PLAXINOL

(Oxaliplatin USP)

Composition
***PLAXINOL* 50mg/10ml Injection**
Each vial contains:
Oxaliplatin USP.....50mg.
Product complies USP specifications.

Indications
Oxaliplatin in combination with 5-fluorouracil (5-FU) and folinic acid (FA) is indicated for:
- Adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of primary tumor.
- Treatment of advanced/metastatic colorectal cancer.

Oxaliplatin in combination with 5-FU/FA and bevacizumab is indicated for:
- First line treatment of metastatic colorectal cancer.

Dosage & Administration
General
For adults only
Recommended dosage
The recommended dose for Oxaliplatin in adjuvant setting of colon cancer is 85 mg/m^2 intravenously repeated every two weeks for 12 cycles (6 months). The recommended dose for Oxaliplatin in treatment of advanced/metastatic colorectal cancer is 85mg/m^2 intravenously repeated every two weeks until disease progression or unacceptable toxicity. Dosage given should be adjusted according to tolerability. Oxaliplatin should always be administered before fluoropyrimidines (5-FU).Oxaliplatin is administered by intravenous infusion. The administration of Oxaliplatin does not require hyper hydration. Oxaliplatin diluted in 250 to 500 mL of 5% glucose solution to give a concentration not less than 0.2 mg/mL must be infused either via a peripheral vein or central venous line at the same time as folinic acid intravenous infusion in 5% glucose solution, over 2 to 6 hours, using a Y-line placed immidiately before the site of infusion. These two medicinal products should not be combined in the same infusion bag. Folinic acid must not contain trometamol as an excipient and must only be diluted using isotonic 5% glucose solution, never in alkaline solutions or sodium chloride or chloride containing sloutions. Oxaliplatin infusion should always precede that of 5-FU. When used in combination with 5-FU/FA and bevacizumab, oxaliplatin should be administered after bevacizumab but prior to administration of 5-FU. In the event of extravasation, administration must be discontinued immediately.

Instructions for use:
Oxaliplatin must be reconstituted and further diluted before use.

Special Populations
Elderly
No increase in severe toxicities was observed when Oxaliplatin was used as a single agent or in combination with 5-fluorouracil (5-FU)in patients over the age of 65 in consequence,no specific dose adaptation is required for elderly patients.
Hepatic impairment
A phase I study of Oxaliplatin single agent, 2-hour IV infusion q3w, included adult cancer patients with different degrees of hepatic impairment (none to severe). The initial Oxaliplatin dose was based upon the degree of liver dysfunction and was then increased up to 130mg/m^2 whatever the degree of liver impairment (none to severe). Overall the severity and types of toxicities observed were toxicities expected with Oxaliplatin (see Adverse Reactions). A correlation between increase of overall toxicity and worsening of hepatic function has not been observed. There were no differences in frequencies of events between the different treatment groups based upon liver impairment degree. No specific dose adjustment for patients with abnormal liver function tests was performed during clinical development.
Renal impairment
In patients with normal renal function or mild to moderate renal impairment, the recommended dose of is 85 mg/m^2. In patients with severe renal impairment, the initial recommended dose should be reduced to 65mg/m^2.

Administration
Intravenous infusion

Contraindications
- History of allergy to oxaliplation
- Breast-feeding

Precautions
Oxaliplatin should only be used in specialized department of oncology and administered under the supervision of an experienced oncologist.
- Due to limited information on safety in patients with severely impaired renal function, administration should be considered after suitable appraisal of the benefit/risk for the patient. In this situation,renal function should be closely monitored and the recommended initial oxaliplatin dose is 65 mg/m^2.
- Patients with a history of allergic reaction to platinum compounds should be monitored for allergic symptoms. Allergic reactions can occur during any cycle. In case of an anaphylactic-like reaction to Oxaliplatin, the infusion should be immediately discontinued and appropriate symptomatic treatment initiated. Oxaliplatin rechallenge is contraindicated.
- In case of Oxaliplatin extravasation, the infusion must be stopped immediately and usual local symptomatic treatment initiated. If neurological symptoms (paraesthesia, dysaesthesia) occur, the following recommended Oxaliplatin dosage adjustment, based on the duration and severity of these symptoms, should be performed:
- if symptoms last longer than 7 days and are troublesome, or if paraesthesia without functional impairment persists until the next cycle, the subsequent Oxaliplatin dose should be reduced by 25%.
- if paraesthesia with functional impairment persists until the next cycle, Oxaliplatin administration should be discontinued.
- if these symptoms improve following discontinuation of Oxaliplatin therapy, resumption of therapy may be considered.
- Gastrointestinal toxicity, which manifests as nausea and vomiting, warrants prophylactic and/or therapeutic anti-emetic therapy. Dehydration, ileus, intestinal obstruction, hypokaliaemia, metabolic acidosis, and even renal disorders, may be associated with severe diarrhoea/emesis, particularly when combining Oxaliplatin with 5-FU.
- if hematological toxicity (evidenced by baseline blood count values, e.g. neutrophils <1.5 x 10^9/L or platelets <75 x 10^9/L) occures after a course of therapy or if myelosupression is present' prior to the start (1st course) of therapy, administration of the next or the first course of therapy should be postponed until the blood count returns to acceptable levels. A full blood count with white cell differential should be performed prior to the start of therapy and before each subsequent course.
- Patients must be adequately informed of the risk of diarrhea/emesis and neutropenia after Oxaliplatin /5-FU administration in order to contact urgently their treating physician for appropriate management.
- For Oxaliplatin combined with 5-FU (with or without folinic acid), the usual dose adjustments for 5-FU associated toxicities should apply.
- If severe/life-threatening diarrhoea, severe neutropenia (neutrophils <1.0 x 10^9/L), severe thrombocytopenia (platelets <50 x 10^9/L) occure,Oxaliplatin must be discontinued until improvement or resolution, and the dose of Eloxatin should be reduced by 25% at subsequent cycles, in addition to any 5-FU dose reductions required.
- In case of unexplained respiratory symptoms such as non-productive cough, dyspnea, crackles or radiological pulmonary infiltrates, Oxaliplatin should be discontinued until further pulmonary investigations exclude an interstitial lung disease.
- 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.

Interactions
In patients who have received a single dose of 85 mg/m^2 of Oxaliplatin immediately before administration of 5-FU, no change in the level of exposure to 5-FU has been observed.

Pregnancy
To date ther is no available information on safety use in pregnant women. Based on preclinical findings, Oxaliplatin is likely to be lethal and/or teratogenic to the human foetus at the recommended therapeutic doses, and, is consequently not recommended during pregnancy, and should only be considered after suitable appraising the patient of the risk to the fetus and with the patient's consent. As with other cytotoxic agents, effective contraceptive measures should be taken in potentially fertile patients prior to initiating chemotherapy with Oxaliplatin.

Lactation
Excretion in breast milk has not been studied. Breast-feeding is contraindicated during Oxaliplatin therapy.

Driving a vehicle or performing other hazardous tasks
No studies on the ability to drive and use machines have been performed. However oxaliplatin treatment resulting in an increase risk of dizziness,nausea and vomiting and other neurologic symptoms that effect gait and balance may lead to a minor or moderate influence on the ability to drive and use machines, Vision abnormalities, in particular transient vision loss (reversible following therapy discontinuation), may affect patients' ability to drive and use machines. Therefore, patients should be warned of the potential effect of these events on the ability to drive or use machines.

Adverse Reactions
Combination Therapy of Oxaliplatin with 5-FU/FA (FOLFOX)
Investigations
- Mild to mderate elevation of transminases and alkaline phosphatases activities.

Blood and lymphatic system disorders
- anaemia, neutropenia, thrombocytopenia The frequency increases when Oxaliplatin is administered (85 mg/m^2 every 2 weeks) in combination with 5-FU +/- folinic acid, as compared to a single agent administration (130 mg/m^2 every 3 weeks), e.g. anemia (80% vs 60% of patients), neutropenia (70% vs 15%), thrombocytopenia (80% vs 40%).
- Severe anaemia (Haemoglobin <8.0g/dL) or thrombocytopenia (platelets <50 x 10^9/L) occures with a similar frequency (<5% of patients) when Oxaliplatin is administered as a signal agent or in combination with 5-FU.
- Severe neutropenia (neutrophils <1.0 x 109/L) occures with a greater frequency when Oxaliplatin is administered in combination with 5-FU than as a single agent (40% vs <3% of patients)
- Immuno-allergic haemolytic anaemia and thrombocytopenia

Nervous system disorders
- acute neuro-sensory manifestations. These symptoms usually develop at the end of the 2-hour Oxaliplatin or within a few hours, abate spontaneously within the next hours or days, and frequently reoccure with further cycles. They may be precipitated or exacerbated by exposure to cold temperatures or objects. They usually present as transient paraesthesia, dysaesthesia and hypoaesthesia. An acute syndrome of pharyngilaryngeal dysaesthesia occures in 1-2% of patients and is characterized by subjective sensations of dysphagia or dyspnea/feeling of suffocation, without any evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm (no stridor or wheezing). Other symptoms occasionally observed, particularly of cranial nerve dysfunction may be either associated with above mentioned events, or also occur isolated such as ptosis,diplopia, aphonia/dysphonia/hoarseness, sometimes described as vocal cord paralysis, abnormal tongue sensation or dysarthria, sometimes described as aphasia, trigeminal neuralgia/facial pain/eye pain, decrease of visual acuity, visual field disorders. In addition, the following symptoms have been observed: jaw spasm/muscle spasm/muscle contractions-involuntary/muscle twitching/myoclonus coordination abnormal/gaint abnormal/ ataxia/balance disorders, throat or chest tightness/pressure/ discomfort/pain.
- Dysaesthesia/paraesthesia of extremities and peripheral neuropathy.
- The limithing toxicity of Oxaliplatin is neurological. It involves a sensory peripheral neuropathy characterized by peripheral dysaesthesia and/or paraesthesia with or without cramps. Often triggered by the cold (85 to 95% of patients).
- The duration of these symptoms, which usually recede between the cycles of treatment, increases with the number of treatment cycles. The onset of pain and.or a functional disorder and their duration are indications for dose adjustment, or even treatment discontinuation. This functional disorder, including difficulties in executing delicate movements, is a possible consequence of sensory impairment. The risk of occurrency of a functional disorder for a cumulative dose of approximately 800 mg/m^2 (i.e. 10 cycles) is 15% or less. The neurological signs and symptoms improve when treatment is discontinued in the majority of cases.
- Dysgeusia - Dysarthria - Loss of deep tendon reflexes - Lhermittes' sign
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS, also known as PRES)
- **Eye disorder**
- visual acuity reduced, visual field disturbances, optic neuritis. - transient vission loss, reversible following therapy discontinuation.
- **Ear and labyrinth disorders**
- deafness
- **Respiratory, thoracic and mediastinal disorders**
- cough - hiccups - acute interstitial lung diseases, sometimes fatal; pulmonary fibrosis.
- **Gastrointestinal disorders**
- Nausea, vomiting, diarrhea. Dehydration, hypokalemia, metabolic acidosis, ileus, intestinal obsruction, renal disorders may be associated with severe diarrhea/vomiting, particularly when Oxaliplatin is combined with 5-FU
- Stomatitis/mucositis - Abdominal pain - Gastrointestinal hemorrhage - Colitis, including Clostridium difficile diarrhea - Pancreatitis
- **Renal and urinary disorder**
- Acute tubular necrosis, acute interstitial nephritis and acute renal failure
- **Skin and subcutaneous tissue disorders**
- Alopecia (<5% of patients, as a single agent)
- **Musculoskeletal and connective tissue disorders**
- Back pain. In case of such adverse reaction, hemolysis which has been rarely reported should be investigated. - Arthralgia
- **Metabolism and nutrition disorders**
- Anorexia
- **Vascular disorders**
- Epistaxis - Deep vein thrombosis -Thromboembolic events - Hypertension
- **General disorders and administration site conditions**
- Fatigue - Fever, rigors (tremors), either from infection (with or without febrile neutropenia) or possibly from immunological mechanism.
- Asthenia - Injection site reactions Injection site reactions including local pain, redness, swelling and thrombosis have been reported. Extravasation may also result in local pain and inflammation, which may be severe and lead to complications including necrosis, especially when Oxaliplatin is infused through a peripheral vein.
- **Immune system disorders**
- allergic reactions such as: skin rash (particularly urticaria), conjunctivities, rhinitis - anaphylactic reactions including bronchospasm, angioedema, hypotension, sensation of chest pain and anaphylactic, sensation of chest pain and anaphylactic shock.
- **Hepatobiliary disorders**
- Liver sinusoidal obstruction syndrome, also known as veno-occlusive disease of live, or pathological manifestations related to such liver disorder, including peliosis hepatic, nodular regenerative hyperplasia, perisinusodal fibrosis. Clinical manifestations may be portal hypertension and/or increased transaminases.

Combination therapy of Oxaliplatin with 5-FU/FA (Folfox) and Bevacizumab
The safety of first line oxaliplatin combines with 5-FU/FA and Bevacizumab was evaluated in 71 patients with metastatic colorectal cancer (TREE study). In addition to the adverse events expected with FOLFOX regimen, adverse events reported with FOLFOX/Bevacizumab combinition included bleeding (45.1;G3/4: 2.8%), proteinuria (11.3%; G3/4: 0%), impaired wound healing (5.6%), gastrointestinal perforation (4.2%) and hypertension (1.4%; G3/4: 1.4%).

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.

Dosage :
As directed by the physician.

Instructions :
Store below 30°C. Protect from heat & light. Keep all medicines out of the reach of children. To be sold on prescription only.

How to supplied:
PLAXINOL 50mg/10ml Injection 1vial

پلیگزینول

اوگزالی پلاٹن (یوایس پی)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ہدایات: 30 ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی اور روشنی سے بچائیں۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔
صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

Manufactured by :
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