is irreversible and is greater than 90%. The main binding proteins are albumin and gamma-globulins. Platinum also binds irreversibly and accumulates (approximately 2-fold) in erythrocytes, where it appears to have no relevant activity. No platinum accumulation was observed in plasma ultra filtrate following 85 mg/m$^2$ every two weeks.

**Metabolism**

Oxaliplatin undergoes rapid and extensive nonenzymatic biotransformation. There is no evidence of cytochrome P450-mediated metabolism in vitro.

Up to 17 platinum-containing derivatives have been observed in plasma ultra filtrate samples from patients, including several cytotoxic species (monochloro DACH platinum, dichloro DACH platinum, and monoaquo and diaquo DACH platinum) and a number of noncytotoxic, conjugated species.

**Elimination**

The major route of platinum elimination is renal excretion. At five days after a single 2-hour infusion of Oxaliplatin for Injection, urinary elimination accounted for about 54% of the platinum eliminated, with fecal excretion accounting for only about 2%. Platinum was cleared from plasma at a rate (10 to 17 L/h) that was similar to or exceeded the average human glomerular filtration rate (GFR; 7.5 L/h). There was no significant effect of gender on the clearance of ultrafilterable platinum. The renal clearance of ultrafilterable platinum is significantly correlated with GFR.

**INDICATIONS AND USAGE**

Oxaliplatin for Injection, used in combination with infusional 5-fluorouracil/leucovorin, is indicated for:

- adjuvant treatment of stage III colon cancer in patients who have undergone complete resection of the primary tumor.
- treatment of advanced colorectal cancer.

**DOSAGE AND ADMINISTRATION**

Administer Oxaliplatin for Injection in combination with 5-fluorouracil/leucovorin every 2 weeks. For advanced disease, treatment is recommended until disease progression or unacceptable toxicity. For adjuvant use, treatment is recommended for a total of 6 months (12 cycles):

**Day 1:** Oxaliplatin for Injection 85 mg/m$^2$ intravenous infusion in 250 to 500mL 5% Dextrose injection IP and leucovorin 200 mg/m$^2$ intravenous infusion in 5% Dextrose Injection IP both given over 120 minutes at the same time in separate bags using a Y-line, followed by 5-fluorouracil 400 mg/m$^2$ intravenous bolus given over 2 to 4 minutes, followed by 5-fluorouracil 600 mg/m$^2$ intravenous infusion in 500mL 5% Dextrose Injection IP (recommended) as a 22-hour continuous infusion.

**Day 2:** Leucovorin 200 mg/m$^2$ intravenous infusion over 120 minutes, followed by 5-fluorouracil 400 mg/m$^2$ intravenous bolus given over 2 to 4 minutes, followed by 5-fluorouracil 600 mg/m$^2$ intravenous infusion in 500mL 5% Dextrose Injection IP (recommended) as a 22-hour continuous infusion.

The administration of Oxaliplatin for Injection does not require prehydration. Premedication with antiemetics, including 5-HT3 blockers with or without dexamethasone, is recommended.For information on 5-fluorouracil and leucovorin, see the respective package inserts.

**Preparation of Infusion Solution**

Reconstitution or final dilution must never be performed with a sodium chloride solution or other chloride-containing solutions.

The lyophilized powder is reconstituted by adding 10 mL (for the 50 mg vial) or 20 mL (for the 100 mg vial) of Water for Injection IP or 5% Dextrose Injection IP. Do not administer the reconstituted solution without further dilution. The reconstituted solution must be further diluted in an infusion solution of 250 to 500 mL of 5% Dextrose Injection IP.

After reconstitution in the original vial, the solution may be stored up to 24 hours under refrigeration [2° to 8°C (36° to 46°F)]. After final dilution with 250 to 500 mL of 5% Dextrose Injection IP, the shelf life is 6 hours at room temperature [20° to 25°C (68° to 77°F)] or up to 24 hours under refrigeration [2° to 8°C (36° to 46°F)].

Oxaliplatin for Injection is not light sensitive.

Oxaliplatin for Injection is incompatible in solution with alkaline medications or media (such as basic solutions of 5-fluorouracil) and must not be mixed with these or administered simultaneously through the same infusion line. The infusion line should be flushed with 5% Dextrose Injection IP prior to administration of any concomitant medication.

**Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and discarded if present.**

Needles or intravenous administration sets containing aluminum parts that may come in contact with Oxaliplatin for Injection should not be used for the preparation or mixing of the drug. Aluminum has been reported to cause degradation of platinum compounds.

**WARNINGS AND PRECAUTIONS**

Allergic Reactions Grade 3/4 hypersensitivity, including anaphylactic/anaphylactoid reactions, to Oxaliplatin for Injection has been observed in 2 to 3% of colon cancer patients. These allergic reactions which can 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, such as rash, urticaria, erythema, pruritus, and, rarely, bronchospasm and hypotension. The symptoms associated with hypersensitivity reactions reported in the previously untreated patients were urticaria, pruritus, flushing of the face, diarrhea associated with Oxaliplatin infusion, shortness of breath, bronchospasm, diaphoresis, chest pains, hypotension, disorientation and syncope. These reactions are usually managed with standard epinephrine, corticosteroid, antihistamine therapy, and may require discontinuation of therapy.

**Neuropathy**

Oxaliplatin for Injection is associated with two types of 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.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).

**Pulmonary Toxicity**

Oxaliplatin for Injection has been associated with pulmonary fibrosis (<1% of study patients), which may be fatal. The combined incidence of cough and dyspnea was 7.4% (any grade) and <1% (grade 3) with no grade 4 events in the Oxaliplatin for Injection plus infusional 5-fluorouracil/leucovorin arm compared to 4.5% (any grade) and no grade 3 and 0.1% grade 4 events in the infusional 5-fluorouracil/leucovorin alone arm in adjuvant colon cancer patients. In case of unexplained respiratory symptoms such as non-productive cough, dyspnea, crackles, or radiological pulmonary infiltrates, Oxaliplatin for Injection should be discontinued until further pulmonary investigation excludes interstitial lung disease or pulmonary fibrosis.

**Hepatotoxicity**

Hepatotoxicity as evidenced in the adjuvant study, by increase in transaminases (57% vs. 34%) and alkaline phosphatase (42% vs. 20%) was observed more commonly in the Oxaliplatin for Injection combination arm than in the control arm. The incidence of increased bilirubin was similar on both arms. Changes noted on liver biopsies include: peliosis, nodular regenerative hyperplasia or sinusoidal alterations, perisinusoidal fibrosis, and veno-occlusive lesions. Hepatic vascular disorders should be considered, and if appropriate, should be investigated in case of abnormal liver function test results or portal hypertension, which cannot be explained by liver metastases.

**Use in Pregnancy**

**Pregnancy Category D**

Oxaliplatin for Injection may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of Oxaliplatin for Injection in pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Oxaliplatin for Injection.

**Recommended Laboratory Tests**

Standard monitoring of the white blood cell count with differential, hemoglobin, platelet count, and blood chemistries (including ALT, AST, bilirubin and creatinine) is recommended before each Oxaliplatin for Injection cycle.

There have been reports while on study and from post-marketing surveillance of prolonged prothrombin time and INR occasionally associated with hemorrhage in patients who received Oxaliplatin for Injection plus 5-fluorouracil/leucovorin while on anticoagulants. Patients receiving Oxaliplatin for Injection plus 5-

fluorouracil/leucovorin and requiring oral anticoagulants may require closer monitoring.

## ADVERSE REACTIONS

Serious adverse reactions including anaphylaxis and allergic reactions, neuropathy, pulmonary toxicities and hepatotoxicities can occur. [See Warnings and Precautions].The most common adverse reactions in patients with stage II or III colon cancer receiving adjuvant therapy were peripheral sensory neuropathy, neutropenia, thrombocytopenia, anemia, nausea, increase in transaminases and alkaline phosphatase, diarrhea, emesis, fatigue and stomatitis. The most common adverse reactions in previously untreated and treated patients were peripheral sensory neuropathies, fatigue, neutropenia, nausea, emesis, and diarrhea. [See Warnings and Precautions].

### Thrombocytopenia and Bleeding

Thrombocytopenia was frequently reported with the combination of Oxaliplatin for Injection and infusional 5-fluorouracil/leucovorin. The incidence of all hemorrhagic events in the adjuvant and previously treated patients was higher on the Oxaliplatin for Injection combination arm compared to the infusional 5-fluorouracil/leucovorin arm. These events included gastrointestinal bleeding, hematuria, and epistaxis. In the adjuvant trial, two patients died from intra cerebral hemorrhages.

The incidence of Grade 3/4 thrombocytopenia was 2% in adjuvant patients with colon cancer. In patients treated for advanced colorectal cancer the incidence of Grade 3/4 thrombocytopenia was 3 to 5%, and the incidence of these events was greater for the combination of Oxaliplatin for Injection and 5-fluorouracil/leucovorin over the irinotecan plus 5-fluorouracil/leucovorin or 5-fluorouracil/leucovorin control groups. Grade 3/4 gastrointestinal bleeding was reported in 0.2% of adjuvant patients receiving Oxaliplatin for Injection and 5-fluorouracil/leucovorin. In the previously untreated patients, the incidence of epistaxis was 10% in the Oxaliplatin for Injection and 5-fluorouracil/leucovorin arm, and 2% and 1%, respectively, in the irinotecan plus 5-fluorouracil/leucovorin or irinotecan plus Oxaliplatin for Injection arms.

### Neutropenia

Neutropenia was frequently observed with the combination of Oxaliplatin for Injection and 5-fluorouracil/leucovorin, with Grade 3 and 4 events reported in 29% and 12% of adjuvant patients with colon cancer, respectively. In the adjuvant trial, 3 patients died from sepsis/neutropenic sepsis. Grade 3 and 4 events were reported in 35% and 18% of the patients previously untreated for advanced colorectal cancer, respectively. Grade 3 and 4 events were reported in 27% and 17% of previously treated patients, respectively. In adjuvant patients the incidence of either febrile neutropenia (0.7%) or documented infection with concomitant grade 3/4 neutropenia (1.1%) was 1.8% in the Oxaliplatin for Injection and 5-fluorouracil/leucovorin arm. The incidence of febrile neutropenia in the patients previously untreated for advanced colorectal cancer was 15% (3% of cycles) in the irinotecan plus 5-fluorouracil/leucovorin arm and 4% (less than 1% of cycles) in the Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination arm. Additionally, in this same population, infection with grade 3 or 4 neutropenia was 12% in the irinotecan plus 5-fluorouracil/leucovorin, and 8% in the Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination. The incidence of febrile neutropenia in the previously treated patients was 1% in the 5-fluorouracil/leucovorin arm and 6% (less than 1% of cycles) in the Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination arm.

### Gastrointestinal

In patients receiving the combination of Oxaliplatin for Injection plus infusional 5-fluorouracil/leucovorin for adjuvant treatment for colon cancer the incidence of Grade 3/4 nausea and vomiting was greater than those receiving infusional 5-fluorouracil/leucovorin alone (see table). In patients previously untreated for advanced colorectal cancer receiving the combination of Oxaliplatin for Injection and 5-fluorouracil/leucovorin, the incidence of Grade 3 and 4 vomiting and diarrhea was less compared to irinotecan plus 5-fluorouracil/leucovorin controls (see table). In previously treated patients receiving the combination of Oxaliplatin for Injection and 5-fluorouracil/leucovorin, the incidence of Grade 3 and 4 nausea, vomiting, diarrhea, and mucositis/stomatitis increased compared to 5-fluorouracil/leucovorin controls (see table).

The incidence of gastrointestinal adverse reactions in the previously untreated and previously treated patients appears to be similar across cycles. Premedication with antiemetics, including 5-HT3 blockers, is recommended. Diarrhea and mucositis may be exacerbated by the addition of Oxaliplatin for Injection to 5-fluorouracil/leucovorin, and should be managed with appropriate supportive care. Since cold temperature can exacerbate acute neurological symptoms, ice (mucositis prophylaxis) should be avoided during the infusion of Oxaliplatin for Injection.

### Dermatologic

Oxaliplatin for Injection did not increase the incidence of alopecia compared to 5-fluorouracil/leucovorin alone. No complete alopecia was reported. The incidence of Grade 3/4 skin disorders was 2% in both the Oxaliplatin for Injection plus infusional 5-fluorouracil/leucovorin and the infusional 5-fluorouracil/leucovorin alone arms in the adjuvant colon cancer patients. The incidence of hand-foot syndrome in patients previously untreated for advanced colorectal cancer was 2% in the irinotecan plus 5-fluorouracil/leucovorin arm and 7% in the Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination arm. The incidence of hand-foot syndrome in previously treated patients was 13% in the 5-fluorouracil/leucovorin arm and 11% in the Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination arm.

### Intravenous Site Reactions

Extravasation, in some cases including necrosis, has been reported. Injection site reaction, including redness, swelling, and pain, has been reported.

### Anticoagulation and Hemorrhage

There have been reports while on study and from post-marketing surveillance of prolonged prothrombin time and INR occasionally associated with hemorrhage in patients who received Oxaliplatin for Injection plus 5-fluorouracil/leucovorin while on anticoagulants. Patients receiving Oxaliplatin for Injection plus 5-fluorouracil/leucovorin and requiring oral anticoagulants may require closer monitoring.

### Renal

About 5 to 10% of patients in all groups had some degree of elevation of serum creatinine. The incidence of Grade 3/4 elevations in serum creatinine in the Oxaliplatin for Injection and 5-fluorouracil/leucovorin combination arm was 1% in the previously treated patients. Serum creatinine measurements were not reported in the adjuvant trial.

### Hepatic

Hepatotoxicity (defined as elevation of liver enzymes) appears to be related to Oxaliplatin for Injection combination therapy [see Warnings and Precautions)] . The following tables list the clinical chemistry changes associated with hepatic toxicity occurring in ≥5% of patients, based on adverse reactions reported and NCI CTC grade for adjuvant patients and patients previously untreated for advanced colorectal cancer, laboratory values and NCI CTC grade for previously treated patients.

### Post marketing Experience

The following adverse reactions have been identified during post-approval use of Oxaliplatin for Injection. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Body as a whole:** angioedema, anaphylactic shock.

**Central and peripheral nervous system disorders:** loss of deep tendon reflexes, dysarthria, Lhermitte's sign, cranial nerve palsies, fasciculations, convulsion.

**Liver and Gastrointestinal system disorders:** severe diarrhea/vomiting resulting in hypokalemia, colitis (including Clostridium difficilediarrhea), metabolic acidosis; ileus; intestinal obstruction, pancreatitis; veno-occlusive disease of liver also known as sinusoidal obstruction syndrome, and perisinusoidal fibrosis which rarely may progress.

**Hearing and vestibular system disorders:** Deafness

**Platelet, bleeding, and clotting disorders:** immuno-allergic thrombocytopeniaprolongation of prothrombin time and of INR in patients receiving anticoagulants.

**Red Blood Cell disorders:** hemolytic uremic syndrome, immuno-allergic hemolytic anemia.

**Renal disorders:** Acute tubular necrosis, acute interstitial nephritis and acute renal failure.

**Respiratory system disorders:** Pulmonary fibrosis, and other interstitial lung diseases (sometimes fatal).

**Vision disorders:** Decrease of visual acuity, visual field disturbance, optic neuritis and transient vision loss.(reversible following therapy discontinuation).

### Overdose

There is no known antidote for Oxaliplatin for Injection overdose. In addition to thrombocytopenia, the anticipated complications of an Oxaliplatin for Injection overdose include hypersensitivity reaction, myelosuppression, nausea, vomiting, diarrhea and neurotoxicity.

Several cases of overdoses have been reported with Oxaliplatin for Injection. Adverse reactions observed were Grade 4 thrombocytopenia ($<25{,}000/mm^3$) without any bleeding, anemia, sensory neuropathy such as paresthesia, dysesthesia, laryngospasm and facial muscle spasms, gastrointestinal disorders such as nausea, vomiting, stomatitis, flatulence, abdomen enlarged and Grade 4 intestinal obstruction, Grade 4 dehydration, dyspnea, wheezing, chest pain, respiratory failure, severe bradycardia and death.

Patients suspected of receiving an overdose should be monitored, and supportive treatment should be administered. The maximum dose of Oxaliplatin that has been administered in a single infusion is 825 mg.

## DRUG INTERACTIONS

No specific cytochrome P-450-based drug interaction studies have been conducted. No pharmacokinetic interaction between 85 $mg/m^2$ Oxaliplatin for Injection and 5-fluorouracil/leucovorin has been observed in patients treated every 2 weeks. Increases of 5-fluorouracil plasma concentrations by approximately 20% have been observed with doses of 130 $mg/m^2$ Oxaliplatin for Injection dosed every 3 weeks. Because platinum-containing species are eliminated primarily through the kidney, clearance of these products may be decreased by coadministration of potentially nephrotoxic compounds; although, this has not been specifically studied.

## STORAGE

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

## HOW SUPPLIED

Relbiplat™-50

Oxaliplatin for Injection USP 50mg
Each sterile single use lyophilized vial, individually packed in a carton.

Relbiplat™-100

Oxaliplatin for Injection USP 100mg
Each sterile single use lyophilized vial, individually packed in a carton.

## SHELF LIFE

36 months