For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

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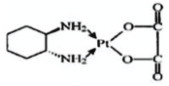
Oxaliplatin Injection IP 50mg/25ml & 100mg/50ml

All medications containing Oxaliplatin as an active ingredient are capable of producing the effects mentioned hereby Oxaliplatin should only be administered by an Oncologist.

Oxplatin 50 mg/25ml :		**Oxplatin 100 mg/50ml :**	
Each ml contains:		Each ml contains:	
Oxaliplatin IP	2 mg	Oxaliplatin IP	2 mg
Water for Injections IP	qs	Water for Injections IP	qs

Description : Oxaliplatin is an antineoplastic agent with the molecular formula C8H14N2O4Pt 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.



THERAPEUTIC ACTION : Cytotoxic Anti neoplastic

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."

Human Pharmacokinetics

The reactive Oxaliplatin derivatives are present as a fraction of the unbound platinum in plasma ultrafiltrate Pharmacokinetic parameters obtained after a single 2-hour IV infusion of Oxaliplatin at a dose of 85mg/m^2 expressed as ultrafilterable platinum are C of 0.814 ug/ml and volume of distribution of 440 L. Interpatient and intrapatient variability in ultrafilterable platinum exposure (AUC 0-48hrs) assessed over 3 cycles is moderate to low (23% and 6% respectively)

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%. No platinum accumulation is observed in plasma ultrafiltrate following 85mg/m^{2}every two weeks.

Metabolism

Oxaliplatin undergoes rapid and extensive non-enzymatic 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 disquo DACH platinum) and a number of noncytotocxic, 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 is cleared from plasma at a rate (10 17 L/h) that is similar to or exceeded the average human glomerular filtration rate (GFR; 7.5L/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.

Pharmacokinetics in special populations

Age and Sex: There was no clinically relevant effect of age or sex on the pharmacokinetics of Oxaliplatin documented in any study.

Renal Impairment - The AUC 0-4 hr of platinum in the plasma ultrafiltrate increases as renal function decreases. The AUC -0-48 hr of platinum in patients with mild (creatinine Clearance, CL cr 50 to 80 mL/min), moderate (CLcr 30 to <50 mL/min) and severer renal (CL cr< 30 mL/min) impairment is increased by about 60% , 140% and 190%, respectively, compared to patients with normal renal function (CLcr>80 mL/min)

INDICATIONS AND USAGE :

Oxaliplatin used in combination with infusional 5-FU/LV is indicated for adjuvant treatment of Stage III colon Cancer patients who have undergone complete resection of the primary tumor.

Oxaliplatin used in combination with infusional 5- FU/LV is indicated for the treatment of advanced carcinoma of the colon of Rectum.

DOSAGE AND ADMINISTRATION :

Adjuvant Therapy in Patients with Stage III Colon Cancer

Adjuvant treatment in patients with stage III Colon Cancer is recommended for a total of 6 months, i.e. 12 cycles, every 2 weeks,

Day (I) Oxaliplatin 85mg/m^2 IV in 250-500 ml. D5W, Leucovorin 200 mg.m^2 in D5W both over 2 hrs. at same time in separate bags using a Y line. Followed by 5 Fluorouracil 400 mg/m^2 IV bolus over 2-4 mins, then 5-Fluorouracil 600 mg/m^2 IV in 500 ml D5W over 22 hrs.

Day 2: Leucovorin 200 mg/m^2 IV over 2 hrs, then 5-Fluorouracil 400 mg/m^2 IV bolus over 2-4 mins, then 5-Fluorouracil 600 mg/m^2 IV over 22 hrs.

Therapy in Previously Untreated and Previously Treated Patients with Advanced Colorectal Cancer

The recommended dose schedule given every two weeks is also follow:

Day 1: Oxaliplatin 85 mg/m^2 IV infusion in 250-500 mL D5W and Leucovorin 200 mg/m^2 IV infusion in D5W both given over 120 minutes at the same time in separate bags using a Y-line, followed by 5 - FU 400 mg/m^2 IV bolus given over 2-4 D5W (recommended) as a 22-hours continuous infusion.

Repeat cycle every 2 weeks.

The administration of Oxaliplatin does not require prehydration. Premedication with anti emetics, including 5-HT$_3$ blockers with or without dexamethasone is recommended.

CONTRAINDICATIONS:

- ✓ Known history of hypersensitivity or allergy to Oxaliplatin, pregnancy, Breast feeding.
- ✓ Myelosuppression prior to starting first course, as evidenced by baseline neutrophils < 1.5 X 10^9/L and / or platelet count of < 100 x 10^9/L.
- ✓ Peripheral Sensory Neuropathy with functional impairment prior to first course.
- ✓ Several impaired renal function (creatinine clearance less than 30 mL/min)

PRECAUTIONS:

General : Oxaliplatin should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents.

Neuropathy-

Previously Untreated and previously Treated Patients with Advanced Colorectal Cancer.

In the previously treated study, neuropathy information was collected to establish that Oxaliplatin is associated with two types of neuropathy:

An acute, reversible, primarily peripheral, sensory neuropathy that is of early onset, occuring within hours or one to two days of dosing, that resolves within 14 days, and that frequently recur 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 has been associated with pulmonary fibrosis (< 1% of study patients), which may be fatal .

Hepatotoxicity - Hepatotoxicity as evidenced by increase in transminases and alkaline phosphatase.

Carcinogenesis, Mutagenesis, Impairment of 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 (L5178 Y mouse lymphoma assay), Oxaliplatin was clastogenic both in vitro (Chromosome aberration in human lymphocytes) and in vivo (mouse bone marrow micronucleus assay) In a fertility study, a dose of 2 mg/kg/day (less than one-seventh the recommended human dose on a body surface area basis) did not affect pregnancy rate, but caused developmental mortality (increased early resorprions, decreased live

fetuses, decreased live births) and delayed growth (decreased fetal weight) Testicular damage, characterized by degeneration, hypoplasia, and atrophy, was observed in dogs administered Oxaliplatin at 0.75 mg/kg/day x5 days every 28 days for three cycles.

Pregnancy Category D- Oxaliplatin may cause fetal harm when administered to a pregnant women.

Nursing Mothers- It is not known whether Oxaliplatin or its 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 delay the use of the drug, taking into account the importance of the drug to the mother.

Pediatric use: The Safety and effectiveness of Oxaliplatin in pediatric patients have not been established.

Patients with Renal Impairment:- The safety and effectiveness of the combination of Oxaliplatin and 5-FU/LV in patients with renal impairment have not been evaluated. The combination of Oxaliplatin and 5-FU/LV should be used with caution in patients with preexisting renal impairment since the primary route of platinum eliminator , is renal, Clearance of Ultra filterable platinum is decreased in patients with mild, moderate and severe renal impairment. A pharmacodynamic relationship between platinum ultra filtrate levels and clinical safety and effectiveness has not been established.

Geriatric Use: No significant effect of age on the clearance of Ultrafilterable platinum has been observed. No adjustment to starting dose was required in patients $\geq$ 65 years old.

Drug Interactions:

No specific cytochrome P450-based drug interactions studies have been conducted. No pharmacokinetic interaction between 85mg/m^2 Oxaliplatin and 5-FU/LV has been observed in patients treated every 2 weeks. Increase of 5-FU plasma concentrations by approximately 20% have been observed with doses of 130 mg/m^2 Oxaliplatin dosed every 3 weeks. Since platinum -Containing species are eliminiated primarily through the kidney, clearance of these products may be decreased by co-adminstration of potentially nephrotoxic compounds; although, this has not been specifically studied.

ADVERSE EFFECTS:

Hematopoetic System.

Oxaliplatin has low hematologic toxicity.

During a monochemotherapy course, the administration of oxaliplatin can lead to the following unwanted effects anaemia, leukopenia, granulocytopenia, thrombocytopenia, sometimes of grade 3 or 4 (Severity of grade 4, neutrophils counts < 500/mm3, platelet counts <25000/mm3, hemoglobin <6.5g/100 ml.).

In association with 5-fluorouracil, the hematological toxicity is increased, and is manifested through neutropenia and thrombocytopenia.

Digestive System.

During a monochemotherapy course, Oxaliplatin produces nausea, vomiting, and diarrhoea. These symptoms can sometimes be severe.

In case of association with 5-Flurouracil, the frequency of said adverse events is increased.

A suitable antiemetic treatment is advised.

Nervous system:

Sometimes, sensitive peripheral neuropathies are observed, characterized by paresthesias of the limbs. This paresthesias can be accompanied by cramps, dysesthesias of the perioral region and of the upper aerodigestive pathway, which can resemble clinical manifestations of larynx spasm without anatomical background, spontaneously reversible without sequelae.

These manifestations are caused and even become worse by cold. Paresthesias are generally regressive between treatment cycles. But they can become permanent and lead to functional discomfort after a cumulative dose generally higher than 800 mg/m^2 (6 cycles).

Neurotoxicity decreases or disappears in most patients in the following months after treatment withdrawl.

The occurrence of spontaneously reversible paresthesias does not require a dose modification when Oxaliplatin is administered later.

Modification of the Oxaliplatin does administered is advised according to the length and severity of the neurologic symptoms observed. In case of persistent paresthesias between two cycles and / or at the onset of a functional disorder, a reduction of 25% of the Oxaliplatin does is recommended (i.e. 100 mg/m^2). If even with a modified does there would not be any modifications of the symptoms, or said symptoms would become worse interruption of administration is advised. A new beginning of the Oxaliplatin treatment at a complete or reduced dose after a totally or partially symptom regression is possible and it is left to the physician's discretion.

OVER DOSAGE :

There is no known antidote for Oxaliplatin overdose.

Patients suspected of receiving an overdose should be administered. In addition to thrombocytopeania, the anticipated complications of Oxaliplatin overdose include myelosuppresssion, nausea and vomiting, diarrhoea and neurotoxicity.

Information For Patients

Patients and patients caregivers should be informed of the expected side effects of Oxaliplatin, particularly its neurologic effects both the acute, reversible effects and the persistent neurosensory toxicity.

Patients should be informed that the acute neurosensory toxicity may be precipitated or exacerbated by exposure to cold or cold objects.

Patients should be instructed to avoid cold drinks, use of ice, and should cover exposed skin prior to exposure to cold temperature or cold objects.

Patients must be adequately informed of the risk of low blood cell counts and instructed to contact their physician immediately should fever, particularly if associated with persistent diarrhoea, or evidence of infection develop.

Patients should be instructed to contact their physician if persistent vomiting, diarrhoea signs of dehydration cough or breathing difficulties occur or signs of allergic reaction appear.

Preparation of Infusion solution/Instruction for use and Handling.

Withdraw appropriate dose and dilute in an infusion solution of 250-500 ml. of 5% Dextrose Injection, IP. Oxaliplatin is incompatible with chlorides & chloride containing solutions.

After dilution with 250-500 ml of 5% Dextrose Injection IP, the shelf life is 6 hours at room temperature [20- 25ºC (68-77°F)] or up to 24 hours under refrigeration [2- 8ºC (36-46ºF)]

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-FU) and must not be mixed with these or administered, simultaneously through the same infusion line.

The infusion line should be flushed with D5W 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. Aluminium has been reported to cause degradation of platinum compounds.

HOW SUPPLIED

Oxaliplatin is supplied in amber colour glass single-use vials containing 50 mg/100 mg. of Oxaliplatin IP in Water for injections IP.

Oxaliplatin injection IP 50 mg / 25 ml in 30 ml glass Amber vial.

Oxaliplatin injection IP 100 mg / 50 ml in 50 ml glass Amber vial.

Storage : Store protected from light, at a temperature below 30ºC.

(Keep in Original outer carton)

Manufactured by :
Beta Drugs Ltd,
Kharuni - Lodhimajra Road, Vil. Nandpur,
Baddi, Distt Solan, Himachal Pradesh -173205

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