SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Oxaliplatin 5 mg/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of concentrate for solution for infusion contains 5 mg oxaliplatin.

10 ml of concentrate for solution for infusion contain 50 mg of oxaliplatin

20 ml of concentrate for solution for infusion contain 100 mg of oxaliplatin

40 ml of concentrate for solution for infusion contain 200 mg of oxaliplatin

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion

Clear, colourless liquid

pH: 4.0 – 7.0

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 tumor
- Treatment of metastatic colorectal cancer.

4.2 Posology and method of administration

The preparation of injectable solutions of cytotoxic agents must be carried out by trained specialist personnel with knowledge of the medical product used, in conditions that guarantee the integrity of the medical product, the protection of the environment and in particular the protection of the personnel handling the medicinal products, in accordance with the hospital policy. It requires a preparation area reserved for this purpose. It is forbidden to smoke, eat or drink in this area (see section 6.6 for detailed information).

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 (see section 4.4).

Oxaliplatin should always be administered before fluoropyrimidines-i.e. 5-fluorouracil (5FU).

Oxaliplatin is administered as a 2- to 6-hour intravenous infusion in 250 to 500 ml of 5% glucose solution (50mg/ml) to give a concentration between 0.2 mg/ml and 0.70 mg/ml; 0.7 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 (see section 4.3 and 5.2).

In patients with mild or moderate renal impairment, treatment may be initiated at the normally recommended dose 85 mg/ m2 (see section 4.4 and 5.2).

- Hepatic impairment:

In a 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.

- Pediatric patients:

There is no relevant indication for use of oxaliplatin in children. The effectiveness of oxaliplatin single agent in the paediatric populations with solid tumors has not been established (see section 5.1).

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 should always precede that of 5-fluorouracil.

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

Instructions for use

Oxaliplatin must be further diluted before use. Only 5% glucose diluent is to be used to dilute the concentrate for solution for infusion. (see section 6.6).

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 < 2 x 109/l and/or platelet count of < 100 x 109/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.

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 medications 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 several hours after a 2-hour infusion, the subsequent oxaliplatin infusion must 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/m^2 (metastatic setting) or 75 mg/m^2 (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/m^2 (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 about 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 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 haematological changes

Gastrointestinal toxicity of oxaliplatin, i.e. symptoms such as nausea and vomiting, requires prophylactic and/or therapeutic use of antiemetics (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-fluorouracil (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 < 1.5 x 10^9/l or platelets < 50 x 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 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.

Patients must be adequately informed about the risk of diarrhoea/emesis, mucositis/stomatitis and neutropenia following oxaliplatin and 5-fluorouracil (5-FU) administration so 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 I 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), the usual dose adjustments for 5-fluorouracil 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°C or a sustained temperature of >38°C for more than one hour), or grade 3-4 thrombocytopenia (platelets $< 50 \times 10^9$/l) occur, the dose of oxaliplatin should be reduced from 85 mg/m^2 to 65 mg/m^2 (metastatic setting) or 75 mg/m2 (adjuvant setting), in addition to any 5-fluorouracil (5-FU) dose reductions required.

Pulmonary

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

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 hypokalaemia, 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 gastrointestinal haemorrhage and perforation, which can be fatal. In case of gastrointestinal 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 results 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 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 haemorrhage may occur when oxaliplatin is administered by intraperitoneal route (off- label route of administration).

4.5 Interaction with other medicinal products 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 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 vaccines 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.

Breast feeding

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

Fertility

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

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 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.

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 and folinic acid (5- FU and FA) were of gastrointestinal (diarrhoea, nausea, vomiting and mucositis), haematological (neutropenia, thrombocytopenia) and neurological (acute and dose cumulative peripheral sensory neuropathy) nature.

Overall, these adverse events were more frequent and severe when 5-FU/FA was administered in combination with oxaliplatin compared to 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 (≥ 1/1,000 < 1/100), rare (≥ 1/10,000 < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Further details are given following this table.

MedDRA classification	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Infections and Infestations *	• Infection	• Rhinitis • Upper respiratory tract infection • Neutropenic sepsis+	• Sepsis+			• Septic shock
Blood and lymphatic system disorders *	• Anemia • Neutropenia • Thrombo-cytopenia • Leukopenia • Lymphopenia	• Febrile neutropenia		• Haemolytic anemia • Immunoallergic thrombocytopenia • Disseminated intravascular coagulation		• Autoimmune pancytopenia • hemolytic uremic syndrome, pancytopenia, secondary leukemia

Immune system disorders*	• Allergy/allergic reaction++					
Metabolism and nutrition disorders	• Anorexia • Hyperglycemia, • Hypokalaemia • Hypernatraemia	• Dehydration • Hypocalcaemia	• Metabolic acidosis			
Psychiatric disorders		• Depression • Insomnia	• Nervousness			
Nervous system disorders *	• Peripheral sensory neuropathy • Headache • Sensory disturbance • Dysgeusia	• Dizziness • Motor neuritis • Meningism		• Dysarthria, • Reversible Posterior Leukoencephalopathy syndrome (RPLS also known as PRES)**		• Convulsion, ischaemic or haemorragic cerebrovascular disorder
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		
Vascular disorders		• Haemorrhage • Flushing • Deep vein thrombosis • Hypertension				• QT prolongation • Acute coronary syndrome
Respiratory, thoracic and	• Dyspnoea • Cough	• Hiccups • Pulmonary		• Interstitial lung disease,		• Laryngospasm, pneumonia

mediastinal disorders	• Epistaxis	embolism		sometimes fatal • Pulmonary fibrosis**		and bronchopneumonia
Gastrointestinal disorders*	• Diarrhea • Nausea • Vomiting • Stomatitis / Mucositis • Abdominal pain • Constipation	• Dyspepsia • Gastroesophageal reflux • Gastrointestinal haemorrhage • Rectal haemorrhage	• Ileus • Intestinal obstruction	• Colitis including *Clostridium difficile* diarrhea • Pancreatitis		• Intestinal ischaemia, gastrointestinal ulcer and perforation, oesophagitis
Hepato-biliary disorders	• Hepatic enzyme increase, blood bilirubin increase				• Liver sinusoidal obstruction syndrome (also known as veno-occlusive disease of liver)	• Focal nodular hyperplasia
Skin and subcutaneous tissue disorders	• Skin disorder • Alopecia	• Skin exfoliation (i.e. hand and foot syndrome) • Rash erythematous • Rash • Hyperhidrosis • Nail disorder				• Hyper-sensitivity vasculitis
Musculoskeletal system, connective tissue and bone disorders	• Back pain	• Arthralgia • Bone pain				• Rhabdomyolysis
Renal and urinary disorders		• Haematuria • Dysuria • Micturition frequency abnormal				• Acute tubular necrosis, acute interstitial nephritis, acute renal failure

General disorders and administration site conditions	• Fever+++ • Injection site reaction++++ • Fatigue • Asthenia • Pain					
Investigations	• Blood alkaline phosphatase increase • Blood bilirubin increase • Blood lactate dehydrogenase (LDH) increase • Hepatic enzymes increase • Weight increase (adjuvant setting)	• Blood creatinine increase • Weight decrease (metastatic setting)				
Injury,poisoning And procedural complications		• Fall;				

* See detailed information in the section below

** See section 4.4.

\+ Common neutropenic sepsis, 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, angioedema, 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 (see section 4.4).

Description of selected adverse reactions

Blood and lymphatic system disorders:

Incidence by patient (%) and by grade

Oxaliplatin/5 FU/FA, 85 mg/m^2 every 2 weeks	Treatment of metastases			Adjuvant therapy		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 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

Rare (>1/10,000 to <1/1,000)
Disseminated intravascular coagulation (DIC), including fatal outcomes (see section 4.4).

Postmarketing experience with frequency not known

Hemolytic uremic syndrome

Autoimmune pancytopenia

Pancytopenia

Secondary leukemia

Infections and infestations:

Incidence by patient (%)

Oxaliplatin and 5-FU/FA 85 mg/m^2 Every 2 weeks	**Metastatic Setting All grades**	**Adjuvant Setting 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 (%) and by grade

Oxaliplatin/5 FU/FA, 85mg/m^2 every 2 weeks	Treatment of metastases			Adjuvant therapy		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 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 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 functional disorders is an indication for dose adjustments or even treatment discontinuation, depending on the duration of these symptoms (see section 4.4).

These functional disorders include difficulties in executing delicate movements and are a possible consequence of sensory impairment. The risk of occurrence of persistent symptoms for a cumulative dose of 850mg/m^2 (10 cycles) is approximately 10% and 20% for a cumulative dose of 1,020 mg/m^2 (12 cycles).

In the majority of the cases, the neurological signs and symptoms improved or totally recovered when treatment was 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 persistent localised paraesthesia of moderate intensity (2.3%) or with paraesthesia 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, dysaesthesia and hypoesthesia. An acute syndrome of pharyngolaryngeal dysaesthesia occurs in 1% and 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 were rapidly reversible even in the absence of treatment. Prolongation of the infusion helps to reduce the incidence of this syndrom (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 the 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 not known

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 (see section 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).

Respiratory, thoracic and mediastinal disorders:

Post-marketing experience with frequency not known

Laryngospasm

Pneumonia and bronchopneumonia, including fatal outcomes

Gastrointestinal disorders:

Incidence by patient (%) and by grade

Oxaliplatin/5 FU/FA, 85 mg/m^2 every 2 weeks	Treatment of metastases			Adjuvant therapy		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 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, hypokalemia, 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).

Post-marketing experience with frequency not known

Intestinal ischaemia, including fatal outcomes (see section 4.4).

Gastrointestinal ulcer and perforation, which can be fatal (see section 4.4).

Oesophagitis

Hepatobiliary disorders:

Very rare (< 1/10,000): Hepatic sinusoidal obstruction syndrome, also known as veno-occlusive liver disease, or pathological manifestations related to such liver disorder, including peliosis hepatis, nodular regenerative hyperplasia and 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 (see section 4.4).

Renal and urinary disorders:

Very rare (<1/10,000):

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

Skin and subcutaneous tissue disorders:

Post-marketing experience with frequency not known

Hypersensitivity vasculitis

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 Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

4.9 Overdose

Symptoms
There is no known antidote to oxaliplatin. In cases of overdose, exacerbation of adverse events can be expected.

Management
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

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, 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.

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.

Clinical efficacy and safety

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, a 2-arm comparative phase III study, EFC2962, 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, a 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, an uncontrolled phase II study, EFC2964, 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 in front-line therapy, EFC2962, and in pretreated patients (EFC4584 study), 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 the study of EFC4584performed in refractory pretreated patients, the difference in median overall survival (OS) between the combination of oxaliplatin and 5-FU/FA versus 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 (42-56)	NA*
	P value = 0.0001		
Pretreated patients EFC4584 (refractory to CPT-11 + 5-FU/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 + 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 (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 EFC4584(TTP) (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 (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 randomised 2246 patients (899 stage II / Duke's B2 and 1347 stage III / Duke's C) further to complete resection of the primary tumor 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).

MOSAIC-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).

MOSAIC-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 (80.9-87.7)	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)	
Stratified 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.

Paediatric population

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

5.2 Pharmacokinetic properties

Adsorption and distribution

The pharmacokinetics of individual active compounds have not been determined. The pharmacokinetics of ultrafiltrable platinum, representing a mixture of all unbound, active and inactive platinum species, following a two-hour infusion of oxaliplatin at 130 mg/m^2 every three weeks for 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**	**$t_{1/2\alpha}$**	**$t_{1/2\beta}$**	**$t_{1/2\gamma}$**	**V_{ss}**	**CL**

	µg/ml	µg * h /ml	µg * h /ml	h	h	h	l	l / h
85 mg/m^2								
Mean	0.814	4.19	4.68	0.43	16.8	391	440	17.4
SD	0.193	0.647	1.40	0.35	5.74	406	199	6.35
130 mg/m^2								
Mean	1.21	8.20	11.9	0.28	16.3	273	582	10.1
SD	0.10	2.40	4.60	0.06	2.90	19.0	261	3.07

Mean AUC_{0-48} and C_{max} values were determined on Cycle 3 (85 mg/m2) or Cycle 5 (130 mg/m2). Mean AUC, V_{ss}, CL, and CLR_{0-48} 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. $t_{1/2\alpha}$, $t_{1/2\beta}$, $t_{1/2\gamma}$ were determined by compartmental analysis (Cycles 1-3 combined).

At the end of a 2-hour infusion, 15 % of the administered platinum is present in the systemic circulation, the remaining 85 % 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/m^2 every two weeks or 130 mg/m^2 every three weeks and steady state was attained by Cycle one in this matrix. Inter- and intra-subject variability is generally low.

Biotransformation

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.

Special populations

Renal impairment

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 (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/m2 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 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

Water for injections

6.2 Incompatibilities

The diluted medicinal product should not be mixed with other medications in the same infusion bag or infusion line. Under instructions for use described in section 6.6, oxaliplatin can be co- administered with folinic acid (FA) via a Y-line.

- DO NOT mix with alkaline medicinal products or solutions, in particular 5-fluorouracil, trometamol and folinic acid products containing trometamol as an excipient and trometamol salts of other medicinal products. Alkaline medicinal products 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 mix with other medicinal products in the same infusion bag or infusion line (see section 6.6 for instructions concerning simultaneous administration with folinic acid).
- DO NOT use injection equipment containing aluminium.

6.3 Shelf life

Medicinal product as packaged for sale: 24 months

In-use stability after dilution

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 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 to 8 °C when diluted to the concentrations of 0.25 mg/ml and with glucose 5% as well as for 6 hours at 20-25 °C when diluted to the concentration of 0.25 mg/ml with glucose 5%.

6.4 Special precautions for storage

Keep the vial in the outer carton in order to protect from light.

Do not freeze.

Do not store above 25°C.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Colourless glass vials with grey Chlorobutyl rubber stoppers and aluminium seals with plastic flip-off caps, with or without a protective plastic overwrap.

Pack sizes:

50mg/10ml: 1 vial

100mg/20ml: 1 vial

200mg/40ml: 1 vial

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

Instructions for Handling

The handling of this cytotoxic agent by healthcare personnel requires every precaution to guarantee the protection of the handler and his surroundings.

The preparation of injectable solutions of cytotoxic agents must be carried out by trained specialist personnel with knowledge of the medicines used, in conditions that guarantee the integrity of the product, the protection of the environment and in particular the protection of the personnel handling the medicines, in accordance with the hospital policy. 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 agents.

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 section “Disposal”.

If oxaliplatin concentrate or solution for infusion should come into contact with skin, wash immediately and thoroughly with water.

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

Special precautions for administration

- DO NOT use injection material containing aluminium.

- DO NOT administer undiluted.
- Only glucose 5% infusion solution is to be used as a diluent. DO NOT dilute for infusion with sodium chloride or chloride containing solutions.
- DO NOT mix with any other medicinal products in the same infusion bag or administer simultaneously by the same infusion line.
- DO NOT mix with alkaline medicinal products or solutions, in particular 5-fluorouracil, folinic acid products containing trometamol as an excipient and trometamol salts of other products. Alkaline medicinal products or solution will adversely affect the stability of oxaliplatin.

Instructions for use with folinic acid (as calcium folinate or disodium folinate)

Oxaliplatin 85mg/m² IV infusion in 250 to 500 ml of 5% glucose solution is given at the same time as folinic acid IV infusion in 5% glucose solution, over 2 to 6 hours, using a Y-line placed immediately before the site of infusion. These two medicinal products 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, never in alkaline solutions or sodium chloride or chloride containing solutions.

Instruction for use with 5-fluorouracil

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

After oxaliplatin administration, flush the line and then administer 5-fluorouracil.

For additional information on medicinal products combined with oxaliplatin, see the corresponding manufacturer's summary of product characteristics.

Concentrate for solution for infusion

Inspect visually prior to use. Only clear solutions free from visible particles should be used. This medicinal product is for single use only. Any unused concentrate should be discarded.

Dilution for intravenous infusion

Withdraw the required amount of concentrate from the vial(s) and then dilute with 250 ml to 500 ml of a 5 % glucose solution to give an oxaliplatin concentration not less than 0.25 mg/ml.

Administer by intravenous infusion.

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 2 - 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 to 8 °C when diluted to the concentrations of 0.25 mg/ml with glucose 5% as well as for 6 hours at 20-25 °C when diluted to the concentration of 0.25 mg/ml with glucose 5%.

Inspect visually prior to use. Only clear solutions free from visible particles should be used.

The medicinal product is for single use only. Any unused infusion solution should be discarded (see chapter “disposal” below).

NEVER use sodium chloride solution for dilution.

Infusion

The administration of oxaliplatin does not require prehydration.

Oxaliplatin diluted in 250 to 500 ml of a 5 % glucose solution to give a concentration not less than 0.2 mg/ml must be infused either by peripheral vein or central venous line over 2 to 6 hours. When oxaliplatin is administered with 5-fluorouracil, the oxaliplatin infusion must precede the administration of 5-fluorouracil.

Disposal

Remnants of the medicinal product as well as all materials that have been used for dilution and administration must be destroyed according to hospital standard procedures applicable to cytotoxic agents and in accordance with local requirements related to the disposal of hazardous waste.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 15413/0107

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09/08/2021

10 DATE OF REVISION OF THE TEXT

13/04/2022