Oxiplat
Oxaliplatin USP

DRUG INTERNATIONAL LTD.

COMPOSITION:

Oxiplat 50 Injection: Each vial contains 10ml solution containing Oxaliplatin USP 50mg (5mg/ml).

Oxiplat 100 Injection: Each vial contains 20ml solution containing Oxaliplatin USP 100mg (5mg/ml).

Oxiplat 200 Injection: Each vial contains 40ml solution containing Oxaliplatin USP 200mg (5mg/ml).

DESCRIPTION: Oxaliplatin is slightly soluble in water, very slightly soluble in methanol and practically insoluble in ethanol.

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.

In vivo studies have shown antitumor activity of oxaliplatin against colon carcinoma. In combination with 5-fluorouracil, oxaliplatin exhibits in vitro and in vivo antiproliferative activity greater than either compound alone in several tumor models [HT29 (colon), GR (mammary), and L1210 (leukemia)].

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). Pharmacokinetic parameters obtained after a single 2-hour intravenous infusion of oxaliplatin at a dose of 85 mg/m² expressed as ultrafilterable platinum were C max of 0.814 mcg /mL and volume of distribution of 440 L.

Interpatient and intrapatient variability in ultrafilterable platinum exposure ($AUC_{0\text{-}48hr}$) 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/m² 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 ultrafiltrate 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, 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.

INDICATIONS: Oxaliplatin, used in combination with infusional 5-fluorouracil/folinic acid, 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:

Dosage: Administer oxaliplatin in combination with 5-fluorouracil/folinic acid 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/m² intravenous infusion in 250-500 mL 5% Dextrose injection, USP and folinic acid 200 mg/m² 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/m² intravenous bolus given over 2-4 minutes, followed by 5-fluorouracil 600 mg/m² intravenous infusion in 500 mL 5% Dextrose Injection, USP (recommended) as a 22-hour continuous infusion.

Day 2: Folinic acid 200 mg/m² intravenous infusion over 120 minutes, followed by 5-fluorouracil 400 mg/m² intravenous bolus given over 2-4 minutes, followed by 5-fluorouracil 600 mg/m² intravenous infusion in 500 mL 5% Dextrose Injection, USP (recommended) as a 22-hour continuous infusion.

Dosage Modification: Prior to subsequent therapy cycles, patients should be evaluated for clinical toxicities and recommended laboratory tests.

Adjuvant Therapy in Patients with Stage III Colon Cancer: For patients who experience persistent Grade 2 neurosensory events that do not resolve, a dose reduction of oxaliplatin to 75 mg/m² should be considered. For patients with persistent Grade 3 neurosensory events, discontinuing therapy should be considered. The infusional 5-fluorouracil/folinic acid regimen need not be altered.

A dose reduction of oxaliplatin to 75 mg/m² and infusional 5-fluorouracil to 300 mg/m² bolus and 500 mg/m² 22 hour infusion is recommended for patients after recovery from grade 3/4 gastrointestinal (despite prophylactic treatment), or grade 4 neutropenia, or febrile neutropenia, or grade 3/4 thrombocytopenia. The next dose should be delayed until: neutrophils ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L.

Previously Untreated and Previously Treated Patients with Advanced Colorectal Cancer: For patients who experience persistent Grade 2 neurosensory events that do not resolve, a dose reduction of oxaliplatin to 65 mg/m² should be considered. For patients with persistent Grade 3 neurosensory events, discontinuing therapy should be considered. The 5-fluorouracil/folinic acid regimen need not be altered.

A dose reduction of oxaliplatin to 65 mg/m² and 5-fluorouracil by 20% (300 mg/m² bolus and 500 mg/m² 22-hour infusion) is recommended for patients after recovery from grade 3/4 gastrointestinal (despite prophylactic treatment), or grade 4 neutropenia, or febrile neutropenia, or grade 3/4 thrombocytopenia. The next dose should be delayed until: neutrophils ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L.

Patients with Renal Impairment: In patients with normal renal function or mild to moderate renal impairment, the recommended dose of oxaliplatin is 85 mg/m². In patients with severe renal impairment, the initial recommended oxaliplatin dose should be reduced to 65 mg/m².

PREPARATION OF INFUSION SOLUTION

Do not freeze and protect from light the concentrated solution.

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)]. 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.

CONTRAINDICATIONS: It is contraindicated in patients with known allergy to oxaliplatin or other platinum compounds.

PRECAUTIONS:Allergic Reactions: Grade 3/4 hypersensitivity, including anaphylactic/anaphylactoid reactions, to oxaliplatin has been observed in 2-3% of colon cancer patients. These allergic reactions which can be fatal, can occur within minutes of administration and at any cycle. These reactions are usually managed with standard epinephrine, corticosteroid, antihistamine therapy, and require discontinuation of therapy. Rechallenge is contraindicated in these patients.

Neurological Toxicity: Neurological toxicity of oxaliplatin should be carefully monitored, especially if co-administered with other medications with specific neurological toxicity. A neurological examination should be performed before initiation of each administration, and periodically thereafter. It is not known whether patients with pre-existing medical conditions associated with peripheral nerve damage have a reduced threshold for oxaliplatin induced peripheral neuropathy.

For patients who develop acute laryngopharyngeal dysaesthesias, during or within 48 hours following the two hour infusion, the next oxaliplatin infusion should be administered over six hours. To prevent such dysaesthesia, advise the patient to avoid exposure to cold and to avoid ingesting cold food and/or beverages during or within 48 hours following oxaliplatin administration.

Pulmonary Toxicity: Oxaliplatin has been associated with pulmonary fibrosis (< 1% of study patients), which may be fatal. In case of unexplained respiratory symptoms such as non-productive cough, dyspnea, crackles, or radiological pulmonary infiltrates, oxaliplatin should be discontinued until further pulmonary investigation excludes interstitial lung disease or pulmonary fibrosis.

Hepatotoxicity: Reactions related to liver sinusoidal obstruction syndrome, including nodular regenerative hyperplasia, have been reported. In the case of abnormal liver function test results or portal hypertension which could not be explained by liver metastases, reactions related to liver sinusoidal obstruction syndrome should be investigated, and very rare cases of drug induced hepatic vascular disorders should be considered.

Cardiovascular Toxicity: QT prolongation and ventricular arrhythmias including fatal Torsade de Pointes have been reported in postmarketing experiences following oxaliplatin administration. ECG monitoring is recommended if therapy is initiated in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics, and electrolyte abnormalities. Correct hypokalemia or hypomagnesemia prior to initiating oxaliplatin and monitor these electrolytes periodically during therapy. Avoid oxaliplatin in patients with congenital long QT syndrome.

Use in Pregnancy: Pregnancy Category D

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

Use in Lactation: It is not known whether this drug or it derivatives are excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from oxaliplatin, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

OVERDOSE: There is no known antidote for oxaliplatin overdose. In addition to thrombocytopenia, the anticipated complications of an oxaliplatin overdose include hypersensitivity reaction, myelosuppression, nausea, vomiting, diarrhea and neurotoxicity. Several cases of overdoses have been reported with oxaliplatin. Adverse reactions observed were Grade 4 thrombocytopenia (<25,OOO/mm3) 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.

ADVERSE EFFECTS: Most common adverse reactions (incidence 40%) were peripheral sensory neuropathy, neutropenia, thrombocytopenia, anemia, nausea, increase in transaminases and alkaline phosphatase, diarrhea, emesis, fatigue and stomatitis. Other adverse reactions, including serious adverse reactions, have been reported.

DRUG INTERACTIONS: No specific cytochrome P-450-based drug interaction studies have been conducted. No pharmacokinetic interaction between 85 mg/m² oxaliplatin and 5-fluorouracil/folinic acid 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/m² oxaliplatin 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.

PHARMACEUTICAL INFORMATION: Storage condition: Store the vial in original carton at 25°C. Protect from light. Do not freeze. Keep out of the reach of the children.

Packing : Oxiplat 50 Injection: Each box contains 1 vial of 10ml solution.
Oxiplat 100 Injection: Each box contains 1 vial of 20ml solution.
Oxiplat 200 Injection: Each box contains 1 vial of 40ml solution.