

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Oxaliplatin Vianex 5 mg/ml powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml reconstituted solution contains 5 mg oxaliplatin.

50 mg vial: one vial contains 50 mg oxaliplatin for reconstitution with 10 ml solvent.

100 mg vial: one vial contains 100 mg oxaliplatin for reconstitution with 20 ml 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.

4.2 Posology and method of administration

Posology

Oxaliplatin Vianex must only be used in adults.

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

The recommended dose for treatment of metastatic colorectal cancer is 85 mg/m² administered intravenously every second week.

The dose should be adjusted according to the patient's tolerance towards the medicinal product (see section 4.4).

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

Oxaliplatin Vianex is normally administered as a 2 to 6-hour intravenous infusion in 250 to 500 ml of glucose solution 5% (50 mg/ml) with a concentration of oxaliplatin of between 0.2 mg/ml and 0.7 mg/ml; 0.7 mg/ml is the highest concentration used in clinical practice at a dose of 85 mg/m².

Oxaliplatin is mainly used in combination with continuous infusion of 5-fluorouracil (5-FU) based regimens. For the every second week oxaliplatin dosing schedule, 5-fluorouracil (5-FU) is administered as a combination of bolus and continuous infusion.

Special Populations

Renal impairment: Oxaliplatin has not been studied in patients with severely impaired renal function (see section 4.3).

In patients with moderately impaired renal function, treatment may be initiated at the usually recommended dose (see section 4.4). There is no need for dose adjustment in patients with mild renal impairment.

Hepatic impairment: In a phase I study including patients with various degrees of reduced hepatic impairment, the frequency and severity of hepatic and biliary tract diseases were related to progressive disease and reduced liver function values prior to oxaliplatin treatment.

No specific dose adjustment for patients with abnormal liver function tests was necessary during clinical development.

Elderly: No increase in severe toxicity was observed when oxaliplatin was used as a single agent or in combination with 5-fluorouracil (5-FU) in patients older than 65 years. Therefore, no specific dose adjustment is necessary in elderly patients.

Children: There is no relevant indication for use of oxaliplatin in children. The effect of oxaliplatin in monotherapy in children with solid tumours has not been established (see section 5.1).

Method of administration

Oxaliplatin Vianex is administered as intravenous infusion.

The administration does not require previous hydration.

Oxaliplatin Vianex dissolved in 250 to 500 ml of glucose solution 5% with a concentration not less than 0.2 mg/ml must be administered via a peripheral vein or a central venous line over 2 to 6 hours. Oxaliplatin Vianex infusion must *always* precede that of 5-fluorouracil (5-FU).

In case of extravasation, discontinue use immediately.

Instruction for use:

As with other potentially toxic compounds caution should be exercised, when handling and preparing Oxaliplatin Vianex solutions (See section 6.6).

Oxaliplatin Vianex must be reconstituted and diluted further before use. Only the recommended solvents should be used to reconstitute and dilute the lyophilised substance. (See section 6.6).

4.3 Contraindications

Oxaliplatin Vianex is contraindicated in patients who:

- are hypersensitive to the active substance or to any of the excipients listed in section 6.1;

- are breastfeeding;
- have myelosuppression prior to first treatment, demonstrated by baseline neutrophils $<2 \times 10^9/l$ and/or platelet count of $<100 \times 10^9/l$;
- have a peripheral sensory neuropathy with functional impairment prior to first treatment;
- have a severely impaired renal function (creatinine clearance less than 30 ml/min).

4.4 Special warnings and precautions for use

Oxaliplatin Vianex should only be used in hospital units specialised in administration of cytostatics and the medicinal product should only be administered under the supervision of an experienced oncologist.

Renal impairment

Due to limited information on safety in patients with moderately impaired renal function, administration should only be considered following careful consideration of the benefit/risk for the patient.

In this case, renal function should be closely monitored and the dose adjusted according to toxicity.

Hypersensitive reactions

Patients with a history of hypersensitivity to any platinum compound should be monitored for potential allergic symptoms. In case of an anaphylactic reaction during treatment with Oxaliplatin Vianex, the infusion should be immediately discontinued and symptomatic treatment initiated. Re-administration of oxaliplatin to such patients is contraindicated. Cross reactions, sometimes fatal, have been reported with all platinum compounds.

In case of extravascular infusion, the administration must be stopped immediately and local symptomatic treatment initiated.

Neurological Symptoms

Administration of Oxaliplatin Vianex, especially with concomitant administration of other potentially neurotoxic medicinal products, the patients should be closely monitored due to the risk of neurological adverse reactions. Neurological examination should be performed before each new administration and periodically thereafter.

In case of development of acute laryngopharyngeal dysaesthesia (see section 4.8) during or within the proximate hours following the 2-hour infusion, the next 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 severe, the dose should be reduced from 85 to 65 mg/m² (treatment of metastatic cancer) or 75 mg/m² (adjuvant treatment).
- If paraesthesia without functional impairment persists until next cycle, the dose should be reduced from 85 to 65 mg/m² (treatment of metastatic cancer) or 75 mg/m² (adjuvant treatment).
- If paraesthesia with functional impairment persists until next cycle, the treatment with oxaliplatin should be discontinued.
- If these symptoms improve following discontinuation of the therapy, continuation of therapy with Oxaliplatin Vianex may be considered.

Patients should be informed of the possibility of persistent symptoms of peripheral sensory neuropathy after termination of the treatment. Localized moderate paraesthesias or paraesthesias that may interfere with functional activities can persist up to 3 years after termination of the adjuvant treatment.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Cases of Reversible Posterior Leukoencephalopathy Syndrome (RPLS also known as PRES or Posterior Reversible Encephalopathy Syndrome) have been reported in patients receiving oxaliplatin in combination chemotherapy. RPLS is a rare, reversible, rapidly evolving neurological condition, which can include seizure, hypertension, headache, confusion, blindness, and other visual and neurological disturbances (see section 4.8). Diagnosis of RPLS is based upon confirmation by brain imaging, preferably MRI (Magnetic Resonance Imaging).

Nausea, vomiting, diarrhoea and dehydration

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/vomiting particularly when combining oxaliplatin with 5-fluorouracil (5-FU).

If haematological toxicity occurs (neutrophils $<1.5 \times 10^9/l$ or blood platelets $<50 \times 10^9/l$), administration of the next treatment 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 course of treatment.

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

As Oxaliplatin Vianex is administered with 5-fluorouracil (5-FU) (with or without folinic acid), the dose adjustments for 5-fluorouracil (5-FU) should as usually depend on toxicity. 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 Vianex should be reduced from 85 to 65 mg/m² (treatment of metastatic cancer) or 75 mg/m² (adjuvant treatment), in addition to required 5-fluorouracil (5-FU) dose reductions.

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

Hepatic

In cases of abnormal test results of liver function or portal hypertension that does not directly result from liver metastases, the possibility of rare medicinal product induced vascular disorder in the liver should be considered.

Pregnancy

For use during pregnancy, see section 4.6.

Fertility

Genotoxic effects were observed with oxaliplatin in the preclinical studies. Male patients treated with oxaliplatin are advised not to father a child during and up to 6 months after treatment. As oxaliplatin may cause infertility that may be irreversible, male patients are advised to seek advice on conservation of fresh sperm prior to initiation of treatment.

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

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 (5-FU), no change in the concentration of 5-fluorouracil (5-FU) has been observed.

In vitro, no significant changes in oxaliplatin binding to plasma proteins have been observed with the following agents: erythromycin, salicylates, granisetron, paclitaxel, and sodium valproate.

4.6 Fertility, pregnancy and lactation

There are no experiences with use of oxaliplatin in pregnant women. In animal trials reproduction toxicity was observed. Consequently, oxaliplatin is not recommended during pregnancy and in women of childbearing potential should be advised to use contraceptive measures. 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. Appropriate contraceptive measures must be taken during and after cessation of therapy during 4 months for women and 6 months for men.

Excretion of oxaliplatin in breast milk has not been studied.

Breast-feeding is contraindicated during treatment with Oxaliplatin Vianex.

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

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 may result in an increased risk of dizziness, nausea and vomiting, and other neurological symptoms that affect the patient's gait and balance which may lead to a minor or moderate influence on the ability to drive and use machines.

Visual disturbances, predominantly transient reduced vision (reversible after discontinuation of the treatment) may affect the patient's ability to drive and use machines. The patient should be warned of this potential effect which may affect ability to drive and use machines.

4.8 Undesirable effects

The most frequent adverse reactions of oxaliplatin in combination with 5-fluorouracil (5-FU)/folinic acid are gastrointestinal (diarrhoea, nausea, vomiting and mucositis), haematological (neutropenia, thrombocytopenia) and neurological (acute and dose depending peripheral sensory neuropathy). Usually, these adverse events occur more frequently and severely when oxaliplatin is combined with 5-fluorouracil (5-FU)/folinic acid than in a treatment with 5-fluorouracil (5-FU)/folinic acid alone.

The frequencies of adverse reactions reported in the table below are partly based on post marketing experience and partly on clinical trials in the metastatic treatment and adjuvant therapy (416 and 1108 patients, respectively, in the oxaliplatin and 5-FU/FA -arm).

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

Further details are given after the table.

Very common	Common	Uncommon	Rare	Very rare	Unknown
<i>Infections and infestations*</i>					
- Infection	- Rhinitis - Upper respiratory tract infection - Neutropenic sepsis				
<i>Blood and the lymphatic system disorders*</i>					
- Anaemia - Neutropenia - Thrombocytopenia - Leukopenia - Lymphopenia	Febrile neutropenia		- Immunoallergic thrombocytopenia - Haemolytic anaemia		
<i>Immune system disorders*</i>					
- Allergy/ allergic reactions+					
<i>Metabolism and nutrition disorders</i>					
- Anorexia - Hyperglycaemia - Hypokalaemia - Hyponatraemia	- Dehydration	- Metabolic acidosis			
<i>Psychiatric disorders</i>					
	- Depression - Insomnia	- Nervousness			
<i>Nervous system disorders*</i>					
- Peripheral sensory neuropathy - Sensory disturbance - Dysgeusia - Headache	- Dizziness - Motor neuritis - Meningism		- Dysarthria - Reversible Posterior Leukoencephalopathy syndrome (RPLS~or PRES) (see section 4.4)		
<i>Eye disorders</i>					
	- Conjunctivitis		- Visual acuity		

	- Visual disturbance		reduced transiently - Visual field disturbances - Optic neuritis - Transient decreased vision (reversible after discontinuation of the treatment)		
<i>Ear and labyrinth disorders</i>					
		- Ototoxicity	- Deafness		
<i>Vascular disorders</i>					
	- Haemorrhage - Flushing - Deep vein thrombosis - Hypertension				
<i>Respiratory, thoracic and mediastinal disorders</i>					
- Dyspnoea - Cough - Epistaxis	- Hiccups - Pulmonary embolism		- Interstitial lung disease sometimes fatal - Pulmonary fibrosis**		
<i>Gastrointestinal disorders*</i>					
- Nausea - Diarrhoea - Vomiting - Stomatitis /mucositis - Abdominal pain - Constipation	- Dyspepsia - Gastro-esophageal reflux - Gastrointestinal bleeding - Rectal haemorrhage	- Ileus - Intestinal obstruction	- Colitis including <i>Clostridium difficile</i> -caused diarrhoea -Pancreatitis		
<i>Hepatobiliary disorders</i>					
<i>Skin and subcutaneous tissue disorders</i>					
- Skin disorder - Alopecia	- Skin exfoliation (hand & foot syndrome) - Erythematous rash				

	- Rash - Hyperhidrosis - Nail disorder				
Musculoskeletal, connective tissue and bone disorders					
- Back pain	- Arthralgia - Bone pain				
Renal and urinary disorders					
	- Haematuria - Dysuria - Micturition frequency abnormal				
General disorders and administration site conditions					
- Fatigue - Fever++ - Asthenia - Pain - Injection site reaction+++					
Investigations					
- Hepatic enzyme increase - Blood alkaline phosphatase increase - Blood bilirubin increase - Blood lactate dehydrogenase increase - Weight increase (adjuvant treatment)	- Creatinine increase - Loss of weight (treatment of metastatic cancer)				

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* See detailed table below

** See section 4.4.

+ Very common: frequent allergy/allergic reactions, occurring during mainly perfusion, sometimes fatal. Frequent allergic reactions such as skin rash (particularly urticaria), conjunctivitis, rhinitis.

Common anaphylactic reactions, including bronchospasm, sense of chest pain, angioedema, hypotension 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 administered through a peripheral vein (see section 4.4).

Blood and the lymphatic system disorders

Incidence by patient (%), by grade

Oxaliplatin and 5-FU/FA 85 mg/m ² every second week	Treatment of metastatic cancer			Adjuvant treatment		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Anaemia	82.2	3	<1	75.6	0.7	0.1
Neutropenia	71.4	28	14	78.9	28.8	12.3
Thrombocytopenia	71.6	4	<1	77.4	1.5	0.2
Febrile neutropenia	5.0	3.6	1.4	0.7	0.7	0.0
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/m ² every second week	Treatment of metastatic cancer			Adjuvant treatment		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Allergic reactions / allergy	9.1	1	<1	10.3	2.3	0.6

Nervous system disorders:

Neurological side effects are dose limiting during treatment with oxaliplatin. They involve 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 the patients. 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 depending on the duration of the symptoms, indications, for dose adjustment, or discontinuation of the medication (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 cumulative doses of app. 850 mg/m² (10 cycles) and 1020 mg/m² (12 cycles) is approximately 10% and 20% respectively. In the majority of the patients, the neurological symptoms recover when treatment is discontinued. In the adjuvant setting of colon cancer 87 % of patients had no or mild symptoms 6 months after discontinuation of treatment. After a follow up 3 years later, about 3 % of patients presented either persisting localized paraesthesias of moderate severity (2.3%) or paraesthesias with decreased functional activities (0.5%).

Acute neurosensory manifestations (see section 5.3.) have been reported. Usually the symptoms start within hours of administration and often occur on exposure to cold. These symptoms may be presented as transient paraesthesia, dysaesthesia and hypoesthesia. Acute syndrome of laryngopharyngeal dysaesthesia, which occur in 1-2% of the patients, and is characterised by subjective sensations of dysphagia or dyspnoea/feeling of suffocation, without any 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 time helps to reduce the incidence of this syndrome (see section 4.4). Occasionally other symptoms that have been observed include jaw spasm/muscle spasms/involuntary muscle contractions/muscle twitching/myoclonus, abnormal coordination/gait disturbances/ataxia/balance disturbances, feeling of tightness/pressure/discomfort/pain in the throat or chest, even in association with cranial nerve dysfunctions that may occur as isolated events such as ptosis, diplopia, aphonia/dysphonia/hoarseness, sometimes described as paresis of the vocal chords, abnormal feeling in the tongue or dysarthria, sometimes described as aphasia, trigeminal neuralgia/facial pain/eye pain, reduced visual acuity, disturbances in the field of vision.

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/m ² every second week	Treatment of metastatic cancer			Adjuvant treatment		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Nausea	69.9	8	<1	73.7	4.8	0.3
Diarrhoea	60.8	9	2	56.3	8.3	2.5
Vomiting	49.0	6	1	47.2	5.3	0.5
Mucositis/Stomatitis	39.9	4	<1	42.1	2.8	0.1

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

Dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/vomiting particularly when combining oxaliplatin with 5-fluorouracil (5-FU) (see section 4.4).

Hepato-biliar 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 disorder

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. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system** listed in [Appendix V](#).

4.9 Overdose

There is no known antidote to oxaliplatin. In cases of overdose increase 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 cytostatics /cytotoxics, platinum compounds.

ATC code: L01XA 03

Oxaliplatin is an antineoplastic 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'] [ethandioate(2-) kO^l , kO^2] platinum].

Oxaliplatin exhibits a wide spectrum of cytotoxic activity both *in vitro* and *in vivo* in a variety of different tumour types including human colorectal cancer models. Oxaliplatin also demonstrates *in vitro* and *in vivo* activity in various cisplatin resistant tumour models.

A synergistic cytotoxic effect has been observed in combination with 5-fluorouracil (5-FU) both *in vitro* and *in vivo*.

Mechanism of action of oxaliplatin is not completely known but studies support the opinion that the aqua-derivatives resulting from the biotransformation of oxaliplatin, interact with DNA to form both cross-links (intrastrand and interstrand), resulting in the disruption of DNA synthesis leading to cytotoxic and antitumour effects.

The effect of oxaliplatin (85 mg/m² every two weeks) combined with 5-fluorouracil (5-FU) and folinic acid(5-FU/FA) in treatment of metastatic colorectal cancer has been reported in three clinical studies:

- 420 previously non-treated patients were randomised in a 2-arm comparative phase III study, EFC2962, either to 5-fluorouracil (5-FU)/FA (FA5FU2, N=210) or to the combination of oxaliplatin + 5-FU/FA (FOLFOX4, N=210).

- 821 patients, not responding to an irinotecan (CPT-11) + 5-fluorouracil (5-FU)/FA were randomised in the comparative three arms phase III study (EFC4584) either to A. 5-fluorouracil (5-FU)/FA (FA5FU2, N=275), B. oxaliplatin alone (N=275), or C. oxaliplatin + 5-fluorouracil (5-FU)/FA (FOLFOX4, N=271).

- In an uncontrolled phase II study EFC2964 with patients not responding to treatment with 5-fluorouracil (5-FU)/FA alone, a combined treatment with oxaliplatin + 5-fluorouracil (5-FU)/FA (FOLFOX4, N=57) was administered.

The two randomised trials, EFC2962 and EFC4584 demonstrated a significantly higher response rate and a prolonged progression free survival/time to progression (PFS/TTP) as compared to treatment with 5-fluorouracil (5-FU)/FA alone. In EFC4584 performed in not responding, pre-treated patients, the difference in median survival between the combination of oxaliplatin and 5-FU/FA did not reach statistical significance.

Response rate FOLFOX4 versus FA5FU2

Response rate, % (95% CI) Independent radiological review ITT analysis (ITT = intention to treat)	FA5FU2	FOLFOX4	Oxaliplatin (alone)
Not pre-treated patients 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)	0.7 (0.0-2.7)	11.1 (7.6-15.5)	1.1 (0.2-3.2)
Response assessment every 6 weeks	P-value= $\leq$ 0.0001		
Pre-treated patients	NA		NA

EFC2964 (refractory to 5-FU/FA)		23 (13-36)	
Response assessment every 12 weeks			

NA: Not applicable

Median Progression Free Survival / Time (PFS)/Median Time to Progression (PFS/TTP)

FOLFOX4 vs FA5FU2

Median PFS/TTP, Months (95% CI) Independent radiological review ITT analysis	FA5FU2	FOLFOX4	Oxaliplatin (alone)
Not pre-treated patients 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		
Pretreated patients EFC2964 (refractory to 5- FU/FA)	NA	5.1 (3.1-5.7)	NA

NA: Not applicable

Median Overall Survival (OS), FOLFOX4 versus FA5FU2

Median OS,			
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months (95% CI) ITT analysis	FA5FU2	FOLFOX4	Oxaliplatin (alone)
Not pre-treated patients EFC2962	14.7 (13.0-18.2)	16.2 (14.7-18.2)	NA*
	Log rank P-value= 0.12		
Pre-treated patients EFC4584 (TTP) (not responding 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 (not responding to 5-FU/FA)	NA	10.8 (9.3-12.8)	NA

*NA: Not Applicable

In those patients, who showed disease-related symptoms at baseline, a higher proportion of those treated with oxaliplatin/5-fluorouracil (5-FU)/FA (EFC4584) experienced a significant improvement of their disease-related symptoms compared to patients treated with 5-fluorouracil (5-FU)/FA alone (27.7% vs. 14.6% p = 0.0033).

In the group of non pre-treated patients (EFC2962), no statistically significant difference between the two treatment regimes was found for the quality of life dimensions. 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.

2246 patients (899 stage II/Duke's B2 and 1347 stage III/Duke's C) were randomised in the MOSAIC comparative phase III study (EFC3313) in an adjuvant treatment either to 5-FU/FA alone (FA5FU2, N=1123 (B2/C = 448/675) or to combination of oxaliplatin and 5-FU/FA (FOLFOX4, N=1123 (B2/C) = 451/672) following complete resection of the primary tumour of colon cancer.

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

Treatment arm	FA5FU2	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 MOSAIC-study demonstrated an overall significant advantage in 3-year disease free survival for the oxaliplatin and 5-FU/FA combination (FOLFOX4) compared with 5-FU/FA (FA5FU2).

EFC 3313, 3-years of Disease Free Survival (ITT)* according to the stage of disease

Patient stage	Stage II (Duke's B2)		Stage III (Duke's C)	
Treatment arm	FA5FU2	FOLFOX4	FA5FU2	FOLFOX4
Percent 3-years 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):

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 compared with 83.8% of the patient in the FA5FU2 arm. This had no statistical significance (hazard ratio = 0.90), but can be translated into an overall reduction in mortality risk of 10% in favour of FOLFOX4. The survival data for stage II (Duke's B2) was 92.2% compared with 92.4% (hazard ratio = 1.01) and 80.4% compared with 78.1% in patients in stage III (Duke's C, hazard ratio = 0.87), for FOLFOX4 and FA5FU2, respectively.

Oxaliplatin as monotherapy has been assessed in children in 2 phase I clinical studies (69 patients) and in 2 phase II clinical studies (90 patients). In total 159 patients (from 7 months to 22 years of age) with solid tumours were treated. The efficacy of oxaliplatin in monotherapy in children has not been demonstrated. Both type II studies were terminated before time due to lack of tumour response.

5.2 Pharmacokinetic properties

The pharmacokinetics of individual active compounds have not been studied. The pharmacokinetics of ultrafiltrable platinum, representing a mixture of all unbound, active and inactive platinum compounds, following a two-hour infusion at 130 mg/m² every three weeks for 1 to 5 cycles and at 85 mg/m² every two weeks for 1 to 3 cycles are stated in the following table:

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} , 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.

$t_{1/2\alpha}$, $t_{1/2\beta}$, and $t_{1/2\gamma}$, were determined by compartmental analysis (cycles 1-3).

Following 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 urine. Irreversible binding to red blood cells and plasma, results in half-lives that are close to the natural life time of erythrocytes and serum albumin. No accumulation was observed in plasma ultrafiltrate following 85 mg/m² every two weeks or 130 mg/m² every three weeks and steady state was achieved 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. There is no evidence of cytochrome P450-mediated metabolism of the diaminocyclohexane ring (DACH).

Oxaliplatin undergoes extensive metabolism and no unchanged active substance was detectable in plasma ultrafiltrate following a 2-hour infusion. Several cytotoxic biotransformation products including the monochloro, dichloro and diaqua DACH platinum compounds have been identified in the systemic circulation together with a number of inactive conjugates at later times.

Platinum is predominantly excreted in urine, mainly within the first 48 hours following infusion.

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

In patients with an impaired renal function a significant decrease in clearance (Cl) from 17.6 ± 2.18 l/h to 9.95 ± 1.91 l/h was observed together with a statistically significant decrease in distribution volume (Vd) from 330 ± 40.9 L to 241 ± 36.1 L. The effect of severe renal impairment on platinum clearance has not been evaluated.

5.3 Preclinical safety data

The target organs identified in mice, rats, dogs, and/or monkeys in single- and multiple-dose studies included the bone marrow, the gastrointestinal system, the kidneys, the testes, the nervous system, and the heart. The target organ toxicities observed in animals are comparable 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 only observed in the dogs 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 sodium-channels.

Oxaliplatin was mutagenic and clastogenic in mammalian test systems and caused embryo-foetal toxicity in rats. Oxaliplatin is considered to be 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 must not be mixed with other medicinal products in the same infusion bag or infusion line. Oxaliplatin may be administered concomitantly with folinic acid (FA) by using an Y-line, see section 6.6.

- Do not mix with alkaline medicinal products or solutions particularly not with (5-fluorouracil (5-FU), folinic acid (FA) products containing trometamol as excipient or medicinal products containing trometamol salts. Alkaline medicinal products or solutions reduce the stability of oxaliplatin (see section 6.6).
- Oxaliplatin Vianex must not be reconstituted or diluted for infusion with sodium chloride solution or solutions containing chloride ions (including calcium chloride, potassium chloride or sodium chloride).
- Oxaliplatin Vianex must not be mixed with other medicinal products in the same infusion bag or infusion line (see Section 6.6 for instructions concerning simultaneous administration with folinic acid).
- Injection equipment containing aluminium must not be used.

6.3 Shelf life

2 years.

Reconstituted solution in the original vial:

From a microbiological and chemical point of view, the reconstituted solution should be diluted immediately.

Solution for infusion:

After reconstitution with glucose solution 5% (50 mg/ml) 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 and during use are the responsibility of the user. This storage should normally not be longer than 24 hours at 2°C to 8°C unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Medicinal product packed in original package: No special storage conditions.

Reconstituted solution: must be diluted immediately (see section 6.3)

Solution for infusion: store at 2°C to 8°C for maximum 24 hours.

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

The medicinal product is for single use only. Any unused solution must be discarded.

6.5 Nature and contents of container

Glass vial for injection with stopper of bromobutyl elastomer, containing 50 mg of oxaliplatin.
Glass vial for injection with stopper of bromobutyl elastomer, containing 100 mg of oxaliplatin.

Pack sizes:

1 x 50 mg vial
1 x 100 mg vial.

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 Vianex solutions.

Instructions for handling

The handling of Oxaliplatin Vianex 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, under conditions that guarantee the stability of the medicinal product, protection of the environment and in particular of the person who is handling the medicinal product, in accordance with guidelines of the hospital. It should be carried out at a place reserved for this purpose. It is forbidden to smoke, eat or drink in this area.

Personnel must be provided with appropriate protecting clothes, such as long sleeved gowns, protection masks, caps, protective goggles, sterile single-use gloves, protective covers for the work area and containers for contaminated waste.

Body fluids like vomit and faeces from patients who recently were treated with cytotoxic agents must be handled with care.

Pregnant women must avoid handling cytotoxic agents.

Any broken container must be treated with the same precaution and considered as contaminated waste.

Contaminated waste should be incinerated in suitably labelled rigid containers. See section below "Disposal".

If Oxaliplatin Vianex powder, reconstituted solution or solution for infusion, should come into contact with skin or mucosa, wash immediately and thoroughly with water.

Special precautions for administration:

- Do not use injection material containing aluminium.
- Do not administer Oxaliplatin Vianex undiluted.
- Use only glucose solution 5% (50 mg/ml) for dilution. Oxaliplatin Vianex must not be reconstituted or diluted for infusion with sodium chloride solution or other chloride containing solutions.
- Do not mix Oxaliplatin Vianex with other medicinal products in the same infusion bag or administer other medicinal products simultaneously by the same infusion line.
- Do not mix Oxaliplatin Vianex with alkaline medicinal products or solutions, in particular not 5-fluorouracil (5-FU), folinic acid (FA)-products containing trometamol as excipient or medicinal products containing trometamol salts. Alkaline medicinal products and solutions reduce the stability of oxaliplatin.

Instruction for concomitant use of oxaliplatin and folinic acid (FA)(as calcium folinate or disodium folinate)

Oxaliplatin 85 mg/m² as intravenous infusion in 250 to 500 ml of glucose solution 5% (50 mg/ml) can be administered at the same time as folinic acid (FA) intravenous infusion in glucose solution 5% (50 mg/ml), over 2 to 6 hours, when using a Y-line. Oxaliplatin and folinic acid must not be combined in the same infusion bag.

Trometamol must not be included as an excipient in the folinic acid (FA) product, and the folinic acid (FA) product must only be diluted with glucose solution 5% (50 mg/ml). Alkaline solutions or solutions containing sodium chloride or other chloride containing solutions must never be used.

Instruction for concomitant use of oxaliplatin and 5-fluorouracil (5-FU)

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

After administration of Oxaliplatin Vianex flush the line before administration of 5-fluorouracil (5-FU).

For additional information on concomitant administration of other medicinal products see the corresponding summary of product characteristics.

- Only use recommended solvents (see below).
- Reconstituted solution that shows evidence of precipitation must not be used and must be discarded with due regard to current legal requirements for disposal of hazardous waste (see below).

Reconstitution of the solution:

Water for injections or glucose solution 5% (50 mg/ml) must be used to reconstitute the solution.

- Oxaliplatin Vianex 50 mg: add 10 ml solvent to obtain a solution with a concentration of 5 mg oxaliplatin/ml.
- Oxaliplatin Vianex 100 mg: add 20 ml solvent to obtain a solution with a concentration of 5 mg oxaliplatin/ml.

From a microbiological and chemical point of view, the reconstituted solution must be diluted immediately with glucose solution 5% (50 mg/ml).

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

The medicinal product is for single use only. Any unused solution must be discarded.

Dilution before infusion:

Withdraw the required amount of reconstituted solution from the vial(s) and then dilute with 250 ml to 500 ml of glucose solution 5% (50 mg/ml) to give an oxaliplatin concentration of 0.2-0.7 mg/ml. Chemical and physical stability of oxaliplatin has been demonstrated for concentrations between 0.2 mg/ml and 2 mg/ml.

Administer by intravenous infusion.

After reconstitution with glucose solution 5% (50 mg/ml) chemical and physical stability has been demonstrated for 24 hours at 2°C to 8°C.

From a microbiological point of view, the infusion preparation must be used immediately.

If not used immediately, the user is responsible for the storage times and the storage conditions prior to use and in-use. This storage should normally not be longer than 24 hours at 2°C to 8°C unless dilution has taken place under controlled and validated aseptic conditions.

Inspect visually prior to use. Only clear solutions without particles must be used. For single use only. Any unused solution must be discarded, see the section on disposal below.

Never use sodium chloride solution or chloride containing solutions for reconstitution or dilution.

The compatibility of oxaliplatin solution for infusion has been tested with representative, PVC based infusion aggregates.

Infusion:

The administration of Oxaliplatin Vianex does not require pre-hydration.

Oxaliplatin Vianex reconstituted in 250 to 500 ml of a glucose solution 5% (50 mg/ml) with a concentration of at least 0.2 mg/ml oxaliplatin must be infused either in a peripheral vein or by a central venous line within 2 to 6 hours. When Oxaliplatin Vianex is administered with 5-fluorouracil (5-FU), the Oxaliplatin Vianex infusion must precede that of 5-fluorouracil (5-FU).

Disposal:

Remainder of the medicinal product as well as all materials that have been used for reconstitution, for dilution and administration must be discarded according to official standard procedures applicable to cytotoxic agents.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 November 2008/28 November 2013

10. DATE OF REVISION OF THE TEXT

29 March 2014