140mm

210mm

Injection

# OXALISOL

( O X A L I P L A T I N )

انجکشن

# آگزالیسول

( آگزیلیپلاٹین )

**COMPOSITION**

**Oxalisol Injection 50mg/10ml**

Each 10ml contains:

Oxaliplatin……50mg

**(USP Specifications)**

**Oxalisol Injection 100mg/20ml**

Each 20ml contains:

Oxaliplatin……100mg

**(USP Specifications)**

**DESCRIPTION**

Oxaliplatin is a platinum-based chemotherapy drug in the same family as cisplatin and carboplatin. It is typically administered in combination with fluorouracil and leucovorin in a combination known as Folfox for the treatment of colorectal cancer. Compared to cisplatin the two amine groups are replaced by cyclohexyldiamine for improved antitumour activity. The chlorine ligands are replaced by the oxalato bidentate derived from oxalic acid in order to improve water solubility.

**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 interand intrastrand Pt-DNA crosslinks are formed. Crosslinks are formed between the $N^7$ 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.

**INDICATIONS**

Oxaliplatin is 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 & ADMINISTRATION**

Oxaliplatin injection should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

Administer OXALIPLATIN 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 85 mg/$m^2$ intravenous infusion in 250-500 mL 5% Dextrose injection, USP and Leucovorin 200 mg/$m^2$ intravenous infusion in 5% Dextrose Injection, USP 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 2-4 minutes, followed by 5-fluorouracil 600 mg/$m^2$ intravenous infusion in 500 mL 5% Dextrose Injection, USP (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 2-4 minutes, followed by 5-fluorouracil 600 mg/$m^2$ intravenous infusion in 500 mL 5% Dextrose Injection, USP (recommended) as a 22-hour continuous infusion.

The administration of OXALIPLATIN does not require rehydration. Premedication with antiemetics, including 5-HT3 blockers with or without dexamethasone, is recommended.

**Dose Modification Recommendations**

Prior to subsequent therapy cycles, patients should be evaluated for clinical toxicities and recommended laboratory tests. Prolongation of infusion time for OXALIPLATIN from 2 hours to 6 hours may mitigate acute toxicities. The infusion times for 5-fluorouracil and Leucovorin do not need to be changed.

***Adjuvant Therapy in Patients with Stage III Colon Cancer***

Neuropathy and other toxicities were graded using the NCI CTC scale version 1 For patients who experience persistent Grade 2 neurosensory events that do not resolve, a dose reduction of OXALIPLATIN to 75 mg/$m^2$ should be considered. For patients with persistent Grade 3 neurosensory events, discontinuing therapy should be considered. The infusional 5-fluorouracil/Leucovorin regimen need not be altered.

A dose reduction of OXALIPLATIN to 75 mg/$m^2$ and infusional 5-fluorouracil to 300 mg/$m^2$ bolus and 500 mg/$m^2$ 22 hour infusion is recommended for patients after recovery from grade 3/4 gastrointestinal (despite prophylactic treatment) or grade 4 neutropenia or grade 3/4 thrombocytopenia. The next dose should be delayed until: neutrophils ≥1.5 x 109 /L and platelets ≥75 x 109 /L.

***Dose Modifications in Therapy in Previously Untreated and Previously Treated Patients with Advanced Colorectal Cancer***

Neuropathy was graded using a study-specific neurotoxicity scale. Other toxicities were graded by the NCI CTC, Version 2.0. For patients who experience persistent Grade 2 neurosensory events that do not resolve, a dose reduction of OXALIPLATIN to 65 mg/$m^2$ should be considered. For patients with persistent Grade 3 neurosensory events, discontinuing therapy should be considered. The 5-fluorouracil/Leucovorin regimen need not be altered.

A dose reduction of OXALIPLATIN to 65 mg/$m^2$ and 5-fluorouracil by 20% (300 mg/$m^2$ bolus and 500 mg/$m^2$ 22-hour infusion) is recommended for patients after recovery from grade 3/4 gastrointestinal (despite prophylactic treatment) or grade 4 neutropenia or grade 3/4 thrombocytopenia. The next dose should be delayed until: neutrophils ≥1.5 x 109 /L and platelets ≥75 x 109 /L.

***Dose Modifications in Therapy for Patients with Renal Impairment***

In patients with normal renal function or mild to moderate renal impairment, the recommended dose of OXALIPLATIN is 85 mg/$m^2$. In patients with severe renal impairment, the initial recommended OXALIPLATIN dose should be reduced to 65 mg/$m^2$.

**Preparation of Infusion Solution**

Do not freeze and protect the concentrated solution from light.

A final dilution must never be performed with a sodium chloride solution or other chloride containing solutions. The solution must be further diluted in an infusion solution of 250-500 mL of 5% Dextrose Injection, USP.

After dilution with 250-500 mL of 5% Dextrose Injection, USP, the shelf life is 6 hours at room temperature [20-25°C (68-77°F)] or up to 24 hours under refrigeration [2-8°C (36-46°F)]. However, from a microbiological point of view, the diluted infusion prepration must be used immediately.

After final dilution, protection from light is not required.

OXALIPLATIN 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, USP 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 should not be used for the preparation or mixing of the drug. Aluminum has been reported to cause degradation of platinum compounds.

**Handling and Disposal**

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions prepared from OXALIPLATIN. The use of gloves is recommended If a solution of OXALIPLATIN contacts the skin, wash the skin immediately and thoroughly with soap and water. If OXALIPLATIN contacts the mucous membranes, flush thoroughly with water. Procedures for the handling and disposal of anticancer drugs should be considered. Several guidelines on the subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

**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 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. Interpatient and intrapatient variability in ultrafilterable platinum exposure (AUC0-48hr) assessed over 3 cycles was moderate to low (23% and 6%, respectively). A pharmacodynamic relationship between platinum ultrafiltrate levels and clinical safety and effectiveness has not been established.

**Distribution**

At the end of a 2-hour infusion of OXALIPLATIN, 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 ultrafiltrate following 85 mg/$m^2$ every two weeks.

**Elimination**

The major route of platinum elimination is renal excretion. 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 a rate (10 – 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.

**WARNINGS AND PRECAUTIONS**

**Oxaliplatin should only be used in specialized departments of oncology and should be administered under the supervision of an experienced oncologist.**

**Renal impairment**

Patients with mild to moderate renal impairment should be closely monitored for adverse reactions and the dose adjusted according to toxicity.

**Hypersensitivity reactions**

Special surveillance should be ensured for patients with a history of allergic manifestations to other products containing platinum. In case of anaphylactic manifestations the infusion should be interrupted immediately and an appropriate symptomatic treatment started. Re-administration of Oxaliplatin is contra-indicated. Cross reactions, sometimes fatal, have been reported with all platinum compounds.

In case of Oxaliplatin extravasation, the infusion must be stopped immediately and usual local symptomatic treatment initiated.

**Neurological symptoms**

Neurological toxicity of oxaliplatin should be carefully monitored, especially if co-administered with other medicinal products with specific neurological toxicity. A neurological examination should be performed before each administration and periodically thereafter.

For patients who develop acute laryngopharyngeal dysaesthesia, during or within the hours following the 2-hour infusion, the next oxaliplatin infusion should be administered over 6 hours.

**Peripheral neuropathy**

If neurological symptoms (paraesthesia, dysaesthesia) occur, the following recommended oxaliplatin dosage adjustment should be based on the duration and severity of these symptoms:

if symptoms last longer than seven days and are troublesome, the subsequent oxaliplatin dose should be reduced from 85 to 65 mg/$m^2$ (metastatic setting) or 75 mg/$m^2$ (adjuvant setting)

If paraesthesia without functional impairment persists until the next cycle, the subsequent oxaliplatin dose should be reduced from 85 to 65 mg/$m^2$ (metastatic setting) or 75 mg/$m^2$ (adjuvant setting)

If paraesthesia with functional impairment persists until the next cycle, oxaliplatin should be discontinued

If these symptoms improve following discontinuation of oxaliplatin therapy, resumption of therapy may be considered.

Patients should be informed of the possibility of persistent symptoms of peripheral sensory neuropathy after the end of the treatment. Localized moderate paresthesias or paresthesias that

may interfere with functional activities can persist after up to 3 years following treatment cessation in the adjuvant setting.

**Reversible Posterior Leukoencephalopathy Syndrome (RPLS)**

Cases of Reversible Posterior Leukoencephalopathy Syndrome (RPLS also known as PRES, Posterior Reversible Encephalopathy Syndrome) have been reported in patients receiving oxaliplatin in combination chemotherapy. RPLS is a rare, reversible, rapidly evolving neurological condition, which can include seizure, hypertension, headache, confusion, blindness, and other visual and neurological disturbances. Diagnosis of RPLS is based upon confirmation by brain imaging, preferably MRI (Magnetic Resonance Imaging).

**Nausea, vomiting, diarrhoea, dehydration and haematological changes**

Gastrointestinal toxicity, which manifests as nausea and vomiting, warrants prophylactic and/or therapeutic anti-emetic therapy.

Dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis particularly when combining oxaliplatin with 5-fluorouracil.

Cases of intestinal ischemia, including fatal outcomes, have been reported with oxaliplatin treatment. In case of intestinal ischemia, oxaliplatin treatment should be discontinued and appropriate measures initiated.

If haematological toxicity occurs (neutrophils < 1.5x109/l or platelets < 50x109/l), administration of the next course of therapy should be postponed until haematological values return to acceptable levels. A full blood count with white cell differential should be performed prior to start of therapy and before each subsequent course. Myelosuppressive effects may be additive to those of concomitant chemotherapy. Patient with severe and persistent myelosuppression are at high risk of infectious complications. Sepsis, neutropenic sepsis and septic shock have been reported in patients treated with oxaliplatin including fatal outcomes. If any of these events occurs, oxaliplatin should be discontinued.

Patients must be adequately informed of the risk of diarrhoea/emesis, mucositis/ stomatitis and neutropenia after oxaliplatin and 5-fluorouracil administration so that they can urgently contact their treating physician for appropriate management.

If mucositis/ stomatitis occurs with or without neutropenia, the next treatment should be delayed until recovery from mucositis/ stomatitis to grade 1 or less and/or until the neutrophil count is ≥ 1.5 x 109/l.

For oxaliplatin combined with 5-fluorouracil (with or without folinic acid), the usual dose adjustments for 5-fluorouracil associated toxicities should apply.

If grade 4 diarrhoea, grade 3-4 neutropenia (neutrophils <1.0x109/l), febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection with an absolute neutrophil count < 1.0 x 109/L, a single temperature of > 38.3°C or a sustained temperature of > 38°C for more than one hour), or grade 3-4 thrombocytopenia (platelets < 50x109/l) occur, the dose of oxaliplatin should be reduced from 85 to 65 mg/m² (metastatic setting) or 75 mg/m² (adjuvant setting), in addition to any 5-fluorouracil dose reductions required.

**Pulmonary**

In the case of unexplained respiratory symptoms such as non-productive cough, dyspnoea, crackles or radiological pulmonary infiltrates, oxaliplatin should be discontinued until further pulmonary investigations exclude an interstitial lung disease or pulmonary fibrosis.

**Blood disorders**

Haemolytic-uraemic syndrome (HUS) is a life-threatening side effect (frequency not known). Oxaliplatin should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required. Disseminated intravascular coagulation (DIC), including fatal outcomes, has been reported in association with oxaliplatin treatment. If DIC is present, oxaliplatin treatment should be discontinued and appropriate treatment should be administered.

**QT prolongation**

QT prolongation may lead to an increased risk for ventricular arrhythmias including Torsade de Pointes, which can be fatal. The QT interval should be closely monitored on a regular basis before and after administration of oxaliplatin. Caution should be exercised in patients with a history or a predisposition for prolongation of QT, those who are taking medicinal products known to prolong QT interval, and those with electrolyte disturbances such as hypokalemia, hypocalcaemia, or hypomagnesaemia. In case of QT prolongation, oxaliplatin treatment should be discontinued.

**Rhabdomyolysis**

Rhabdomyolysis has been reported in patients treated with oxaliplatin, including fatal outcomes. In case of muscle pain and swelling, in combination with weakness, fever or darkened urine, oxaliplatin treatment should be discontinued. If rhabdomyolysis is confirmed, appropriate measures should be taken. Caution is recommended if medicinal products associated with rhabdomyolysis are administered concomitantly with oxaliplatin.

**Gastrointestinal ulcer/ gastrointestinal haemorrhage and perforation**

Oxaliplatin treatment can cause gastrointestinal ulcer and potential complications, such as gastrointestinal haemorrhage and perforation, which can be fatal. In case of gastrointestinal ulcer, oxaliplatin treatment should be discontinued and appropriate measures taken.

**Hepatic**

In case of abnormal liver function test results or portal hypertension which does not obviously result from liver metastases, very rare cases of drug-induced hepatic vascular disorders should be considered.

**Fertility**

Genotoxic effects were observed with oxaliplatin in the preclinical studies. Therefore male patients treated with oxaliplatin are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment because oxaliplatin may have an anti-fertility effect which could be irreversible.

Women should not become pregnant during treatment with oxaliplatin and should use an effective method of contraception.

**Pregnancy**

There is no data from the use of oxaliplatin in pregnant women. Animal studies, have shown reproductive toxicity.

Oxaliplatin is not recommended during pregnancy and in women of childbearing potential not using contraception.

The use of oxaliplatin should only be considered after suitably appraising the patient of the risk to the fetus and with the patient's consent.

Appropriate contraceptive measures must be taken during and after cessation of therapy during 4 months for women and 6 months for men.

**Breastfeeding**

It is unknown whether oxaliplatin is excreted in human milk.

Oxaliplatin is contra-indicated during breast-feeding

**Immunosuppressant effects/increased susceptibility to infections:**

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including oxaliplatin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving oxaliplatin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Peritoneal hemorrhage may occur when oxaliplatin is administered by intraperitoneal route (off-label route of administration).

**SIDE EFFECTS**

**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, Reversible Posterior Leukoencephalopathy Syndrome (RPLS, also known as PRES).

**Liver and Gastrointestinal system disorders:** severe diarrhea/vomiting resulting in hypokalemia, colitis (including Clostridium difficile diarrhea), metabolic acidosis; ileus;

**intestinal obstruction, pancreatitis;** veno-occlusive disease of liver also known as sinusoidal obstruction syndrome, and per sinusoidal fibrosis which rarely may progress.

**Hearing and vestibular system disorders:** deafness

**Platelet, bleeding, and clotting disorders:** immuno-allergic thrombocytopenia prolongation 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).

**DRUG INTERACTIONS**

In patients who have received a single dose of 85 mg/m² of oxaliplatin, immediately before administration of 5-fluorouracil, no change in the level of exposure to 5-fluorouracil has been observed. In vitro, no significant displacement of oxaliplatin binding to plasma proteins has been observed with the following agents: erythromycin, salicylates, granisetron, paclitaxel, and sodium valproate.

Caution is advised when oxaliplatin treatment is co-administered with other medicinal products known to cause QT interval prolongation. In case of combination with such medicinal products, the QT interval should be closely monitored.

Caution is advised when oxaliplatin treatment is administered concomitantly with other medicinal products known to be associated with rhabdomyolysis.

**OVERDOSE**

There is no known antidote to oxaliplatin. In cases of overdose, exacerbation of adverse events can be expected. Monitoring of haematological parameters should be initiated and symptomatic treatment given.

**CONTRAINDICATIONS**

Oxaliplatin is contraindicated in patients who:

- Have a known history of hypersensitivity to the active substance or to any of the excipients.
- Are breast feeding.
- Have myelosuppression prior to starting first course, as evidenced by baseline neutrophils <2x109/l and/or platelet count of <100x109l
- Have a peripheral sensitive neuropathy with functional impairment prior to first course
- Have a severely impaired renal function (creatinine clearance less than 30 ml/min)

**STORAGE & INSTRUCTIONS**

Store below 30°C before dilution.

DO NOT INJECT WITHOUT PRIOR DILUTION. After dilution use within 48 hours if store between 2-8°C and for 24 hours at 25°C.

Protect from heat, sunlight and moisture.

Do not freeze.

Keep out of the reach of children.

**For intravenous use only.**

**To be sold on the prescription of a registered oncologist or on demand from cancer hospitals and institutions only.**

**HOW SUPPLIED**

**Oxalisol Injection 500mg/5ml**
1 vial

**Oxalisol Injection 100mg/20ml**
1 vial

## خوراک وطریقہ استعمال:

سرطان کے ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

## ہدایات:

ڈائیلوشن سے پہلے دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔ ڈائیلوشن کے بعد دوا کو ۸-۲ ڈگری سینٹی گریڈ درجہ حرارت پر رکھنے کی صورت میں ۴۸ گھنٹے میں استعمال کریں اور ۲۵ ڈگری سینٹی گریڈ درجہ حرارت پر رکھنے کی صورت میں ۲۴ گھنٹے میں استعمال کریں۔

دھوپ، گرمی، نمی اور منجمد ہونے سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

صرف وریدی استعمال کے لیئے ہے۔ صرف مستند اونکولوجسٹ یا کینسر ہسپتال کے نسخے پر فروخت کریں۔

Manufactured by:

PHARMASOL

**PRIVATE LIMITED**

Plot # 549,Sundar Industrial Estate,
Lahore, Pakistan.