For the use of an Oncologist or a Hospital or a Laboratory only

OXALTOR

1. Generic Name

Oxaliplatin Injection I.P.

2. Qualitative and quantitative Composition:

OXALTOR 50

Each ml Contains:

Oxaliplatin I.P…….. 2 mg

Water for injection I.P……..... q.s.

OXALTOR 100

Each ml Contains:

Oxaliplatin I.P…….. 2 mg

Water for injection I.P……..... q.s.

The excipients are Mannitol and Sodium hydroxide

3. Dosage form and strength

Dosage form: Injection

Strength: 2mg/ ml

4. Clinical particulars

4.1 Therapeutic indication

It is indicated for the treatment of advanced colorectal cancer.

4.2 Posology and method of administration

Posology

FOR ADULTS ONLY

The recommended dose for oxaliplatin in adjuvant setting is 85 mg/m² intravenously repeated every two weeks for 12 cycles (6 months).

The recommended dose for oxaliplatin in treatment of metastatic colorectal cancer is 85 mg/m² intravenously repeated every 2 weeks until disease progression or unacceptable toxicity.

Dosage given should be adjusted according to tolerability.

Oxaliplatin should always be administered before fluoropyrimidines – i.e. 5-fluorouracil.

Oxaliplatin is administered as a 2- to 6-hour intravenous infusion in 250 to 500 ml of 5% glucose solution to give a concentration between 0.2 mg/ml and 0.70 mg/ml; 0.70 mg/ml is the highest concentration in clinical practice for an oxaliplatin dose of 85 mg/m².

Oxaliplatin was mainly used in combination with continuous infusion 5-fluorouracil based regimens. For the two-weekly treatment schedule 5-fluorouracil regimens combining bolus and continuous infusion were used.

Special Populations

Renal impairment

Oxaliplatin must not be administered in patients with severe renal impairment. In patients with mild to moderate renal impairment, the recommended dose of oxaliplatin is 85 mg/m².

Hepatic impairment

As per reported phase I study including patients with several levels of hepatic impairment, frequency and severity of hepato-biliary disorders appeared to be related to progressive disease and impaired liver function tests at baseline. No specific dose adjustment for patients with abnormal liver function tests was performed during clinical development.

Elderly patients

No increase in severe toxicities was observed when oxaliplatin was used as a single agent or in combination with 5-fluorouracil in patients over the age of 65. In consequence no specific dose adaptation is required for elderly patients.

Paediatric population

There is no relevant indication for use of oxaliplatin in children. The effectiveness of oxaliplatin single agent in the paediatric populations with solid tumours has not been established.

Method of administration

Oxaliplatin is administered by intravenous infusion.

The administration of oxaliplatin does not require hyperhydration.

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 via a central venous line or peripheral vein over 2 to 6 hours.

Oxaliplatin infusion must always precede the administration of 5-fluorouracil.

Instruction for use

Oxaliplatin must be diluted before use. Only 5% glucose diluent is to be used to dilute the concentrate for solution for infusion product. For instructions on dilution of the medicinal product before administration.

In the event of extravasation, administration must be discontinued immediately.

Method of Administration: For oral administration.

4.3 Contraindications

Oxaliplatin is contraindicated in patients who:

- have a known history of hypersensitivity to the active substance or to any of the excipients.

- are breast feeding

- have myelosuppression prior to starting first course, as evidenced by baseline neutrophils <2x109/l and/or platelet count of <100x109l

- have a peripheral sensitive neuropathy with functional impairment prior to first course

- have a severely impaired renal function (creatinine clearance less than 30 ml/min)

4.4 Special warnings and precautions for use

Oxaliplatin should only be used in specialized departments of oncology and should be administered under the supervision of an experienced oncologist.

Renal impairmen

Patients with mild to moderate renal impairment should be closely monitored for adverse reactions and the dose adjusted according to toxicity.

Hypersensitivity reactions

Special surveillance should be ensured for patients with a history of allergic manifestations to other products containing platinum. In case of anaphylactic manifestations the infusion should be interrupted immediately and an appropriate symptomatic treatment started. Re-administration of oxaliplatin is contra-indicated. Cross reactions, sometimes fatal, have been reported with all platinum compounds.

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

Neurological symptoms

Neurological toxicity of oxaliplatin should be carefully monitored, especially if co-administered with other medicinal products with specific neurological toxicity. A neurological examination should be performed before each administration and periodically thereafter.

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

Peripheral neuropathy

If neurological symptoms (paraesthesia, dysaesthesia) occur, the following recommended oxaliplatin dosage adjustment should be based on the duration and severity of these symptoms:

- if symptoms last longer than seven days and are troublesome, the subsequent oxaliplatin dose should be reduced from 85 to 65 mg/m2 (metastatic setting) or 75 mg/m2 (adjuvant setting)

- if paraesthesia without functional impairment persists until the next cycle, the subsequent oxaliplatin dose should be reduced from 85 to 65 mg/m2 (metastatic setting) or 75 mg/m2 (adjuvant setting)

- if paraesthesia with functional impairment persists until the next cycle, oxaliplatin should be discontinued

- if these symptoms improve following discontinuation of oxaliplatin therapy, resumption of therapy may be considered.

Patients should be informed of the possibility of persistent symptoms of peripheral sensory neuropathy after the end of the treatment. Localized moderate paresthesias or paresthesias that may

interfere with functional activities can persist after up to 3 years following treatment cessation in the adjuvant setting.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Cases of Reversible Posterior Leukoencephalopathy Syndrome (RPLS also known as PRES, Posterior Reversible Encephalopathy Syndrome) have been reported in patients receiving oxaliplatin in combination chemotherapy. RPLS is a rare, reversible, rapidly evolving neurological condition, which can include seizure, hypertension, headache, confusion, blindness, and other visual and neurological disturbances. Diagnosis of RPLS is based upon confirmation by brain imaging, preferably MRI (Magnetic Resonance Imaging).

Nausea, vomiting, diarrhoea, dehydration and haematological changes

Gastrointestinal toxicity, which manifests as nausea and vomiting, warrants prophylactic and/or therapeutic anti-emetic therapy.

Dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis particularly when combining oxaliplatin with 5-fluorouracil.

Cases of intestinal ischemia, including fatal outcomes, have been reported with oxaliplatin treatment. In case of intestinal ischemia, oxaliplatin treatment should be discontinued and appropriate measures initiated.

If haematological toxicity occurs (neutrophils < 1.5x109/l or platelets < 50x109/l), administration of the next course of therapy should be postponed until haematological values return to acceptable levels. A full blood count with white cell differential should be performed prior to start of therapy and before each subsequent course. Myelosuppressive effects may be additive to those of concomitant chemotherapy. Patient with severe and persistent myelosuppression are at high risk of infectious complications. 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.

Patients must be adequately informed of the risk of diarrhoea/emesis, mucositis/ stomatitis and neutropenia after oxaliplatin and 5-fluorouracil administration so that they can urgently contact their treating physician for appropriate management.

If mucositis/ stomatitis occurs with or without neutropenia, the next treatment should be delayed until recovery from mucositis/ stomatitis to grade 1 or less and/or until the neutrophil count is ≥ 1.5 x 109/l.

For oxaliplatin combined with 5-fluorouracil (with or without folinic acid), the usual dose adjustments for 5-fluorouracil associated toxicities should apply.

If grade 4 diarrhoea, grade 3-4 neutropenia (neutrophils <1.0x109/l), febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection with an absolute neutrophil count < 1.0 x 109/L, a single temperature of > 38.3°C or a sustained temperature of > 38°C for more than one hour), or grade 3-4 thrombocytopenia (platelets < 50x109/l) occur, the

dose of oxaliplatin should be reduced from 85 to 65 mg/m² (metastatic setting) or 75 mg/m² (adjuvant setting), in addition to any 5-fluorouracil dose reductions required.

Pulmonary

In the case of unexplained respiratory symptoms such as non-productive cough, dyspnoea, crackles or radiological pulmonary infiltrates, oxaliplatin should be discontinued until further pulmonary investigations exclude an interstitial lung disease or pulmonary fibrosis.

Blood disorders

Haemolytic-uraemic syndrome (HUS) is a life-threatening side effect (frequency not known). 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. Disseminated intravascular coagulation (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.

QT prolongation

QT prolongation may lead to an increased risk for ventricular arrhythmias including Torsade de Pointes, which can be fatal. The QT interval should be closely monitored on a regular basis before and after administration of oxaliplatin. 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.

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.

Gastrointestinal ulcer/ Gastrointestinal haemorrhage and perforation

Oxaliplatin treatment can cause gastrointestinal ulcer and potential complications, such as gastrointestinal haemorrhage and perforation, which can be fatal. In case of gastrointestinal ulcer, oxaliplatin treatment should be discontinued and appropriate measures taken.

Hepatic

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.

Pregnancy

For use in pregnant women,

Fertility

Genotoxic effects were observed with oxaliplatin in the preclinical studies. Therefore male patients treated with oxaliplatin are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment because oxaliplatin may have an anti-fertility effect which could be irreversible.

Women should not become pregnant during treatment with oxaliplatin and should use an effective method of contraception.

Immunosuppressant effects/increased susceptibility to infections:

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

Peritoneal hemorrhage may occur when oxaliplatin is administered by intraperitoneal route (off-label route of administration).

4.5 Drugs interactions

In patients who have received a single dose of 85 mg/m² of oxaliplatin, immediately before administration of 5-fluorouracil, no change in the level of exposure to 5-fluorouracil has been observed. In vitro, no significant displacement of oxaliplatin binding to plasma proteins has been observed with the following agents: erythromycin, salicylates, granisetron, paclitaxel, and sodium valproate.

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.

Caution is advised when oxaliplatin treatment is administered concomitantly with other medicinal products known to be associated with rhabdomyolysis.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

There is no data from the use of oxaliplatin in pregnant women. Animal studies, have shown reproductive toxicity.

Oxaliplatin is not recommended during pregnancy and in women of childbearing potential not using contraception.

The use of oxaliplatin should only be considered after suitably appraising the patient of the risk to the foetus and with the patient's consent.

Appropriate contraceptive measures must be taken during and after cessation of therapy during 4 months for women and 6 months for men.

Breastfeeding

It is unknown whether oxaliplatin is excreted in human milk.

Oxaliplatin is contra-indicated during breast-feeding.

Fertility

Oxaliplatin may have an anti-fertility effect.

Contraception in males and females

Due to the potential genotoxic effects of oxaliplatin, appropriate contraceptive measures must be taken during and after cessation of therapy during 4 months for women and 6 months for men.

4.7 Effects on ability to drive and use machines

No Reported studies on the effects 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 affect 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.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse events of oxaliplatin in combination with 5-fluorouracil/folinic acid (5-FU/FA) were gastrointestinal (diarrhoea, nausea, vomiting and mucositis), haematological (neutropenia, thrombocytopenia) and neurological (acute and dose cumulative peripheral sensory neuropathy). Overall, these adverse events were more frequent and severe with oxaliplatin and 5-FU/FA combination than with 5-FU/FA alone.

Tabulated list of adverse reactions

The frequencies reported in the table below are derived from clinical trials in the metastatic and adjuvant settings (having included 416 and 1108 patients respectively in the oxaliplatin + 5-FU/FA treatment arms) and from post marketing experience.

Frequencies in this table are defined using the following convention: very common (≥1/10) common (≥1/100, <1/10), uncommon (≥1/1000, ≤1/100), rare (≥1/10000, ≤1/1000), very rare (≤1/10000), not known (cannot be estimated from the available data).

Further details are given after the table.

MedDRA system organ classes	Very common	Common	Uncommon	Rare	Not known
Infections and infestations*	Infection	Rhinitis Upper respiratory tract infection Neutropenic sepsis+	Sepsis +		
Blood and lymphatic	Anaemia Neutropenia	Febrile neutropenia		Immunoallergic thrombocytopenia	

system disorders*	Thrombocytopenia Leukopenia Lymphopenia			Haemolytic anaemia	
Immune system disorders*	Allergy/allergic reaction ++				
Metabolism and nutrition disorders	Anorexia Hyperglycaemia Hypokalaemia Hyponatraemia	Dehydration Hypocalcaemia	Metabolic acidosis		
Psychiatric disorders		Depression Insomnia	Nervousness		
Nervous system disorders*-	Peripheral sensory neuropathy Sensory disturbance Dysgeusia Headache	Dizziness Motor neuritis Meningism		Dysarthria Reversible Posterior Leukoencephalopathy syndrome (RPLS, or PRES)	
Eye disorders		Conjunctivitis Visual disturbance		Visual acuity reduced transiently Visual field disturbances Optic neuritis Transient vision loss, reversible following therapy discontinuation	
Ear and labyrinth disorders			Ototoxicity	Deafness	
Cardiac disorders					Acute coronary syndrome (Vasospasm), including myocardial infarction and coronary arteriospasm and angina pectoris in patients treated with

					oxaliplatin in combination with 5-FU and bevacizumab
Vascular disorders		Haemorrhage Flushing Deep vein thrombosis Hypertension			
Respiratory, thoracic and mediastinal disorders	Dyspnoea Cough Epistaxis	Hiccups Pulmonary embolism		Interstitial lung disease, sometimes fatal Pulmonary fibrosis**	
Gastrointestinal disorders*	Nausea Diarrhoea Vomiting Stomatitis /Mucositis Abdominal pain Constipation	Dyspepsia Gastroesophageal reflux Gastrointestinal haemorrhage Rectal haemorrhage	Ileus Intestinal obstruction	Colitis including clostridium difficile diarrhoea Pancreatitis	Oesophagitis
Skin and subcutaneous tissue disorders	Skin disorders Alopecia	Skin exfoliation (i.e. Hand & Foot syndrome) Rash erythematous Rash Hyperhidrosis Nail disorder			
Musculoskeletal and connective tissue disorders	Back pain	Arthralgia Bone pain			
Renal and urinary disorders		Haematuria Dysuria Micturition frequency abnormal			
General disorders and administration site conditions	Fatigue Fever+++ Asthenia Pain				

	Injection site reaction++++				
Investigations	Hepatic enzyme increase Blood alkaline phosphatase increase Blood bilirubin increase Blood lactate dehydrogenase increase Weight increase (adjuvant setting)	Blood creatinine increase Weight decrease (metastatic setting)			
Injury, poisoning and procedural complications		Fall			

* See detailed section below
** See section 4.4.
+ including fatal outcomes
++ Very common allergies/allergic reactions, occurring mainly during infusion, sometimes fatal. Common allergic reactions include skin rash, particularly urticaria, conjunctivitis ,and rhinitis. Common anaphylactic or anaphylactoid reactions, include bronchospasm, angiooedema, hypotension, sensation of chest pain and anaphylactic shock. Delayed hypersensitivity has also been reported with oxaliplatin hours or even days after the infusion.
+++ Very common fever, rigors (tremors), either from infection (with or without febrile neutropenia) or possibly from immunological mechanism.
++++ 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.

Description of selected adverse reactions

Blood and lymphatic system disorders

Incidence by patient (%), by grade

Oxaliplatin and 5-FU/FA 85 mg/m² every 2 weeks	**Metastatic Setting**			**Adjuvant Setting**		
	All grades	Gr 3	Gr 4	All grades	Gr 3	Gr 4
Anemia	82.2	3	<1	75.6	0.7	0.1
Neutropenia	71.4	28	14	78.9	28.8	12.3
Thrombocytopenia	71.6	4	<1	77.4	1.5	0.2

Febrile neutropenia	5.0	3.6	1.4	0.7	0.7	0.0

Rare (>1/10000, <1/1000)

Disseminated intravascular coagulation (DIC), including fatal outcomes.

Post- marketing experience with frequency unknown

Hemolytic uremic syndrome, autoimmune pancytopenia, pancytopenia, secondary leukemia.

Infections and infestations

Incidence by patient (%), by grade

Oxaliplatin and 5-FU/FA 85 mg/m² every 2 weeks	**Metastatic Setting**			**Adjuvant Setting**		
	All grades			All grades		
Sepsis (including sepsis and neutropenic sepsis)	1.5			1.7		

Post-marketing experience with frequency not known

Septic shock, including fatal outcomes.

Immune system disorders

Incidence of allergic reactions by patient (%), by grade

Oxaliplatin and 5-FU/FA 85 mg/m² every 2 weeks	**Metastatic Setting**			**Adjuvant Setting**		
	All grades	Gr 3	Gr 4	All grades	Gr 3	Gr 4
Allergic reactions / Allergy	9.1	1	<1	10.3	2.3	0.6

Nervous system disorders

The dose limiting toxicity of oxaliplatin is neurological. It involves a sensory peripheral neuropathy characterized by dysaesthesia and/or paraesthesia of the extremities with or without cramps, often triggered by the cold.

These symptoms occur in up to 95% of patients treated. The duration of these symptoms, which usually regress between courses of treatment, increases with the number of treatment cycles.

The onset of pain and/or a functional disorder are indications, depending on the duration of the symptoms, for dose adjustment, or even treatment discontinuation.

This functional disorder includes difficulties in executing delicate movements and is a possible consequence of sensory impairment. The risk of occurrence of persistent symptoms for a cumulative dose of 850 mg/m² (10 cycles) is approximately 10% and 20% for a cumulative dose of 1020 mg/m² (12 cycles).

In the majority of the cases, the neurological signs and symptoms improve or totally recover when treatment is discontinued. In the adjuvant setting of colon cancer, 6 months after treatment cessation, 87 % of patients had no or mild symptoms. After up to 3 years of follow up, about 3 % of patients presented either with persisting localized paresthesias of moderate intensity (2.3%) or with paresthesias that may interfere with functional activities (0.5%).

Acute neurosensory manifestations have been reported. They start within hours of administration and often occur on exposure to cold. They usually present as transient paresthesia, dysesthesia and hypoesthesia. An acute syndrome of pharyngolaryngeal dysesthesia occurs in 1% - 2% of patients and is characterised by subjective sensations of dysphagia or dyspnoea/feeling of suffocation, without any objective evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm (no stridor or wheezing). Although antihistamines and bronchodilators have been administered in such cases, the symptoms are rapidly reversible even in the absence of treatment. Prolongation of the infusion helps to reduce the incidence of this syndrome. Occasionally other symptoms that have been observed include jaw spasm/muscle spasms/muscle contractions-involuntary/muscle twitching/myoclonus, coordination abnormal/gait abnormal/ ataxia/ balance disorders, throat or chest tightness/ pressure/ discomfort/pain. In addition, cranial nerve dysfunctions may be associated with above mentioned events, or also occur as an isolated event 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 in visual acuity, visual field disorders.

Other neurological symptoms such as dysarthria, loss of deep tendon reflex and Lhermitte's sign were reported during treatment with oxaliplatin. Isolated cases of optic neuritis have been reported.

Post- marketing experience with frequency unknown

Convulsion, ischemic or haemorrhagic cerebrovascular disorder

Cardiac disorders

Post-marketing experience with frequency not known

QT prolongation, which may lead to ventricular arrhythmias including Torsade de Pointes, which may be fatal.

Acute coronary syndrome, including myocardial infarction and coronary arteriospasm and angina pectoris in patients treated with oxaliplatin in combination with 5- FU and bevacizumab.

Respiratory, thoracic and mediastinal disorders

Post-marketing experience with frequency not known:

Laryngospasm, pneumonia and bronchopneumonia, including fatal outcomes

Gastrointestinal disorders

Incidence by patient (%), by grade

Oxaliplatin and 5-FU/FA 85 mg/m² every 2 weeks	**Metastatic Setting**			**Adjuvant Setting**		
	All grades	Gr 3	Gr 4	All grades	Gr 3	Gr 4
Nausea	69.9	8	<1	73.7	4.8	0.3
Diarrhoea	60.8	9	2	56.3	8.3	2.5
Vomiting	49.0	6	1	47.2	5.3	0.5
Mucositis/Stomatitis	39.9	4	<1	42.1	2.8	0.1

Prophylaxis and/or treatment with potent antiemetic agents is indicated.

Dehydration, paralytic ileus, intestinal obstruction, hypokalaemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis particularly when combining oxaliplatin with 5 fluorouracil (5 FU).

Post marketing experience with frequency not known

Intestinal ischaemia, including fatal outcomes.

Gastrointestinal ulcer and perforation, which can be fatal

Hepato-biliary disorders

Very rare (≤ 1/10000)

Liver sinusoidal obstruction syndrome, also known as veno-occlusive disease of liver, or pathological manifestations related to such liver disorder, including peliosis hepatis, nodular regenerative hyperplasia, perisinusoidal fibrosis. Clinical manifestations may be portal hypertension and/or increased transaminases.

Musculoskeletal and connective tissue disorders

Post-marketing experience with frequency not known

Rhabdomyolysis, including fatal outcomes.

Skin and subcutaneous tissue disorders

Post-marketing experience with frequency not known

Hypersensitivity vasculitis.

Renal and urinary disorders

Very rare (≤ 1/10000)

Acute tubular necrosis, acute interstitial nephritis and acute renal failure.

Reporting of suspected adverse reactions

Torrent Pharma available at: https://torrentpharma.com/index.php/site/info/adverse_event_reporting
By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 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.

5 Pharmacological properties

5.1 Mechanism of Action

Oxaliplatin is an antineoplastic active substance 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, (SP-4-2)-[(1R,2R)-Cyclohexane-1,2-diamine-kN, kN'] [ethanedioato(2-)-kO1, kO2] platinum.

Oxaliplatin exhibits a wide spectrum of both in vitro cytotoxicity and in vivo anti-tumour 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 5-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 anti-tumour effects.

5.2 Pharmacodynamic properties

Pharmacotherapeutic group: other antineoplastic agents, platinum compounds

ATC code: L01XA 03

Clinical efficacy and safety

In patients with metastatic colorectal cancer, the efficacy of oxaliplatin (85 mg/m2 repeated every two weeks) combined with 5-fluorouracil/folinic acid (5-FU/FA) is reported in three clinical studies:

- in front-line treatment, the 2-arm comparative phase III EFC2962 study randomised 420 patients either to 5-FU/FA alone (LV5FU2, N=210) or the combination of oxaliplatin with 5-FU/FA (FOLFOX4, N=210)

- in pretreated patients, the comparative three arms phase III study EFC4584 randomised 821 patients refractory to an irinotecan (CPT-11) + 5-FU/FA combination either to 5-FU/FA alone (LV5FU2, N=275), oxaliplatin single agent (N=275), or combination of oxaliplatin with 5-FU/FA (FOLFOX4, N=271).

- finally, the uncontrolled phase II EFC2964 study included patients refractory to 5-FU/FA alone, that were treated with the oxaliplatin and 5-FU/FA combination (FOLFOX4, N=57).

The two randomised clinical trials, EFC2962 in front-line therapy and EFC4584 in pretreated patients, demonstrated a significantly higher response rate and a prolonged progression free

survival (PFS)/time to progression (TTP) as compared to treatment with 5-FU/FA alone. In EFC4584 performed in refractory pretreated patients, the difference in median overall survival (OS) between the combination of oxaliplatin and 5-FU/FA did not reach statistical significance.

Response rate under FOLFOX4 versus LV5FU2

Response rate, % (95% CI) independent radiological review ITT analysis	**LV5FU2**	**FOLFOX4**	**Oxaliplatin Single agent**
Front-line treatment EFC2962	22 (16-27)	49 (42-56)	NA*
Response assessment every 8 weeks	P value = 0.0001		
Pretreated patients EFC4584 (refractory to CPT-11 + 5-FU/FA)	0.7 (0.0-2.7)	11.1 (7.6-15.5)	1.1 (0.2-3.2)
Response assessment every 6 weeks	P value < 0.0001		
Pretreated patients			
EFC2964	NA*	23	NA*
(refractory to 5-FU/FA)		(13-36)	
Response assessment every 12weeks			

* NA : Not Applicable

Median Progression Free Survival (PFS) / Median Time to Progression (TTP) FOLFOX4 versus LV5FU2

Median PFS/TTP Months (95% CI) independent radiological review ITT analysis	**LV5FU2**	**FOLFOX4**	**Oxaliplatin Single agent**
Front-line treatment EFC2962 (PFS)	6.0 (5.5-6.5)	8.2 (7.2-8.8)	NA*
	Log-rank P value = 0.0003		
Pretreated patients EFC4584 (TTP) (refractory to CPT-11 + 5-FU/FA)	2.6 (1.8-2.9)	5.3 (4.7-6.1)	2.1 (1.6-2.7)
	Log-rank P value < 0.0001		
Pretreated patients			
EFC2964	NA*	5.1	NA*
(refractory to 5-FU/FA)		(3.1-5.7)	

*NA : Not Applicable

Median Overall Survival (OS) under FOLFOX4 versus LV5FU2

Median OS, months (95% CI) ITT analysis	**LV5FU2**	**FOLFOX4**	**Oxaliplatin Single agent**
Front-line treatment EFC2962	14.7 (13.0-18.2)	16.2 (14.7-18.2)	NA*

	Log-rank P value = 0.12		
Pretreated patients EFC4584 (refractory to CPT-11 + 5-FU/FA)	8.8 (7.3-9.3)	9.9 (9.1-10.5)	8.1 (7.2-8.7)
	Log-rank P value = 0.09		
Pretreated patients			
EFC2964	NA*	10.8	NA*
(refractory to 5-FU/FA)		(9.3-12.8)	

*NA : Not Applicable

In pretreated patients (EFC4584), who were symptomatic at baseline, a higher proportion of those treated with oxaliplatin and 5-FU/FA experienced a significant improvement of their disease related symptoms compared to those treated with 5-FU/FA alone (27.7% versus 14.6% p = 0.0033).

In non-pretreated patients (EFC2962), no statistically significant difference between the two treatment groups was found for any of the quality of life dimensions. However, the quality of life scores were generally better in the control arm for measurement of global health status and pain and worse in the oxaliplatin arm for nausea and vomiting. In the adjuvant setting, the MOSAÏC comparative phase III study (EFC3313) randomised 2246 patients (899 stage II/Dukes' B2 and 1347 stage III/Dukes' C) further to complete resection of the primary tumour of colon cancer either to 5-FU/FA alone (LV5FU2, N=1123 (B2/C = 448/675) or to combination of oxaliplatin and 5-FU/FA (FOLFOX4, N=1123 (B2/C) = 451/672).

EFC 3313 3-year disease free survival (ITT analysis)* for the overall population.

Treatment arm FOLFOX4	LV5FU2	FOLFOX4
Percent 3-year disease free survival (95% CI)	73.3 (70.6-75.9)	78.7 (76.2-81.1)
Hazard ratio (95% CI)	0.76 (0.64-0.89)	
Stratified log rank test	P=0.0008	

* median follow up 44.2 months (all patients followed for at least 3 years)

The study demonstrated an overall significant advantage in 3-year disease free survival for the oxaliplatin and 5-FU/FA combination (FOLFOX4) over 5-FU/FA alone (LV5FU2).

EFC 3313 3-year disease free survival (ITT analysis)* according to stage of disease

Patient stage	**Stage II (Dukes' B2)**		**Stage III (Dukes' C)**	
Treatment arm	LV5FU2	FOLFOX4	LV5FU2	FOLFOX4
Percent 3-year disease	84.3	87.4	65.8	72.8
Free survival	(80.9-87.7)	(84.3-90.5)	(62.2-69.5)	(69.4-76.2)
(95% CI)				
Hazard ratio (95% CI)	0.79 (0.57-1.09)		0.75 (0.62 – 0.90)	
Log-rank test	P=0.151		P=0.002	

* median follow up 44.2 months (all patients followed for at least 3 years)

Overall Survival (ITT analysis)

At time of the analysis of the 3-year disease free survival, which was the primary endpoint of the MOSAIC trial, 85.1% of the patients were still alive in the FOLFOX4 arm versus 83.8% in the LV5FU2 arm. This translated into an overall reduction in mortality risk of 10% in favour of FOLFOX4 not reaching statistical significance (hazard ratio = 0.90). The figures were 92.2% versus 92.4% in the stage II (Dukes' B2) sub-population (hazard ratio = 1.01) and 80.4% versus 78.1% in the stage III (Dukes' C) sub-population (hazard ratio = 0.87), for FOLFOX4 and LV5FU2, respectively.

Paediatric population

Oxaliplatin single agent has been evaluated in paediatric population in 2 Phase I (69 patients) and 2 Phase II (166 patients) studies. A total of 235 paediatric patients (7 months - 22 years of age) with solid tumours have been treated. The effectiveness of oxaliplatin single agent in the paediatric populations treated has not been established. Accrual in both Phase II studies was stopped for lack of tumour response.

5.3 Pharmacokinetic properties

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 /m² every three weeks for 1 to 5 cycles and oxaliplatin at 85 mg/m² every two weeks for 1 to 3 cycles are as follows:

Summary of Platinum Pharmacokinetic Parameter Estimates in Ultrafiltrate Following Multiple Doses of Oxaliplatin at 85 mg/m2 Every Two Weeks or at 130 mg/m2 Every Three Weeks

Dose 85 mg/m²	**C_{max} µg/mL**	**AUC_{0-48} µg.h/mL**	**AUC µg.h/mL**	**$t_{1/2\alpha}$ h**	**$t_{1/2\beta}$ h**	**$t_{1/2\gamma}$ h**	**Vss L**	**CL L/h**
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/m²								
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 AUC0-48, and Cmax values were determined on Cycle 3 (85 mg/m²) or cycle 5 (130 mg/m²).

Mean AUC, Vss, CL, and CLR0-48 values were determined on Cycle 1.

Cend, Cmax, AUC, AUC0-48, Vss and CL values were determined by non-compartmental analysis.

t1/2α, t1/2β, and t1/2γ, 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% being 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 accumulation was observed in plasma ultrafiltrate following 85 mg/m² every two weeks or 130 mg/m² 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 2h-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.

The effect of renal impairment on the disposition of oxaliplatin was studied in patients with varying degrees of renal function. Oxaliplatin was administered at a dose of 85 mg/m^2 in the control group with a normal renal function (CLcr > 80 ml/min, n=12) and in patients with mild (CLcr = 50 to 80 ml/min, n=13) and moderate (CLcr = 30 to 49 ml/min, n=11) renal impairment, and at a dose of 65 mg/m^2 in patients with severe renal impairment (CLcr < 30 ml/min, n=5). Median exposure was 9, 4, 6, and 3 cycles, respectively, and PK data at cycle 1 were obtained in 11, 13, 10, and 4 patients respectively.

There was an increase in plasma ultrafiltrate (PUF) platinum AUC, AUC/dose and a decrease in total and renal CL and Vss with increasing renal impairment especially in the (small) group of patients with severe renal impairment: point estimate (90% CI) of estimated mean ratios by renal status versus normal renal function for AUC/dose were 1.36 (1.08, 1.71), 2.34 (1.82, 3.01) and 4.81 (3.49, 6.64) for patients with mild and moderate and in severe renal failure respectively.

Elimination of oxaliplatin is significantly correlated with the creatinine clearance. Total PUF platinum CL was respectively 0.74 (0.59, 0.92), 0.43 (0.33, 0.55) and 0.21 (0.15, 0.29) and for Vss respectively 0.52 (0.41, 0.65), 0.73 (0.59, 0.91) and 0.27 (0.20, 0.36) for patients with mild, moderate and severe renal failure respectively. Total body clearance of PUF platinum was therefore reduced by respectively 26% in mild, 57% in moderate, and 79% in severe renal impairment compared to patients with normal function.

Renal clearance of PUF platinum was reduced in patients with impaired renal function by 30% in mild, 65% in moderate, and 84% in severe renal impairment compared to patients with normal function.

There was an increase in beta half-life of PUF platinum with increasing degree of renal impairment mainly in the severe group. Despite the small number of patients with severe renal dysfunction, these data are of concern in patients in severe renal failure and should be taken into account when prescribing oxaliplatin in patients with renal impairment.

6. Nonclinical properties

6.1 Animal toxicology or Pharmacology

The target organs identified in preclinical species (mice, rats, dogs, and/or monkeys) in single- and multiple-dose studies included the bone marrow, the gastrointestinal system, the kidney, the testes, the nervous system, and the heart. The target organ toxicities observed in animals are consistent with those produced by other platinum-containing drugs and DNA-damaging, cytotoxic drugs used in the treatment of human cancers with the exception of the effects produced on the heart. Effects on the heart were observed only in the dog and included electrophysiological disturbances with lethal ventricular fibrillation. Cardiotoxicity is considered specific to the dog

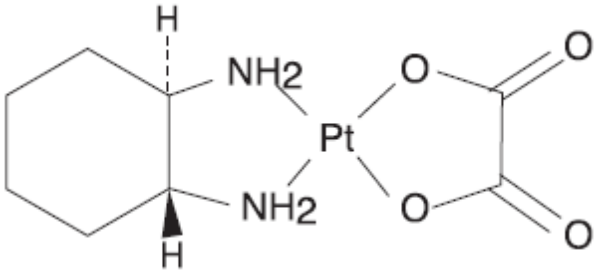
not only because it was observed in the dog alone but also because doses similar to those producing lethal cardiotoxicity in dogs (150 mg/m²) were well-tolerated by humans. Preclinical studies using rat sensory neurons suggest that the acute neurosensory symptoms related to Oxaliplatin may involve an interaction with voltage-gated Na+ channels.

Oxaliplatin was mutagenic and clastogenic in mammalian test systems and produced embryo-fetal toxicity in rats. Oxaliplatin is considered a probable carcinogen, although carcinogenic studies have not been conducted.

7. Description

Oxaliplatin

Oxaliplatin is cis-[(1R, 2R)-1,2-cyclohexanediamine-N,N'][oxalate(2-)- O,O']platinum. Its empirical formula is $C_8H_{14}N_2O_4Pt$ and its structural formula is:



Oxaliplatin is a white to off white crystalline powder with a molecular weight is 397.3. Oxaliplatin is slightly soluble in water, very slightly soluble in methanol, and insoluble in ethanol.

OXALTOR

A clear colorless solution.

The excipients are Mannitol and Sodium hydroxide.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not Applicable

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

OXALTOR 50

Available in pack of 25 ml vial.

OXALTOR 100

Available in pack of 50 ml vial.

8.4 Storage and handing instructions

Store below 25°C. Protect from light.

Do not freeze.

Keep out of reach of children

9. Patient Counselling Information

Package leaflet: Information for the user

OXALTOR

Oxaliplatin Injection I.P.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

9.1 What is OXALTOR and what it is used for

Oxaliplatin is an anticancer drug that contains platinum.

It is used for the treatment of advanced colorectal cancer.

9.2 What you need to know before you take OXALTOR

Do not take OXALTOR

- you are allergic to oxaliplatin or any of the other ingredients of this medicine.

- you are breast feeding

- you already have a reduced number of blood cells (white blood cells and/or platelets)

- you already have tingling and numbness in the fingers and/or toes, and have difficulty performing delicate tasks, such as buttoning clothes

- you have severe kidney problems.

Even if you are male, please ensure that you read the section of this leaflet that concerns pregnancy and breast-feeding.

Warnings and precautions

Talk to your doctor or pharmacist before taking OXALTOR

Talk to your doctor or pharmacist before using Oxaliplatin if

- you have ever suffered an allergic reaction to platinum-containing medicines such as carboplatin or cisplatin

- you have moderate kidney problems, you have any liver problems or abnormal liver function test results during your treatment

- if you have or had heart disorders such as an abnormal electrical signal called prolongation of the QT interval, an irregular heartbeat, or a family history of heart problems.

If any of the following applies to you at any time, tell your doctor immediately. Your doctor may need to treat you for these events. Your doctor may need to reduce the dose of Oxaliplatin, or delay or stop your treatment with Oxaliplatin.

- If you have an unpleasant sensation in the throat, in particular when swallowing, and have a sensation of shortness of breath, during the treatment, tell your doctor.

- If you have nerve problems in your hands or feet, such as numbness or tingling, or decreased sensations in your hands or feet, tell your doctor.

- If you have headache, altered mental functioning, seizures and abnormal vision from blurriness to vision loss, tell your doctor.

- If you feel or are sick (nausea or vomiting), tell your doctor.

- If you have severe diarrhoea, tell your doctor.

- If you have sore lips or mouth ulcers (mucositis/ stomatitis), tell your doctor.

- If you have diarrhoea, or a reduction in white blood cells or platelets, tell your doctor. Your doctor may reduce the dose of Oxaliplatin or postpone your treatment with Oxaliplatin.

- If you have unexplained respiratory symptoms such as cough, or any difficulties in breathing, tell your doctor. Your doctor may stop your treatment with Oxaliplatin.

- If you develop an extreme tiredness, shortness of breath, or kidney disease where you pass little or no urine (symptoms of acute renal failure), tell your doctor.

- If you have fever (temperature greater than or equal to 38°C), or chills, which could be signs of infection, tell your doctor immediately. You may be at risk of getting an infection of the blood.

- If you have fever > 38°C, tell your doctor. Your doctor may determine you also have a reduction in white blood cells.

- If you experience unexpected bleeding or bruising (disseminated intravascular coagulation), tell your doctor as these could be signs of blood clots throughout the small vessels of your body.

- If you faint (lose consciousness) or have an irregular heartbeat while being given Oxaliplatin, tell your doctor immediately as this may be a sign of a serious heart condition.

- If you experience muscle pain and swelling, in combination with weakness, fever, or red-brown urine, tell your doctor. These could be signs of muscle damage (rhabdomyolysis) and could lead to kidney problems or other complications.

- If you have abdominal pain, nausea, bloody vomit or vomit that looks like "coffee-grounds", or dark-coloured/ tarry stools, which may be signs of an ulcer of the bowel (gastrointestinal ulcer, with potential bleeding or perforation), tell your doctor.

- If you have abdominal (tummy) pain, bloody diarrhoea, and nausea and/or vomiting, which may be caused by a reduction of blood flow to your gut wall (intestinal ischaemia), tell your doctor.

Children

Oxaliplatin should not be used in children and adolescents below 18 years of age.

Other medicines and OXALTOR

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Pregnancy, breast-feeding and fertility

Pregnancy

- It is not recommended that you become pregnant during treatment with oxaliplatin and must use an effective method of contraception. Female patients should take appropriate contraceptive measures during and after cessation of therapy continuing for 4 months.

- If you are pregnant or planning a pregnancy it is very important that you discuss this with your doctor before you receive any treatment.

- If you get pregnant during your treatment, you must immediately inform your doctor.

Breast-feeding

- You must not breast-feed while you are treated with oxaliplatin.

Fertility

- Oxaliplatin may have an anti-fertility effect, which could be irreversible. Male patients should seek advice on conservation of sperm prior to treatment.
- Male patients are advised not to father a child during treatment and until 6 months after treatment, and to take appropriate contraceptive measures during this time.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Oxaliplatin treatment may result in an increased risk of dizziness, nausea and vomiting, and other neurological symptoms that affect walking and balance. If this happens you should not drive or operate machinery. If you have vision problems while being given oxaliplatin, do not drive, operate heavy machines, or engage in dangerous activities.

9.3 How to take OXALTOR

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Oxaliplatin may only be given to adults.

For single use only.

If you take more OXALTOR than you should:

As this medicine is administered by a healthcare professional it is highly unlikely that you will be given too much or too little.

In case of overdose, you may experience increased side effects. Your doctor may give you appropriate treatment for these side effects.

If you have any further questions on the use of this medicine, ask your doctor.

Frequency of administration

You should usually receive your infusion once every two weeks.

Duration of treatment

The duration of the treatment will be determined by your doctor.

Your treatment will last a maximum of 6 months when used after complete resection of your tumour.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. If you experience any side effect it is important that you inform your doctor before your next treatment.

You will find described below the side effects that you could experience.

Most serious side effects

Tell your doctor immediately if you notice any of the following:

Very common: may affect more than 1 in 10 people

- allergies/allergic reactions, occurring mainly during infusion, sometimes fatal
- stomatitis / mucositis (sore lips or mouth ulcers)
- low platelet count, abnormal bruising (thrombocytopenia). Your doctor will take blood to check that you have sufficient blood cells before you start treatment and before each subsequent course.
- unexplained respiratory symptoms such as dry cough, difficulties in breathing or crackles.

Common: may affect up to 1 in 10 people

- serious infection of the blood in addition to a reduction in white blood cells (neutropenic sepsis), which may be fatal
- reduction in white blood cells accompanied by fever > 38.3°C or a prolonged fever > 38°C for more than one hour (febrile neutropenia)
- symptoms of an allergic or anaphylactic reaction with sudden signs such as rash, itching or hives on the skin, difficulties in swallowing, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing, extreme tiredness (you may feel you are going to faint). In the majority of cases, these symptoms occurred during the infusion or immediately after but delayed allergic reactions have also been observed hours or even days after the infusion.
- pain in the chest or upper back, difficulty breathing and coughing up blood (symptoms of clots in the lungs).

Uncommon: may affect up to 1 in 100 people

- serious infection of the blood (sepsis), which may be fatal
- blockage or swelling of the bowel
- difficulty in hearing, vertigo, ringing in ears.

Rare: may affect up to 1 in 1,000 people

- unexpected bleeding or bruising due to widespread blood clots throughout the small blood vessels of the body (disseminated intravascular coagulation), which may be fatal
- abnormal bruising, bleeding or signs of infection such as a sore throat and high temperature
- persistent or severe diarrhoea or vomiting
- reversible short-term loss of vision
- a group of symptoms such as headache, altered mental functioning, seizures and abnormal vision from blurriness to vision loss (symptoms of reversible posterior leukoencephalopathy syndrome, a rare neurological disorder)
- extreme tiredness with decreased number of red blood cells, and shortness of breath (haemolytic anaemia), alone or combined with low platelet count, abnormal bruising (thrombocytopenia) and kidney disease where you pass little or no urine (symptoms of Haemolytic-uraemic syndrome)
- scarring and thickening in the lungs with difficulties in breathing, sometimes fatal (interstitial lung disease)
- pain in upper abdomen and pain associated with nausea and vomiting.

Very rare: may affect up to 1 in 10,000 people

- kidney disease where you pass little or no urine (symptoms of acute renal failure)
- vascular disorders of the liver (symptoms include abdominal pain and swelling, weight gain and tissue swelling of the feet, ankles or other parts of the body).
Not known: frequency cannot be estimated from the available data
- serious infection of the blood and low blood pressure (septic shock), which may be fatal
- abnormal heart rhythm (QT prolongation), that can be seen on electrocardiogram (ECG), which may be fatal
- muscle pain and swelling, in combination with weakness, fever, or red-brown urine (symptoms of muscle damage called rhabdomyolysis), which may be fatal
- abdominal pain, nausea, bloody vomit or vomit that looks like "coffee grounds", or dark-coloured/tarry stools (symptoms of gastrointestinal ulcer, with potential bleeding or perforation), which may be fatal
- decreased blood flow to the intestine/bowel (intestinal ischaemia), which may be fatal
- spasm of the throat causing difficulty in breathing
- auto-immune reaction leading to reduction of all blood cell lines (autoimmune pancytopenia) (symptoms include easy bleeding, easy bruising, shortness of breath, extreme lethargy and weakness, and an increased risk of infection due to the immune compromised state)
- stroke symptoms (including sudden severe headache, confusion, trouble seeing in one or both eyes, numbness or weakness of face, arm or leg usually on one side, face drooping, trouble walking, dizziness, loss of balance and speech difficulty)
- pneumonia (serious lung infection) which may be fatal.
Other known side effects

Very common: may affect more than 1 in 10 people

- Oxaliplatin can affect the nerves (peripheral neuropathy). You may feel a tingling and/or numbness in the fingers, toes, around the mouth or in the throat, which may sometimes occur in association with cramps. These effects are often triggered by exposure to cold e.g. opening a refrigerator or holding a cold drink. You may also have difficulty in performing delicate tasks, such as buttoning clothes. Although in the majority of cases these symptoms disappear completely, there is a possibility of persistent symptoms of peripheral sensory neuropathy after the end of the treatment. Some people have experienced a tingling shock-like sensation passing down the arms or trunk when the neck is flexed.
- Oxaliplatin can sometimes cause an unpleasant sensation in the throat, in particular when swallowing, and give the sensation of shortness of breath. This sensation, if it happens, usually occurs during or within hours of the infusion and may be triggered by exposure to the cold. Although unpleasant, it will not last long and goes away without the need for any treatment. Your doctor may decide to alter your treatment as a result.
- Oxaliplatin may cause diarrhoea, mild nausea (feeling sick) and vomiting (being sick); however medication to prevent the sickness is usually given before treatment and may be continued after treatment.

- Oxaliplatin causes temporary reduction in the number of blood cells. The reduction of red cells may cause anaemia (a reduction of red cells), abnormal bleeding or bruising (due to a reduction in platelets). The reduction in white blood cells may make you prone to infections. Your doctor will take blood to check that you have sufficient blood cells before you start treatment and before each subsequent course.

- sensation of discomfort close to or at the injection site during the infusion
- fever, rigors (tremors), mild or severe tiredness, body pain
- weight changes, loss or lack of appetite, taste disorders, constipation
- headache, back pain
- abnormal tongue sensation possibly altering speech
- stomach pain
- abnormal bleeding including nose bleeds
- allergic reactions, skin rash including red and itchy skin, mild hair loss (alopecia)
- alteration in blood tests including those relating to abnormalities on liver function.

Common: may affect up to 1 in 10 people

- indigestion and heart burn, hiccups, flushing and dizziness
- increased sweating and nail disorders, flaking skin
- chest pain
- lung disorders and runny nose
- joint pain and bone pain

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://torrentpharma.com/index.php/site/info/adverse_event_reporting
By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store OXALTOR

Store below 25°C. Protect from light.

Do not freeze.

Keep out of reach of children

9.6 Contents of the pack and other information

The active substance in OXALTOR is Oxaliplatin and it is available in strength of 2mg/ ml.

OXALTOR 50 and 100

The excipients are Mannitol and Sodium hydroxide.

OXALTOR 50

Available in pack of 25 ml vial.

OXALTOR 100

Available in pack of 50 ml vial.

10. Details of manufacturer

Naprod Life Sciences Pvt. Ltd.

G-17/1, M.I.D.C., Tarapur Industrial Area,

Boisar, Dist : Thane – 401 506, India.

11. Details of permission or license number with date

Mfg Lic No.: KD-141 issued on 08 Feb 2018

12. Date of revision

MAR 2022

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ OXALTOR 50, 100 mg/MAR 22/02/PI