Professional Information

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

ELOPLAT 50 (concentrate for solution for infusion)

ELOPLAT 100 (concentrate for solution for infusion)

ELOPLAT 150 (concentrate for solution for infusion)

ELOPLAT 200 (concentrate for solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Eloplat 50: Each vial contains 50 mg oxaliplatin per 10 mL.

Eloplat 100: Each vial contains 100 mg oxaliplatin per 20 mL.

Eloplat 150: Each vial contains 150 mg oxaliplatin per 30 mL.

Eloplat 200: Each vial contains 200 mg oxaliplatin per 40 mL.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

ELOPLAT concentrate for solution for infusion is a clear, colourless to light yellow solution, practically free from particles.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

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

4.2. Posology and method of administration

Posology

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For single use only.

The preparation of ELOPLAT must be carried out by trained specialist personnel with knowledge of the medicines used, in conditions that guarantee the protection of the environment and in particular the protection of the personnel handling the medicines. It requires a preparation area reserved for this purpose. It is forbidden to smoke, eat or drink in this area.

For adults only:

Treatment of metastatic colorectal cancer:

The recommended dose is 85 mg/m^2 intravenously repeated every 2 weeks.

Adjuvant treatment of colon cancer:

The recommended dose is 85 mg/m^2 intravenously repeated every 2 weeks for 12 cycles (6 months). Dosage given should be adjusted according to tolerability (see section 4.4 and 4.8).

ELOPLAT should always be administered before fluoropyrimidines (5FU).

ELOPLAT is administered as a 2 to 6- hour intravenous infusion in 250 to 500 mL of 5 % glucose solution. ELOPLAT is mainly used in combination with continuous infusion of 5-fluorouracil based regimens. For the two-weekly treatment schedule 5-fluorouracil regimens combining bolus and continuous infusion were used.

Special Populations:

Renal impairment:

In gastrointestinal cancer patients with varying degrees of renal impairment, treated with ELOPLAT (2 -hour IV infusion every two weeks for a maximum of 12 cycles) in combination with 5FU/FA (FOLFOX4), ELOPLAT showed minimal clinical impact on renal function as assessed by mean creatinine clearance (see section 4.3, 4.4 and 4.8).

The duration of exposure was shorter in patients with renal impairment. The median exposure was 4, 6 and 3 cycles for mild, moderate and severe renal impairment patients, respectively. In patients with normal renal

function, the median exposure was 9 cycles. However, 7/13 with mild and 5/11 with moderate severe renal impairment withdrew due to adverse effects.

In patients with normal renal function or mild to moderate renal impairment, the recommended dose of ELOPLAT is 85 mg/m^2. In patients with severe renal impairment, ELOPLAT should not be used.

Hepatic impairment:

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

Elderly patients:

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

Method of administration:

ELOPLAT is administered by intravenous infusion.

The administration of ELOPLAT does not require hyperhydration.

ELOPLAT infusion should always precede that of 5-fluorouracil (5-FU).

ELOPLAT diluted in 250 to 500 mL of 5 % glucose solution to give a concentration of not less than 0,2 mg/mL must be infused either via a peripheral vein or central venous line at the same time as folinic acid intravenous infusion in 5 % glucose solution, over 2 to 6 hours, using a Y-line placed immediately before the site of infusion. The two medicines should not be combined in the same infusion bag. Folinic acid must not contain trometamol as an excipient and must only be diluted using isotonic 5 % glucose solution and NOT in alkaline solutions or sodium chloride or chloride containing solutions (see section 6.2 for Incompatibilities).

Flush the line after ELOPLAT administration.

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

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Instructions for use

ELOPLAT must be further diluted before use. DO NOT administer undiluted. Only the recommended diluent (5 % glucose) should be used (see Method of administration above and section 6.2: Incompatibilities).

Precautions to be taken before manipulation or administering the product

Caution should be exercised when handling and preparing ELOPLAT solutions, see section 6.6.

4.3. Contraindications

- Hypersensitivity to oxaliplatin or to any of the excipients of ELOPLAT.
- Pregnancy and breastfeeding.
- Bone marrow failure.
- Myelosuppression prior to starting treatment.
- Peripheral sensitive neuropathy with functional impairment before treatment.
- Severely impaired renal function (creatinine clearance less than 30 mL/min).

4.4 Special warnings and precautions for use

General:

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

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

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

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Renal impairment:

Due to limited information on safety in patients with severely impaired renal function, administration should only be considered after suitable appraisal of the benefit/risk for the patient. In this situation, renal function should be closely monitored and the recommended initial ELOPLAT dose is 65 mg/m^2 (see section 4.2: Special populations).

Hypersensitivity reactions:

Patients with a history of allergic reaction to platinum compounds should be monitored for allergic symptoms. Allergic reactions can occur during any cycle.

In case of an anaphylactic-like reaction to ELOPLAT, the infusion should be immediately discontinued and appropriate symptomatic treatment initiated. ELOPLAT re-challenge is contraindicated**.**

Neurological toxicity:

Sensory peripheral neurotoxicity of ELOPLAT should be carefully monitored, especially if co-administered with other medications with specific neurological toxicity. A neurological examination should be performed before each administration and periodically thereafter.

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

- If symptoms last longer than seven days and are troublesome, the subsequent ELOPLAT dose should be reduced from 85 to 65 mg/m^2 (metastatic setting) or 75 mg/m^2 (adjuvant setting).
- If paraesthesia without functional impairment persists until the next cycle, the subsequent ELOPLAT dose should be reduced from 85 to 65 mg/m^2 (metastatic setting) or 75 mg/m^2 (adjuvant setting).
- If paraesthesia with functional impairment persists until the next cycle, ELOPLAT administration should be discontinued.
- If these symptoms improve following discontinuation of ELOPLAT therapy, resumption of therapy may be considered.

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

For patients who develop acute laryngopharyngeal dysaesthesia (see section 4.8), during or within the hours following the 2-hour infusion, the next ELOPLAT infusion should be administered over 6 hours. To reduce such dysaesthesia, inform the patient to avoid exposure to cold and to avoid ingesting fresh/cold food and/or beverages during or within hours following ELOPLAT administration.

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, as in ELOPLAT, in combination chemotherapy.

Signs and symptoms of Reversible Posterior Leukoencephalopathy Syndrome (RPLS, also known as PRES, Posterior Reversible Encephalopathy Syndrome) include headache, altered mental functioning, seizures, abnormal vision from blurriness to blindness, associated with or without hypertension (see section 4.8). Diagnosis of RPLS/PRES is based upon confirmation by brain imaging.

Gastrointestinal toxicity:

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, hypokalaemia, metabolic acidosis and renal impairment may be associated with severe diarrhoea/emesis particularly when combining ELOPLAT with 5-fluorouracil (5-FU).

Intestinal ischaemia:

Cases of intestinal ischaemia, including fatal outcomes, have been reported with ELOPLAT treatment. In case of intestinal ischaemia, ELOPLAT treatment should be discontinued and appropriate measures initiated (see section 4.8).

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Haematological toxicity:

If haematological toxicity occurs (neutrophils < 1,5 x 10^9 /L or platelets < 50 x 10^9 /L), after a course of therapy or if myelosuppression is present prior to the start (first course) of therapy (see section 4.3), administration of the next course or the first course of therapy should be postponed until the haematological values return to acceptable levels. A full blood count with white cell differential should be performed prior to the start of therapy and before each subsequent course. 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 (see section 4.8). If any of these events occurs, oxaliplatin should be discontinued.

If severe/life-threatening diarrhoea, severe neutropenia (neutrophils < 1,0 x 10^9/L), febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection with an absolute neutrophil count < 1,0 x 10^9/L, a single temperature of > 38,3 °C or a sustained temperature of > 38 °C for more than one hour), or severe thrombocytopenia (platelets < 50 x 10^9/L) occurs, ELOPLAT must be discontinued until improvement or resolution, and the dose of ELOPLAT should be reduced from 85 to 65 mg/m^2 (metastatic setting) or 75 mg/m^2 (adjuvant setting) at subsequent cycles, in addition to any 5-fluorouracil dose reductions required.

Patients must be adequately informed of the risk of diarrhoea/emesis and neutropenia after ELOPLAT/5-fluorouracil administration in order to contact urgently their treating doctor 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 10^9 /L.

Infection:

Sepsis, neutropenic sepsis and septic shock have been reported in patients treated with ELOPLAT, including fatal outcomes (see section 4.8). If any of these events occurs, ELOPLAT should be discontinued.

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Pulmonary toxicity:

In the case of unexplained respiratory symptoms such as non-productive cough, dyspnoea, crackles or radiological pulmonary infiltrates, ELOPLAT should be discontinued until further pulmonary investigations exclude an interstitial lung disease (see section 4.8).

Haemolytic-uraemic syndrome (HUS):

Haemolytic-uraemic syndrome (HUS) is a life-threatening side effect (see section 4.8). 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)

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). Caution should be exercised in patients with disorders related to DIC, such as infections, sepsis etc.

Hepatic toxicity:

In case of abnormal liver function test results or portal hypertension which does not obviously result from liver metastases, ELOPLAT-induced hepatic vascular disorders should be considered.

QT prolongation:

QT prolongation may lead to an increased risk for ventricular arrhythmias including Torsade de Pointes, which can be fatal. Caution should be exercised in patients with a history or a predisposition for prolongation of QT, those who are taking medicines known to prolong QT interval and those with electrolyte disturbances such as

hypokalaemia, hypocalcaemia, or hypomagnesaemia. In case of QT prolongation, oxaliplatin treatment should be discontinued (see section 4.5 and 4.8).

Cardiac disorders:

Post-marketing reports with ELOPLAT use include acute coronary syndrome (including myocardial infarction, coronary arteriospasm, and cardiac arrest). In case of acute coronary syndrome, treatment with ELOPLAT may need to be interrupted or discontinued based on the individual benefit-risk assessment (see section 4.8).

Post-marketing reports with oxaliplatin include cardiac dysrhythmias (including bradyarrhythmia, tachycardia and ELOPLAT may need to be interrupted or discontinued based on the individual benefit-risk assessment (see section 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 section 4.5 and 4.8).

Duodenal ulcer:

Oxaliplatin treatment can cause duodenal 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).

Immunosuppressant effects/increased susceptibility to infections:

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic medicines including oxaliplatin such as ELOPLAT, may result in serious or fatal infections. Vaccination with a

live vaccine should be avoided in patients receiving ELOPLAT. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Do not use intraperitoneal route of administration:

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

Fertility:

Male patients treated with ELOPLAT 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 OELOPLAT may have an anti-fertility effect which could be irreversible.

Pregnancy:

Women should not become pregnant during and up to 4 months after treatment with OXALIWIN and should use an effective method of contraception (see section 4.6).

4.5 Interaction with other medicines and other forms of interaction

In patients who have received a single dose of 85 mg/m^2 of oxaliplatin, immediately before administration of 5-fluorouracil (5-FU), no change in plasma levels of 5-fluorouracil (5-FU) has been observed.

In vitro, no significant displacement of oxaliplatin binding to plasma proteins has been observed with the following medicines: 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).

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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 vaccines should be avoided in patients receiving oxaliplatin (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Effective contraceptive measures should be taken in potentially fertile patients prior to initiating chemotherapy with ELOPLAT. Further, barrier contraceptive measures must be taken during and after cessation of therapy (4 months for women and 6 months for men) (see section 4.4)

Pregnancy

To date there is no available information on the safety of use in pregnant women. Based on pre-clinical findings, ELOPLAT is likely to be lethal and/or teratogenic to the human foetus at the recommended therapeutic doses and is consequently not recommended during pregnancy and should only be considered after suitably appraising the patient of the risk to the foetus and with the patient's consent.

Lactation:

Excretion in breast milk has not been studied. Breastfeeding is contraindicated during ELOPLAT therapy.

Fertility:

ELOPLAT may have an anti-fertility effect which could be irreversible, and patients are advised to seek advice on conservation of sperm prior to treatment (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 results 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.

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

COMBINATION THERAPY OF ELOPLAT WITH 5-FU/FA (FOLFOX):

MedDRA System Organ Classes	**Frequency category**		
	Frequent	**Less frequent**	**Frequency unknown**
Infections and Infestations	Infection, rhinitis, upper respiratory tract infection, neutropenic sepsis.	Sepsis, including fatal outcomes.	Septic shock, including fatal outcomes.
Blood and lymphatic system disorders	Anaemia, neutropenia, thrombocytopenia, leukopenia, lymphopenia, febrile neutropenia.	Haemolytic anaemia, immune-allergic thrombocytopenia, disseminated intravascular coagulation (DIC), including fatal outcomes (see section 4.4)	Haemolytic-uremic syndrome, autoimmune pancytopenia, pancytopenia, secondary leukaemia.
Immune system disorders	Allergic reactions such as: skin rash (particularly urticaria), conjunctivitis, rhinitis, anaphylactic reactions including bronchospasm, angioedema,		Delayed hypersensitivity.

	hypotension, sensation of chest pain and anaphylactic shock.		
Metabolism and nutrition disorders	Anorexia, hyperglycaemia, hypokalaemia, hypernatraemia, dehydration, hypocalcaemia.	Metabolic acidosis.	
Psychiatric disorders	Depression, insomnia.	Nervousness.	
Nervous system disorders	Dysesthesia/paraesthesia of extremities and peripheral sensory neuropathy, headache, sensory disturbance, acute neuro sensory manifestations (see section 4.4), dysgeusia, dizziness, motor neuritis, flushing and meningism.	Dysarthria, loss of deep tendon reflexes, Lhermitte's sign, reversible posterior leukoencephalopathy syndrome (RPLS, also known as PRES) (see section 4.4).	Convulsions, ischemic or haemorrhagic cerebrovascular disorder.
Eye disorders	Conjunctivitis and abnormal vision.	Visual acuity reduced transiently, visual field disturbances and optic neuritis, transient vision loss, reversible following therapy discontinuation.	

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Ear and labyrinth disorders		Ototoxicity, deafness.	
Cardiac disorders	Chest pain.		QT prolongation, which may lead to ventricular dysrhythmias including Torsade de Pointes, which may be fatal (see sections 4.4 and 4.5), acute coronary syndrome including myocardial infarction and coronary arteriospasm and cardiac arrest; cardiac dysrhythmias including bradyarrhythmia, tachycardia and atrial fibrillation.
Vascular disorders	Epistaxis, haematuria, deep thrombophlebitis, rectum haemorrhage, flushing, deep vein thrombosis, thromboembolic events (including pulmonary embolism) and hypertension.		

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Respiratory, thoracic and mediastinal disorders	Dyspnoea, cough, epistaxis, rhinitis, hiccups, upper respiratory infection and pulmonary embolism.	Interstitial lung diseases, which may be fatal and pulmonary fibrosis (see section 4.4).	Laryngospasm, pneumonia and bronchopneumonia, including fatal outcomes.
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, stomatitis/mucositis, abdominal pain, constipation, dyspepsia, gastroesophageal reflux, gastrointestinal haemorrhage, rectal haemorrhage, dehydration, hypokalaemia, metabolic acidosis, ileus, intestinal obstruction, renal disorders may be associated with severe diarrhoea/vomiting, particularly when ELOPLAT is combined with 5-FU (see section 4.4).	Ileus, intestinal obstruction, colitis including *Clostridium difficile* diarrhoea, pancreatitis.	Intestinal ischaemia, including fatal outcomes, duodenal ulcer, and complications, such as duodenal ulcer haemorrhage or perforation, which can be fatal (see section 4.4), oesophagitis.
Hepato-biliary disorders		Liver sinusoidal obstruction syndrome, also known as veno-occlusive disease of	Focal nodular hyperplasia.

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		liver, or pathological manifestations related to such liver disorder, including peliosis hepatitis, nodular regenerative hyperplasia, perisinusoidal fibrosis. Clinical manifestations may be portal hypertension and/or increased transaminases.	
Skin and subcutaneous tissue disorders	Skin disorder and alopecia, skin exfoliation (hand and foot syndrome), rash, erythematous rash, sweating increased and nail disorder.		Hypersensitivity vasculitis.
Musculoskeletal, connective tissue and bone disorders		Back pain, bone pain, arthralgia.	Rhabdomyolysis, including fatal outcomes (see sections 4.4 and 4.5).
Renal and urinary disorders	Dysuria, haematuria, abnormal micturition frequency.	Acute tubular necrosis, acute interstitial nephritis and acute renal failure.	

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General disorders and administration site conditions	Fatigue, fever, rigors (tremors) either from infection (with or without febrile neutropenia) or possibly from immunological mechanism, asthenia, pain, injection site reactions including local pain, redness, swelling and thrombosis. Extravasation may result in local pain and inflammation, which may be severe and lead to complications including necrosis, especially when ELOPLAT is infused through a peripheral vein.		
Investigations	Hepatic enzyme increase, alkaline phosphatase increase, creatinine increase, bilirubin increase, lactate dehydrogenase (LDH) increase, weight increase (adjuvant setting), weight		

	decrease (metastatic setting).		
Injury, poisoning, and procedural complications		Fall.	

Description of selected adverse reactions

Nervous system disorders

Dysaesthesia/paraesthesia of extremities and peripheral neuropathy:

The dose-limiting toxicity of ELOPLAT is neurological (see section 4.4). It involves a sensory peripheral neuropathy characterised by peripheral dysaesthesia and/or paraesthesia with or without cramps, often triggered by the cold. The symptoms occur in 95 % of patients treated. The duration of these symptoms, which usually recede between the cycles of treatment, increases with the number of treatment cycles.

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

This functional disorder includes difficulties in executing delicate movements and is a possible consequence of sensory impairment. The risk of occurrence of a functional disorder for a cumulative dose of approximately 850 mg/m2 (10 cycles) is 10 % and 20 % for a cumulative dose of 1 020 mg/m2 (12 cycles).

In the majority of cases, the neurological signs and symptoms improve or totally recover when treatment is discontinued. In the adjuvant setting of colon cancer, 6 months after recovery 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 localised paraesthesias of moderate intensity (2,3 %) or with paraesthesias that interfere with functional activities (0,5 %).

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Acute neurosensory manifestations:

These symptoms usually develop at the end of the 2-hour ELOPLAT infusion or within a few hours, abate spontaneously within the next hours or days, and frequently recur with further cycles. They may be precipitated or exacerbated by exposure to cold temperatures or objects. They usually present as transient paraesthesia, dysaesthesia and hypoaesthesia.

An acute syndrome of pharyngolaryngeal dysaesthesia occurs in 1 - 2 % of patients and is characterised by subjective sensations of dysphagia or dyspnoea/feeling of suffocation, without any 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.

Other symptoms occasionally observed, particularly of cranial nerve dysfunction may be either associated with above-mentioned events, or also occur isolated such as ptosis, diplopia, aphonia/dysphonia/hoarseness, sometimes described as vocal cord paralysis, abnormal tongue sensation or dysarthria, sometimes described as aphasia, trigeminal neuralgia/facial pain/eye pain, decrease of visual acuity and visual field disorders. In addition, the following symptoms have been observed: jaw spasm/muscle spasms/involuntary muscle contractions/muscle twitching/myoclonus, abnormal coordination/abnormal gait/ataxia/balance disorders, throat or chest tightness/pressure/discomfort/pain.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of ELOPLAT. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

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Suspected adverse reactions can also be reported directly to the HCR via the link: https://pvi1j.solutions.iqvia.com or the e-mail address, adverse.event.sac@sandoz.com

4.9 Overdose

There is no known antidote to ELOPLAT. 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 Pharmacodynamic properties:

Pharmacotherapeutic group: other antineoplastic agents, platinum compounds, ATC code: L01XA03

Pharmacological Classification: A 26 Cytostatic agents

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

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

A synergistic cytotoxic action has been observed in combination with 5-fluorouracil both *in vitro* and *in vivo*.

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, oxaliplatin at 85 mg/m^2 every two weeks for 1 to 3 cycles are as follows:

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Summary of platinum pharmacokinetic parameter estimates in ultrafiltrate following multiple doses of oxaliplatin at 85 mg/m² every 2 weeks.

Dose	**C_{max} (ug,h/mL)**	**AUC_{0-48} (ug,h/mL)**	**AUC (ug,h/ml)**	**$T_{1/2}$ α (h)**	**$T_{1/2}$β (h)**	**$T_{1/2}$ɣ (h)**	**V_{ss} L**	**CL (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

Mean AUC_{0-48}, and C_{max} values were determined on Cycle 3 (85 mg/m²) or cycle 5 (130 mg/m²).

Mean AUC, V_{ss}, CL and CL_{R0-48} values were determined on Cycle 1.

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

$T_{1/2}$α, $T_{1/2}$β, and $T_{1/2}$ ɣ 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 and steady state was attained by cycle one in this matrix.

Inter- and intra-subject variability is generally low.

Biotransformation and elimination*:*

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.

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

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

A significant decrease in clearance from 17,6 ± 2,18 L/h to 9,95 ± 1,91 L/h in renal impairment was observed together with a statistically significant decrease in distribution volume from 330 ± 40,9 to 241 ± 36,1 L.

Special populations:

Renal impairment patients:

The disposition of oxaliplatin was studied in patients with varying degrees of renal function. Elimination of oxaliplatin is significantly correlated with the creatinine clearance (CIcr). Total body clearance of plasma ultrafiltrate (PUF) platinum was reduced in patients with impaired renal function by 26 % in mild (CIcr = 50 to 80 mL/min), 57 % in moderate (CIcr = 30 to 49 mL/min), and 79 % in severe (CIcr < 30 mL/min) renal impairment compared to patients with normal function (CIcr > 80 mL/min). There was a trend of increased beta and gamma half-lives of PUF platinum with increasing degree of renal impairment and mainly in the severe group. However, the results were not conclusive due to the large inter-patient variability and the small number (4) of patients with severe renal impairment. Urinary excretion of platinum and renal clearance of PUF platinum also decreases with impaired renal function (see sections section 4.2 and 4.4).

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.

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In patients with metastatic colorectal cancer, the efficacy of oxaliplatin (85 mg/m^2 repeated every two weeks) combined with 5-fluorouracil/folinic acid is reported in three clinical studies: The two randomised clinical trials, EFC2962 in front-line therapy and EFC4584 in pre-treated patients, demonstrated a significantly higher response rate and a prolonged progression-free survival (PFS)/time to progression (TTP) as compared to treatment with 5- fluorouracil/folinic acid alone.

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 (42-46)	NA
	P value = 0,0001		
Pre-treated patients EFC4584 (refractory to CPT-11+5-FU/LV)	0,0 (0,0-2,5)	9,9 (5,6-15,8)	1,3 (0,1-4,6)
	P value = 0,0001		
Pre-treated patients EFC2964 (refractory to 5-FU/LV)	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	6,0	8,2	

EFC2962 (PFS)	(5,5-6,5)	(7,2-8,8)	NA
	Log-rank P value = 0,0003		
Pre-treated patients EFC4584 (TTP) (refractory to CPT-11+5-FU/LV)	2,7 (1,8-3,0)	4,6 (4,2-6,1)	1,6 (1,4-2,7)
	Log-rank P value = 0,0001		
Pre-treated patients EFC2964 (refractory to 5-FU/LV)	NA	5,1 (3,1-5,7)	NA

Median overall survival (OS) under FOLFOX4 versus LV5FU2

Median OS, months (95 % CI) ITT analysis	**LV5FU2**	**FOLFOX4**	**Oxaliplatin single agent**
Front-line treatment EFC2962 (PFS)	14,7 (13,0-18,2)	16,2 (14,7-18,2)	NA
	Log-rank P value = 0,12		
Pre-treated patients EFC4584* (refractory to CPT-11+5-FU/LV)	8,8 (7,3-9,3)	9,9 (9,1-10,5)	8,1 (7,2-8,7)
	Log-rank P value = 0,0001		
Pre-treated patients EFC2964 (refractory to 5-FU/LV)	NA	10,8 (9,3-12,8)	NA

NA: Not applicable
*Survival data with 90 % of the events (deaths) reported

In pre-treated patients 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 5FU/FA alone (32,6 % vs 11,9 %).

Professional Information

In non pre-treated patients no statistically significant difference was observed between the two treatment groups in terms of quality of life. However, the quality of life scores were generally better in the control group with respect to global state of health and pain and worse in the oxaliplatin group with respect to nausea and vomiting.

In the adjuvant setting the MOSAIC comparative phase III study (EFC3313) randomised 2 246 patients (899 stage II/Duke's B2 and 1 347 stage III/Duke's C) further to complete resection of the primary tumour of colon cancer either to 5-FU/FA alone (LV5FU2, N = 1 123, B2/C = 448/675) or to combination of oxaliplatin and 5-FU/FA (FOLFOX4, N = 1 123, 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	72,9	78,2
(95 % CI)	(70,2-75,7)	(75,6-80,7)
Hazard ratio (95 % CI)	0,77 (0,65-0,91)	
Stratified log rank test	P = 0,002	

* Median (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 (Duke's B2)**		**Stage III (Duke's C)**	
Treatment arm	LV5FU2	FOLFOX4	LV5FU2	FOLFOX4

Percent 3-year disease free survival (95 % CI)	84,3 (80,6-87,9)	87,0 (83,6-90,3)	65,3 (61,6-69,1)	72,2 (68,6-75,8)
Hazard ratio (95 % CI)	0,8 (0,56-1,15)		0,76 (0,62-0,92)	
Log-rank test	P = 0,151		P = 0,002	

* Median (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, 87,7 % of the patients were still alive in the FOLFOX4 arm versus 86,6 % 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 93,2 % versus 93,6 % in the stage II (Duke's B2) sub-population (hazard ratio = 1,06) and 84,4 % versus 81,9 % in the stage III (Duke's C) sub-population (hazard ratio = 0,86), for FOLFOX4 and LV5FU2, respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection

6.2 Incompatibilities

DO NOT use with alkaline medicines or solutions (in particular 5-fluorouracil, basic solutions, trometamol and folinic acid products containing trometamol as an excipient).

ELOPLAT can be co-administered with folinic acid infusion using a Y-line placed immediately before the site of infusion. These two medicines should not be combined in the same infusion bag. Folinic acid must be

diluted using isotonic infusion solutions such as 5 % glucose solution but NOT sodium chloride solutions, chloride containing solutions or alkaline solutions. Flush the line after ELOPLAT administration.

- DO NOT dilute for infusion with saline solution.
- DO NOT mix with other medicines in the same infusion bag or infusion line.
- Refer to the instructions concerning the simultaneous administration with folinic acid.

DO NOT use injection equipment containing aluminium.

6.3 Shelf life

24 months

Chemical and physical in-use stability of Oxaliplatin 5mg/ml, concentrate for solution for infusion solutions at concentrations of 0,2 mg/ml and 1,0 mg/ml has been demonstrated for 96 hours at 2 to 8 °C when protected from light and for 24 hours at room temperature (20 °C to 25 °C), protected from light. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at room temperature (20 °C to 25 °C), unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store at or below 30 ºC.

Protect from light.

Keep vial in outer carton until required for use.

For single use only.

Any unused solution should be discarded.

6.5 Nature and contents of container

ELOPLAT concentrate for solution for infusion; 50 mg/10 mL, 100 mg/20 mL, 150 mg/30 mL and 200 mg/40 mL is packed in 10 mL, 20 ml and 50 mL type I, colourless glass vials respectively, with a rubber stopper and sealed with an aluminium crimp cap.

Professional Information

The vials may be packed additionally in a plastic clear protective covering around the primary pack.

The vials are packed into an outer cardboard carton.

The pack sizes for Eloplat 50 is 1's or 5's or 10's and the other strengths are packed as 1's.

Not all packs may be marketed.

6.6 Special precautions for disposal and other handling

Caution should be exercised when handling and preparing ELOPLAT solutions.

The preparation of ELOPLAT must be carried out by trained specialist personnel with knowledge of the medicines used, in conditions that guarantee the protection of the environment and in particular the protection of the personnel handling the medicines. It requires a preparation area reserved for this purpose. It is forbidden to smoke, eat or drink in this area. Personnel must be provided with appropriate handling materials, notably long-sleeved gowns, protection masks, caps, protective goggles, sterile single-use gloves, protective covers for the work area, containers and collection bags for waste.

Excreta and vomit must be handled with care.

Pregnant women must be warned to avoid handling cytotoxic medicines.

Any broken container must be treated with the same precautions and considered as contaminated waste. Contaminated waste should be incinerated in suitably labelled rigid containers (see below "Disposal").

If ELOPLAT concentrate or infusion solution should come into contact with skin, was immediately and thoroughly with water.

If ELOPLAT concentrate or infusion solution should come into contact with mucous membranes, wash immediately and thoroughly with water.

Concentrate for solution for infusion and dilution for intravenous infusion

Inspect visually prior to use. Only clear solutions without particles should be used. The medicinal product is for single use only. Any unused solution should be discarded.

Professional Information

Disposal:

Remnants of ELOPLAT as well as all materials that have been used for dilution and administration must be destroyed according to hospital standard procedures applicable to cytotoxic medicines with due regard to current laws related to the disposal of hazardous waste.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

2090

8. REGISTRATION NUMBER(S)

ELOPLAT 50: 46/26/0919

ELOPLAT 100: 46/26/0920

ELOPLAT 150: 46/26/0921

ELOPLAT 200: 46/26/0922

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 November 2017

10. DATE OF REVISION OF THE TEXT

03 December 2024

[1]Company Reg. No.: 1990/001979/07