

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Celdach 50, Oxaliplatin for Injection USP 50 mg

2.0 Qualitative and quantitative composition

Each vial contains:

Oxaliplatin50 mg

Excipient of known effect:

Lactose Monohydrate450.0 mg per vial

For full list of excipients see section 6.1

3.0 Pharmaceutical form

White to off white, crystalline powder for Injection

4.0 Clinical particulars

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

FOR ADULTS ONLY

The recommended dose for oxaliplatin in adjuvant setting is 85 mg/m² intravenously repeated every two weeks for 12 cycles (6 months).

The recommended dose for oxaliplatin in treatment of metastatic colorectal cancer is 85 mg/m² intravenously repeated every 2 weeks until disease progression or unacceptable toxicity.

Dosage given should be adjusted according to tolerability.

Oxaliplatin should always be administered before fluoropyrimidines – i.e. 5-fluorouracil. Oxaliplatin is administered as a 2- to 6-hour intravenous infusion in 250 to 500 mL of 5% glucose 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/m².

Oxaliplatin was mainly used in combination with continuous infusion 5-fluorouracil based regimens. For the two-weekly treatment schedule 5-fluorouracil regimens combining bolus and continuous infusion were used.

Special Populations

- Renal impairment:

Oxaliplatin must not be administered in patients with severe renal impairment. In patients with mild to moderate renal impairment, the recommended dose of oxaliplatin is 85 mg/m².

- Hepatic insufficiency:

In a phase I study including patients with several levels of hepatic impairment, frequency and severity of hepato-biliary disorders appeared to be related to progressive disease and impaired liver function tests at baseline. No specific dose adjustment for patients with abnormal liver function tests was performed during clinical development.

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

- *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 tumors has not been established.

Method of administration

Oxaliplatin is administered by intravenous infusion.

The administration of oxaliplatin does not require hyperhydration.

Oxaliplatin diluted in 250 to 500 mL of 5% glucose solution to give a concentration not less than 0.2 mg/mL must be infused via a central venous line or peripheral vein over 2 to 6 hours.

Oxaliplatin infusion 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.

4.3 Contraindications

Oxaliplatin is contraindicated in patients who

- have a known history of hypersensitivity to oxaliplatin.
- are breast feeding.
- have myelosuppression prior to starting first course, as evidenced by baseline neutrophils $<2 \times 10^9/l$ and/or platelet count of $<100 \times 10^9/l$.
- have a peripheral 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.

Hypersensitivity reactions

Special surveillance should be ensured for patients with a history of allergic manifestations to other products containing platinum. In case of anaphylactic manifestations the infusion should be interrupted immediately and an appropriate symptomatic treatment started. Re-administration of oxaliplatin to such patients is contra-indicated. 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, during or within the hours following the 2-hour infusion, the next oxaliplatin infusion should be administered over 6 hours.

Peripheral neuropathy

If neurological symptoms (paraesthesia, dysaesthesia) occur, the following recommended oxaliplatin dosage adjustment should be based on the duration and severity of these symptoms: - If symptoms last longer than seven days and are troublesome, the subsequent oxaliplatin dose should be reduced from 85 to 65 mg/m² (metastatic setting) or 75 mg/m² (adjuvant setting). - If paraesthesia without functional impairment persists until the next cycle, the subsequent oxaliplatin dose should be reduced from 85 to 65 mg/m² (metastatic setting) or 75 mg/m² (adjuvant setting).

- If paraesthesia with functional impairment persists until the next cycle, oxaliplatin should be discontinued.
- If these symptoms improve following discontinuation of oxaliplatin therapy, resumption of therapy may be considered.

Patients should be informed of the possibility of persistent symptoms of peripheral sensory neuropathy after the end of the treatment. Localized moderate 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 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. 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.

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.

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 haematological values return to acceptable levels. A full blood count with white cell differential should be performed prior to start of therapy and before each subsequent course.

Patients must be adequately informed of the risk of diarrhoea/emesis, mucositis/stomatitis and neutropenia after oxaliplatin 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), the usual dose adjustments for 5-fluorouracil associated toxicities should apply.

If grade 4 diarrhoea, grade 3-4 neutropenia (neutrophils $< 1.0 \times 10^9/l$), grade 3-4 thrombocytopenia (platelets $< 50 \times 10^9/l$) occur, the dose of oxaliplatin should be reduced from 85 to 65 mg/m² (metastatic setting) or 75 mg/m² (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 should be discontinued until further pulmonary investigations exclude an interstitial lung disease.

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.

Fertility

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

Women should not become pregnant during treatment with oxaliplatin and should use an effective method of contraception.

4.5 Interaction with other medicinal products and other forms of interaction

In patients who have received a single dose of 85 mg/m² of oxaliplatin, immediately before administration of 5-fluorouracil, no change in the level of exposure to 5-fluorouracil 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.

4.6 Pregnancy and lactation

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

The use of oxaliplatin should only be considered after suitably appraising the patient of the risk to the foetus and with the patient's consent.

Appropriate contraceptive measures must be taken during and after cessation of therapy during 4 months for women and 6 months for men.

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

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 increase risk of dizziness, nausea and vomiting, and other neurologic symptoms that affect gait and balance may lead to a minor or moderate influence on the ability to drive and use machines.

Vision abnormalities, in particular transient vision loss (reversible following therapy discontinuation), may affect patient's ability to drive and use machines. Therefore, patients should be warned of the potential effect of these events on the ability to drive or use machines

4.8 Undesirable effects

The most frequent adverse events of oxaliplatin in combination with 5-fluorouracil/folinic acid (5-FU/FA) were 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 oxaliplatin and 5-FU/FA combination than with 5-FU/FA alone.

The frequencies reported in the table below are derived from clinical trials in the metastatic and adjuvant settings (having included 416 and 1108 patients respectively in the oxaliplatin + 5FU/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 Organ system classes	Very common	Common	Uncommon	Rare
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)		

Blood and lymphatic system disorders*	- Anaemia - Neutropenia - Thrombocytopenia - Leukopenia - Lymphopenia	- Febrile neutopenia		- Immunoallergic thrombocytopenia - Haemolytic anaemia
Nervous system disorders*	- Peripheral sensory neuropathy - Sensory disturbance - Dysgeusia - Headache	- Dizziness - Motor neuritis - Meningism		- Dysarthria - Reversible Posterior Leukoencephalopathy syndrome (RPLS, or PRES)
Eye disorders		- Conjunctivitis - Visual		- Visual acuity reduced transiently

		disturbance		- Visual field disturbances - Optic neuritis - Transient vision loss, reversible following therapy discontinuation
Ear and labyrinth disorders			- Ototoxicity	- Deafness

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 hemorrhage - Rectal haemorrhage	- Ileus - Intestinal obstruction	- Colitis including clostridium difficile diarrhea - Pancreatitis
Renal and urinary disorders		- Haematuria - Dysuria - Micturition frequency abnormal		

Skin and subcutaneous tissue disorders	- Skin disorder - Alopecia	- Skin exfoliation (i.e. Hand & Foot syndrome) - Rash erythematous - Rash - Hyperhidrosis - Nail disorder		
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Musculoskeletal and connective tissue disorders	- Back pain	- Arthralgia - Bone pain		
Metabolism and nutrition disorders	- Anorexia - Hyperglycaemia - Hypokalaemia - Hypernatraemia	- Dehydration	- Metabolic acidosis	
Infections and infestations *	- Infection	- Rhinitis - Upper respiratory tract infection - Neutropenic sepsis		
Vascular disorders		- Haemorrhage - Flushing - Deep vein thrombosis - Hypertension		
General disorders and administration site conditions	- Fatigue - Fever++ - Asthenia - Pain - Injection site reaction+++			
Immune system disorders*	- Allergy/ allergic reaction+			
Psychiatric disorders		- Depression - Insomnia	- Nervousness	

* See detailed section below

+ Very common allergies/allergic reactions, occurring mainly during infusion, sometimes fatal.

Common allergic reactions include skin rash, particularly urticaria, conjunctivitis, and rhinitis. Common anaphylactic or anaphylactoid reactions, include bronchospasm, angioedema, hypotension, sensation of chest pain and anaphylactic shock.

++ 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.

Blood and lymphatic system disorders

Incidence by patient (%), by grade

Oxaliplatin and 5-FU/FA 85 mg/m²	Metastatic Setting			Adjuvant Setting		
	All grades	Gr 3	Gr 4	All grades	Gr 3	Gr 4
every 2 weeks						
Anemia	82.2	3	<1	75.6	0.7	0.1
Neutropenia	71.4	28	14	78.9	28.8	12.3
Thrombocytopenia	71.6	4	<1	77.4	1.5	0.2
Febrile neutropenia	5.0	3.6	1.4	0.7	0.7	0.0
Neutropenic sepsis	1.1	0.7	0.4	1.1	0.6	0.4

Postmarketing experience with frequency unknown

Hemolytic uremic syndrome

Immune system disorders

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

Oxaliplatin and 5-FU/FA 85 mg/m²	Metastatic Setting	Adjuvant Setting
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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 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.

This functional disorder includes difficulties in executing delicate movements and is a possible consequence of sensory impairment. The risk of occurrence of persistent symptoms for a cumulative dose of 850 mg/m² (10 cycles) is approximately 10% and 20% for a cumulative dose of 1020 mg/m² (12 cycles).

In the majority of the cases, the neurological signs and symptoms improve or totally recover when treatment is discontinued. In the adjuvant setting of colon cancer, 6 months after treatment cessation, 87 % of patients had no or mild symptoms. After up to 3 years of follow up, about 3 % of patients presented either with persisting localized paresthesias of moderate intensity (2.3%) or with paresthesias that may interfere with functional activities (0.5%).

Acute neurosensory manifestations 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. Occasionally other symptoms that have been observed include jaw spasm/muscle spasms/muscle contractions-

involuntary/muscle twitching/myoclonus, coordination abnormal/gait abnormal/ ataxia/ balance disorders, throat or chest tightness/ pressure/ discomfort/pain. In addition, cranial nerve dysfunctions may be associated with above mentioned events, or also occur as an isolated event such as ptosis, diplopia, aphonia/ dysphonia/ hoarseness, sometimes described as vocal cord paralysis, abnormal tongue sensation or dysarthria, sometimes described as aphasia, trigeminal neuralgia/ facial pain/ eye pain, decrease in visual acuity, visual field disorders.

Other neurological symptoms such as dysarthria, loss of deep tendon reflex and Lhermitte's sign were reported during treatment with oxaliplatin. Isolated cases of optic neuritis have been reported.

Postmarketing experience with frequency unknown

Convulsion

Gastrointestinal disorders

Incidence by patient (%), by grade

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

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

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

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.

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 authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>

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.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties Pharmacotherapeutic group: other antineoplastic agents, platinum compounds

ATC code: L01XA 03

Oxaliplatin is an antineoplastic active substance belonging to a new class of platinum-based compounds in which the platinum atom is complexed with 1, 2-diaminocyclohexane ("DACH") and an oxalate group.

Oxaliplatin is a single enantiomer, (SP-4-2)-[(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 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.

In patients with metastatic colorectal cancer, the efficacy of oxaliplatin (85mg/m² repeated every two weeks) combined with 5-fluorouracil/folinic acid (5-FU/FA) is reported in three clinical studies:

- In front-line treatment, the 2-arm comparative phase III EFC2962 study 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 three arms phase III study EFC4584 randomised 821 patients refractory to an irinotecan (CPT-11) + 5-FU/FA combination either to 5-FU/FA alone (LV5FU2, N=275), oxaliplatin single agent (N=275), or combination of oxaliplatin with 5FU/FA (FOLFOX4, N=271).
- Finally, the uncontrolled phase II EFC2964 study included patients refractory to 5-FU/FA alone, that were treated with the oxaliplatin and 5-FU/FA combination (FOLFOX4, N=57) The two 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 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
	22 (16-27)	49 (42-56)	NA*

Front-line treatment EFC2962 Response assessment every 8 weeks	P value = 0.0001		
Pretreated patients EFC4584 (refractory to CPT-11 + 5FU/FA) Response assessment every 6 weeks	0.7 (0.0-2.7)	11.1 (7.6-15.5)	1.1 (0.2-3.2))
	P value < 0.0001		
Pretreated patients EFC 2964 (refractory to 5-FU/FA) Response assessment every 12weeks	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	LV5FU2	FOLFOX4	Oxaliplatin Single agent
review ITT analysis			
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*
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*NA: Not Applicable

Median Overall Survival (OS) under FOLFOX4 versus LV5FU2

Median OS, months (95% CI) ITT analysis	LV5FU2	FOLFOX 4	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 two treatment groups was found for any of the quality of life dimensions. However, the quality of life scores were generally better in the control arm for measurement of global health status and pain and worse in the oxaliplatin arm for nausea and vomiting. In the adjuvant setting, the MOSAIC comparative phase III study (EFC3313) randomised 2246 patients (899 stage II/Duke's B2 and 1347 stage III/Duke's C) further to complete resection of the primary tumor of colon cancer either to 5-FU/FA alone (LV5FU2, N=1123 (B2/C = 448/675) or to combination of oxaliplatin and 5-FU/FA (FOLFOX4, N=1123 (B2/C) = 451/672).

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.

Oxaliplatin single agent has been evaluated in paediatric population in 2 Phase I (69 patients) and 2 Phase II (166 patients) studies. A total of 235 paediatric patients (7 months-

22 years of age) with solid tumors 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 tumor response.

5.2 Pharmacokinetic properties

The pharmacokinetics of individual active compounds have not been determined. The pharmacokinetics of ultrafilterable 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 _{1/2α} h	t _{1/2β} h	t _{1/2γ} 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 AUC₀₋₄₈, and C_{max} values were determined on Cycle 3 (85 mg/m²) or cycle 5 (130 mg/m²).

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

C_{max}, AUC, AUC₀₋₄₈, V_{ss} and CL values were determined by non-compartmental analysis.

t_{1/2α}, t_{1/2β}, and t_{1/2γ}, were determined by compartmental analysis (Cycles 1-3 combined).

At the end of a 2-hour infusion, 15% of the administered platinum is present in the systemic circulation, the remaining 85% being rapidly distributed into tissues or eliminated in the urine. Irreversible binding to red blood cells and plasma, results in half-lives in these matrices that are close to the natural turnover of red blood cells and serum albumin. No

accumulation was observed in plasma ultrafiltrate following 85 mg/m² every two weeks or 130mg/m² every three weeks and steady state was attained by cycle one in this matrix. Inter- and intra-subject variability is generally low.

Biotransformation 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 drug was detectable in plasma ultra filtrate 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.

Platinum is predominantly excreted in urine, with clearance mainly in the 48 hours following administration.

By day 5, approximately 54% of the total dose was recovered in the urine and < 3% in the faeces.

The effect of renal impairment on the disposition of oxaliplatin was studied in patients with varying degrees of renal function. Oxaliplatin was administered at a dose of 85 mg/m² in the control group with a normal renal function (CL_{Cr} > 80 mL/min, n=12) and in patients with mild (CL_{Cr} = 50 to 80 mL/min, n=13) and moderate (CL_{Cr} = 30 to 49 mL/min, n=11) renal impairment, and at a dose of 65mg/m² in patients with severe renal impairment (CL_{Cr} < 30 mL/min, n=5). Median exposure was 9, 4, 6, and 3 cycles, respectively, and PK data at cycle 1 were obtained in 11, 13, 10, and 4 patients respectively.

There was an increase in plasma ultrafiltrate (PUF) platinum AUC, AUC/dose and a decrease in total and renal CL and V_{ss} with increasing renal impairment especially in the (small) group of patients with severe renal impairment: point estimate (90% CI) of estimated mean ratios by renal status versus normal renal function for AUC/dose were 1.36 (1.08, 1.71), 2.34 (1.82, 3.01) and

4.81 (3.49, 6.64) for patients with mild and moderate and in severe renal failure respectively. Elimination of oxaliplatin is significantly correlated with the creatinine clearance. Total PUF platinum CL was respectively 0.74 (0.59, 0.92), 0.43 (0.33, 0.55) and 0.21 (0.15, 0.29) and for V_{ss} respectively 0.52 (0.41, 0.65), 0.73 (0.59, 0.91) and 0.27 (0.20, 0.36) for patients with mild, moderate and severe renal failure respectively. Total body

clearance of PUF platinum was therefore reduced by respectively 26% in mild, 57% in moderate, and 79% in severe renal impairment compared to patients with normal function. Renal clearance of PUF platinum was reduced in patients with impaired renal function by 30% in mild, 65% in moderate, and 84% in severe renal impairment compared to patients with normal function.

There was an increase in beta half life of PUF platinum with increasing degree of renal impairment mainly in the severe group. Despite the small number of patients with severe renal dysfunction, these data are of concern in patients in severe renal failure and should be taken into account when prescribing oxaliplatin in patients with renal impairment.

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 drugs and DNA-damaging, cytotoxic drugs used in the treatment of human cancers with the exception of the effects produced on the heart. Effects on the heart were observed only in the dog and included electrophysiological disturbances with lethal ventricular fibrillation. Cardiotoxicity is considered specific to the dog not only because it was observed in the dog alone but also because doses similar to those producing lethal cardiotoxicity in dogs (150 mg/m²) were well-tolerated by humans. Preclinical studies using rat sensory neurons suggest that the acute neurosensory symptoms related to Oxaliplatin may involve an interaction with voltage-gated Na⁺ channels. Oxaliplatin was mutagenic and clastogenic in mammalian test systems and produced embryofetal toxicity in rats. Oxaliplatin is considered a probable carcinogen, although carcinogenic studies have not been conducted.

6.0 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate, Water for injections

6.2 Incompatibilities: The diluted medicinal product should not be mixed with other medications in the same infusion bag or infusion line. Oxaliplatin can be coadministered with folinic acid via a Y-line.

- DO NOT mix with alkaline drugs or solutions, in particular 5-fluorouracil, folinic acid preparations containing trometamol as an excipient and trometamol salts of others drugs. Alkaline drugs or solutions will adversely affect the stability of oxaliplatin.
- DO NOT dilute oxaliplatin with saline or other solutions containing chloride ions (including calcium, potassium or sodium chlorides).
- DO NOT mix with other drugs in the same infusion bag or infusion line -
- DO NOT use injection equipment containing aluminium.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

30 mL clear USP-Type-1 tubular vial having 20 mm grey coloured bromo butyl slotted rubber stopper and sealed with 20 mm red colored aluminum flip off seal.

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 medicines used, in conditions that guarantee the integrity of the product, the protection of the environment and in particular the protection of the personnel handling the medicines, in accordance with the hospital policy. It requires a preparation area reserved for this purpose. It is forbidden to smoke, eat or

drink in this area. Personnel must be provided with appropriate handling materials, notably long sleeved gowns, protection masks, caps, protective goggles, sterile single-use gloves, protective covers for the work area, containers and collection bags for waste.

Excreta and vomit must be handled with care.

Pregnant women must be warned to avoid handling cytotoxic agents.

Any broken container must be treated with the same precautions and considered as contaminated waste. Contaminated waste should be incinerated in suitably labeled rigid containers. See below section "Disposal". If oxaliplatin concentrate or infusion solution, should come into contact with skin, wash immediately and thoroughly with water.

If oxaliplatin concentrate or infusion solution, 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% 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 medication in the same infusion bag or administer simultaneously by the same infusion line.
- DO NOT mix with alkaline drugs or solutions, in particular 5-fluorouracil, folinic acid preparations containing trometamol as an excipient and trometamol salts of others drugs. Alkaline drugs 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 to 500 mL of 5% glucose solution is given at the same time as folinic acid IV infusion in 5% glucose solution, over 2 to 6 hours, using a Y-line placed immediately before the site of infusion. These two drugs should not be combined in the same infusion bag. Folinic acid must not contain trometamol as excipients 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.

Concentrate for solution for infusion

Inspect visually prior to use. Only clear solutions without particles should be used.

The medicinal product is for single use only. Any unused concentrate should be discarded.

Preparation of Infusion Solution RECONSTITUTION OR FINAL DILUTION MUST NEVER BE PERFORMED WITH A SODIUM CHLORIDE

SOLUTION OR OTHER CHLORIDE-CONTAINING SOLUTIONS.

The lyophilized powder is reconstituted by adding 10 mL (for the 50 mg vial) of Water for Injection, USP or 5% Dextrose Injection, USP. Do not administer the reconstituted solution without further dilution. The reconstituted solution must be further diluted in an infusion solution of 250 to 500 mL of 5% Dextrose Injection, USP.

After reconstitution in the original vial, the solution may be stored up to 24 hours under refrigeration [2° to 8°C (36° to 46°F)]. After final dilution with 250 to 500 mL of 5% Dextrose Injection, USP, the shelf life is 6 hours at room temperature [20° to 25°C (68° to 77°F)] or up to 24 hours under refrigeration [2° to 8°C (36° to 46°F)].

Oxaliplatin for injection is not light sensitive.

Oxaliplatin for injection is incompatible in solution with alkaline medications or media (such as basic solutions of 5-fluorouracil) and must not be mixed with these or administered simultaneously through the same infusion line. The infusion line should be flushed with 5% Dextrose Injection, USP prior to administration of any concomitant medication.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and discarded if present.

Needles or intravenous administration sets containing aluminum parts that may come in contact with Oxaliplatin for injection should not be used for the preparation or mixing of the drug.

Aluminum has been reported to cause degradation of platinum compounds.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

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