SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

OXALIPLATIN MEDAC 50 MG
OXALIPLATIN MEDAC 100 MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial with powder for solution for infusion contains 50 mg or 100 mg oxaliplatin.

One ml of reconstituted concentrate solution contains 5 mg oxaliplatin.

50 mg vial: Each vial contains 50 mg oxaliplatin for reconstitution in 10 ml of solvent.
100 mg vial: Each vial contains 100 mg oxaliplatin for reconstitution in 20 ml of solvent.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion

White to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Oxaliplatin in combination with leucovorin, irinotecan and 5-fluorouracil is indicated for the first-line treatment of patients with metastatic pancreatic adenocarcinoma (based on NCCN guidelines, version 2.2014).

4.2 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 recommended dose of oxaliplatin for the treatment of metastatic pancreatic adenocarcinoma is 85 mg/m^2 given as a 2-hour intravenous infusion, immediately followed by leucovorin (400 mg/m^2, 2-hour intravenous infusion) with the addition after 30 minutes of irinotecan (180 mg/m^2, 90-minute intravenous infusion through a Y-connector) and immediately followed by 5-fluorouracil (400 mg/m^2 intravenous bolus followed by 2,400 mg/m^2 continuous intravenous infusion for 46 hours), in 2-week cycles up to 6 months.

Dosage given should be adjusted according to tolerability (see section 4.4).

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

Oxaliplatin is administered as a 2- to 6-hour intravenous infusion in 250 ml to 500 ml of 5% glucose solution to give a concentration between 0.2 mg/ml and 0.7 mg/ml; 0.70 mg/ml is the highest concentration in clinical practice for an oxaliplatin dose of 85 mg/m^2.

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.

Oxaliplatin in combination with leucovorin, irinotecan and 5-fluorouracil should only be administered to patients less than 76 years-old, with ECOG performance status (Eastern Cooperative Oncology Group) 0-1, who have no cardiac ischemia, and normal or nearly normal level of bilirubin.

Special Populations

- Renal impairment:
Oxaliplatin must not be administered in patients with severe renal impairment (see sections 4.3 and 5.2). In patients with mild to moderate renal impairment, the recommended dose of oxaliplatin is 85 mg/m^2 (see sections 4.3 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 adaption is required for elderly patients.

- Paediatric population:
There is no relevant indication for use of oxaliplatin in children. The effectiveness of oxaliplatin single agent in the paediatric populations with solid tumours has not been established (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 ml 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 a peripheral vein over 2 to 6 hours. Oxaliplatin infusion must always precede the administration of 5-fluorouracil.

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

Instructions for use

Oxaliplatin must be diluted before use. Only 5% glucose diluent is to be used to dilute the concentrate for solution for infusion product. (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 excipient(s) listed in section 6.1.
- are breastfeeding.
- have myelosuppression prior to starting first course, as evidenced by baseline neutrophils < 2 x 10^9/l and/or platelet count of < 100 x 10^9/l.
- have a peripheral sensitive neuropathy with functional impairment prior to first course.
- have a severely impaired renal function (creatinine clearance less than 30 ml/min).

4.4 Special warnings and precautions for use

Oxaliplatin should only be used in 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 the dose adjusted according to toxicity (see section 5.2).

Hypersensitivity reactions
Special surveillance should be ensured for patients with a history of allergic reactions 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 medicinal products with specific neurological toxicity. A neurological examination should be performed before each administration and periodically thereafter.

For patients who develop acute laryngopharyngeal dysaesthesia (see section 4.8), during or within the hours following the 2-hour infusion, the next oxaliplatin infusion should be administered over 6 hours.

Peripheral neuropathy
If neurological symptoms (paraesthesia, dysaesthesia) occur, the following recommended oxaliplatin dosage adjustment should be based on the duration and severity of these symptoms:
- If symptoms last longer than 7 days and are troublesome, the subsequent oxaliplatin dose should be reduced from 85 mg/m^2 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 mg/m^2 to 65 mg/m^2 (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 of the possibility of persistent symptoms of peripheral sensory neuropathy after the end of the treatment. Localised moderate paresthesias or paresthesias that may interfere with functional activities can persist after up to 3 years following treatment cessation in the adjuvant setting.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
Cases of Reversible Posterior Leukoencephalopathy Syndrome (RPLS) 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, which manifests as nausea and vomiting, warrants prophylactic and/or therapeutic anti-emetic therapy (see section 4.8).

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

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

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 4.8). If any of these events occurs, oxaliplatin should be discontinued.

Patients must be adequately informed of the risk of diarrhoea/emesis, mucositis/stomatitis and neutropenia after oxaliplatin and 5-fluorouracil administration so that they can urgently contact their treating physician for appropriate management.
If mucositis/stomatitis occurs with or without neutropenia, the next treatment should be delayed until recovery from mucositis/stomatitis to grade 1 or less and/or until the neutrophil count is $\geq 1.5 \times 10^9$/l.

For oxaliplatin combined with 5-fluorouracil (with or without folinic acid (FA)), 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, temperature > 38.3°C or a sustained temperature > 38°C for more than 1 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/m^2 (adjuvant setting), in addition to any 5-fluorouracil (5-FU) dose reductions required.

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

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

Blood disorders
Haemolytic-uraemic syndrome (HUS) is a life-threatening side effect (frequency not known). Oxaliplatin should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required. Disseminated intravascular coagulation (DIC), including fatal outcomes, has been reported in association with oxaliplatin treatment. If DIC is present, oxaliplatin treatment should be discontinued and appropriate treatment should be administered (see section 4.8).

QT prolongation
QT prolongation may lead to an increased risk for ventricular arrhythmias including Torsade de Pointes, which can be fatal (see section 4.8). The QT interval should be closely monitored on a regular basis before and after administration of oxaliplatin. Caution should be exercised in patients with a history or a predisposition for prolongation of QT, those who are taking medicinal products known to prolong QT interval, and those with electrolyte disturbances such as 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 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 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.

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 the level of exposure to 5-fluorouracil (5-FU) has been observed.
In vitro, no significant displacement of oxaliplatin binding to plasma proteins has been observed with the following agents: erythromycin, salicylates, granisetron, paclitaxel, and sodium valproate.

Caution is advised when oxaliplatin treatment is co-administered with other medicinal products known to cause QT interval prolongation. In case of combination with such medicinal products, the QT interval should be closely monitored (see section 4.4). Caution is advised when oxaliplatin treatment is administered concomitantly with other medicinal products known to be associated with rhabdomyolysis (see section 4.4).

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of oxaliplatin in pregnant women.
Studies in animals have shown reproductive toxicity (see section 5.3). Consequently, oxaliplatin is not recommended during pregnancy and in women of childbearing potential not using contraception.
The use of oxaliplatin should only be considered after suitably apprising the patient of the risk to the foetus and with the patient's consent.

Contraception in males and females
Due to the genotoxic potential of oxaliplatin (see section 5.3), women of childbearing potential have to use effective contraception during and up to 9 months after treatment. Men have to use effective contraception during and up to 6 months after treatment.

Breastfeeding
Excretion in human milk has not been studied. Breastfeeding is contra-indicated during oxaliplatin therapy.

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

Oxaliplatin may have an anti-fertility effect.

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 neurologic symptoms that affect gait and balance may lead to minor or moderate influence on the ability to drive and use machines.
Vision abnormalities, in particular transient vision loss (reversible following therapy discontinuation), may affect patients´ ability to drive and use machines. Therefore, patients should be warned of the potential effect of these events on the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile
The most frequent adverse events of oxaliplatin in combination with 5-fluorouracil/folinic acid (5-FU/FA) were gastrointestinal (diarrhoea, nausea, vomiting and mucositis), haematological (neutropenia,

thrombocytopenia) and neurological (acute and dose cumulative peripheral sensory neurophathy). Overall, these adverse events were more frequent and severe with oxaliplatin and 5-FU/FA combination than with 5-FU/FA alone.

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

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

Further details are given after the table.

MedDRA system organ class	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)
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 - Gastroesophageal reflux - Gastrointestinal haemorrhage - Rectal haemorrhage	- Ileus - Intestinal obstruction	- Colitis including clostridium difficile diarrhoea - 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 phosphatise increase - Blood bilirubin increase - Blood lactate dehydrogenase increase - Weight increase (adjuvant setting)	- Blood creatinine increase - Weight decrease (metastatic setting)		
Injury, poisoning and procedural complications		Fall		

* See detailed section below.

** See section 4.4.

\+ Very common: frequent allergy/allergic reactions, occurring mainly during perfusion, sometimes fatal (frequent allergic reactions such as skin rash, in particularly urticaria, conjunctivitis, rhinitis). Common anaphylactic reactions, including bronchospasm, angioedema, low blood pressure 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).
++++ Common neutropenic sepsis, including fatal outcomes.

Description of selected adverse reactions

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

Blood and lymphatic system disorders

Incidence by patient (%), by grade

Oxaliplatin and 5-FU/FA 85 mg/m² every 2 weeks	**Metastatic Setting**			**Adjuvant Setting**		
	All grades	Gr 3	Gr 4	All grades	Gr 3	Gr 4
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, <1/1,000)
Disseminated intravascular coagulation (DIC), including fatal outcomes (see section 4.4).

Postmarketing experience with frequency not known
Haemolytic uremic syndrome, autoimmune pancytopenia, pancytopenia, secondary leukaemia

Immune system disorders

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

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

Nervous system disorders

The dose limiting toxicity of oxaliplatin is neurological. It involves a sensory peripheral neuropathy 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 a functional disorder are indications, depending on the duration of the symptoms, for dose adjustment, or even treatment discontinuation (see section 4.4).

This functional disorder includes difficulties in executing delicate movements and is a possible consequence of sensory impairment. The risk of occurrence of persistent symptoms for a cumulative dose of 850 mg/m^2 (10 cycles) is approximately 10 % and 20 % for a cumulative dose of 1020 mg/m^2 (12 cycles).
In the majority of the cases, the neurological signs and symptoms improve or totally recover when treatment is discontinued. In the adjuvant setting of colon cancer, 6 months after treatment cessation, 87 % of patients had no or mild symptoms. After up to 3 years of follow up, about 3 % of patients presented either with persisting localised paresthesias of moderate intensity (2.3 %) or with paresthesias 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 paresthesia, dysesthesia and hypoesthesia. An acute syndrome of pharyngolaryngeal dysesthesia occurs in 1 % - 2 % of patients and is characterised by subjective sensations of dysphagia or dyspnoea/feeling of suffocation, without any objective evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm (no stridor or wheezing). Although antihistamines and bronchodilators have been administered in such cases, the symptoms are rapidly reversible even in the absence of treatment. Prolongation of the infusion helps to reduce the incidence of this syndrome (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, 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.

Postmarketing experience with frequency not known
Convulsion, ischaemic and 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 (%), by grade

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

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

Dehydration, paralytic ileus, intestinal obstruction, 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 ischemia, including fatal outcomes (see section 4.4). Gastrointestinal ulcer and perforation, which can be fatal (see section 4.4). Oesophagitis.

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.

Post marketing experience with frequency not known
Focal nodular hyperplasia.

Skin and subcutaneous tissue disorders

Postmarketing experience with frequency not known
Hypersensitivity vasculitis
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.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/

4.9 Overdose

There is no known antidote to oxaliplatin. In cases of overdose, exacerbation of adverse events can be expected. Monitoring of haematological parameters should be initiated and symptomatic treatment given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, platinum compounds, ATC code: L01XA 03

Mechanism of action
Oxaliplatin is an antineoplastic medicinal product 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 (85 mg/m^2 repeated every 2 weeks) combined with 5-fluorouracil/folinic acid (5-FU/FA) is reported in 3 clinical studies:

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

- In pretreated patients, the comparative 3 arms phase III study EFC4584 randomised 821 patients refractory to an irinotecan (CPT-11) + 5-FU/FA combination either to 5-FU/FA alone (LV5FU2, N=275), oxaliplatin single agent (N=275), or combination of oxaliplatin with 5-FU/FA (FOLFOX4, N=271).

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

The 2 randomised clinical trials, EFC2962 in front-line therapy and EFC4584 in pretreated patients, demonstrated a significantly higher response rate and a prolonged progression free survival (PFS) / time to progression (TTP) as compared to treatment with 5-FU/FA alone. In EFC4584 performed in refractory pretreated patients, the difference in median overall survival (OS) between the combination of oxaliplatin and 5-FU/FA 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 (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 2 treatment groups was found for any of the quality of life dimensions. However, the quality of life scores were generally better in the control arm for measurement of global health status and pain and worse in the oxaliplatin arm for nausea and vomiting.

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

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

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

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

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

EFC 3313- 3-year disease free survival (ITT analysis)* according 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)
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 the paediatric population in 2 Phase I (69 patients) and 2 Phase II (166 patients) studies. A total of 235 paediatric patients (7 months – 22 years of age) with solid tumours have been treated. The effectiveness of oxaliplatin single agent in the paediatric populations treated has not been established. Accrual in both Phase II studies was stopped for lack of tumour response.

5.2 Pharmacokinetic properties

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 2-hour infusion of oxaliplatin at 130 mg/m^2 every 3 weeks for 1 to 5 cycles and oxaliplatin at 85 mg/m^2 every 2 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/m^2 Every 2 Weeks or at 130 mg/m^2 Every 3 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/m^2) or cycle 5 (130 mg/m^2).
Mean AUC, Vss , CL, and CL_{R0-48} values were determined on cycle 1.
C_{end}, C_{max}, AUC, AUC_{0-48}, V_{ss} and CL values were determined by non-compartmental analysis.
$t_{1/2\alpha}$, $t_{1/2\beta}$, $t_{1/2\gamma}$ were determined by compartmental analysis (cycles 1-3 combined).

Distribution
At the end of a 2-hour infusion, 15 % of the administered platinum is present in the systemic circulation, the remaining 85 % being rapidly distributed into tissues or eliminated in the urine. Irreversible binding to red blood cells and plasma, results in half-lives in these matrices that are close to the natural turnover of red blood cells and serum albumin. No accumulation was observed in plasma ultrafiltrate following 85 mg/m^2 every 2 weeks or 130 mg/m^2 every 3 weeks and steady state was attained by cycle 1 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 medicinal product 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.

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 % Cl) 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 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/m^2) 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-foetal toxicity in rats. Oxaliplatin is considered a probable carcinogen, although carcinogenic studies have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate.

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 via a Y-line.

- DO NOT mix with alkaline medicinal agents or solutions, in particular 5-fluorouracil, folinic acid preparations containing trometamol as an excipient and trometamol salts of other medicinal products. Alkaline medicinal agents 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:
The expiry date of the product is indicated on the packaging materials.

Reconstituted concentrate solution in the original vial:
The reconstituted concentrate solution should be diluted immediately.

Solution for infusion after dilution:
After dilution of the reconstituted solution in 5 % glucose solution, chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°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.

6.4 Special precautions for storage

Medicinal product as packaged for sale: Store below 25°C.
For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I glass vials with stoppers of chlorobutyl elastomer.
Supplied in packs of 1 vial containing oxaliplatin 50 mg or 100 mg.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Instructions for handling

The handling of this cytotoxic agent by nursing or medical 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 medicinal products used, in conditions that guarantee the integrity of the medicinal 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.

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 powder, reconstituted solution or infusion solution should come into contact with skin, wash immediately and thoroughly with water.

If oxaliplatin powder, reconstituted solution or infusion solution 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 (50 mg/ml) is to be used as a diluent.
- DO NOT reconstitute or dilute for infusion with sodium chloride or chloride containing solutions.
- DO NOT administer extravascularly.
- DO NOT mix with any other medication in the same infusion bag or administer simultaneously by the same infusion line.
- DO NOT mix with alkaline medicinal agents or solutions, in particular 5-fluorouracil, folinic acid preparations containing trometamol as an excipient and trometamol salts of other medicinal products. Alkaline medicinal agents or solutions will adversely affect the stability of oxaliplatin.

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

Oxaliplatin 85mg/m² IV infusion in 250 ml to 500 ml of 5% glucose solution (50 mg/ml) 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 2 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.

Any reconstituted solution that shows evidence of precipitation should not be used and should be destroyed with due regard to legal requirements for disposal of hazardous waste (see below).

Reconstitution of the powder

- Water for injections or 5 % glucose solution (50 mg/ml) should be used to reconstitute the solution.
- For a vial of 50 mg: add 10 ml of solvent to obtain a concentration of 5 mg oxaliplatin/ml.
- For a vial of 100 mg: add 20 ml of solvent to obtain a concentration of 5 mg oxaliplatin/ml.

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

Dilution before infusion

Withdraw the required amount of reconstituted concentrate solution from the vial(s) and then dilute with 250 ml to 500 ml of a 5 % glucose solution to give an oxaliplatin concentration between not less than 0.2 mg/ml and 0.7 mg/ml, concentration range for which the physico-chemical stability of oxaliplatin has been demonstrated.
Administer by IV infusion.
After dilution in 5% glucose, chemical and physical in-use stability has been demonstrated for 24 hours at +2°C to +8°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.
Inspect visually prior to use. Only clear solutions without particles should be used.
The medicinal product is for single use only. Any unused solution should be discarded.
NEVER use sodium chloride solution for either reconstitution or dilution.

The compatibility of Oxaliplatin solution for infusion has been tested with representative, PVC-based, administration sets.

Infusion
The administration of oxaliplatin does not require prehydration.
Oxaliplatin diluted in 250 ml 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 reconstitution, for dilution and administration must be destroyed according to hospital standard procedures applicable to cytotoxic agents with due regard to current laws related to the disposal of hazardous waste.

7. MANUFACTURER

medac Gesellschaft für klinische Spezialpräparate mbH
Wedel, Germany.

8. MARKETING AUTHORISATION HOLDER

Tzamal Bio-Pharma Ltd.,
20 Hamagshimim St., Kiryat Matalon,
Petah-Tikva.

9. MARKETING AUTHORISATION NUMBERS

Oxaliplatin Medac 50 mg: 137 24 31503
Oxaliplatin Medac 100 mg: 137 25 31504

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