

Summary of Product Characteristics

1. Name of the medicinal product

Zildox 100 (Oxaliplatin) 100 mg lyophilised mass for solution for injection

2. Qualitative and quantitative composition

Oxaliplatin USP 100 mg

Lactose USP q.s

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Sterile White Lyophilized mass for solution for injection

4. Clinical particulars

4.1 Therapeutic indications

Oxaliplatin in combination with 5-fluorouracil (5-FU) and folinic acid (FA) is indicated for:

- Adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of primary tumour.
- Treatment of metastatic colorectal cancer.

4.2 Posology and method of administration

Adjuvant Therapy in Patients with Stage III Colon Cancer

Adjuvant treatment in patients with stage III colon cancer is recommended for a total of 6 months, i.e., 12 cycles, every 2 weeks, according to the dose schedule.

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

The recommended dose schedule to be given every two weeks is as follows:

Day 1: Oxaliplatin for injection 85 mg/m² IV infusion in 250-500 mL D5W and leucovorin 200 mg/m² IV infusion in D5W both given over 120 minutes at the same time in separate bags using a Y-line, followed by 5-FU 400 mg/ m² IV bolus given over 2–4 minutes, followed by 5-FU 600 mg/m² IV infusion in 500 mL D5W (recommended) as a 22-hour continuous infusion.

Day 2: Leucovorin 200 mg/ m² IV infusion over 120 minutes, followed by 5-FU 400 mg/ m² IV bolus given over 2–4 minutes, followed by 5-FU 600 mg/ m² IV infusion in 500 mL D5W (recommended) as a 22-hour continuous infusion. Repeat cycle every 2 weeks.

The administration of Oxaliplatin for injection does not require prehydration. Premedication with antiemetics, including 5-HT₃ blockers with or without dexamethasone, is recommended. Dose Modification Recommendations Prior to subsequent therapy cycles, patients should be evaluated for clinical toxicities and laboratory tests. Prolongation of infusion time for Oxaliplatin for injection from 2 hours to 6 hours decreases the C_{max} and may mitigate acute toxicities. The infusion times for 5-FU and leucovorin do not need to be changed.

Preparation of Infusion Solution

Reconstitution or final dilution must never be performed with a sodium chloride solution or other chloride-containing solutions.

The lyophilized injection is reconstituted by adding 10 mL (for the 50 mg vial) or 20 mL (for the 100 mg vial) of Water for Injection or 5% Dextrose Injection.

Do not administer the reconstituted solution without further dilution. The reconstituted solution must be further diluted in an infusion solution of 250–500 mL of 5% Dextrose Injection. After reconstitution in the original vial, the solution may be stored up to 24 hours under refrigeration [2°C–8°C (36°F–46°F)]. After final dilution with 250–500 mL of 5% Dextrose Injection, the shelf life is 6 hours at room temperature [20°C–25°C (68°F– 77°F)] or up to 24 hours under refrigeration [2°C–8°C (36°F–46°F)].

Oxaliplatin for injection is not light sensitive. Oxaliplatin for injection is incompatible in solution with alkaline medications or media (such as basic solutions of 5-FU) and must not be mixed with these or administered simultaneously through the same infusion line.

The infusion line should be flushed with D5W prior to administration of any concomitant medication. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and discarded if present. Needles or intravenous administration sets containing aluminum parts that may come in contact with Oxaliplatin for injection should not be used for the preparation or mixing of the drug. Aluminum has been reported to cause degradation of platinum compounds.

4.3 Contraindications

Oxaliplatin is contraindicated in patients who

- have a known history of hypersensitivity to oxaliplatin or to any of the excipients listed in section 6.1.
- are breast feeding.
- have myelosuppression prior to starting first course, as evidenced by baseline neutrophils $<2 \times 10^9/l$ and/or platelet count of $<100 \times 10^9/l$.
- have a peripheral sensory neuropathy with functional impairment prior to first course.
- have a severely impaired renal function (creatinine clearance less than 30 ml/min) (see section 5.2).

4.4 Special warnings and precautions for use

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

Renal impairment

Patients with mild to moderate renal impairment should be closely monitored for adverse reactions and dose adjusted according to toxicity (see section 5.2).

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 to such patients is contraindicated. Cross reactions, sometimes fatal, have been reported with all platinum compounds.

Extravasation

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 (see section 4.8), 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 paraesthesias or paraesthesias 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 (see section 4.8). Diagnosis of RPLS is based upon confirmation by brain imaging, preferably MRI (Magnetic Resonance Imaging).

Nausea, vomiting, diarrhoea, dehydration, and haematologic changes

Gastrointestinal toxicity, which manifests as nausea and vomiting, warrants prophylactic and/or therapeutic anti-emetic therapy (see section 4.8).

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

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 section 4.8).

If haematological toxicity occurs (neutrophils $\leq 1.5 \times 10^9/l$ or platelets $\leq 50 \times 10^9/l$), 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.

Patients must be adequately informed of the risk of diarrhoea/emesis, mucositis/stomatitis and neutropenia after oxaliplatin /5-fluorouracil (5-FU) 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 $\geq 1.5 \times 10^9/l$.

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

If grade 4 diarrhoea, grade 3-4 neutropenia (neutrophils $< 1.0 \times 10^9/l$), febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection with an absolute neutrophil count $< 1.0 \times 10^9/l$, a single temperature of $> 38.3^\circ\text{C}$ or a sustained temperature of $> 38^\circ\text{C}$ for more than one hour), or grade 3-4 thrombocytopenia (platelets $\leq 50 \times 10^9/l$) occur, the dose of oxaliplatin should be reduced from 85 to 65 mg/m^2 (metastatic setting) or 75 mg/m^2 (adjuvant setting), in addition to any 5-FU 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 (see section 4.8).

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. (see section 4.8).

QT prolongation

QT prolongation may lead to an increased risk for ventricular arrhythmias including Torsade de Pointes, which can be fatal (see section 4.8). 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. (see sections 4.5 and 4.8).

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 sections 4.5 and 4.8).

Gastrointestinal ulcer/ Gastrointestinal haemorrhage and perforation

Oxaliplatin treatment can cause gastrointestinal ulcer 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 section 4.8)

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.

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.

Pregnancy

For use in pregnant women, see section 4.6.

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 (see section 4.6).

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

Excipient information

This medicinal product contains less than 1 mmol sodium (23 mg) per vial. Patients on low sodium diets can be informed that this medicinal product is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

In patients who have received a single dose of 85 mg/m² of oxaliplatin, immediately before administration of 5-fluorouracil (5-FU), no change in the level of exposure to 5-fluorouracil (5-FU) 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 (see section 4.4). Caution is advised when oxaliplatin treatment is administered concomitantly with other medicinal products known to be associated with rhabdomyolysis. (see section 4.4).

Vaccination with live or live-attenuated vaccine should be avoided in patients receiving oxaliplatin (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

To date there is no available information on safety of use in pregnant women. In animal studies, reproductive toxicity was observed. Consequently, oxaliplatin is not recommended during pregnancy and in women of childbearing potential not using contraceptive measures.

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.

Breast-feeding

Excretion in breast milk has not been studied. Breast-feeding is contra-indicated during oxaliplatin therapy.

Fertility

Oxaliplatin may have an anti-fertility effect (see section 4.4).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However oxaliplatin treatment resulting in an increased risk of dizziness, nausea and vomiting, and other neurological symptoms that affect gait and balance may lead to a minor or moderate influence on the ability to drive and use machines.

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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

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

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-fluorouracil (5FU)/folinic acid (FA) arm) and from post-marketing experience.

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

Further details are given after the table.

Infections and infestations*	
Very Common	Infection
Common	Rhinitis, Upper respiratory tract infection, Neutropenic sepsis
Uncommon	Sepsis ²
Not Known ¹	Septic shock (including fatal outcomes)
Blood and lymphatic system disorders*	
Very Common	Anaemia, Neutropenia, Thrombocytopenia, Leukopenia, Lymphopenia
Common	Febrile neutropenia
Rare	Immunoallergic thrombocytopenia, Haemolytic anaemia, Disseminated intravascular coagulation (DIC), including fatal outcomes ³
Not Known ¹	Secondary leukaemia, Haemolytic-uraemic syndrome, Autoimmune pancytopenia, Pancytopenia
Immune system disorders*	
Very Common	Allergy/allergic reaction ²
Metabolism and nutrition disorders	
Very Common	Anorexia, Hyperglycaemia, Hypokalaemia, Hyponatraemia
Common	Dehydration, Hypocalcaemia
Uncommon	Metabolic acidosis
Psychiatric disorders	
Common	Depression, Insomnia
Uncommon	Nervousness
Nervous system disorders*	
Very Common	Peripheral sensory neuropathy, Sensory disturbance, Dysgeusia, Headache
Common	Dizziness, Motor neuritis, Meningism
Rare	Dysarthria, Reversible Posterior Leukoencephalopathy Syndrome (RPLS or PRES) ³
Not Known ¹	Ischemic or haemorrhagic cerebrovascular disorder, Convulsion
Eye disorders	
Common	Conjunctivitis, Visual disturbance
Rare	Visual acuity reduced transiently, Visual field disturbances, Optic neuritis, Transient vision loss reversible, following therapy discontinuation
Ear and labyrinth disorders	
Uncommon	Ototoxicity
Rare	Deafness
Cardiac disorders	
Not Known ¹	Acute coronary syndrome ⁴ , QT Prolongation ⁵
Vascular disorders	
Common	Haemorrhage, Flushing, Deep vein thrombosis, Hypertension
Respiratory, thoracic and mediastinal disorders	
Very Common	Dyspnoea, Cough, Epistaxis

Common	Hiccups, Pulmonary embolism
Rare	Interstitial lung disease (sometimes fatal), Pulmonary fibrosis ³
Not Known ¹	Laryngospasm, Pneumonia and bronchopneumonia (including fatal outcomes)
Gastrointestinal disorders*	
Very Common	Nausea, Diarrhoea, Vomiting, Stomatitis/Mucositis, Abdominal pain, Constipation
Common	Dyspepsia, Gastroesophageal reflux, Gastrointestinal haemorrhage, Rectal haemorrhage
Uncommon	Ileus, Intestinal obstruction
Rare	Colitis including <i>Clostridium difficile</i> diarrhoea, Pancreatitis
Not Known ¹	Intestinal ischaemia (including fatal outcomes) ³ , Gastrointestinal ulcer and perforation (which can be fatal) ³ , Oesophagitis
Hepato-biliary disorders*	
Very Rare	Liver sinusoidal obstruction syndrome (also known as veno-occlusive disease of liver) ⁶
Not Known ¹	Focal nodular hyperplasia
Skin and subcutaneous tissue disorders	
Very Common	Skin disorder, Alopecia
Common	Skin exfoliation (i.e. Hand and Foot syndrome), Rash erythematous, Rash, Hyperhidrosis, Nail disorder
Not Known ¹	Hypersensitivity vasculitis
Musculo-skeletal and connective tissue disorders	
Very Common	Back pain
Common	Arthralgia, Bone pain
Not Known ¹	Rhabdomyolysis (including fatal outcomes) ³
Renal and urinary disorders	
Common	Haematuria, Dysuria, Micturition frequency abnormal
Very Rare	Acute tubular necrosis, Acute interstitial nephritis, Acute renal failure
General disorders and administration site conditions	
Very Common	Fatigue, Fever ⁷ , Asthenia, Pain, Injection site reaction ⁸ , Rigors
Investigations	
Very Common	Hepatic enzyme increase, Blood alkaline phosphatase increase, Blood bilirubin increase, Blood lactate dehydrogenase increase, Weight increase (adjuvant setting)
Common	Blood creatinine increase, Weight decrease (metastatic setting)
Injury, poisoning and procedural complications	
Common	Fall
* See detailed section below	
¹ Post-marketing experience with frequency unknown	
² 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, angioedema, hypotension, sensation of chest pain and anaphylactic shock. Delayed hypersensitivity has also been reported with oxaliplatin hours or even days after the infusion.

³ See section 4.4

⁴ Acute coronary syndrome, including myocardial infarction and coronary arteriospasm and angina pectoris in patients treated with oxaliplatin in combination with 5-FU and bevacizumab.

⁵ QT prolongation, which may lead to ventricular arrhythmias including Torsade de Pointes, which may be fatal (see section 4.4).

⁶ 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

⁷ Very common fever, rigors (tremors), either from infection (with or without febrile neutropenia) or possibly from immunological mechanism.

⁸ 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 (see section 4.4).

Blood and lymphatic system disorders

Incidence by patient (%), by grade

Oxaliplatin/5-FU/FA 85 mg/m ² every 2 weeks	Metastatic setting			Adjuvant setting		
	All grades	gr 3	gr 4	All grades	gr 3	gr 4
Anaemia	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
Neutropenic sepsis	1.1	0.7	0.4	1.1	0.6	0.4

Infections and infestations

Incidence by patients (%)

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

Immune system disorders

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

Oxaliplatin/5-FU/FA 85 mg/m ² 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 characterised by dysaesthesia and/or parasthesia 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 (see section 4.4).

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 paraesthesias of moderate intensity (2.3%) or with paraesthesias that may interfere with functional activities (0.5%).

Acute neurosensory manifestations (see section 5.3) have been reported. They start within hours of administration and often occur on exposure to cold. They usually present as transient paraesthesia, 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 (see section 4.4). 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.

Gastrointestinal disorders

Incidence by patient (%), by grade

Oxaliplatin/5FU/FA mg/m ²	85	Metastatic setting			Adjuvant setting		
		All grades	gr 3	gr 4	All grades	gr 3	gr 4
every 2 weeks							
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) (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antineoplastic agents, platinum compounds.

ATC code: L01XA 03

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)-[(1*R*,2*R*)-Cyclohexane-1,2-diamine-*kN*, *kN'*] [ethanedioato(2-)-*kO*¹, *kO*²] 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 5-fluorouracil both *in vitro* and *in vivo*.

Mechanism of action

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.

In patients with metastatic colorectal cancer, the efficacy of oxaliplatin (85mg/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 randomized 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 randomized 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 randomized 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 EFC 4584 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 Response assessment every 8 weeks	22 (16-27)	49 (42-546)	NA*
	P value = 0.0001		
Pretreated patients EFC4584 (refractory to CPT-11 + 5FU/FA) Response assessment every 6 weeks	0.7 (0.0-2.7)	11.1 (7.6-15.5)	1.1 (0.2-3.2)
	P value < 0.0001		
Pretreated patients EFC2964 (refractory to 5-FU/FA) Response assessment every 12 weeks	NA*	23 (13-36)	NA*

* 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 + 5FU/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 (refractory to 5-FU/FA)	NA*	5.1 (3.1-5.7)	NA*

* 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	8.8	9.9	8.1

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

* 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% vs 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 MOSAIC comparative phase III study (EFC3313) randomised 2246 patients (899 stage II/Duke's B2 and 1347 stage III/Duke's 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	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 of disease stage

Patient stage	Stage II (Duke's B2)		Stage III Duke's C	
	LV5FU2	FOLFOX4	LV5FU2	FOLFOX4
Percent 3-year disease free survival (95% CI)	84.3 (80.9-87.7)	87.4 (84.3-90.5)	65.8 (62.2-69.5)	72.8 (69.4-76.2)
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 (Duke's B2) sub-population (hazard ratio = 1.01) and 80.4% versus 78.1% in the stage III (Duke's C) sub-population (hazard ratio = 0.87), for FOLFOX4 and LV5FU2, respectively.

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

5.2 Pharmacokinetic properties

Absorption

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	C _{max}	AUC ₀₋₄₈	AUC	t _{1/2α}	t _{1/2β}	t _{1/2γ}	V _{ss}	CL
	μg/ml	μg.h/ml	μg.h/ml	h	h	h	L	L/h
85 mg/m²								
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 C_{max} values were determined on Cycle 3 (85 mg/m²) or cycle 5 (130 mg/m²). Mean AUC, V_{ss} and CL values were determined on Cycle 1.

C_{max}, AUC, AUC₀₋₄₈, V_{ss} and CL values were determined by non-compartmental analysis. t_{1/2α}, t_{1/2β}, and t_{1/2γ}, were determined by compartmental analysis (Cycles 1-3 combined).

Distribution

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 130mg/m² every three weeks and steady state was attained by cycle one in this matrix. Inter- and intra-subject variability is generally low.

Biotransformation

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 active substance 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.

Elimination

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/m² in the control group with a normal renal function (CL_{cr} > 80 ml/min, n=12) and in patients with mild (CL_{cr} = 50 to 80 ml/min, n=13) and moderate (CL_{cr} = 30 to 49 ml/min, n=11) renal impairment, and at a dose of 65 mg/m² in patients with severe renal impairment (CL_{cr} < 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 V_{ss} 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 V_{ss} 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 (see sections 4.2, 4.3 and 4.4).

5.3 Preclinical safety data

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 medicinal products and DNA-

damaging, cytotoxic medicinal products 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.

6. Pharmaceutical particulars

6.1 List of excipients

6.2 Incompatibilities

This medicinal product should not be mixed with other medicinal products except for those mentioned in section 6.6. Oxaliplatin can be co-administered with folinic acid via a Y-line.

- DO NOT mix with alkaline medicinal products or solutions, in particular 5-fluorouracil, folinic acid preparations containing trometamol as an excipients and trometamol salts of other medicinal products. Alkaline drugs or solutions will adversely affect the stability of oxaliplatin (see section 6.6).
- DO NOT dilute oxaliplatin with saline or other solutions containing chloride ions (including calcium, potassium or sodium chlorides).
- DO NOT use injection equipment containing aluminium.
- DO NOT mix with other medicinal products in the same infusion bag or line (see section 6.6 to check instructions related to co-administration with folinic acid)

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30 °C.

6.5 Nature and contents of container

Flint tubular vial type I with 20mm rubber stopper sealed with aluminum seal lacquered 20mm flip off top magenta plain.

6.6 Special precautions for disposal and other handling

As with other potentially toxic compounds, caution should be exercised when handling and preparing oxaliplatin solutions.

7. Marketing authorisation holder

Miracalus Pharma Pvt. Ltd. 213,
Shivai Dongre Industrial Premises,
Andheri Kurla Rd, Andheri (E),
Mumbai 400 072.

8. Marketing authorisation number(s)

TAN 20 HM 0124

9. Date of first authorisation/renewal of the authorisation

July 09, 2020

10. Date of revision of the text

October 12, 2023