เอกสารกำกับยาภาษาอังกฤษ

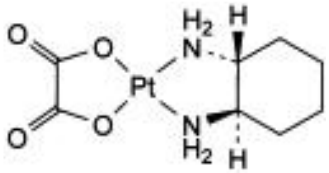
Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion

PRODUCT NAME

Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion

DESCRIPTION

Oxaliplatin is designated chemically as [*SP*-4-2]-(1R,2R)-(cyclohexane-1,2-diamine-k^2*N*,*N*′(oxalato(2-)-K^2*O*^{1},*O*^{2}]platinum (II).



The empirical formula of oxaliplatin is $C_8H_{14}N_2O_4Pt$ and its molecular weight is 397.3.

CAS Number: 61825-94-3

Oxaliplatin is a white or almost white, crystalline powder. Slightly soluble in water; practically insoluble in dehydrated alcohol; very slightly soluble in methyl alcohol.

Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion contains oxaliplatin, tartaric acid, sodium hydroxide and water for injections. It is clear colourless sterile solution for injection.

PHARMACOLOGY

Pharmacodynamics

Oxaliplatin is an antineoplastic drug belonging to a new class of platinum based compounds in which the platinum atom is complexed with 1,2-diaminocyclohexane (DACH) and an oxalate group. Oxaliplatin is a single enantiomer, the Cis-[oxalato(trans-*l*-1,2-DACH) platinum].

Oxaliplatin exhibits a wide spectrum of both *in vitro* cytotoxicity and *in vivo* antitumour activity in a variety of tumour model systems, including human colorectal cancer models. Oxaliplatin also demonstrates *in vitro* and *in vivo* activity in various cisplatin resistant models.

A synergistic cytotoxic action has been observed in combination with fluorouracil both *in vitro* and *in vivo*.

Studies on the mechanism of action of oxaliplatin, although not completely elucidated, show that the aqua-derivatives resulting from the biotransformation of oxaliplatin interact with DNA to form both inter- and intra-strand cross links, resulting in the disruption of DNA synthesis leading to cytotoxic and antitumour effects.

Pharmacokinetics

The pharmacokinetics of individual active compounds have not been determined. The pharmacokinetics of ultrafiltrable platinum, representing a mixture of all unbound, active and inactive platinum species, following a two hour infusion of oxaliplatin at 130 mg/m^2 every three weeks for one to five cycles and at 85 mg/m^2 every two weeks for one to three cycles are as follows:

Summary of platinum pharmacokinetic parameter estimates in ultrafiltrate following multiple doses of oxaliplatin at 85 mg/m^2 every two weeks or at 130 mg/m^2 every three weeks

Dose	C_{max} (µg/mL)	AUC_{0-48} (µg/mL.h)	AUC_{0-inf} (µg/mL.h)	$t_{1/2}\alpha$ (h)	$t_{1/2}\beta$ (h)	$t_{1/2}\gamma$ (h)	V_{ss} (L)	CL (L/h)
85 mg/m^2 Mean	0.814	4.19	4.68	0.43	16.8	391	440	17.4
SD	0.193	0.647	1.40	0.35	5.74	406	199	6.35
130 mg/m^2 Mean	1.21	8.20	11.9	0.28	16.3	273	582	10.1
SD	0.10	2.40	4.60	0.06	2.90	19.0	261	3.07

Mean AUC_{0-48}, C_{max} values were determined on Cycle 3 (85 mg/m^2) or Cycle 5 (130 mg/m^2)

Mean $AUC_{0-\infty}$, V_{ss} and CL values were determined on Cycle 1

C_{max}, AUC, AUC_{0-48}, V_{ss} and CL values were determined by non-compartmental analysis

$t_{½}\alpha$, $t_{½}\beta$ and $t_{½}\gamma$ were determined by compartmental analysis (Cycles 1-3 combined)

At the end of a 2-hour infusion, 15% of the administered platinum is present in the systemic circulation, the remaining 85% is rapidly distributed into tissues or eliminated in the urine.

Irreversible binding to red blood cells and plasma, results in half-lives in these matrices that are close to the natural turnover of red blood cells and serum albumin. No platinum accumulation was observed in plasma ultrafiltrate following 85 mg/m^2 every two weeks or 130 mg/m^2 every three weeks and steady state was attained by cycle one in this matrix. Inter- and intra-subject variability is generally low.

Biotransformation *in vitro* is considered to be the result of non-enzymatic degradation and there is no evidence of cytochrome P450-mediated metabolism of the diaminocyclohexane (DACH) ring.

Oxaliplatin undergoes extensive biotransformation in patients, and no intact drug was detectable in plasma ultrafiltrate at the end of a 2 hour infusion. Several cytotoxic biotransformation products including the monochloro, dichloro and diaquo DACH platinum species have been identified in the systemic circulation together with a number of inactive conjugates at later time points.

Platinum is predominantly excreted in urine, with clearance mainly in the 48 hours following administration. By day 5, approximately 54% of the total dose was recovered in the urine and < 3% in the faeces.

A significant decrease in clearance of ultrafilterable platinum from 17.6 ± 2.18 L/h to 9.95 ± 1.91 L/h in renal impairment (creatinine clearance 12-57 mL/min) was observed together with a statistically significant decrease in distribution volume from 330 ± 40.9 to 241 ± 36.1 L. The effect of severe renal impairment on platinum clearance has not been evaluated.

INDICATION

• Adjuvant treatment of stage III colon cancer: In combination with infusion fluorouracil/leucovorin for adjuvant treatment of stage III colon cancer patients who have undergone complete resection of the primary tumor.
• Advanced carcinoma of the colon or rectum: In combination with infusion fluorouracil/leucovorin for the treatment of advanced carcinoma of the colon or rectum.
• Unresectable advanced or metastatic gastric cancer
• Treatment of unresectable hepatocellular carcinoma (HCC)

DOSAGE AND ADMINISTRATION

Dosage

1. Adjuvant treatment in stage III colon cancer: Recommended for a total of 6 months (i.e. 12

cycles, every 2 weeks), according to the dose schedule for previously treated patients with advanced colorectal cancer.

2. Advanced colorectal cancer (previously untreated and previously treated patients):
Day 1: oxaliplatin 85 mg/m^2 intravenous (IV) infusion in 5% dextrose in water (D5W) 250 to 500 ml 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 fluorouracil 400 mg/m^2 IV bolus given over 2 to 4 minutes, followed by fluorouracil 600 mg/m^2 IV infusion in D5W 500 ml (recommended) as a 22 hour continuous infusion.
Day 2: leucovorin 200 mg/m^2 IV infusion over 120 minutes, followed by fluorouracil 400 mg/m^2 IV bolus given over 2 to 4 minutes, followed by fluorouracil 600 mg/m^2 IV infusion in D5W 500 ml (recommended) as a 22 hour continuous infusion.
Repeat cycle every 2 weeks.

3. Unresectable advanced or metastatic gastric cancer
- 100 mg/m^2 intravenously repeated every two weeks in combination with infusional 5-FU and folinic acid
- 85 mg/m^2 intravenously (FLO regimen) every 2 weeks in combination with fluorouracil 2,600 mg/m^2 and leucovorin 200 mg/m^2
- 85 mg/m^2 intravenously (Modified FOLFOX regimen) every 2 weeks in combination with fluorouracil 1,000 mg/m^2 and leucovorin 200 mg/m^2
- 130 mg/m^2 intravenously (EOX or EOF regimen) every 3 weeks cycle in combination with Epirubicin 50 mg/m^2 and Capecitabine 625 mg/m^2 or fluorouracil 200 mg/m^2

4. The recommended dose of oxaliplatin in combination with fluorouracil and folinic acid (FOLFOX) in the treatment of unresectable hepatocellular carcinoma is 85 mg/m^2 intravenously, repeated every 2 weeks until disease progression or unacceptable toxicity.

Premedication

Premedication with antiemetics, including 5-HT3 blockers with or without dexamethasone, is recommended.

Dosage Modification

Prior to subsequent therapy cycles, patients should be evaluated for clinical toxicities and laboratory tests. Prolongation of infusion time for oxaliplatin from 2 to 6 hours decreased the maximum drug

concentration (C_{max}) by an estimated 32% and may mitigate acute toxicities. The infusion times for infusional fluorouracil and leucovorin do not need to be changed.

Adjuvant therapy in stage III colon cancer: For patients who experience persistent grade 2 neurosensory events that do not resolved, 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 fluorouracil/leucovorin regimen need not be altered.

A dose reduction of oxaliplatin to 75 mg/m^2 and infusional fluorouracil to 300 mg/m^2 bolus and 500 mg/m^2 22-hour infusion is recommended for patients after recovery from grade ¾ GI (despite prophylactic treatment) or grade 4 neutropenia or grade ¾ thrombocytopenia. The next dose should be delayed until neutrophils are 1.5 x 10^9/L or more and platelets are 75 x 10^9/L or more.

Advanced colorectal cancer (previously untreated and previously treated patients): 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 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 and 500 mg/m^2 22-hour infusion) is recommended for patients after recovery from grade ¾ GI (despite prophylactic treatment), grade 4 neutropenia, or grade ¾ thrombocytopenia. The next dose should be delayed until: neutrophils are greater than or equal to 1.5 x 10^9/L and platelets are greater than or equal to 75 x 10^9/L.

Preparation and Administration:

Special precautions for administration:

• DO NOT use any injection material containing aluminium
• DO NOT administer undiluted
• DO NOT mix or administer with sodium chloride injection or any other solution containing chlorides
• DO NOT mix with any other medication or administer simultaneously by the same infusion line (in particular fluorouracil and folinic acid). A Y-tube may be used
• USE ONLY the recommended diluents

Any reconstituted solution that shows evidence of precipitation should not be used and should be

destroyed.

Handling:

Procedure for proper handling of anti-cancer medicines should be considered.

- The handling of this cytotoxic agent by health care personnel requires every precaution to guarantee the protection of the handler and their surroundings. It is essential to use appropriate protective clothing, including protective goggles, mask and gloves.
- Direct contact may cause irritation of the skin, eyes and mucous membrane.

If oxaliplatin concentrate, premixed solution or infusion solution should come into contact with skin, mucous membranes or eyes, wash immediately and thoroughly with water.

- Safe and aseptic handling of parenteral chemotherapeutic drug by medical personnel involved in preparation and administration of these agents is mandatory.
- Potential risks from repeated contact with parenteral antineoplastics can be controlled by a combination of specific containment equipment and proper work techniques.
- Excess drug should be returned to the drug vial or discarded into a closed container. Placing excess drug in any type of open container, even while working in the biohazard cabinet, is inappropriate.
- All contaminated materials should be placed in leakproof, puncture-resistant containers within the biohazard cabinet and then placed in larger containers outside the biohazard cabinet for disposal. To minimize aerosolization, needles should be discarded in puncture-resistant containers without being clipped.
- Pregnant women must be warned to avoid handling cytotoxic agents.

Preparation of Infusion Solution:

(i) Oxaliplatin injection vials contain no preservative and are for single use only. Discard any remaining contents.

(ii) Dilution before Infusion

The reconstituted solution must be further diluted in an infusion solution of 250-500 mL of 5% glucose injection. From a microbiological and chemical point of view, this infusion preparation should be used immediately. Inspect visually prior to use. Only clear solutions without particles should be used. The product is for single use only. Discard any remaining contents. **NEVER** use sodium chloride solution for either reconstitution or dilution.

Infusion:

- The administration of oxaliplatin does not require prehydration.

- Oxaliplatin diluted in 250 to 500 mL of a glucose 5% injection must be infused either by central venous line or peripheral vein over 2 to 6 hours.
- When oxaliplatin is administered with fluorouracil, the oxaliplatin infusion should precede that of fluorouracil.
- Oxaliplatin can be co-administered with folinic acid infusion using a Y-tube placed immediately before the site of injection. The medicines should not be combined in the same infusion bag. Folinic acid must be diluted using isotonic infusion solutions such as 5% glucose solution but **NOT** sodium chloride solutions or alkaline solutions.
- Flush the line after oxaliplatin administration.
- While oxaliplatin has minimal to no vesicant potential, extravasation may result in local pain and inflammation which may be severe and lead to complications especially when oxaliplatin is infused through a peripheral vein. In case of oxaliplatin extravasation, the infusion must be stopped immediately and the usual local symptomatic treatment initiated.
- To reduce microbiological hazard, use as soon as practicable after reconstitution. If storage is necessary, hold at 2°-8°C for not more than 24 hours.

Disposal:

All materials that have been used for reconstitution, for dilution and administration must be destroyed according to local statutory requirements.

CONTRAINDICATION

Oxaliplatin is contraindicated in patients who:

- have a known history of hypersensitivity to oxaliplatin, any of the excipients or other platinum compounds
- are pregnant
- are breastfeeding
- have myelosuppression prior to starting first course, as evidenced by baseline neutrophils < 1.5 x 10^9/L and/or platelet count of < 75 x 10^9/L
- have a peripheral sensory neuropathy with functional impairment prior to first course
- have severely impaired renal function (creatinine clearance less than 30 mL/min)
- if contraindications exist to any of the agents in combination regimens, that agent should not be used

PRECAUTIONS

General

Oxaliplatin should be administered only by or under the supervision of an experienced clinical oncologist.

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

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

Allergic Reactions

Hypersensitivity, anaphylactic reactions and/or allergic reactions to oxaliplatin have been reported. These allergic reactions which may be fatal and can occur within minutes of oxaliplatin injection administration are similar in nature and severity to those reported with other platinum-containing compounds, such as rash, urticaria, erythema, pruritus and rarely, bronchospasm and hypotension. Patients with a history of allergic reactions to platinum compounds should be monitored for allergic symptoms. Allergic reactions can occur during any cycle. In case of an anaphylactic-type reaction to oxaliplatin, the infusion should be immediately discontinued and appropriate symptomatic treatment initiated. Rechallenge with oxaliplatin is contraindicated. Cross reactions, sometimes fatal, have been reported with all platinum compounds.

Immunosuppressant Effects/Increased Susceptibility to Infections

Administration of live or live attenuated vaccines in patients immunocompromised by chemotherapeutic agents, 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.

Neurological Toxicity

Neurological toxicity (see **Adverse Effects**) 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. Dose modification may be required (see **DOSAGE AND ADMINISTRATION**). 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.

Patients should be informed of the possibility of persistent symptoms of peripheral sensory neuropathy after the end of the treatment. Localised moderate paraesthesias or paraesthesias that may interfere with functional activities can persist up to 3 years following treatment cessation in the adjuvant setting.

If sensory loss or paraesthesia persists longer than 7 days or interferes with function (grade 2 toxicity), reduce oxaliplatin dose by 25%.

If sensory loss or paraesthesia interferes with activities of daily living (grade 3 toxicity), oxaliplatin should be discontinued.

For patients who develop acute laryngopharyngeal dysaesthesias, during or within 48 hours following the 2-hour infusion, the next oxaliplatin infusion should be administered over 6 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.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) Cases of Reversible Posterior Leukoencephalopathy Syndrome (RPLS also known as Posterior Reversible Encephalopathy Syndrome [PRES]) have been reported in patients receiving oxaliplatin in combination chemotherapy. RPLS is a rare, reversible, rapidly evolving neurological condition. Signs and symptoms of RPLS can include headache, altered mental functioning, seizures, hypertension, confusion, neurological disturbances and abnormal vision from blurriness to blindness (see **Adverse Effects**). Diagnosis of RPLS is based upon confirmation by brain imaging, preferably MRI (Magnetic Resonance Imaging).

Gastrointestinal Toxicity

Gastrointestinal toxicity, which manifests as nausea and vomiting, warrants prophylactic anti-emetic therapy, including 5-HT3 antagonists and corticosteroids. Dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis, particularly when combining oxaliplatin with fluorouracil (see **Dosage and Administration**).

Intestinal Ischaemia

Cases of intestinal ischaemia, including fatal outcomes, have been reported with oxaliplatin

treatment. In case of intestinal ischaemia, oxaliplatin treatment should be discontinued and appropriate measures initiated (see **Adverse Effects**).

Haematological Toxicity

Monitor haematological toxicity with a full blood count and white cell differential count prior to starting therapy and before each subsequent course. Idiosyncratic haematological toxicity may occur, especially in patients who have received previous myelotoxic treatment (see **Dosage and Administration**). If severe/life threatening diarrhoea, severe neutropenia, febrile neutropenia or severe thrombocytopenia occur, oxaliplatin must be discontinued until improvement or resolution and appropriate dose adjustments may apply.

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

Infection

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 (see **Adverse Effects**).

Disseminated Intravascular Coagulation (DIC)

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 (see **Adverse Effects**).

Pulmonary Toxicity

Oxaliplatin has been associated with pulmonary fibrosis (0.7% of study patients), which may be fatal. In the case of unexplained respiratory symptoms such as non-productive cough, dyspnoea, crackles or radiological pulmonary infiltrates, oxaliplatin should be discontinued temporarily until further pulmonary investigation excludes an interstitial lung disease or pulmonary fibrosis (see **Adverse Effects**).

Haemolytic-Uraemic Syndrome (HUS)

Haemolytic-uraemic syndrome (HUS) is a life-threatening side effect (see **Adverse Effects**). 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.

Hepatic Toxicity

Reactions related to liver sinusoidal obstruction syndrome, including nodular regenerative hyperplasia, have been reported (see **Adverse Effects**). 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.

QT Prolongation

QT prolongation may lead to an increased risk for ventricular arrhythmias including Torsade de Pointes, which can be fatal (see **Adverse Effects**). 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 (see **Interactions with Other Medicines** and **Adverse Effects**).

Cardiac Disorders

Post-marketing reports with oxaliplatin use include acute coronary syndrome (including myocardial infarction, coronary arteriospasm, and cardiac arrest). In case of acute coronary syndrome, treatment with oxaliplatin may need to be interrupted or discontinued based on the individual benefit-risk assessment (see **Adverse Effects**).

Post-marketing reports with oxaliplatin include cardiac arrhythmias (including bradyarrhythmia, tachycardia and atrial fibrillation). In case of cardiac arrhythmias, treatment with oxaliplatin may need to be interrupted or discontinued based on the individual benefit-risk assessment (see **Adverse Effects**).

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 (see **Interactions with Other Medicines** and **Adverse Effects**).

Duodenal Ulcer

Oxaliplatin treatment can cause duodenal ulcer (DU) and potential complications, such as duodenal ulcer haemorrhage and perforation, which can be fatal. In case of duodenal ulcer, oxaliplatin treatment should be discontinued and appropriate measures taken (see **Adverse Effects**).

Off-label Route of Administration

Do not use oxaliplatin intraperitoneally. Peritoneal hemorrhage may occur when oxaliplatin is administered by intraperitoneal route (off-label route of administration).

Renal Impairment

Oxaliplatin has not been studied in patients with severe renal impairment. It is therefore contraindicated in patients with severe renal impairment.

There is limited information on safety in patients with moderately impaired renal function, and administration should only be considered after suitable appraisal of the benefit/risk for the patient, however, treatment may be initiated at the normally recommended dose. In this situation, renal function should be closely monitored and dose adjusted according to toxicity.

There is no need for dose adjustment in patients with mild renal dysfunction.

Hepatic Insufficiency

Oxaliplatin has not been studied in patients with severe hepatic impairment. No increase in oxaliplatin acute toxicities was observed in the subset of patients with abnormal liver function tests at baseline. No specific dose adjustment for patients with abnormal liver function tests was performed during clinical development.

Carcinogenicity, Mutagenicity and Impairment of Fertility

Oxaliplatin was shown to be mutagenic and clastogenic in mammalian test systems *in vitro* and *in vivo.* The carcinogenic potential of oxaliplatin has not been studied, but compounds with similar mechanisms of action and genotoxicity profiles have been reported to be carcinogenic. Oxaliplatin should be considered a probable carcinogen.

In dogs dosed with oxaliplatin, a decrease in testicular weight accompanied with testicular hypoplasia approaching aplasia was seen at doses ≥15 mg/m^2. However, no effects on fertility were seen in male and female rats at doses up to 12 mg/m^2/day for 5 days/cycle.

Contraception in males and females

Based on reproductive toxicity and genetic toxicity findings, women of childbearing potential should be advised to use effective contraception during treatment with oxaliplatin and for at least 9 months after the last dose.

Based on genetic toxicity findings, male patients with female partners of childbearing potential should be advised to use effective contraception during treatment with oxaliplatin and for at least 6 months after the last dose.

Use in Pregnancy

Category D[1]

Reproductive toxicity studies showed no teratogenic activity in rats or rabbits at intravenous doses up to 6 and 9 mg/m^2/day respectively (1/20 of the maximum recommended clinical dose, based on body surface area). However, increased embryonic deaths, decreased foetal weight and delayed ossifications were observed in rats. Related compounds with similar mechanisms of action have been reported to be teratogenic. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Oxaliplatin is probably toxic to the human fetus at the recommended therapeutic dose, and is therefore contraindicated during pregnancy. Oxaliplatin is not recommended in women of childbearing potential not using contraceptive measures.

As with other cytotoxic agents, effective contraceptive measures should be taken in potentially fertile patients prior to initiating chemotherapy with oxaliplatin.

Use in Lactation

There are no data on the excretion of oxaliplatin into milk of animals or humans. Oxaliplatin is

[1] *Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.*

contraindicated in breast feeding women and for 3 months after the last dose.

Children

Oxaliplatin is not recommended for use in children as safety and efficacy have not been established in this group of patients.

Elderly

No increase in severe toxicities was observed when oxaliplatin was used as a single agent or in combination with fluorouracil in patients over the age of 65. In consequence no specific dose adaptation is required for elderly patients.

Interactions with Other Medicines

In patients who have received a single dose of 85 mg/m^2 of oxaliplatin, immediately before administration of fluorouracil, no change in the level of exposure to fluorouracil has been observed. However, in patients dosed with fluorouracil weekly and oxaliplatin 130 mg/m^2 every 3 weeks, increases of 20% in fluorouracil plasma concentrations have been observed.

In vitro, little or no displacement of oxaliplatin binding to plasma proteins has been observed with the following agents; erythromycin, salicylates, granisetron, paclitaxel, and sodium valproate.

Oxaliplatin is incompatible with chloride containing solutions and basic solutions (including fluorouracil), therefore oxaliplatin should not be mixed with these or administered simultaneously via the same IV line. There is no data for compatibility with other medicines.

The lack of Cytochrome P450 mediated metabolism indicates that oxaliplatin is unlikely to modulate the P450 metabolism of concomitant medications through a competitive mechanism.

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 (see **Precautions**).

Caution is advised when oxaliplatin treatment is administered concomitantly with other medicinal products known to be associated with rhabdomyolysis (see **Precautions**).

Advice to Patients

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

Patients and caregivers should be informed of the expected side effects of oxaliplatin and, in particular, patients should be advised to:

- Avoid cold foods and drinks and cover skin prior to exposure to cold during or within 48 hours following oxaliplatin administration, since neurological effects may be precipitated or exacerbated by exposure to cold.
- Contact their doctor immediately if they develop fever, particularly in association with persistent diarrhoea or evidence of infection since this may indicate low blood count.
- Contact their doctor if persistent vomiting, diarrhoea, signs of dehydration, cough or breathing difficulties or signs of allergic reaction occur.

Vision abnormalities, in particular transient vision loss (reversible following therapy discontinuation), may affect patient's 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 EFFECTS

Note:	*very common*	≥1/10 (≥10%)
	common	≥1/100 and <1/10 (≥1% and <10%)
	uncommon	≥1/1000 and <1/100 (≥0.1% and <1.0%)
	rare	≥1/10,000 and <1/1000 (≥0.01% and <0.1%)
	very rare	<1/10,000 (<0.01%)

Neurological

	Adjuvant	**Advanced**
Very common:	Sensory peripheral neuropathy, dysgeusia, neuritis	Primarily sensory peripheral neuropathy (e.g., loss of deep tendon reflexes, dysaesthesia, paraesthesia, Lhermitte's sign), dysgeusia, neuritis
Common:		Pharyngolaryngeal dysaesthesia,

		jaw spasm, abnormal tongue sensation, feeling of chest pressure
Rare:		Dysarthria Reversible Posterior Leukoencephalopathy Syndrome (RPLS, also known as PRES) (see **Precautions**)

Neurological adverse effects are the dose-limiting toxicity. A primarily sensory peripheral neuropathy occurs in 85-95% of patients. These symptoms usually develop at the end of the 2-hour oxaliplatin infusion or within few hours, abate spontaneously within the next hours or days, and frequently recur with further cycles. They may be precipitated by or exacerbated by exposure to cold temperatures or objects. They usually present as transient paraesthesia, dysaesthesia and hypoaesthesia. There may be functional impairment such as difficulty in executing fine movements. The duration of symptoms increases with the number of treatment cycles. Symptoms usually recede between courses of treatment.

If symptoms persist or pain or functional impairment develops, the dose should be reduced or treatment discontinued (see **Dosage and Administration**).

Psychiatric Disorders

Common:	Depression, insomnia

Vascular Disorders

	Adjuvant	**Advanced**
Very common:	Epistaxis	Epistaxis
Common:	Deep vein thrombosis, thromboembolic events, hypertension	Deep vein thrombosis, thromboembolic events, hypertension

Common:	Hemorrhage, flushing

Infections and Infestations

Common:	Neutropenic sepsis, including fatal outcomes
Uncommon:	Sepsis, including fatal outcomes

Haematological

	Adjuvant	**Advanced**
Very common:	Epistaxis, anaemia (all grades), neutropenia (all grades), thrombocytopenia (all grades)	Anaemia (all grades), neutropenia (all grades), thrombocytopenia (all grades)
Common:	Febrile neutropenia	Febrile neutropenia
Rare:	Disseminated intravascular coagulation (DIC), including fatal outcomes	Disseminated intravascular coagulation (DIC), including fatal outcomes Autoimmune hemolytic anaemia and thrombocytopenia

Very common:	Leukopenia, lymphopenia

Gastrointestinal

	Adjuvant	**Advanced**
Very common:	Diarrhoea, nausea, vomiting, stomatitis, abdominal pain, mucositis, constipation	Diarrhoea, nausea, vomiting, stomatitis, abdominal pain, mucositis, dehydration, ileus, intestinal obstruction, hypokalemia, metabolic acidosis, constipation
Common:	Dyspepsia, gastrointestinal haemorrhage	Gastrointestinal haemorrhage
Rare:		Colitis, including *Clostridium difficile* diarrhoea

	Adjuvant	Advanced
		Pancreatitis

Common:	Gastroesophageal reflux, rectal haemorrhage

Dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis, particularly when combining oxaliplatin with fluorouracil (see **Precautions**). Rectal haemorrhage, gastro-oesophageal reflux disease and melena have been observed.

Metabolism and Nutrition Disorders

Very common:	Anorexia, hyperglycaemia, hypernatremia
Common:	Hypocalcaemia

Hepatobiliary

	Adjuvant	Advanced
Very common:	Increased bilirubin, elevation of transaminases and alkaline phosphatases activities	Increased bilirubin, elevation of transaminases and alkaline phosphatases activities
Very rare:	Reactions related to liver sinusoidal obstruction syndrome, including peliosis hepatis, nodular regenerative hyperplasia, perisinusoidal fibrosis. Clinical manifestations may be portal hypertension and/or increased transaminases.	Reactions related to liver sinusoidal obstruction syndrome, including peliosis hepatis, nodular regenerative hyperplasia, perisinusoidal fibrosis. Clinical manifestations may be portal hypertension and/or increased transaminases.

Musculoskeletal

	Adjuvant	Advanced
Very common:	Arthralgia	Back pain*, arthralgia

* Back pain. If associated with haemolysis, which has been rarely reported, should be investigated.

Common:	Bone pain

Hypersensitivity

	Adjuvant	**Advanced**
Very common:	Skin rash (particularly urticaria), conjunctivitis, rhinitis, injection site reactions	Skin rash (particularly urticaria), conjunctivitis, rhinitis, injection site reactions
Common:	Bronchospasm, sensation of chest pain, angioedema, hypotension, anaphylactic shock	Bronchospasm, sensation of chest pain, angioedema, hypotension, anaphylactic shock

Sensory

	Adjuvant	**Advanced**
Very common:	Taste perversion	
Common:	Conjunctivitis	
Uncommon:		Ototoxicity
Rare:	Deafness, optic neuritis, loss of visual acuity, visual field disturbances, transient vision loss (reversible following therapy discontinuation).	Deafness, optic neuritis, loss of visual acuity, visual field disturbances, transient vision loss (reversible following therapy discontinuation).

Renal

	Adjuvant	**Advanced**
Common:		Altered renal function
Very rare:		Renal tubular necrosis

In clinical and post-marketing setting: very rare – Acute tubular necrosis, acute interstitial nephritis and acute renal failure.

Common:	Haematuria, dysuria, micturition frequency abnormal

Respiratory

	Adjuvant	**Advanced**
Very common	Cough	Cough
Common:	Rhinitis, dyspnoea, hiccups	Hiccups
Rare:		Acute interstitial lung disease (sometimes fatal), pulmonary fibrosis

Immune system

	Adjuvant	**Advanced**
Very common:	Infections, fever, rigors (tremors) fatigue, asthenia	Infections, fever, rigors (tremors) fatigue, asthenia

Skin

	Adjuvant	**Advanced**
Very common:	Alopecia, rash	
Common:		Alopecia, rash

Moderate alopecia has been reported in 2% of patients treated with oxaliplatin as a single agent; the combination of oxaliplatin and fluorouracil did not increase the incidence of alopecia observed with fluorouracil alone.

Common:	Rash erythematous, skin exfoliation, hand and foot syndrome, hyperhidrosis, nail disorder

General disorders and administration site conditions

Very common:	Pain, injection site reaction

Investigations

Very common:	Hepatic enzyme increase, blood bilirubin increase, blood lactate dehydrogenase increase, weight increase (adjuvant setting)
Common:	Blood creatinine increase, weight decrease (metastatic setting)

Care of Intravenous Site

Extravasation may result in local pain and inflammation that may be severe and lead to complications, including necrosis, especially when oxaliplatin is infused through a peripheral vein. Injection site reaction, including redness, swelling, thrombosis and local pain, have been reported.

Post-marketing experience with frequency not known:

The following additional adverse events were observed following the marketing of oxaliplatin when used with various chemotherapy regimens:

Infections and infestations

Septic shock, including fatal outcomes

Blood and lymphatic system disorders

Haemolytic-uraemic syndrome, autoimmune pancytopenia, pancytopenia, secondary leukemia

Immune system disorders

Delayed hypersensitivity

Nervous system disorders

Convulsion, ischemic and hemorrhagic cerebrovascular disorder

Cardiac disorders

QT prolongation, which may lead to ventricular arrhythmias including Torsade de Pointes, which may be fatal (see **Precautions**).

Acute coronary syndrome including myocardial infarction, coronary arteriospasm, and cardiac arrest.

Cardiac arrhythmias including bradyarrhythmia, tachycardia and atrial fibrillation.

Respiratory, thoracic and mediastinal disorders

Laryngospasm, pneumonia and bronchopneumonia, including fatal outcomes

Gastrointestinal disorders

Intestinal ischaemia, including fatal outcomes (see **Precautions**), ascites

Esophagitis

Duodenal ulcer, and complications, such as duodenal ulcer haemorrhage or perforation, which can be fatal (see **Precautions**).

Hepatobiliary

Focal nodular hyperplasia, hepatic failure

Skin and subcutaneous tissue disorders

Hypersensitivity vasculitis

Injury, poisoning, and procedural complications

Fall and fall-related injuries

Musculoskeletal and connective tissue disorders

Rhabdomyolysis, including fatal outcomes (see **Precautions**).

OVERDOSE

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

Warning (based on the Ministry of Public Health's Announcement)

This drug may cause serious harm, should be used under the supervision of a physician.

STORAGE CONDITION

Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion - Store below 30°C. Protect from light.

PRESENTATION

Oxaliplatin is available as a sterile concentrated solution for infusion in 50 mg/10 mL and 100 mg/20 mL. (one vial per box)

NAME AND ADDRESS OF MANUFACTURING

Zydus Hospira Oncology Pvt. Ltd.
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MARKETING AUTHORIZATION HOLDER

Pfizer (Thailand) Limited

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