Package insert
OXACCORD
Oxaliplatin Injection USP 5mg/mL, 10mL and 20mL Vial

NAME OF THE MEDICINAL PRODUCT
OXACCORD
Oxaliplatin Injection USP 5mg/mL, 10mL and 20mL Vial

QUALITATIVE AND QUANTITATIVE COMPOSITION
1 ml concentrate for solution for infusion contains 5 mg oxaliplatin.
10 ml of concentrate for solution for infusion contains 50 mg of oxaliplatin
20 ml of concentrate for solution for infusion contains 100 mg of oxaliplatin
For full list of excipients see, see section *List of excipients*

PHARMACEUTICAL FORM
Concentrate for solution for infusion.
Clear, colourless solution

CLINICAL PARTICULARS
Therapeutic indications
Oxaliplatin in combination with 5-fluorouracil (5-FU) and folinic acid (FA) is indicated for:
- Adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of primary tumour
- Treatment of metastatic colorectal cancer.

Posology and method of administration
Posology
FOR ADULTS ONLY
The recommended dose for oxaliplatin in adjuvant setting is 85 mg/m^2 intravenously, repeated every two weeks for 12 cycles (6 months).
The recommended dose for oxaliplatin in treatment of metastatic colorectal cancer is 85 mg/m^2 intravenously, repeated every 2 weeks until disease progression or unacceptable toxicity.
The dose should be adjusted according to tolerability (see section *Special warnings and precautions for use*).

Oxaliplatin should always be administered before fluoropyrimidines – i.e. 5-fluorouracil (5-FU).
Oxaliplatin is administered as a 2-to 6-hour intravenous infusion in 250 to 500 ml of glucose 5% (50mg/ml) solution to give a concentration between 0.2 mg/ml and 0.70 mg/ml; 0.70 mg/ml is the highest concentration in clinical practice for an oxaliplatin dose of 85 mg/m^2.

Oxaliplatin has mainly been used in combination with continuous infusion 5-fluorouracil (5-FU) based regimens. For the two-weekly treatment schedule 5-fluorouracil (5-FU) 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 *Contraindications* and *Pharmacokinetic properties*). In patients with mild to moderate renal impairment, the recommended dose of oxaliplatin is 85 mg/m^2 (see section *Special warnings and precautions for use* and *Pharmacokinetic properties*).

Hepatic insufficiency
In a phase I study including patients with several levels of hepatic impairment, the frequency and severity of hepatobiliary 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 (5-FU) in patients over the age of 65. Therefore, no specific dose adjustment is required for elderly patients.

Paediatric patients
There is no relevant indication for use of oxaliplatin in children. The effectiveness of oxaliplatin single agent in the paediatric populations with solid tumours has not been established (see section *Pharmacodynamic properties*).

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 glucose 5% (50mg/ml) solution to obtain a concentration not less than 0.2 mg/ml must be infused either via a central venous line or into a peripheral vein over 2 to 6 hours.
Oxaliplatin infusion must always precede the administration of 5-fluorouracil (5-FU).
In the event of extravasation, administration must be discontinued immediately.

Instructions for use
Oxaliplatin must be diluted before use. Only glucose 5% (50mg/ml) solution should be used to dilute the concentrate for solution for infusion product. (see section *Special precautions for disposal and other handling*).

Contraindications
Oxaliplatin is contraindicated in patients who:
- have a known history of hypersensitivity to the active substance or to any of the excipients listed in section List of excipients
- are breast feeding
- have myelosuppression prior to starting first course, as evidenced by baseline neutrophils < 2 x 10^9/L and/or platelet count of < 100x 10^9/L
- have a peripheral sensory neuropathy with functional impairment prior to first course

- have a severely impaired renal function (creatinine clearance <30 ml/min) (see section *Pharmacokinetic properties*).

Special warnings and special 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 *Pharmacokinetic properties*).

Hypersensitivity reactions
Special surveillance should be ensured for patients with a history of allergic manifestations to other products containing platinum. Allergic reactions can occur during any cycle. 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.

Anaphylactic-like reactions such as difficulty in breathing, stridor, flushing, skin rash particularly urticaria, conjunctivitis, rhinitis, bronchospasm, angioedema, hypotension, tachycardia (possible consequence of hypotension) and anaphylactic shock have been reported, and this may occur within minutes of Oxaliplatin administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms.

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

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

For patients who develop acute laryngopharyngeal dysaesthesia (see section *Undesirable effects*), during or within the hours following a two-hour infusion, subsequent oxaliplatin infusion should be administered over 6 hours.

Peripheral neuropathy
If neurological symptoms (paraesthesia, dysaesthesia) occur, the following recommended oxaliplatin dose 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 to 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/m^2 (metastatic setting) or to 75 mg/m^2 (adjuvant setting).
- If paraesthesia with functional impairment persists until the next cycle, oxaliplatin treatment should be discontinued.

- If symptoms improve following discontinuation of oxaliplatin therapy, resuming the treatment can be considered.

Patients should be informed of the possibility of persistent symptoms of peripheral sensory neuropathy after the end of the treatment. Localized moderate paresthesia or paresthesia 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 *Undesirable effects*). Diagnosis of RPLS is based upon confirmation by brain imaging, preferably MRI (Magnetic Resonance Imaging).

Nausea, vomiting, diarrhoea, dehydration, and haematologic changes
Gastrointestinal toxicity, which manifests as nausea and vomiting, warrants prophylactic and/or therapeutic antiemetic treatment (see section *Undesirable effects*).

Dehydration, paralytic ileus, intestinal occlusion, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis, particularly when oxaliplatin is used in combination 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 *Undesirable effects*).

If haematological toxicity occurs (neutrophils $< 1.5 \times 10^9$/L or platelets $< 50 \times 10^9$/L), administration of the next course of therapy should be postponed until haemotological values return to acceptable levels. A full blood count with white cell differential should be performed prior to start of therapy and before each subsequent course.

Myelosuppressive effects may be additive to those of concomitant chemotherapy. Patient with severe and persistent myelosuppression are at high risk of infectious complications. Sepsis, neutropenic sepsis and septic shock have been reported in patients treated with oxaliplatin including fatal outcomes (see section *Undesirable effects*). If any of these events occurs, oxaliplatin should be discontinued.

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

If mucositis/stomatitis occurs with or without neutropenia, the next administration should be delayed until recovery from mucositis/stomatitis to grade 1 or lower and/or until the neutrophil count is $\geq 1.5 \times 10^9$/L.

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

If grade 4 diarrhoea, grade 3 - 4 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 grade 3 - 4 thrombocytopenia (platelets < 50 x 10^9/L) occur, the oxaliplatin dose should be reduced from 85 to 65 mg/m^2 (metastatic setting) or 75 mg/m^2 (adjuvant setting), in addition to any 5-fluorouracil dose reductions required.

Pulmonary

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

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 *Undesirable effects*) Caution should be exercised in patients with conditions that are associated with 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 *Undesirable effects*). The QT interval should be closely monitored on a regular basis before and after administration of oxaliplatin. Caution should be exercised in patients with a history or a predisposition for prolongation of QT, those who are taking medicinal products known to prolong QT interval, and those with electrolyte disturbances such as hypokalemia, hypocalcaemia, or hypomagnesaemia. In case of QT prolongation, oxaliplatin treatment should be discontinued. (see sections *Interaction with other medicinal products and other forms of interaction* and *Undesirable effects*).

Rhabdomyolysis

Rhabdomyolysis has been reported in patients treated with oxaliplatin, including fatal outcomes. In case of muscle pain and swelling, in combination with weakness, fever or darkened urine, oxaliplatin treatment should be discontinued. If rhabdomyolysis is confirmed, appropriate measures should be taken. Caution is recommended if medicinal products associated with

rhabdomyolysis are administered concomitantly with oxaliplatin. (see sections *Interaction with other medicinal products and other forms of interaction* and *Undesirable effects*)

Gastrointestinal ulcer/ Gastrointestinal ulcer 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 *Undesirable effects*)

Hepatic
In the event of abnormal liver function test results or portal hypertension which does not obviously result from liver metastases, very rare cases of drug-induced hepatic vascular disorders should be considered.

Pregnancy
For use in pregnant women, see section *Fertility, pregnancy and lactation*.

Fertility
Genotoxic effects have been observed with oxaliplatin in the preclinical studies. Therefore male patients treated with oxaliplatin are advised not to father children during and up to 6 months after treatment, and also to seek advice on conservation of sperm before treatment, since oxaliplatin may have an anti-fertility effect, which could be irreversible.
Women should not become pregnant during oxaliplatin treatment and should use an effective method of contraception (see section *Fertility, pregnancy and lactation*).

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

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 the level of exposure to 5-fluorouracil (5-FU) has been observed. *In vitro*, no significant displacement of oxaliplatin plasma protein binding 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 *Special warnings and precautions for use*). Caution is advised when oxaliplatin treatment is administered concomitantly with other medicinal products known to be associated with rhabdomyolysis. (see section *Special warnings and precautions for use*).

Fertility, pregnancy and lactation
Pregnancy
There is no information available to date on the safety of use of oxaliplatin in pregnant women.

In animal studies, reproductive toxicity was observed. Oxaliplatin is therefore not recommended during pregnancy and in women of child-bearing 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 treatment and up to 4 months after cessation of therapy 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 *Special warnings and precautions for use*).
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.

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, vomiting and other neurologic symptoms affecting gait and balance may lead to a minor or moderate impact on the ability to drive and use machines.
Vision abnormalities, in particular transient loss of vision (reversible upon treatment discontinuation) may affect the ability to drive and to use machines. Patients must therefore be warned of the potential effect of these events on the ability to drive or use machines.

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

Tabulated list of adverse reactions
The frequencies reported in the table below were obtained from clinical studies in the metastatic and adjuvant settings (including 416 and 1108 patients, respectively, in the oxaliplatin + 5-fluorouracil (5-FU) /folinic acid (FA) arm) and from post-marketing experience.

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

Further details are given after the table.

MedDRA Organ system classes	Very common	Common	Uncommon	Rare
Infections and infestations *	- Infection	- Rhinitis - Upper respiratory tract infection - Neutropenic sepsis+	Sepsis+	
Blood and lymphatic system disorders*	- Anaemia - Neutropenia - Thrombocytopenia - Leukopenia - Lymphopenia	-Febrile neutropenia		- Immunoallergic thrombocytopenia - Haemolytic anaemia
Immune system disorders*	- Allergy/ allergic reaction++			
Metabolism and nutrition disorders	- Anorexia - Hyperglycaemia - Hypokalaemia - Hypernatraemia	- Dehydration - Hypocalcaemia	- Metabolic acidosis	
Psychiatric disorders		- Depression - Insomnia	- Nervousness	
Nervous system disorders*	- Peripheral sensory neuropathy - Sensory disturbance - Dysgeusia - Headache	- Dizziness - Motor neuritis - Meningism		- Dysarthria - Reversible Posterior Leukoencephalopathy syndrome (RPLS, or PRES) (see section *Special warnings and precautions for use*)
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		

Respiratory, thoracic and mediastinal disorders	- Dyspnoea - Cough - Epistaxis	- Hiccups - Pulmonary embolism		- Interstitial lung disease sometimes fatal - Pulmonary fibrosis**
Gastrointestinal disorders*	- Nausea - Diarrhoea - Vomiting - Stomatitis /Mucositis - Abdominal pain - Constipation	- Dyspepsia -Gastro esophageal reflux - Gastrointestinal hemorrhage - Rectal haemorrhage	- Ileus - Intestinal obstruction	- Colitis including clostridium difficile diarrhea - Pancreatitis
Skin and subcutaneous tissue disorders	- Skin disorder - Alopecia	- Skin exfoliation (i.e. Hand & Foot syndrome) - Rash erythematous - Rash - Hyperhidrosis - Nail disorder		
Musculoskeletal and connective tissue disorders	- Back pain	- Arthralgia - Bone pain		
Renal and urinary disorders		-Haematuria - Dysuria - Micturition frequency abnormal		
General disorders and administration site conditions	- Fatigue - Fever+++ - Asthenia - Pain - Injection site reaction++++			
Investigations	- Hepatic enzyme increase - Blood alkaline phosphatase increase - Blood bilirubin increase - Blood lactate dehydrogenase increase - Weight increase (adjuvant setting)	- Blood creatinine increase - Weight decrease (metastatic setting)		

* see detailed section below
** see section *Special Warnings and Special Precautions for Use*
+ 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, angioeodema, hypotension, sensation of chest pain and anaphylactic shock.

+++ Very common fever, rigors (tremors), either from infection (with or without febrile neutropenia) or possibly of 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, particularly when oxaliplatin is infused through a peripheral vein (see section *Special Warnings and Special Precautions for Use*).

Description of selected adverse reactions

Blood and lymphatic system disorders

Incidence by patient (%), by grade

Oxaliplatin and 5 FU/FA 85 mg/m^2 every 2 weeks	**Metastatic setting**			**Adjuvant setting**		
	All grades	**Gr 3**	**Gr 4**	**All grades**	**Gr 3**	**Gr 4**
Anaemia	82.2	3	<1	75.6	0.7	0.1
Neutropenia	71.4	28	14	78.9	28.8	12.3
Thrombocytopenia	71.6	4	<1	77.4	1.5	0.2
Febrile neutropenia	5.0	3.6	1.4	0.7	0.7	0.0

Rare (>1/10000, <1/1000)
Disseminated intravascular coagulation (DIC), including fatal outcomes (see section *Special warnings and precautions for use*)

Post-marketing experience with frequency not known:
Haemolytic uremic syndrome
Autoimmune pancytopenia
Pancytopenia
Secondary leukemia

Infections and infestations

Incidence by patient (%)

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

Postmarketing experience with frequency not known
Septic shock, including fatal outcomes.

Immune system disorders

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

Oxaliplatin and 5-FU/FA	**Metastatic Setting**	**Adjuvant Setting**

85 mg/m^2 every 2 weeks	All grades	Gr 3	Gr 4	All grades	Gr 3	Gr 4
Allergic reactions / Allergy	9.1	1	<1	10.3	2.3	0.6

Nervous system disorders

The dose limiting toxicity of oxaliplatin is neurological. It involves peripheral sensory neuropathy characterized by dysesthesia and/or paresthesia 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 cycles, increases with the number of treatment cycles.

The onset of pain and/or a functional disorder are indications, depending on the duration of the symptoms, for dose adjustment, or even treatment discontinuation (see section *Special warnings and precautions for use*).

This functional disorder includes difficulties in executing delicate movements and is a possible consequence of sensory impairment. The risk of occurrence of persistent symptoms at a cumulative dose of 850 mg/m^2 (i.e. 10 cycles) is about 10%, and about 20% at a cumulative dose of 1020 mg/m^2 (12 cycles).

In the majority of cases, the neurological signs and symptoms improve or resolve completely when treatment is discontinued. In the adjuvant treatment of colon cancer, 87% of patients have either no or mild symptoms 6 months after discontinuing treatment. After up to 3 years of follow up, about 3% of patients have either persistent, localized paresthesia of moderate intensity (2.3%) or with paresthesia that may interfere with functional activities (0.5%).

Acute neurosensory effects have been reported (see section *Preclinical Safety Data*). These symptoms appear within hours of administration and often occur on exposure to cold. The usual signs are transient paresthesia, dysesthesia or hypoesthesia. An acute syndrome of pharyngolaryngeal dysesthesia occurs in 1% to 2% of patients, and is characterized by subjective sensations of dysphagia or dyspnoea/feeling of suffocation, with no objective signs of respiratory distress (with no cyanosis or hypoxia), or by laryngospasm or bronchospasm (with no stridor or wheezing). Although antihistamines and bronchodilators have been administered in such cases, these symptoms are rapidly reversible even if no treatment is given. Extending the infusion time during subsequent cycles helps to reduce the incidence of this syndrome (see section *Special warnings and precautions for use*).

Other symptoms have occasionally been observed: jaw spasm, muscle spasm, involuntary muscle contractions, muscle twitching, myoclonus, coordination disorders, abnormal gait, ataxia, balance disorders, throat or chest tightness, pressure, discomfort, and pain. Furthermore, cranial nerve dysfunctions may be associated with above-mentioned events, or also occur as an isolated event such as ptosis, diplopia, aphonia, dysphonia, hoarseness, occasionally described as vocal cord paralysis, abnormal tongue sensation or dysarthria occasionally described as aphasia, trigeminal neuralgia, facial or ocular pain, reduced visual acuity, visual field disturbances.

Other neurological symptoms such as dysarthria, loss of deep tendon reflex and Lhermitte's sign have been 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 *Special warnings and precautions for use*).

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

Skin and Subcutaneous tissue disorders
Post-marketing experience with frequency not known
Hypersensitivity vasculitis

Gastrointestinal disorders

Incidence by patient (%), by grade

Oxaliplatin and 5-FU/FA 85 mg/m^2 every 2 weeks	**Metastatic Setting**			**Adjuvant Setting**		
	All grades	Gr 3	Gr 4	All grades	Gr 3	Gr 4
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 and/or emesis particularly when oxaliplatin is combined with 5-fluorouracil (5-FU) (see section *Special warnings and precautions for use*).

Postmarketing experience with frequency not known
Intestinal ischaemia, including fatal outcomes (see section *Special warnings and precautions for use*).
Gastrointestinal ulcer and perforation, which can be fatal. (see section *Special warnings and precautions for use*).

Hepato-biliary disorders
Very rare (<1/10,000)

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

Musculoskeletal and connective tissue disorders
Post-marketing experience with frequency not known
Rhabdomyolysis, including fatal outcomes (see section *Special warnings and precautions for use*).

Renal and urinary disorders
Very rare (<1/10,000)
Acute tubular necrosis, acute interstitial nephritis and acute renal failure

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

Management
Monitoring of haematological parameters should be initiated and symptomatic treatment given.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: other antineoplastic agents, platinum compounds
ATC code: L01XA 03

Mechanism of action
Oxaliplatin is an antineoplastic agent belonging to a new class of platinum-based compounds in which the platinum atom is complexed with 1,2-diaminocyclohexane ("DACH") and an oxalate group.
Oxaliplatin is a single enantiomer, (SP-4-2)-[(1R,2R)-cyclohexane-1,2-diamine-kN, kN'] [ethanedioato(2-)-kO1, kO2] platinum.

Oxaliplatin exhibits a wide spectrum of both *in vitro* cytotoxicity and *in vivo* antitumour activity in various tumour model systems, including human colorectal cancer models.
Oxaliplatin has also shown *in vitro* and *in vivo* activity in various cisplatin-resistant cell lines.
Synergistic cytotoxic activity with 5-fluorouracil has been demonstrated both *in vitro* and *in vivo*.
Studies on the mechanism of action, although not completely elucidated, have shown that the aqua derivatives resulting from the biotransformation of oxaliplatin, interact with DNA to form both inter and intra-and inter-strand cross-links, resulting in the disruption of DNA synthesis, which underlines the cytotoxic and antitumour effects.

Clinical efficacy and safety
In patients with metastatic colorectal cancer, the efficacy of oxaliplatin (85 mg/m^2 repeated every two weeks) in combination with 5-fluorouracil/folinic acid (5-FU/FA) has been reported in three clinical studies:

- as first-line treatment, in a 2-arm comparative phase III (EFC2962) study, 420 patients were randomised either to 5-FU/FA alone (LV5FU2, N=210) or to the combination of oxaliplatin with 5-FU/FA (FOLFOX4, N=210);
- in pretreated patients, in a 3-arm, comparative, phase III study (EFC4584), 821 patients refractory to the irinotecan (CPT-11) + 5-FU/FA combination were randomised to 5-FU/FA alone (LV5FU2, N=275), single agent oxaliplatin (N=275), or oxaliplatin + 5-FU/FA (FOLFOX4, N=271).
- finally, in a non-controlled phase II study (EFC2964) patients refractory to 5-FU/FA alone were treated with the oxaliplatin + 5-FU/FA combination (FOLFOX4, N=57)

In the two randomised clinical studies (EFC2962 as first-line treatment and EFC4584 in pretreated patients) a significantly superior response rate was demonstrated as well as longer progression-free survival (PFS)/time to progression (TTP) compared to treatment with 5-FU/FA alone.

In EFC4584 performed in refractory pretreated patients, the difference in median overall survival (OS) between the combination of oxaliplatin + 5-FU/FA combination and 5-FU/FA was not statistically significant.

Response rate under FOLFOX4 versus LV5FU2

Response rate % (95% CI) Independent radiological review ITT analysis	**LV5FU2**	**FOLFOX4**	**Oxaliplatin alone**
Front-line treatment EFC2962	22 (16-27)	49 (42-56)	NA*
Response assessment every 8 weeks	P value = 0.0001		
Pretreated patients EFC4584 (refractory to CPT-11 + 5FU/FA)	0.7 (0.0-2.7)	11.1 (7.6-15.5)	1.1 (0.2-3.2)
Response assessment every 6 weeks	P value < 0.0001		
Pretreated patients EFC2964 (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 alone**
Front-line treatment EFC2962 (PFS)	6.0 (5.5-6.5)	8.2 (7.2-8.8)	NA*
	Log-rank P value = 0.0003		
Pretreated patients EFC4584 (TTP) (refractory to CPT-11 + 5FU/FA)	2.6 (1.8-2.9)	5.3 (4.7-6.1)	2.1 (1.6-2.7)
	Log-rank P value < 0.0001		

Pretreated patients EFC2964 (refractory to 5-FU/FA)	NA*	5.1 (3.1-5.7)	NA*

*NA: Not Applicable

Median Overall Survival (OS) under FOLFOX4 versus LV5FU2

Median OS, Months (95% CI) ITT analysis	**LV5FU2**	**FOLFOX4**	**Oxaliplatin alone**
Front-line treatment EFC2962	14.7 (13.0-18.2)	16.2 (14.7-18.2)	NA*
	Log-rank P value = 0.12		
Pretreated patients EFC4584 (refractory to CPT-11 + 5FU/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 who were symptomatic at baseline (EFC4584), a higher proportion of those treated with oxaliplatin + 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 group for measurement of global health status and pain and less favourable in the oxaliplatin arm for nausea/vomiting.

In the adjuvant setting, the MOSAÏC comparative phase III study (EFC3313) randomised 2246 patients (899 stage II/Duke's B2 and 1347 stage III/Duke's C) further to complete resection of the primary tumour of colon cancer either to 5-FU/FA alone (LV5FU2, N=1123 (B2/C = 448/675) or to combination of oxaliplatin and 5-FU/FA (FOLFOX4, N=1123 (B2/C = 451/672).

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

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

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

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

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

Patient stage	**Stage II**	**Stage III**

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

Paediatric population
Oxaliplatin single agent has been evaluated in paediatric population in 2 Phase I (69 patients) and 2 Phase II (166 patients) studies. A total of 235 paediatric patients (7 months to 22 years of age) with solid tumours were treated. The efficacy of oxaliplatin administered alone was not established in the treated population.
Enrolment in these two phase II studies was stopped due to lack of tumour response.

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

Summary of Platinum Pharmacokinetic Parameter Estimates in Ultrafiltrate Following Multiple Doses of Oxaliplatin at 85 mg/m² every two weeks or at 130 mg/m² every three weeks

Dose	C_{max} µg/ml	**AUC_{0-48}** µg.h/ml	**AUC** µg.h/ml	**$t_{1/2}\alpha$** h	**$t_{1/2}\beta$** h	**$t_{1/2}\gamma$** h	**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
130 mg/m²								
Mean	1.21	8.20	11.9	0.28	16.3	273	582	10.1
SD	0.10	2.40	4.60	0.06	2.90	19.0	261	3.07

Mean AUC_{0-48}, and C_{max} values were determined on Cycle 3 (85 mg/m^2) or cycle 5 (130 mg/m_2).
Mean AUC, V_{ss} and CL values were determined on Cycle 1.
C_{max}, AUC, AUC_{0-48}, V_{ss} and CL values were determined by non-compartmental anablysis.
$t_{1/2}\alpha$, $t_{1/2}\beta$, and $t_{1/2}\gamma$, were determined by compartmental analysis (Cycles 1-3 combined).

Following a 2-hour infusion, 15% of the administered platinum is found in the systemic circulation, the remaining 85% having been rapidly distributed into tissues or excreted 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 of platinum was observed in plasma ultrafiltrate following an 85 mg/m^2 infusion every two weeks or 130mg/m2 every 3 weeks, and steady state was attained in cycle 1 in this matrix. Inter- and intra-individual 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 metabolites including the monochloro-, dichloro- and diaquo-DACH platinum species have been identified in the systemic circulation, as have a number of inactive metabolites at later time points.

Elimination

Platinum is predominantly excreted in urine, with clearance mainly in the 48 hours following administration.
At day 5, approximately 54% of the dose is recovered in the urine and less than 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/m^2 in the control group with a normal renal function (CLcr >80 ml/min, n=12) and in patients with mild (CLcr = 50 to 80 ml/min, n=13) and moderate (CLcr = 30 to 49 ml/min, n=11) renal impairment, and at a dose of 65 mg/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 Vss respectively 0.52 (0.41, 0.65), 0.73 (0.59, 0.91) and 0.27 (0.20, 0.36) for patients with mild, moderate and severe renal failure respectively. Total body clearance of PUF platinum was therefore reduced by respectively 26% in mild, 57% in moderate, and 79% in severe renal impairment compared to patients with normal function.

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

There was an increase in beta half-life of PUF platinum with increasing degree of renal impairment mainly in the severe group. Despite the small number of patients with severe renal dysfunction, these data are of concern in patients in severe renal failure and should be taken into account when prescribing oxaliplatin in patients with renal impairment (see sections *Posology and method of administration, Contraindications,* and *Special warnings and precautions for use*).

Preclinical safety data

The target organs identified in the species used in preclinical studies (mice, rats, dogs, and/or monkeys) in single-dose and repeated dose studies included the bone marrow, the gastrointestinal system, the kidney, the testes, the nervous system and the heart. The toxicities in the target organ observed in animals are similar to those observed with other platinum-based agents and DNA-damaging, cytotoxic drugs used in the treatment of human cancers, with the exception of those on the heart. Effects on the heart were only observed in the dog and included electrophysiological abnormalities with lethal ventricular fibrillation. Cardiotoxicity is considered specific to the dog, not only because it was only observed in this species, but also because doses similar to lethal doses in the dog (150 mg/m^2) were well tolerated in 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 is mutagenic and clastogenic in mammalian test systems and has demonstrated embryo-foetal toxicity in rats. Oxaliplatin is considered a probable carcinogen, although carcinogenic studies have not been conducted.

PHARMACEUTICAL PARTICULARS

List of excipients

Water for injections

Incompatibilities

The diluted medicinal product should not be mixed with other medications in the same infusion bag or infusion line. Oxaliplatin may be co-administered with folinic acid using a Y-line, according to the instructions for use presented in section *Special precautions for disposal and other handling*.

- DO NOT mix with alkaline medicinal products or solutions, particularly 5-fluorouracil (5-FU), folinic acid (FA) preparations containing trometamol as an excipient, and trometamol salts of other medicines. Alkaline drugs or solutions will adversely affect the stability of oxaliplatin (see section *Special precautions for disposal and other handling*).
- DO NOT dilute oxaliplatin with saline solutions or other solutions containing chloride ions (including calcium, potassium or sodium chloride).
- DO NOT mix with other medicinal products in the same infusion bag or infusion line (see section *Special precautions for disposal and other handling* for instructions on simultaneous administration with folinic acid (FA)).
- DO NOT use injection equipment containing aluminium.

Shelf life

Please refer to the expiry date on the carton.

After dilution in glucose 5% (50mg/ml) solution, chemical and physical in-use stability has been demonstrated for 48 hours at +2°C to +8°C and for 24 hours at +25°C.
From a microbiological point of view, the solution for infusion 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°C to 8°C unless dilution has taken place in controlled and validated aseptic conditions.

Special precautions for storage
Store below 30°C. Store the vial in its outer packaging, protected from light.
Do not freeze.
For storage conditions of the diluted medicinal product, see section *Shelf life*.

Nature and contents of container
10 ml concentrate in a vial (Type I clear glass) with siliconized rubber stopper
20 ml concentrate in a vial (Type I clear glass) with siliconized rubber stopper
Pack size: 1 vial per box.

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

Instructions for Handling
Handling of this cytotoxic agent by healthcare personnel requires a set of precautions to ensure the protection of the handler and his/her 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 ensuring drug integrity, the protection of the environment and in particular the protection of the personnel handling the medicines, according to hospital practice. 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, particularly 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 must be incinerated in suitably labelled rigid containers. (see section *Disposal* below).
If oxaliplatin concentrate or solution for infusion should come into contact with the 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 equipment containing aluminium.

- DO NOT administer undiluted.
- Only glucose 5% (50mg/ml) 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 medications or solutions, particularly 5-fluorouracil (5-FU), folinic acid (FA) preparations containing trometamol as an excipients, and trometamol salts of other drugs.

Alkaline drugs or solutions will adversely affect the stability of oxaliplatin.

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

Oxaliplatin 85 mg/m² IV infusion in 250 to 500 ml of glucose 5% (50mg/ml) solution is given at the same time as folinic acid (FA) intravenous infusion in glucose 5% (50mg/ml) solution, over 2 to 6 hours, using a Y-line placed immediately before the site of infusion.

These two medicinal products should not be mixed in the same infusion bag. Folinic acid (FA) must not contain trometamol as an excipient and must only be diluted in isotonic glucose 5% (50mg/ml) solution, never in alkaline solutions or sodium chloride or chloride containing solutions.

Instruction for use with 5-fluorouracil (5-FU)

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

After oxaliplatin administration, rinse the infusion line and then administer 5-fluorouracil (5-FU).

For more information on medicinal products combined with oxaliplatin, see the respective manufacturer's package insert.

Concentrate for solution for infusion

Inspect visually before use. Only clear solutions with no particles can be used.

The 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 to 500 ml of glucose 5% (50mg/ml) solution to obtain an oxaliplatin concentration of between 0.2 mg/ml and 0.7 mg/ml. The concentration range for which the physico-chemical stability of oxaliplatin has been demonstrated is 0.2 mg/ml to 2.0 mg/ml.

Administer by IV infusion.

After dilution in glucose 5 % (50 mg/ml) solution, chemical and physical in-use stability has been demonstrated for 48 hours at +2°C to +8°C and for 24 hours at +25°C.

From a microbiological point of view, this infusion preparation 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°C to 8°C unless dilution has taken place in controlled and validated aseptic conditions (not to exceed 48 hours).

Inspect visually before use. Only clear solutions with no particles should be used.

The medicinal product is for single use only. Any unused infusion solution should be discarded (see section on *Disposal* below).
NEVER use solutions containing chloride or sodium chloride for dilution.
The compatibility of oxaliplatin solution for infusion has been tested with standard PVC-based, administration sets.

Infusion
The administration of oxaliplatin does not require prehydration.
Oxaliplatin diluted in 250 to 500 ml of glucose 5 % (50 mg/ml) solution to obtain a concentration not less than 0.2 mg/ml must be infused either in peripheral a vein or using central venous line over 2 to 6 hours.
When oxaliplatin is administered with 5-fluorouracil (5-FU), the oxaliplatin infusion must be given before 5-fluorouracil (5-FU).

Disposal
Any unused 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.

MANUFACTURER
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