SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

OXALPIN 50 mg/10 ml Lyophilized Powder for Solution for IV Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Each vial contains 50 mg oxaliplatin.
Each 1 ml of reconstituted solution contains 5 mg oxaliplatin before dilution.
Excipient(s):
For the full list of excipients see 6.1.

3. PHARMACEUTICAL FORM

Vial containing lyophilized powder for solution for intravenous infusion
White or off-white powdery mass

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

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

OXALPIN in combination with bevacizumab and 5-FU/FA or capecitabine is indicated for first-line treatment of patients with metastatic colon cancer who have not received previous adjuvant chemotherapy.

4.2. Posology and method of administration

Posology/frequency and duration of administration
FOR ADULTS ONLY.
OXALPIN is administered as a 2- to 6- hour intravenous infusion in 250 to 500 ml of 5% dextrose solution (50 mg/ml) 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 OXALPIN dose of 85 mg/m^2.
OXALPIN was mainly used in combination with continuous infusion 5-fluorouracil (5-FU) based regimens. For the 2-weekly treatment schedule 5-fluorouracil regimens combining bolus and continuous infusion were used.

Frequency and duration of administration:
The recommended dose for OXALPIN in adjuvant setting is 85 mg/m^2 intravenously repeated every 2 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 and 100-130 mg/m^2 intravenously repeated every 3 weeks until disease progression or unacceptable toxicity.

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

Method of administration:
OXALPIN is administered via a central venous line or peripheral vein by intravenous infusion.
The administration of OXALPIN does not require hyperhydration.

OXALPIN should always be administered before 5-fluorouracil (5FU) infusion.

In the event of extravasation, administration must be discontinued immediately.
OXALPIN must be diluted before use. Only 5% dextrose solution (50 mg/ml) is to be used to dilute the lyophilized powder for solution for infusion (see section 6.6).

Additional information on special populations:

Renal/Hepatic impairment:
5 -In patients with gastrointestinal cancer treated with oxaliplatin in combination with FU/FA (FOLFOX4) (up to 12 cycles of 2-hour intravenous infusion every two weeks) and with varying degrees of renal impairment, oxaliplatin had minimal clinical effect on renal impairment as assessed by mean creatinine clearance (see Section 5.2).

Safety results have been found to be similar between patient groups. However, median exposure time was shorter in patients with impaired renal function. Median exposure was 4, 6 and 3 cycles in patients with mild, moderate and severe renal impairment respectively. Median exposure was 9 cycles in patients with normal renal function. More patients discontinued treatment due to adverse effects in groups of patients with impaired renal function. The initial dose of oxaliplatin should be reduced to 65 mg/m^2 in patients with severely impaired renal function.

In patients with normal renal function or mild to moderate renal impairment, the recommended dose of oxaliplatin is 85 mg/m^2. In patients with severe renal impairment, the initial recommended dose of oxaliplatin should be reduced to 65 mg/m^2.
In a phase I study including patients with several level of hepatic impairment, frequency and severity of hepatobiliary disorders appeared to be related to progressive disease and impaired liver function tests at baseline.
No specific dose adjustment for patients with abnormal liver function tests was performed during clinical development trials.

Pediatric population:
There is no relevant indication for use of oxaliplatin in children. The effectiveness of oxaliplatin single agent in the pediatric populations with solid tumors has not been established (see section 5.1). It should not be used in children and adolescents.

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

4.3. Contraindications
- Patients who have a known history of hypersensitivity to oxaliplatin
- Patients who are breast feeding

- Patients who have myelosuppression prior to starting first course, as evidenced by baseline neutrophils $<2\times10^9$/l and/or platelet count of $<100\times10^9$/l
- Patients who have a peripheral sensory neuropathy with functional impairment prior to first course

4.4. Special warnings and precautions for use

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

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

Special surveillance should be ensured for patients with a history of allergic manifestations to other products containing platinum. Allergic reactions can occur during any course of treatment. If anaphylaxis or an anaphylactoid-like reaction develops to OXALPIN, the infusion should be stopped immediately and appropriate symptomatic treatment initiated. Restarting OXALPIN administration is contraindicated in these patients (see Section 4.3). Cross-allergic reactions, sometimes fatal, have been reported with all platinum compounds.

If OXALPIN leaks outside the vein, the infusion should be stopped immediately and usual local symptomatic treatment should be initiated.

The dose limiting toxicity of oxaliplatin is neurological. It involves a sensory peripheral neuropathy characterized by dysesthesia and/or paresthesia of the extremities with or without cramps, often triggered by the cold (in 85-95% of patients). The duration of these symptoms, which usually recede between the cycles of treatment, increases with the number of treatment cycles.

The onset of pain and/or a functional disorder and continuation may require 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 cumulated 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 treatment of colon cancer, 6 months after treatment cessation, 87% of patients had no or mild symptoms. After up to 3 years of follow up, 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 (see section 5.3). These symptoms usually develop at the end of the 2-hour oxaliplatin infusion or within a few hours, abate spontaneously within the next few hours or days, and frequently recur with further cycles. They may be precipitated by or exacerbated by exposure to cold temperatures or objects. They usually present as transient paresthesia, dysesthesia and hypoesthesia. An acute syndrome of pharyngolaryngeal dysesthesia occurs in 1-2% of patients and is characterized by subjective sensations of dysphagia or

dyspnea/feeling of suffocation, without any objective evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm (no stridor or wheezing).

Occasionally observed and particularly associated with cranial nerve dysfunction, symptoms such as ptosis, diplopia, aphonia/dysphonia/hoarseness (sometimes described as vocal cord paralysis), sensory disturbances in the tongue, or dysarthria (sometimes described as aphasia), trigeminal neuralgia/facial pain/eye pain, decreased visual acuity, visual field defects, among other symptoms, may occur alone or in combination. In addition, the following symptoms have been observed: jaw spasm, muscle spasm, muscle contractions-involuntary, myoclonus, coordination abnormal, gait abnormal, ataxia, balance disorders, throat or chest tightness, pressure, discomfort, pain.

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

When administered concomitantly with other drugs that exhibit specific neurological toxicity, the neurological toxicity of OXALPIN should be carefully monitored. A neurological examination should be performed before and after each administration, as well as periodically.
In patients who develop acute laryngopharyngeal dysesthesia during the 2-hour infusion or in the hours following the infusion, the next OXALPIN infusion should be administered over 6 hours. To prevent such dysesthesia, the patient should be advised to avoid exposure to cold and to refrain from consuming cold/chilled foods and/or beverages during the OXALPIN administration or in the hours following the administration.

If neurological symptoms (paresthesia, dysesthesia) occur, the following OXALPIN 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 OXALPIN dose should be reduced from 85 to 65 mg/m² in metastatic setting, 75 mg/m² in adjuvant setting.
- If paresthesia without functional impairment persists until the next cycle, the subsequent OXALPIN dose should be reduced from 85 to 65 mg/m² in metastatic setting, 75 mg/m² in adjuvant setting.
- If paresthesia with functional impairment persists until the next cycle, OXALPIN should be discontinued.
- If these symptoms improve following discontinuation of OXALPIN 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 paresthesia or paresthesias that may interfere with functional activities can persist after up to 3 years following treatment cessation in the adjuvant setting.

Signs and symptoms of Reversible Posterior Leukoencephalopathy Syndrome (RPLS; Posterior Reversible Leukoencephalopathy Syndrome) could be headache, altered mental functioning, seizures, abnormal vision from blurriness to blindness, associated or not with hypertension (see Section 4.8). Diagnosis of RPLS is based upon confirmation by brain imaging.

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 diarrhea/emesis particularly when combining OXALPIN with 5-fluorouracil (5-FU).

If hematological toxicity occurs (neutrophils $<1.5\times10^9$/l or platelets $<50\times10^9$/l) or bone marrow suppression at the start of therapy (first course), administration of the next course of therapy should be postponed until hematological 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 diarrhea/emesis, mucositis/stomatitis and neutropenia after OXALPIN and 5-fluorouracil (5-FU) administration so that they can urgently contact their treating physician for appropriate management. If mucositis/stomatitis occurs with or without neutropenia, the next treatment should be delayed until recovery from mucositis/stomatitis to grade 1 or less and/or until the neutrophil count is $\geq1.5\times10^9$/l.

As oxaliplatin is combined with 5-fluorouracil (5-FU), (with or without folinic acid [FA]), the usual dose adjustments for 5-fluorouracil associated toxicities should apply hereby.

If grade 4 diarrhea, grade 3-4 neutropenia (neutrophils $<1.0\times10^9$/l), grade 3-4 thrombocytopenia (platelets $<50\times10^9$/l) occur, the dose of OXALPIN should be reduced from 85 to 65 mg/m^2 in metastatic setting or 85 to 75 mg/m^2 in adjuvant setting, in addition to any 5-fluorouracilin 5 FU dose reductions required.

OXALPIN should be discontinued until further pulmonary investigations rule out interstitial lung disease when unexplained respiratory symptoms such as nonproductive cough, dyspnea, crepitant rales, or radiological pulmonary infiltrates are present.

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.

For use in pregnant women, see section “4.6 Pregnancy and lactation”.

Genotoxic effects were observed with oxaliplatin in the preclinical studies. Therefore male patients treated with OXALPIN 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 OXALPIN may have an anti-fertility effect, which could be irreversible.

Women should not become pregnant during treatment with OXALPIN and should use an effective method of contraception (see section 4.6).

During adjuvant setting with OXALPIN weight increase (very common), and in metastatic setting weight decrease (common) may occur.

Laboratory tests
During OXALPIN treatment, standard monitoring of white blood cell count (including hemoglobin, platelet count, and blood chemistry) is recommended. OXALPIN treatment alters laboratory test results as follows:

Very common : Mild or moderate hepatic enzyme increase, serum alkaline phosphates increase, serum bilirubin increase, serum lactate dehydration increase
Common : Serum creatinine increase

4.5. Interaction with other medicinal products and other forms of interaction
Co-administration with nephrotoxic compounds:
Since platinum compounds are eliminated primarily through the kidney, clearance of OXALPIN may be decreased by co-administration of nephrotoxic compounds. Although no studies have been conducted on this subject.

Co-administration with drugs interacting with cytochrome P-450 enzyme system:
In vitro, no significant displacement of OXALPIN binding to plasma proteins has been observed with the following agents: erythromycin, salicylates, granisetron, paclitaxel, and sodium valproate. Accordingly, drug interaction regarding cytochrome P-450 enzyme system is not expected.

Co-administration with 5-fluorouracil (5-FU):
In patients who have received a single dose of 85 mg/m^2 of oxaliplatin every 2 weeks, immediately before administration of 5-FU, no change in the level of exposure to 5-FU has been observed.
In patients dosed with OXALPIN 130 mg/m^2 every 3 weeks, increases of 20% in 5-FU plasma concentrations have been observed.

4.6. Pregnancy and lactation

General Recommendation
Pregnancy category is D

Women of child-bearing potential/Birth Control (Contraception)
As with other cytotoxic agents, effective contraceptive measures should be taken in potentially fertile patients (male and female) prior to initiating chemotherapy with OXALPIN.
Appropriate contraceptive measures must be taken during and after cessation of therapy during 4 months for women and 6 months for men.

Pregnancy
To date, there is no available information on safety of OXALPIN use in pregnant women. In animal studies, reproductive toxicity was observed (see section 5.3). Based on preclinical findings, OXALPIN is likely to be lethal and/or teratogenic to the human fetus at the recommended therapeutic doses. The use of OXALPIN should only be considered after the patient has been adequately informed about the risks to the fetus and has given their consent.

Breast-feeding
There is inadequate/limited data regarding excretion of OXALPIN into animal or human milk. Given the physicochemical and available pharmacodynamic/toxicological data regarding the excretion of OXALPIN in breast milk, a risk to the breastfed infant cannot be ruled out. OXALPIN should not be used during breastfeeding.

Reproductive ability/Fertility
Fertility toxicity has been observed in animal studies (see section 5.3). OXALPIN may have an anti-fertility effect (see section 4.4).

4.7. Effects on ability to drive and use machines

There are no studies on the effects of OXALPIN on the ability to drive or operate machinery. OXALPIN treatment may cause dizziness, nausea, and vomiting, and other neurological symptoms that affect balance, which may mildly or moderately impair the ability to drive or operate machinery. Visual abnormalities, particularly temporary vision loss (reversible following discontinuation of treatment), may affect the ability to drive or operate machinery. Patients receiving this medication should be warned not to drive or operate machinery.

4.8. Undesirable effects

The most frequent adverse events of OXALPIN in combination with 5 fluorouracil/folinic acid (5-FU/FA), were gastrointestinal (diarrhea, nausea, vomiting and mucositis), hematological (neutropenia, thrombocytopenia) and neurological (acute and dose cumulative peripheral sensory neuropathy). Overall, these adverse events were more frequent and severe with OXALPIN and 5-FU/FA combination than with 5- FU/FA alone.

The frequencies reported below are derived from clinical trials in the metastatic and adjuvant settings (having included 416 and 1108 patients respectively in the OXALPIN + 5-FU/FA arm) and from post marketing experience.

Frequencies are defined as: 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).

Infections and infestations

Very common : Infection
Common : Rhinitis, upper respiratory tract infection, febrile neutropenia/neutropenic sepsis

Blood and lymphatic system disorders

Very common : Anemia, neutropenia, thrombocytopenia, leucopoenia, lymphopenia

- Increases more frequently when OXALPIN administered in combination with 5-FU+/- folic acid (85 mg/m^2 every two weeks) in comparison to administration alone (130 mg/m^2 every three weeks); for example anemia (in 80% of patients vs 60 % respectively), neutropenia (15% vs 70%), thrombocytopenia (80% vs 40%)
- Severe anemia (hemoglobin <8.0 g/dl) or thrombocytopenia (trombosit <50×10^9/L) <8.0 g/dL), occur in similar frequency when OXALPIN is administered alone or in combination with 5-FU (in not less than 5% of patients).
- Severe neutropenia (neutrophile <1.0×10^9/L) occurs more frequently when OXALPIN is administered in combination with 5-FU in comparison to administration alone (40% vs <3% respectively)

Rare : Immunoallergic hemolytic anemia and thrombocytopenia
Not known : Hemolytic uremic syndrome

Immunity system disorders

Very common : Allergy/allergic reactions +
Common : Anaphylactic reactions including bronchospasm, angioedema, hypotension, feeling pain on chest and anaphylactic shock

Metabolism and nutrition disorders

Very common : Anorexia, glycemia abnormalities, hypokalemia, natremia abnormalities

Common : Dehydration
Uncommon : Metabolic acidosis

Psychiatric disorders
Common : Depression, insomnia
Uncommon : Nervousness

Nervous system disorders **
Very common : Peripheral sensitive neuropathy, sensory disturbance, dysgeusia, headache
Common : Dizziness, motor neuritis, meningism
Rare : Dysarthria, loss of deep tendon reflexes, Lhermitte's sign, Reversible Posterior Leukoencephalopathy Syndrome (RPLS; also called as Posterior Reversible Leukoencephalopathy Syndrome)**
Not known : Convulsions, laryngospasm

Eye disorders
Common : Conjunctivitis, visual disturbance
Rare : Visual acuity reduced transiently, visual field disturbances, optic neuritis, and transient vision loss, reversible following therapy discontinuation

Ear and labyrinth disorders
Uncommon : Ototoxicity
Rare : Deafness

Cardiovascular disorders
Very common : Epistaxis
Common : Hemorrhage, flushing, deep vein thrombosis, thromboembolic events, pulmonary embolism, hypertension

Respiratory, thoracic and mediastinal disorders
Very common : Dyspnea, cough
Common : Hiccups
Rare : Interstitial lung disease (sometimes fatal), pulmonary fibrosis **

Gastrointestinal disorders
Very common : Nausea, diarrhea, vomiting, stomatitis /mucositis, abdominal pain, constipation
Common : Dyspepsia, gastro-esophageal reflux, gastrointestinal hemorrhage, rectal hemorrhage
Uncommon : Ileus, intestinal obstruction
Rare : Colitis (including *Clostridium difficile* diarrhea), pancreatitis

Hepatobiliary disorders
Very rare : Liver sinusoidal obstruction syndrome, also known as veno-occlusive disease of liver, or pathological manifestations related to such liver disorder, including peliosis, nodular regenerative hyperplasia, perisinusoidal fibrosis and portal hypertension.

Skin and subcutaneous tissue disorders
Very common : Skin disorder, alopecia (when oxaliplatin is administered alone <%5)

Common : Skin exfoliation (i.e. hand & foot syndrome), rash erythematous, rash, hyperhidrosis, nail disorder

Musculoskeletal and connective tissue disorders
Very common : Back pain (in case of such adverse reaction, hemolysis rarely reported should be investigated)
Common : Arthralgia, bone pain

Renal and urinary disorders
Common : Hematuria, dysuria, micturition frequency abnormal, renal dysfunction
Very rare : Acute tubular necrosis, acute interstitial nephritis and acute renal impairment

General disorders and administration site conditions
Very common : Fatigue, fever++, tremor (because of infection– with or without fibril neutropenia- or immunologic mechanism), asthenia, pain, injection site reaction+++, alteration in blood test results including those relating to abnormalities in liver function

** see section 4.4
+ Common allergic reactions, occurring mainly during infusion, sometimes fatal, such as 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, either from infection (with or without febrile neutropenia) or isolated fever possibly from immunological mechanism
+++ Injection site reactions including local pain, redness, swelling and thrombosis have been reported. Extravasation, particularly when oxaliplatin is administered as an infusion into a peripheral vein, can result in local pain and inflammation, including necrosis, which can be serious and lead to complications (see Section 4.4).

Combination therapy of oxaliplatin with 5-FU/FA (FOLFOX) and BEVACIZUMAB
The safety of the first-line oxaliplatin with 5-FU/FA and bevacizumab combination was evaluated in 71 patients with metastatic colorectal cancer (TREE study).
In addition to the expected side effects of the FOLFOX regimen, the FOLFOX/bevacizumab combination was associated with: bleeding (45.1%; G3/4: 2.8%), proteinuria (11.3%; G3/4: 0%), delayed wound healing (5.6%), gastrointestinal perforation (4.2%), and hypertension (1.4%; G3/4: 1.4%).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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

Mechanism of action
OXALPIN is white or off-white powdery mass. Oxaliplatin, its active substance, is an antineoplastic medicine 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) – [(1*R*, 2*R*) – Cyclohexane -1,2-diamin-k*N*, k*N*'] [etanedioato (2-) – kO^1, kO^2] platinum.
Although the mechanism of action of oxaliplatin has not been fully elucidated, studies on this subject have shown that the aqueous derivatives of oxaliplatin, resulting from biotransformation, interact with DNA by forming both inter- and intra-crosslinks, thereby disrupting DNA synthesis and leading to cytotoxic and antitumor effects.
Pharmacodynamic effects
Oxaliplatin exhibits a wide spectrum of both *in vitro* cytotoxicity and *in vivo* anti-tumor activity in a variety of tumor 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 (5 FU) *both in vitro* and *in vivo*.

Clinical efficacy
In patients with metastatic colorectal cancer, the efficacy of oxaliplatin (85 mg/m^2 repeated every 2 weeks) in combination with 5-fluorouracil/ folinic acid (5-FU/FA) has been reported in 3 clinical studies:

- In first-line treatment, the 2-arm comparative phase III EFC2962 study randomized 420 patients either to 5-FU/FA alone (LV5FU2, N=210) or the combination of oxaliplatin with 5-FU/FA (FOLFOX4, N=210)
- In pre-treated patients the comparative 3-arm phase III EFC4584 study randomized 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 non controlled 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 randomized clinical trials, EFC2962 in first-line therapy and EFC4584 in pre-treated patients, demonstrated a significantly higher response rate and a prolonged progression-free survival (PFS)/time to progression (TTP) as compared to treatment with 5-FU/FA alone.
In EFC4584 study performed in refractory pre-treated 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% confidence interval) independent radiological review ITT analysis	**LV5FU2**	**FOLFOX4**	**Oxaliplatin Single agent**
First-line treatment EFC2962	22 (16-27)	49 (42-46)	NA*

Response assessment every 8 weeks	P value = 0.0001		
Pre-treated 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		
Pre-treated 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% confidence interval) independent radiological review ITT analysis	**LV5FU2**	**FOLFOX4**	**Oxaliplatin Single agent**
First-line treatment EFC2962 (PFS)	6.0 (5.5-6.5)	8.2 (7.2-8.8)	NA*
	Log-rank P value = 0.0003		
Pre-treated 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		
Pre-treated 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% confidence interval) ITT analysis	**LV5FU2**	**FOLFOX4**	**Oxaliplatin Single agent**
First-line treatment EFC2962	14.7 (13.0-18.2)	16.2 (14.7-18.2)	NA*
	Log-rank P value = 0.12		
Pre-treated patients EFC4584 (refractory to CPT-11 + 5-FU/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		
Pre-treated patients EFC2964 (refractory to 5-FU/FA)	NA*	10.8 (9.3-12.8)	NA*

*NA: Not applicable.

In pre-treated 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. Additionally, 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 comparative MOSAIC phase III study (EFC3313) randomized 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)*

Treatment arm	**LV5FU2**	**FOLFOX4**
Percent 3-year disease free survival (95% confidence interval)	73.3 (70.6-75.6)	78.7 (76.2-81.1)
Hazard ratio (95% confidence interval)	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).

This study demonstrated that the combination of oxaliplatin and 5-FU/FA (FOLFOX4) has a significant overall advantage in terms of 3-year disease-free survival compared to 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% confidence interval)	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% confidence interval)	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 the 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.

Metastatic colorectal cancer (oxaliplatin/5-FU/FA/bevacizumab):
Combination efficacy of oxaliplatin with 5-FU/FA (FOLFOX) and bevacizumab is evaluated in 2 clinical studies in patients with metastatic colorectal cancer as first-line chemotherapy (TREE study) or second-line chemotherapy (ECOG study).

- In randomized, non-comparative, phase II TREE study, combination of FOLFOX/bevacizumab (by using standard dose of bevacizumab 5 mg/kg body weight every two weeks) (71 patients) and FOLFOX alone course (49 patients) were evaluated. In patient population treated (patients treated randomly), the objective response rate was 52.1% and 40.8% respectively. Mean time to progression (TTP, defined as progression free survival, PFS) was respectively 9.9 and 8.7 months. Overall survival was 26 and 19.2 months respectively.
- In randomized, comparative, phase III ECOG 3200 study, combination of FOLFOX/ bevacizumab (bevacizumab 10 mg/kg body weight every 2 weeks) (293 patients) and FOLFOX

course (292 patients) were compared. Significant improvements in objective response rate (22.2% versus 8.6%), mean progression-free survival (PFS, 7.5 versus 4.5 months), and overall survival (OS, 13.0 versus 10.8 months) were observed in the combination of FOLFOX/ bevacizumab arm.

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

5.2. Pharmacokinetic properties

General properties
Reactive oxaliplatin derivates are available as a mixture of platinum compounds unbound to plasma ultrafiltrate. After administration of oxaliplatin, decreasing of platinum levels which is ultrafiltered are three-stages, and characterized as relatively short two distribution ($t_{1/2\alpha}$=0.43 hour, $t_{1/2\beta}$= l6.8 hour) and long terminal elimination phase ($t_{1/2\gamma}$=391 hour). After infusion of OXALPIN at dosage of 85 mg/m^2 for 2 hours by intravenously, obtained pharmacokinetic parameters as maximum plasma concentration is 0.814 µg/ml and distribution volume is 440 l.

Absorption:
The pharmacokinetics of individual active compounds have not been determined. The pharmacokinetics of ultrafiltrable platinum, representing a mixture of all unbound, active and inactive platinum species, following a 2-hour infusion of oxaliplatin at 130 mg/m² every three weeks for 1 to 5 cycles and oxaliplatin at 85 mg/m² 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/m² every two weeks or at 130 mg/m² every three weeks

Dose	C_{max} µg/ml	AUC_{0-48} µg.s/ml	AUC µg.s/ml	$t_{1/2}\alpha$ s	$t_{1/2}\beta$ s	$t_{1/2}\gamma$ s	V_{ss} l	CI l/s
85 mg/m² Mean± SD	0.814± 0.193	4.19± 0.647	4.68± 1.40	0.43± 0.35	16.8± 5.74	391± 406	440± 199	17.4± 6.35
130 mg/m² Mean± SD	1.21± 0.10	8.20± 2.40	11.9± 4.60	0.28± 0.06	16.3± 2.90	273± 19.0	582± 261	10.1± 3.07

Mean AUC_{0-48} and C_{max} values were determined on Cycle 3 (85 mg/m²) or cycle 5 (130 mg/m²).
Mean AUC, V_{ss}, CI and CI_{R0-48} values were determined on Cycle 1.
C_{final}, C_{max}, AUC, AUC_{0-48}, V_{ss} and CI values were determined by non-compartmental analysis.
$t_{1/2}\alpha$, $t_{1/2}\beta$ and $t_{1/2}\gamma$ (Cycles 1-3 combined) were determined by compartmental analysis.

Distribution:
At the end of a 2-hour infusion, 15% of the administered platinum is present in the systemic circulation, the remaining 85% being rapidly distributed into tissues or eliminated in the urine. Irreversible binding to red blood cells and plasma, results in half-lives in these matrices that are close to the natural turnover of red blood cells and serum albumin. No accumulation was observed in plasma ultrafiltrate following 85 mg/m² every two weeks or 130 mg/m² every 3 weeks and steady state was attained by cycle one in this matrix. Inter- and intra-subject variability is generally low.

Biotransformation:
Biotransformation *in vitro* is considered to be the result of non-enzymatic degradation and there is no evidence of cytochrome P450-mediated metabolism of the diaminocyclohexane (DACH) ring.

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

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 feces.

Linearity/ non-linearity:
In a 1 to 5-cycle treatment regimen, following a 2-hour infusion of 130 mg/m² OXALPIN every 3 weeks, and in a 1 to 3-cycle treatment regimen, following a 2-hour infusion of 85 mg/m² OXALPIN every 2 weeks, C_{max}, AUC_{0-48}, and AUC values for platinum ultrafiltrate, representing a mixture of all active and inactive platinum species, increased proportionally with dose.

Characteristics in patients

Renal impairment:
Disposition of oxaliplatin was studied in patients with varying degrees of renal impairment.
Elimination of oxaliplatin is significantly correlated with the creatinine clearance. Total body clearance of plasma ultrafiltrate (PUF) platinum was reduced in patients with impaired renal function compared to patients with normal function (creatinine clearance >80 ml/min); the reduction rates are 34% in patients with mild renal impairment (creatinine clearance =50 to 80 ml/min), 57% in patients with moderate renal impairment (creatinine clearance = 30 to 49 ml/min) and 79% in patients with severe renal impairment (creatinine clearance <30 ml/min).
There was an increase in beta and gamma half lives of PUF platinum with increasing degree of renal impairment mainly in the severe impairment group. Due to high inter-patient variability and the small number of patients with severe renal impairment (4 patients), no certain results have not been obtained. Renal clearance of PUF platinum and elimination of platinum were reduced depending on impaired renal function (see section 4.2 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, kidney, testes, the nervous system, and the heart. The target organ toxicities observed in animals are consistent with those produced by other platinum-containing medicinal products and DNA-damaging, cytotoxic medicinal products used in the treatment of human cancers with the exception of the effects produced on the heart.
Effects on the heart were observed only in the dog and included electrophysiological disturbances with lethal ventricular fibrillation. Cardiotoxicity is considered specific to the dog not only because it was observed in the dog alone but also because doses similar to those producing lethal cardiotoxicity in dogs (150 mg/m²) were well-tolerated by humans. Preclinical studies using rat sensory neurons suggest that acute symptoms associated with OXALPIN, related to nerves that

transmit signals to the central nervous system, may arise from interaction with voltage-gated Na+ channels.
OXALPIN has been found to be mutagenic and clastogenic in mammals and has caused embryo-fetal toxicity in rats. Although carcinogenic studies have not been conducted, OXALPIN is considered a possible carcinogen.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients
Lactose monohydrate

6.2. Incompatibilities
The diluted medicinal product should not be mixed with other medicines in the same infusion bag or infusion line. Under instructions for use described in Section 6.6 "Special precautions for disposal and other handling" OXALPIN can be co-administered with folinic acid (FA) via a Y-line.

- DO NOT mix with alkaline medicinal products or solutions; in particular 5-fluorouracil (5-FU), folinic acid (FA) preparations containing trometamol as an excipient and trometamol salts of others active substances. Alkaline medicinal products or solutions will adversely affect the stability of OXALPIN (see section 6.6).
- DO NOT dilute OXALPIN with 0.9% sodium chloride or other solutions containing chloride ions (including calcium, potassium or sodium chloride)
- DO NOT mix with any other medicinal products in the same infusion bag or line (see section 6.6 for instruction for simultaneous administration with folinic acid (FA))
- DO NOT use injection equipment containing aluminum.

6.3. Shelf life
Medicinal product: 36 months

Reconstituted solution in the original vial:
From a microbiological and chemical point of view, it should be diluted immediately. It is stable at 2-8°C for 24 hours, if not used immediately.

Solution for infusion:
After dilution of reconstituted solution in glucose 5% solution, chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C. From a microbiological point of view, this infusion solution should be used immediately and not kept at room temperature.

6.4. Special precautions for storage
Lyophilized powder: Store at room temperature below 25°C
For storage conditions of opened sterile product, see section 6.3.

6.5. Nature and contents of packaging
Colorless, Type I glass vial closed with chlorobutyl rubber stopper and aluminum flip-off cap.
Each cardboard box contains 1 vial.

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 healthcare personnel requires every precaution to guarantee the protection of the handler and his surroundings.

The preparation of injectable solutions of cytotoxic agents must be carried out by trained specialist personnel with knowledge of the medicines used, in conditions that guarantee the integrity of the medicinal 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 vial 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 OXALPIN lyophilized powder, reconstituted solution or infusion solution contact with skin or mucosa membranes, wash immediately and thoroughly with water.

Special precautions for administration

- DO NOT use injection equipment containing aluminum.
- DO NOT administer undiluted.
- Only 5% dextrose infusion solution (50 mg/ml) is to be used as a diluent. DO NOT dilute with 0.9 % sodium chloride solution or chloride containing solutions.
- DO NOT mix with any other medicinal products in the same infusion bag or administer simultaneously by the same infusion line.
- DO NOT mix with alkaline medicinal products or solutions; in particular 5-fluorouracil (5-FU), folinic acid (FA) preparations containing trometamol as an excipient and trometamol salts of others active substances. Alkaline medicinal products or solutions will adversely affect the stability of oxaliplatin.

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

OXALPIN 85 mg/m² intravenous infusion in 250 to 500 ml of dextrose 5% (50 mg/ml) solution is given at the same time as folinic acid (FA) intravenous infusion in dextrose 5% (50 mg/ml) solution, over 2 to 6 hours, using a Y-line placed immediately before the site of infusion.
These two medicinal products should not be combined in the same infusion bag. Folinic acid (FA) must not contain trometamol as an excipient and must only be diluted using isotonic dextrose 5% (50 mg/ml) solution, NEVER USE in alkaline solutions or sodium chloride or chloride containing solutions.

Instruction for use with 5 fluorouracil

OXALPIN should always be administered before fluoropyrimidines – i.e. 5 fluorouracil (5-FU).
After OXALPIN administration, flush the line and then administer 5-fluorouracil (5-FU).
For additional information on medicinal products combined with OXALPIN, see the corresponding manufacturer's summary of product characteristics.

Reconstitution of the powder

Water for injection or 5% glucose solution should be used to reconstitution of the powder.

For a 50 mg vial: add 10 ml of solvent to obtain a concentration of 5 mg OXALPIN/ml.
For a 100 mg vial: add 20 ml of solvent to obtain a concentration of 5 mg OXALPIN/ml.
Inspect visually prior to use. Only clear solutions without particles should be used.
The medicinal product is for single use only. Any unused concentrate solution should be discarded.

Dilution for Intravenous Infusion
The required amount of reconstituted solution is withdrawn from the vial(s) and diluted with 250 ml to 500 ml of 5% (50 mg/ml) dextrose solution to achieve an OXALPIN concentration between 0.2 mg/ml and 2 mg/ml. The concentration range at which the physicochemical stability of OXALPIN has been proven is 0.2 mg/ml to 2 mg/ml.
Administer by intravenous infusion.

After dilution in 5% (50 mg/ml) dextrose solution, chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°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 2-8°C unless dilution has taken place in controlled and validated aseptic conditions. Do not store at room temperature and use immediately.
Inspect visually prior to use. Only clear solutions without particles should be used.
The medicinal product is for single use only. Any unused infusion solution should be discarded.
NEVER use sodium chloride solution or chloride containing solutions for dilution.
The compatibility of OXALPIN solution for infusion has been tested with representative, PVC based, administration sets.

Infusion
The administration OXALPIN does not require prehydration.
OXALPIN diluted in 250 to 500 ml of a 5% (50 mg/ml) dextrose solution to give a concentration not less than 0.2 mg/ml must be infused either by peripheral vein or central venous catheter over 2 to 6 hours. When OXALPIN is administered with 5-fluorouracil (5-FU), OXALPIN infusion should precede that of 5-fluorouracil (5-FU).

Disposal
Remnants of the medicinal product as well as all items used for preparation, administration, infusion, or otherwise coming into contact with OXALPIN are **HAZARDOUS WASTE** and should be placed in an appropriate safety container and disposed according to local guidelines for the handling of cytotoxic compounds.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER(S)

224/93

9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF THE AUTHORIZATION

Date of first authorization : 04.06.2010
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10. DATE OF REVISION OF THE TEXT