(PRES) has been reported literatures for patients treated with oxaliplatin and 5-FU/LV although the cause/effect relationship cannot be established with certainty.

WARNING(S) & PRECAUTION(S)

General precautions for the patient

Before using XYLOTIN™ it is recommended to

inform the doctor and pharmacist what prescription and nonprescription medications, vitamins, nutritional supplements, and herbal products you are taking or plan to take including the use of oral anticoagulants ('blood thinners') such as warfarin. The treating doctor may need to change the doses of your medications or monitor you carefully for side effects.

inform your doctor if you have or have ever had kidney disease.

inform your doctor if you are pregnant or plan to become pregnant. Oxaliplatin may harm the fetus. You are advised to use birth control to prevent pregnancy during treatment with oxaliplatin. Talk to the doctor about the types of birth control that will work for you. If you become pregnant while taking oxaliplatin call upon your doctor.

You are advised to not breastfeed during treatment with oxaliplatin.

Inform the doctor or the dentist if you are having surgery, including dental surgery.

Stay away from people who are sick during your treatment with oxaliplatin as it may decrease your ability to fight infection.

Refrain from eating or drinking anything colder than room temperature, touch any cold objects, go near air conditioners or freezers, wash your hands in cold water, or go outside in cold weather unless absolutely necessary for five days after you receive each dose of oxaliplatin. You should know that exposure to cold air or objects may aggravate some of the side effects of oxaliplatin. If you must go outside in cold weather, wear a hat, gloves, and a scarf, and cover your mouth and nose.

General

No studies have been performed to co-relate the effects of the treatment to the ability to drive and operate machinery. However treatment with XYLOTIN™ may result in an increased risk of dizziness, nausea, vomiting, neurologic gait and balance disorders which may influence the ability to drive and operate machinery. Vision abnormalities, in particular transient vision loss (reversible following therapy discontinuation) have been reported with oxaliplatin administration. Transient blindness episodes may last for periods of seconds or minutes and may recur repeatedly during the event duration (usually hours to days). Therefore, patients should be warned of the potential effect of these events on the ability to drive or operate machinery.

Carcinogenesis and Mutagenesis

Oxaliplatin Injection has been shown to be mutagenic and clastogenic in mammalian test systems *in vitro* and *in vivo*. The teratogenic potential of oxaliplatin injection has been manifested by the embryonic mortality, decreased fetal weight and delayed ossifications in rats at doses up to 12 mg/m^2/day which is approximately 1/6th of the daily recommended human dose. Related compounds with similar mechanism of action and genotoxicity profiles have been reported to be teratogenic. Oxaliplatin Injection may increase the risk of genetic defects or fetal malformations and thus oxaliplatin injection is contraindicated in pregnancy, and males are advised not to father a child during treatment and up to 6 months thereafter. Because oxaliplatin injection may cause irreversible infertility, men are advised to seek counseling on sperm storage before starting treatment. Carcinogenicity studies have not been performed with oxaliplatin injection. However given that oxaliplatin injection is genotoxic, it should be considered as a human carcinogen, which should be taken into consideration for the overall risk/benefit in the adjuvant setting.

Cardiovascular

No formal clinical cardiac safety studies have been carried out. Preclinical study data are limited and no standard hERG or purkinje fibre tests have been done. Cardiotoxicity was observed in dogs however no formal clinical QT studies with oxaliplatin for injection have been performed. The effect of oxaliplatin for injection in combination with 5-HT$_3$ blocker antiemetics (given as pre-medication in clinical studies) on QTc has not been formally studied. In case of grade 3 or grade 4 hypersensitivity reaction associated with hemodynamic instability (eg. bradycardia, tachycardia, hypotension, hypertension) ECG monitoring is recommended.

Gastrointestinal

Gastrointestinal toxicity, which manifests as nausea and vomiting, warrants prophylactic and/or therapeutic antiemetic therapy. Dehydration, ileus, intestinal obstruction, hypokalemia, metabolic acidosis and even renal disorders may be associated with severe diarrhea/emesis particularly when combining oxaliplatin for injection with 5-FU. In rare cases colitis, including *Clostridium difficile* diarrhea may occur. Patients ought to be adequately informed of the risk of diarrhea/emesis after oxaliplatin for injection/5-FU administration in order to contact the treating physician for appropriate management.

Hematologic

Patients must be adequately informed of the risk of neutropenia after oxaliplatin injection/5-FU administration in order to contact the treating physician for appropriate management. Thrombocytopenia is commonly seen with oxaliplatin injection combination therapy although the risk of grade 3 or 4 bleeding is low. Anemia (rarely presenting as hemolytic uremic syndrome) may also occur.

Hepatic/Biliary/Pancreatic

Routine monitoring of liver function should be performed on all patients receiving oxaliplatin injection. Hepatotoxicity with the use of oxaliplatin injection plus 5-FU/LV has been noted in clinical studies. Hepatic vascular disorders should be considered and if appropriate should be investigated in cases of abnormal liver function test results or portal hypertension which cannot be explained by liver metastases. There is evidence

that oxaliplatin injection causes liver sinusoidal obstruction syndrome also known as veno-occlusive disease of the liver which on liver biopsy is manifested as peliosis, nodular regenerative hyperplasia and perisinusoidal fibrosis.

Immune

Hypersensitivity, anaphylactic reactions and/or allergic reactions are reported with the use of oxaliplatin injection. In postmarketing experience, some cases of anaphylaxis have been reported fatal. These allergic reactions may occur within minutes of oxaliplatin injection administration and can include rashes, urticaria, erythema, pruritis and rarely bronchospasm and hypotension. Patients with a history of allergic reaction to platinum compounds should be monitored for allergic symptoms. In case of an anaphylactic like reaction to XYLOTIN™, the infusion should be immediately discontinued and appropriate symptomatic treatment initiated. These reactions can usually be managed with epinephrine, corticosteroid, and antihistamine therapy. XYLOTIN™ rechallenge is contraindicated.

Neurologic

Oxaliplatin Injection is consistently associated with two types of sensory neuropathy:

(1) An acute, reversible, sensory peripheral neuropathy can develop which usually resolves between cycles, but frequently recurs with further cycles. Symptoms may be precipitated or exacerbated by exposure to cold temperatures or objects. The symptoms usually present as transient paresthesias, dysesthesias and hypoesthesias in the hands, feet, perioral area or throat. Other symptoms occasionally observed include abnormal tongue sensation, dysarthria, eye pain and throat or chest tightness. In addition, acute motor symptoms, including jaw spasms, muscle spasms, involuntary muscle contractions, ptosis, vocal cord paralysis and cranial nerve dysfunction have been reported. Acute syndrome of pharyngolaryngeal dysesthesia may occur in few 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). Because cold temperatures can precipitate or exacerbate acute neurological symptoms, ice (mucositis prophylaxis) should be avoided during XYLOTIN™ infusion.

(2) A persistent peripheral sensory neuropathy can develop characterised by paresthesias, dysesthesias and/or hypoesthesias, and may include deficits in proprioception, thus resulting in difficulties performing activities of daily living (ADLs). The probability of developing peripheral sensory neuropathy is dependent upon the cumulative dose of oxaliplatin administered. These symptoms may improve in some patients upon discontinuation of oxaliplatin injection.

NCI CTC grading definitions

Grade	Definition
Grade 0	No change or none
Grade 1	Mild paresthesias, loss of deep tendon reflexes
Grade 2	Mild or moderate objective sensory loss, moderate paresthesias
Grade 3	Severe objective sensory loss or paresthesias that interfere with function

Sensory peripheral neurotoxicity of oxaliplatin injection should be carefully monitored, especially if coadministered with other medications with specific neurological toxicity.

Respiratory

Oxaliplatin Injection has been uncommonly associated with pulmonary fibrosis/interstitial lung disease. In case of unexplained respiratory symptoms such as non-productive cough, dyspnea, crackles, or radiological pulmonary infiltrates, oxaliplatin injection should be discontinued until further pulmonary investigation excludes interstitial lung disease. Fatal cases of interstitial lung disease have been reported in the post-market setting.

Skin

In case of XYLOTIN™ extravasation, the infusion must be stopped immediately and usual local symptomatic treatment initiated. Extravasation of XYLOTIN™ may result in local pain and inflammation that may be severe and lead to complications, including necrosis and injection site reaction, including redness, swelling, and pain. In the literature, tissue necrosis has been reported with oxaliplatin injection extravasation.

Special Populations

Geriatrics (= 65 years of age): In patients previously untreated for metastatic colorectal cancer, patients = 65 years receiving oxaliplatin injection in combination with 5-FU/LV experienced more fatigue, dehydration, diarrhea, leukopenia and syncope than patients < 65 years although the difference was not statistically significant even as the starting doses were the same in both age groups. Patients = 65 years receiving the oxaliplatin injection combination therapy experienced more grade 3-4 granulocytopenia and diarrhea than patients < 65 years.

Pediatrics (= 22 years of age): The effectiveness of oxaliplatin single agent in the pediatric populations treated has not been established.

Pregnant Women: To date, there is no available information on safety of use in pregnant women. Based on preclinical findings oxaliplatin injection is likely to be lethal and/or teratogenic to the human foetus at the recommended therapeutic doses and therefore, XYLOTIN™ is contraindicated in pregnancy. As with other cytotoxic agents, effective contraceptive measures should be taken in potentially fertile patients (male and female) prior to initiating chemotherapy with XYLOTIN™.

Nursing Women: Excretion in breast milk has not been studied. Breast-feeding is contraindicated during XYLOTIN™ therapy.

Hepatic Insufficiency: No increase in oxaliplatin for injection acute toxicities has observed in the subset of patients with abnormal liver function tests at baseline. No specific dose adjustment for patients with abnormal liver function tests has been performed during clinical development.

Renal Insufficiency: The primary route of platinum elimination is renal. Clearance of ultrafilterable platinum is decreased in patients with mild, moderate and severe renal impairment. A pharmacodynamic relationship between platinum ultrafiltrate levels and clinical safety and effectiveness has not been established. XYLOTIN™ has not been studied in patients with severe renal impairment. Due to limited information on safety in patients with moderately impaired renal function, administration should be considered after suitable appraisal of the benefit/risk for the patient. In this situation, treatment may be initiated at the normally recommended dose and renal function should be closely monitored and dose adjusted according to toxicity.

Monitoring and Laboratory tests

Complete blood count with differential, hemoglobin, platelets, and blood chemistries, including ALT, AST, bilirubin, creatinine, magnesium and electrolytes should be performed prior to the start of therapy and before each subsequent course. 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 injection plus 5-FU/LV while on anticoagulants. Patients receiving oxaliplatin injection plus 5-FU/LV and requiring oral anticoagulants may require closer monitoring. Patients receiving oxaliplatin injection combination therapy should be monitored for diarrhea, vomiting, and mucositis, which can lead to severe/life-threatening dehydration. If this occurs, discontinue oxaliplatin injection until improvement or resolution. A neurological examination should be performed before each administration and periodically thereafter.

OVERDOSAGE(S)

Reports testify that patients overdosed with oxaliplatin injection experienced Grade 4 thrombocytopenia (< 25,000/mm^3) without any bleeding, dyspnea, wheezing, paresthesia, profuse vomiting, chest pain, respiratory failure, severe bradycardia, and subsequently did not respond to resuscitation efforts. Rapid onset of dysesthesia may be seen in patients mistakenly administered 700 mg dose. Inpatient supportive care includes hydration, electrolyte support, and platelet transfusion. Recovery may take 15 days after overdose. There is no known antidote for XYLOTIN™ overdose. In addition to thrombocytopenia, the anticipated complications of an XYLOTIN™ overdose include myelosuppression, nausea and vomiting, diarrhea, and neurotoxicity. Patients suspected of receiving an overdose should be monitored, and supportive treatment should be administered.

STORAGE

XYLOTIN™ (Oxaliplatin Injection) should be stored between 20-25 °C (68-77 °F); however excursions are permitted between 15-30 °C (59-86 °F). Do not freeze. For long-term storage, protect product from light (keep in original outer carton).

PRESENTATION

XYLOTIN™ is supplied in amber, glass, single use vials with elastomeric stoppers and aluminium flip-off seals containing 50 mg or 100 mg of oxaliplatin as a sterile, preservative free aqueous solutions at a concentration 2 mg/ml. Water for Injection is present as a solvent.

HANDLING & DISPOSAL

As with other potentially toxic anticancer agents care should be exercised in the handling and preparation of infusion solutions prepared from XYLOTIN™. The use of gloves is recommended. If a solution of XYLOTIN™ contacts the skin, wash the skin immediately and thoroughly with soap and water. If XYLOTIN™ 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.

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Getwell Oncology Pvt. Ltd.
(A unit of Getwell)
464, Udyog Vihar, Phase-V, Gurgaon - 122016, Haryana, India

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Getwell Pharmaceuticals
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0700DXP

GETWELL

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

Oxaliplatin Injection

XYLOTIN™

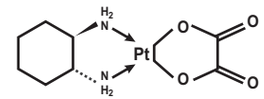
FOR I.V INFUSION AFTER DILUTION

WARNING

XYLOTIN™ should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents.
Anaphylactic Reactions, Hepatotoxicity, Myelosuppression (Neutropenia and Thrombocytopenia), Neuropathy (Sensory & Motor) and Respiratory (Interstitial lung disease including fatalities) has been reported with XYLOTIN™. Epinephrine, corticosteroids and antihistamines may be employed to alleviate anaphylactic symptoms.

DESCRIPTION

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. Oxaliplatin is chemically *cis* - [(1 R, 2 R) - 1, 2 cyclohexanediamine - N, N'] [oxalate (2) - O, O'] platinum and has the molecular formulae $C_8H_{14}N_2O_4Pt$, molecular weight 397.2858 g/mol and the following structure:



Oxaliplatin in slightly soluble in water at 6 mg/ml, very slightly soluble in methanol and practically in soluble in ethanol and acetone.
XYLOTIN™, Oxaliplatin Injection is supplied in vials containing 50 mg or 100 mg of oxaliplatin as a sterile, preservative free aqueous solution for intravenous use after dilution.

COMPOSITION

XYLOTIN™ is present in two strength's, 50 mg/25 ml and 100 mg/50 ml filled in amber glass vial.

Each ml contains

Oxaliplatin BP	2 mg
Water for Injection IP	q.s.

INDICATION(S)

XYLOTIN™ is intended to be used in combination with infusion of 5-Fluorouracil and Leucovorin Calcium and is indicated for:

adjuvant treatment of stage III (Dukes' C) colon cancer in patients who have undergone complete resection of the primary tumor. The indication is based on a demonstrated improvement in disease-free survival.

treatment of advanced metastatic colorectal cancer.

CLINICAL PHARMACOLOGY

Mode of Action

Oxaliplatin undergoes non-enzymatic conversion in physiologic solutions to active derivatives via displacement of the labile oxalate ligand. Several transient reactive species are formed, including mono-aquo and di-aquo DACH platinum, which covalently bind with macromolecules. Both inter and intra strand Pt-DNA crosslinks is 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 (5-FU), 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 & PHARMACODYNAMICS

Absorption: 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 IV infusion of oxaliplatin injection at a dose of 85 mg/m^2 expressed as ultrafilterable platinum were C_{max} of 0.814 µg/ml and volume of distribution of 440 L. Reports from studies that inter-patient and intra-patient variability in ultra filterable platinum exposure (AUC_{0-48hr}) assessed over 3 cycles was moderate to low (23 % and 6 %, respectively), however a pharmacodynamic relationship between platinum ultra filtrate levels and clinical safety and effectiveness has not been established.

Distribution: Reports testify that at the end of 2 hour infusion of oxaliplatin injection, approximately 15 % of the administered platinum is present in the systemic circulation while 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 %; majority of the 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. Studies report no platinum accumulation in plasma ultra filtrate following administration of 85 mg/m^2 dose every two weeks.

Metabolism: Oxaliplatin undergoes rapid and extensive non-enzymatic biotransformation, however there is no evidence of cytochrome P_{450} mediated metabolism *in vitro*. Studies suggest that as many as 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.

Excretion: The major route of platinum elimination is renal excretion. At five days after a single 2 hour infusion of XYLOTIN™, urinary elimination may account for about 5 % of the platinum eliminated while fecal excretion may account for only about 2 %. Reposts suggest that platinum clears 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), however no significant effect of gender on the clearance of ultra filterable platinum has been observed. The renal clearance of ultra filterable platinum is significantly correlated with GFR.

Special Populations

Pregnancy: **Category D**

Based on direct interaction with DNA, oxaliplatin injection may cause fetal harm when administered to pregnant women. There are no reports from adequate and well controlled studies of oxaliplatin use in pregnant women. Reproductive toxicity studies in rats however demonstrate adverse effects on fertility and embryo-fetal development at maternal doses that were below the recommended human dose based on body surface area. Oxaliplatin administered to pregnant rats caused developmental mortality (increased early resorptions) when administered on days 6-10 and 11-16 and adversely affected fetal growth (decreased fetal weight, delayed ossification) when administered on days 6-10. Administration of oxaliplatin to male and female rats prior to mating resulted in 97 % post implantation loss in animals at approximately 1/7th the recommended human dose based on the body surface area. Thus caution is recommended for the usage of this drug during pregnancy; if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant and use effective contraception while receiving treatment with XYLOTIN™.

Nursing mothers: It is not known whether XYLOTIN™ 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 XYLOTIN™, 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 effectiveness of oxaliplatin use in children has not been established. However studies report that oxaliplatin has been tested in various Phase I & II trials *(159 patients; age of 7 months - 22 years with solid tumors)* and no significant activity were observed. Majority of the patients received oxaliplatin for injection at 6 dose levels starting at 40 mg/m² with escalation to 110 mg/m². The dose limiting toxicity (DLT) was sensory neuropathy at the 110 mg/m² dose. Studies also report the administration of oxaliplatin for injection as 2 hour intravenous infusion on day 1 every 3 weeks (1 cycle) at 5 dose levels starting at 100 mg/m² with escalation to 160 mg/m², for a maximum of 6 cycles. Evaluation of pharmacokinetic parameters of ultrafiltrable platinum report the mean clearance in pediatric patients estimated by the population pharmacokinetic analysis as 4.7 L/h with inter-patient variability of platinum clearance in pediatric cancer patients as 41 %. The mean platinum pharmacokinetic parameters in ultrafiltrate reports C_{max} of 0.75 ± 0.24 mcg/ml, AUC_{0-48} of 7.52 ± 5.07 mcg.h/ml and AUC_{inf} of ± 1.57 mcg.h/ml at 85 mg/m² of oxaliplatin for injection and C_{max} of 1.10 ± 0.43 mcg/ml, AUC_{0-48} of ± 2.52 mcg.h/ml and AUC_{inf} of 17.3 ± 5.34 mcg.h/ml at 130 mg/m² of oxaliplatin.

Geriatric use: **Study reports suggest that n**o significant effect of age on the clearance of ultrafilterable platinum has been observed. However it has been reported that patients = 65 years of age receiving oxaliplatin for injection combination therapy experienced more grade 3-4 granulocytopenia than patients < 65 years of age (45 % vs. 39 %) and the incidence of diarrhea, dehydration, hypokalemia, leukopenia, fatigue and syncope were higher in patients = 65 years old. No adjustment to starting dose was required in patients = 65 years old.

Patients with renal impairment: The safety and effectiveness of the combination of oxaliplatin injection and 5-fluorouracil/leucovorin in patients with renal impairment have not been evaluated. The combination of oxaliplatin injection and 5-fluorouracil/leucovorin should be used with caution in patients with preexisting renal impairment since the primary route of platinum elimination is renal. Reports suggest that clearance of ultrafilterable platinum is decreased in patients with mild, moderate, and severe renal impairment. A pharmacodynamic relationship between platinum ultrafiltrate levels and clinical safety and effectiveness has not been established.

Drug-Drug Interactions: Reports suggest no pharmacokinetic interaction between 85 mg/m^2 of oxaliplatin injection and infusional 5-FU in patients treated every 2 weeks, but an increase of 5-FU plasma concentrations by approximately 20 % have been observed with oxaliplatin injection dose of 130 mg/m^2 administered every 3 weeks. *In vitro*,

platinum is not displaced from plasma proteins by the following medications: erythromycin, salicylate, sodium valproate, granisetron, and paclitaxel. *In vitro*, oxaliplatin is not metabolized by nor does it inhibit human cytochrome P450 isoenzymes. No P450 mediated drug-drug interactions are therefore anticipated in patients. Since platinum containing species are eliminated primarily through the kidney, clearance of these products may be decreased by co-administration of potentially nephrotoxic compounds, although this has not been specifically studied.

DOSAGE AND ADMINISTRATION

XYLOTIN™ (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.

It is recommended that XYLOTIN™ be administered in combination with 5-FU/LV 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: XYLOTIN™ 85 mg/m^2 IV infusion in 250-500 ml 5 % Dextrose Injection, IP and leucovorin 200 mg/m^2 IV infusion in Dextrose Injection, IP 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 minutes, followed by 5-FU 600 mg/m^2 IV infusion in 500 ml Dextrose Injection, IP (recommended) as a 22 hour continuous infusion. *Day 2:* Leucovorin 200 mg/m^2 IV infusion over 120 minutes, followed by 5-FU 400 mg/m^2 IV bolus given over 2-4 minutes, followed by 5-FU 600 mg/m^2 IV infusion in 500 ml Dextrose Injection, IP (recommended) as a 22 hour continuous infusion. The administration of XYLOTIN™ does not require prehydration. Premedication with antiemetics, including 5-HT$_3$ blockers with or without dexamethasone is recommended.

Dose modifications

These may be recommended prior to subsequent therapy cycles and patients should be evaluated for clinical toxicities and recommended laboratory tests. Prolongation of infusion time for XYLOTIN™ from 2-6 hours may mitigate acute toxicities; however the infusion times for 5-FU and leucovorin not need be changed.

Adjuvant therapy in patients with stage III colon cancer: Neuropathy and other toxicities are usually 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 XYLOTIN™ to 75 mg/m^2 may need to be considered. For patients with persistent Grade 3 neurosensory events, discontinuing the therapy should be considered. The infusional 5-FU/LV regimen however need not be altered. A dose reduction of XYLOTIN™ to 75 mg/m^2 and infusional 5-FU 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 the neutrophil count = 1.5 × 109/L and the platelet count = 75 × 109/L.

Dose modifications in therapy in previously treated and untreated treated patients with advanced colorectal cancer: *In such patients n*europathy is graded using study-specific neurotoxicity scale while other toxicities are 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 XYLOTIN™ to 65 mg/m^2 is considered and for patients with persistent Grade 3 neurosensory events, discontinuing the therapy is considered however 5- FU/LV regimen need not be altered. A dose reduction of XYLOTIN™ to 65 mg/m^2 and 5-FU 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 the neutrophil count = 1.5 × 109/L and the platelet count = 75 × 109/L.

Preparation of infusion solution

Protect the concentrated solution from light. Do not freeze.

Sodium Chloride solution or other chloride containing solutions must never be used for dilution.

The solution must be further diluted in an infusion solution of 250-500 ml 5 % Dextrose Injection IP. After dilution with 250-500 ml of 5 % Dextrose Injection IP, the shelf life is 6 hours at room temperature 20-25^0 C (68-77^0 F), or upto 24 hours under refrigeration 2-8^0 C (36-46^0 F). The diluted solution need not the protected from light.

XYLOTIN™ 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 Water for 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 intravenousadministration sets containing aluminum parts that may come in contact with XYLOTIN™ should not be used for the preparation or mixing of the drug. Aluminum has been reported to cause degradation of platinum compounds.

CONTRAINDICATION(S)

XYLOTIN™ should not be administered to patients with a history of known allergy to oxaliplatin injection or other platinum compounds. 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, 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 include urticaria, pruritus, flushing of the face, diarrhea associated with oxaliplatin infusion, shortness of breath, bronchospasm, diaphoresis, chest pains, hypotension, disorientation and syncope. These reactions can usually be managed with standard epinephrine, corticosteroid, antihistamine therapy, and may require discontinuation of therapy. Drug related deaths associated with platinum compounds from anaphylaxis have also been reported.

ADVERSE REACTION(S)

Both 5-FU and oxaliplatin are associated with gastrointestinal and hematologic adverse events. When oxaliplatin is administered in combination with 5-FU, the incidence of these events is increased. The most common adverse reactions in patients treated with oxaliplatin in combination with 5-FU for adjuvant colon and metastatic colorectal cancer trials are peripheral sensory neuropathies, fatigue, thrombocytopenia, anemia, neutropenia, nausea, vomiting, diarrhea, stomatitis and increase in hepatic enzymes and alkaline phosphatase.

Blood and Lymphatic system disorders: Anemia, neutropenia and thrombocytopenia are reported for the combination of oxaliplatin and infusional 5-FU/LV. Events of bleeding in the oxaliplatin plus 5-FU/LV are infrequent but may include epistaxis, rectal bleeding, melena, vaginal bleeding, hematuria, and hemoptysis. The incidence of thrombocytopenia in patients previously treated for metastatic colorectal cancer is also reported to be higher in the oxaliplatin plus 5-FU/LV treatment vs. the 5-FU/LV therapy. Hemolytic uremic syndrome has been rarely reported with the use of oxaliplatin.

Gastrointestinal disorders: Anorexia, nausea, vomiting, diarrhea, stomatitis/mucositis and abdominal pain are commonly reported in the adjuvant treatment of patients with colon cancer and in previously untreated and treated patients for metastatic colorectal cancer. Dehydration, hypokalemia, metabolic acidosis, ileus, intestinal obstruction and renal disorders may be associated with severe diarrhea or vomiting, particularly when oxaliplatin is combined with 5-FU.

General disorders and administration site conditions: Fever and rigors (tremors) either from infection (with or without febrile neutropenia) or possibly from immunological mechanism have been reported in the adjuvant treatment of patients with colon cancer and in the previously untreated and treated patients for metastatic colorectal cancer.

Injection site reactions include local pain, redness, swelling and thrombosis. Literatures suggest tissue necrosis with oxaliplatin extravasation.

Immune system disorders: Allergic reactions such as skin rash (particularly urticaria), conjunctivitis, rhinitis and anaphylactic reactions have been reported.

Musculoskeletal and Connective tissue disorders: Back pain has been reported in patients receiving oxaliplatin plus 5-FU/LV as adjuvant therapy and in the previously treated patients for metastatic colorectal cancer. In case of such adverse reaction, hemolysis (as part of Hemolytic Uremic Syndrome) which is rarely reported should be investigated.

Nervous system disorders: Oxaliplatin Injection is frequently associated with acute and chronic sensory peripheral neuropathy. However there have been very rare reports of symptoms compatible with a diagnosis of Guillain-Barre Syndrome, for which a causal relationship has not been established. Peripheral sensory neuropathy has been reported in patients on adjuvant treatment with the oxaliplatin combination, however in patients previously untreated and treated for metastatic colorectal cancer, neuropathy has been reported.

Peripheral / *Acute sensory neuropathy: These symptoms* usually develop at the end of 2 hour oxaliplatin infusion or within a few hours and abate spontaneously within the next hours or days but may frequently recur with further cycles. These may be precipitated or exacerbated by exposure to cold temperatures or objects and are usually present as transient paresthesia, dysesthesia and hypoesthesia. Acute syndrome of pharyngolaryngeal dysesthesia may occurs in few patients and these are 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).

Dysesthesia / paresthesia of extremities and peripheral neuropathy: The dose limiting toxicity of oxaliplatin is neurological and involves sensory peripheral neuropathy characterised by peripheral dysesthesia and or paresthesia with or without cramps, often triggered by cold (in 85 - 95 % of patients) temperature. 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 includes difficulty in executing delicate movements and is a possible consequence of sensory impairment. These neurological signs and symptoms improve when treatment is discontinued in the majority of cases.

Other neurologic manifestations occasionally observed include cranial nerve dysfunction which may occur as a single, isolated event or several events may occur in combination. These include ptosis, diplopia, aphonia, dysphonia, hoarseness sometimes described as vocal cord paralysis, abnormal tongue sensation or dysarthria sometimes described as aphasia, trigeminal neuralgia, facial pain, fasciculations, eye pain, decrease of visual acuity, visual field disorders, transient blindness (reversible following therapy discontinuation), amaurosis and amaurosis fugax. In addition jaw spasm, muscle spasms, involuntary muscle contractions, muscle twitching, myoclonus, abnormal coordination, abnormal gait, ataxia, balance disorders and throat or chest tightness/pressure/ discomfort/pain may be observed

Skin and Subcutaneous tissue disorders: Alopecia in patients receiving oxaliplatin has been reported across clinical studies worldwide, most cases being mild hair loss only.

Body as a whole - general disorders: chest pain

Central & Peripheral nervous system disorders: dizziness

Metabolic/laboratory: magnesium levels were not prospectively tested

Psychiatric disorders: insomnia

Respiratory system disorders: coughing

Vision disorders: abnormal lacrimation

White cell and Reticulo-endothelial system disorders: leukopenia

In patients previously untreated for metastatic colorectal cancer the following additional most common and potentially important adverse events regardless of treatment causality are reported in less than 5 % of the patients previously untreated for metastatic colorectal cancer with oxaliplatin for injection and 5- FU/LV combination.

Cardiovascular: hypertension, hypotension, prothrombin time

Dermatology/skin: nail changes, pigmentation changes, urticaria

Gastrointestinal: gastrointestinal not otherwise specified (NOS)

Hemorrhage: rectal bleeding

Infection/febrile neutropenia: catheter infection, febrile neutropenia, unknown Infection

Metabolic/laboratory: magnesium levels were not prospectively tested

Neurology: syncope, vertigo

Pain: bone pain, chest pain, neuralgia, rectal pain

Pulmonary: hiccups, hypoxia, pneumonitis, pulmonary NOS

Renal/Genitourinary: creatinine, dysuria

In patients previously treated for metastatic colorectal cancer the following additional most common and potentially important adverse events regardless of treatment causality are reported.

Body as a whole: General Disorders*:* ascites

Cardiovascular Disorders, General*:* oedema

Central and Peripheral Nervous System Disorders: ataxia

Gastro-intestinal System Disorders*:* dry mouth, gastroesophageal reflux, tenesmus

Heart Rate and Rhythm Disorders*:* tachycardia

Metabolic/laboratory: magnesium levels were not prospectively tested

Musculo-Skeletal System Disorders*:* bone pain

Platelet, Bleeding and Clotting Disorders*:* bruise, deep thrombophlebitis, melena, rectal hemorrhage

Respiratory System Disorders*:* pneumonia

Skin and Appendage Disorders*:* dry skin, erythematous rash, pruritus, skin disorder

Vision Disorders*:* abnormal vision, conjunctivitis

White Cell and Reticulo-Endothelial System Disorders*:* febrile neutropenia

Other adverse drug reactions reported in Clinical Trial's

Blood and Lymphatic system disorders - *Rare:* hemolysis

Ear and Labyrinth disorders - *Rare:* deafness.

Eye disorders - *Rare:* visual acuity reduced transiently, optic neuritis, transient vision loss reversible following therapy discontinuation, visual field disturbances. Severalcases of positive rechallenge associated with subsequent cycles of chemotherapy were reported indicating probable causal relationship to oxaliplatin.

Gastrointestinal disorders - *Very common:* Dehydration, hypokalemia, metabolic acidosis, ileus, intestinal obstruction, renal disorders may be associated with severe diarrhea/vomiting, particularly when XYLOTIN™ is combined with 5-FU. *Common:* gastrointestinal hemorrhage *Rare:* colitis, including *Clostridium difficile* diarrhea

General disorders and administration site conditions - *Very common:* asthenia. Extravasation may also result in local pain and inflammation, which may be severe and lead to complications including necrosis, especially when oxaliplatin for injection is infused through a peripheral vein.

Hepatobiliary disorders - *Rare:* pancreatitis. *Very rare:* hepatic failure, hepatitis, liver sinusoidal obstruction syndrome, also known as venoocclusive disease of liver, or pathological manifestations related to such liver disorder, including nodular regenerative hyperplasia, peliosis hepatis, perisinusoidal fibrosis. Clinical manifestations of this syndrome may be portal hypertension and/or increased transaminases.

Immune system disorders - *Common*: anaphylactic reactions including bronchospasm, sensation of chest pain, angioedema, hypotension, anaphylactic shock. *Rare:* immuno-allergic hemolytic anemia, immuno-allergic thrombocytopenia.

Nervous system disorders - *Very common:* acute neuro-sensory manifestations, dysesthesia, paresthesia of extremities and peripheral neuropathy. *Rare*: dysarthria, Lhermitte's sign, loss of deep tendon reflexes. *Very rare:* Reports of symptoms compatible with a diagnosis of Guillain-Barre Syndrome. Causal relationship has not been established.

Renal and urinary disorders - *Very rare*: acute tubular necrosis, acute interstitial nephritis and acute renal failure were reported.

Respiratory, Thoracic and Mediastinal disorders - *Rare:* acute interstitial lung diseases (including fatalities), pulmonary fibrosis.

Vascular disorders - *Common:* hypertension, thromboembolic events, including deep vein thrombosis.

Post market adverse drug reactions reported from worldwide post marketing experience include

Blood and Lymphatic system disorders: hemolytic uremic syndrome.

Eye disorders: amaurosis, amaurosis fugax. Cases of positive rechallenge associated with subsequent cycles of chemotherapy reports indicate probable causal relationship to oxaliplatin. Few cases of optic ischemic neuropathy are reported without established causal relationship.

Metabolism and Nutrition disorders: Hypomagnesemia.

Musculoskeletal and Connective tissue disorders: Rhabdomyolysis.

Nervous system disorders: convulsion. Posterior reversible encephalopathy syndrome