FRESENIUS KABI
caring for life

SUMMARY OF PRODUCT CHARACTERISTICS

OXALIPLATIN 5 MG/ML
CONCENTRATE FOR SOLUTION FOR INFUSION

1. NAME OF THE MEDICINAL PRODUCT

Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of concentrate for solution for infusion contains 5 mg oxaliplatin

10 ml of concentrate for solution for infusion contains 50 mg of oxaliplatin

20 ml of concentrate for solution for infusion contains 100 mg of oxaliplatin

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oxaliplatin in combination with 5-fluorouracil (5FU) 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

Posology

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.

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

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

Oxaliplatin is administered as a 2- to 6-hour intravenous infusion in 250 to 500 ml of glucose 5% solution to give a concentration between 0.20 mg/ml and 0.70 mg/ml; 0.70 mg/ml is the highest concentration in clinical practice for an oxaliplatin dose of 85 mg/m^2.

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

Special Populations

- *Renal impairment:*

Oxaliplatin has not been studied in patients with severe renal impairment (see section 4.3).

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

- *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.

Method of administration

Oxaliplatin is administered by intravenous infusion.

The administration of oxaliplatin does not require hyperhydration.

Oxaliplatin diluted in 250 to 500 ml of glucose 5 % solution to give a concentration not less than 0.20 mg/ml must be infused via a central venous line or a peripheral vein over 2 to 6 hours. Oxaliplatin infusion must always precede the administration of 5-fluorouracil.

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

Instructions for use:

Oxaliplatin must be diluted before use. Only glucose 5% diluent is to be used to dilute the concentrated solution for infusion (see section 6.6).

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 $<2x10^9$/l and/or platelet count of $<100x10^9$/l.
- have a peripheral sensory 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.

Due to limited information on safety in patients with moderately impaired renal function, 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 dose adjusted according to toxicity.

Patients with a history of allergic reaction to platinum compounds should be monitored for allergic symptoms. In case of an anaphylactic-like reaction to oxaliplatin, the infusion should be immediately discontinued and appropriate symptomatic treatment initiated. Oxaliplatin rechallenge is contra-indicated.

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

Neurological toxicity of oxaliplatin should be carefully monitored, especially if co-administered with other medicinal products with specific neurological toxicity. A

neurological examination should be performed before each administration and periodically thereafter.

For patients who develop acute laryngopharyngeal dysaesthesia (see section 4.8), during or within the hours following the 2-hour infusion, the next oxaliplatin infusion should be administered over 6 hours.
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 mg/m^2 to 65 mg/m^2 (metastatic setting) or 75 mg/m^2 (adjuvant setting).

- If paraesthesia without functional impairment persists until the next cycle, the subsequent oxaliplatin dose should be reduced from 85 mg/m^2 to 65 mg/m^2 (metastatic setting) or 75 mg/m^2 (adjuvant setting).

- If paraesthesia with functional impairment persists until the next cycle, oxaliplatin should be discontinued.

- If these symptoms improve following discontinuation of oxaliplatin therapy, resumption of therapy may be considered.

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

Gastrointestinal toxicity, which manifests as nausea and vomiting, warrants prophylactic and/or therapeutic anti-emetic therapy (see section 4.8).

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

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/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<1.0x10^9/l), grade 3 to 4 thrombocytopenia (platelets <50x10^9/l) occur, the dose of oxaliplatin should be reduced from 85 mg/m² to 65 mg/m² (metastatic setting) or 75 mg/m^2 (adjuvant setting), in addition to any 5-fluorouracil dose reductions required.
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 or pulmonary fibrosis (see section 4.8).

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.

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 (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/m^2 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 (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 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.

4.8 Undesirable effects

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

The frequencies reported in the table below are derived from clinical trials in the metastatic and adjuvant setting (having included 416 and 1108 patients respectively in the oxaliplatin +5FU/FA treatment arm) 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) including isolated report.

Further details are given after the table.

MedDRA Organ system classes	**Very common**	**Common**	**Uncommon**	**Rare**
Infections and infestations *	**-** Infection	- Rhinitis - Upper respiratory tract infection - Febrile neutropenia /Neutropenic sepsis		
Blood and the lymphatic system disorders*	**-** Anaemia **-** Neutropenia **-** Thrombo-cytopenia **-** Leucopenia **-** Lymphopenia			**-** Autoimmune thrombocyto-penia **-** Haemolytic anaemia
Immune	**-** Allergy/			

system disorders*	allergic reaction+			
Metabolism and nutrition disorders	- Anorexia - Glycaemia abnormalities - Hypokalaemia - Natraemia abnormalities	**-** Dehydration	**-** Metabolic acidosis	
Psychiatric disorders		- Depression - Insomnia	**-** Nervousness	
Nervous system disorders*	- Peripheral sensory neuropathy - Sensory disturbance - Dysgeusia - Headache	- Dizziness - Motor neuritis - Meningism		- Dysarthria
Eye disorders		- Conjunctivitis - Visual disturbance		**-** Visual acuity reduced transiently - Visual field disturbances - Optic neuritis
Ear and labyrinth disorders			**-** Ototoxicity	**-** Deafness
Vascular disorders	- Epistaxis	- Haemorrhage - Flushing - Haematuria - Deep vein thrombosis - Pulmonary embolism - Rectal haemorrhage		
Respiratory, thoracic and mediastinal disorders	**-** Dyspnoea - Cough	**-** Hiccups **-** Chest pain		**-** Interstitial lung disease **-** Pulmonary fibrosis**
Gastrointestinal disorders*	- Nausea - Diarrhoea - Vomiting - Stomatitis /Mucositis - Abdominal pain - Constipation	- Dyspepsia - Gastro-esophageal reflux	**-** Ileus **-** Intestinal obstruction	- Colitis including clostridium difficile diarrhoea
Skin and subcutaneous tissue disorders	**-** Skin disorder - Alopecia	- Skin exfoliation (i.e. Hand & Foot syndrome)		

		- Rash erythematous - Rash - Hyperhidrosis - Nail disorder		
Musculo-skeletal, connective tissue and bone disorders	- Back pain	- Arthralgia - Bone pain		

Renal and urinary disorders		- Dysuria - Micturition frequency abnormal		
General disorders and administration site conditions	- Fatigue - Fever++ - Asthenia - Pain - Injection site reaction+++			
Investigations	- Hepatic enzyme increase - Blood alkaline phosphatase increase - Blood bilirubin increase - Blood lactate dehydrogenase increase - Weight increase (adjuvant setting)	- Blood creatinine increase - Weight decrease (metastatic setting)		

* See detailed section below
** See section 4.4.
+ Common allergic reactions such as skin rash (particularly urticaria), conjunctivitis, rhinitis.
Common anaphylactic reactions, including bronchospasm, angioedema, hypotension and anaphylactic shock.
++ Very common fever, either from infection (with or without febrile neutropenia) or isolated fever from immunological mechanism.
+++ Extravasation may result in local pain and inflammation which may be severe and lead to complications, especially when oxaliplatin is infused through a peripheral vein (see 4.4).

Hepato-biliary disorders

Very rare (≤1/10000):

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 (≤1/10000):

Acute tubulo-interstinal nephropathy leading to acute renal failure

Haematological toxicity:

Incidence by patient (%), by grade

Oxaliplatin/5FU/FA 85 mg/m² every 2 weeks	**Metastatic Setting**			**Adjuvant Setting**		
	All grades	**Gr 3**	**Gr 4**	**All grades**	**Gr 3**	**Gr4**
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

Digestive toxicity:

Incidence by patient (%), by grade

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

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

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

Nervous system:

The dose limiting toxicity of oxaliplatin is neurological. It involves a sensory peripheral neuropathy characterised by dysaesthesia and/or paraesthesia of the extremities with or without cramps, often triggered by the cold. These symptoms occur in up to 95% of patients treated. The duration of these symptoms, which usually regress between courses of treatment, increases with the number of treatment cycles.

The onset of pain and/or a functional disorder are indications, depending on the duration of the symptoms, for dose adjustment, or even treatment discontinuation (see section 4.4). This functional disorder includes difficulties in executing delicate movements and is a possible consequence of sensory impairment. The risk of occurrence of persistent symptoms for a cumulative dose of 850 mg/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 (see section 5.3) have been reported. They start within hours of administration and often occur on exposure to cold. They usually present as transient paraesthesia, dysaesthesia and hypoesthesia, or as an acute syndrome of pharyngolaryngeal dysaesthesia. This acute syndrome of pharyngolaryngeal dysaesthesia, with an incidence estimated between 1% and 2%, is characterised by subjective sensations of dysphagia or dyspnoea, without any objective evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm (no stridor or wheezing); jaw spasm, abnormal tongue sensation, dysarthria and a feeling of chest pressure have also been observed. Although antihistamines and bronchodilators have been administered in such cases, the symptoms are rapidly reversible even in the absence of treatment. Prolongation of the infusion helps to reduce the incidence of this syndrome (see section 4.4).

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.

Allergic reactions:
Incidence by patient (%), by grade

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

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, platinum compounds

ATC code: L01XA03

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)-[(1*R*,2*R*)-Cyclohexane-1,2-diamine-k*N*, k*N*'] [ethanedioato(2-)-kO^1, kO^2] 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 (85 mg/m^2 repeated every two weeks) combined with 5-fluorouracil/folinic acid (5FU/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 3-arm phase III EFC4584 study randomised 821 patients refractory to an irinotecan (CPT-11) + 5FU/FA combination either to 5FU/FA alone (LV5FU2, N = 275), oxaliplatin single agent (N = 275), or combination of oxaliplatin with 5FU/FA (FOLFOX4, N = 271)

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

The two randomized 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 5FU/FA alone. In study EFC4584 performed in pretreated refractory patients, the difference in the median overall survival (OS) between the combination of oxaliplatin and 5FU/FA did not reach statistical significance.

Response rate under FOLFOX4 versus LV5FU2

Response rate, % (95% CI) independent radiological review ITT analysis	**LV5FU2**	**FOLFOX4**	**Oxaliplatin Single agent**
Front-line treatment EFC2962 Response assessment every 8 weeks	22 (16-27)	49 (42-46)	NA
	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 EFC2964 (refractory to 5FU / FA) Response assessment every 12 weeks	NA	23 (13-36)	NA

NA: Not Applicable

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

FOLFOX4 versus LV5FU2

Median PFS/TTP, months (95% CI) independent radiological review ITT analysis	**LV5FU2**	**FOLFOX4**	**Oxaliplatin Single agent**
Front-line treatment EFC2962 (PFS)	6.0 (5.5-6.5)	8.2 (7.2-8.8)	NA
	Log-rank P value = 0.0003		
Pretreated patients EFC4584 (TTP) (refractory to CPT-11 + 5FU/FA)	2.6 (1.8-2.9)	5.3 (4.7-6.1)	2.1 (1.6-2.7)
	Log-rank P value < 0.0001		
Pretreated patients EFC2964 (refractory to 5FU/FA)	NA	5.1 (3.1-5.7)	NA

NA: Not Applicable

Median Overall Survival (OS) under FOLFOX4 versus LV5FU2

Median OS, months (95% CI) ITT analysis	**LV5FU2**	**FOLFOX4**	**Oxaliplatin Single agent**
Front-line treatment EFC2962	14.7 (13.0-18.2)	16.2 (14.7-18.2)	NA
	Log-rank P value = 0.12		
Pretreated patients EFC4584* (refractory to CPT-11 + 5FU/FA)	8.8 (7.3 - 9.3)	9.9 (9.1-10.5)	8.1 (7.2-8.7)
	Log-rank P value = 0.09		
Pretreated patients EFC2964 (refractory to 5FU/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 5FU/FA experienced a significant improvement of their disease-related symptoms compared to those treated with 5FU/FA alone (27.7% vs 14.6%, p<0.0033). In non-pretreated patients (EFC2962), no statistical 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 comparative MOSAIC 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 5FU/FA alone (LV5FU2 N=1123, B2/C = 448/675) or to combination of oxaliplatin and 5FU/FA (FOLFOX 4 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 5FU/FA combination (FOLFOX4) over 5 FU/FA alone (LV5FU2).

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

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 favor 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.

5.2 Pharmacokinetic properties

The pharmacokinetics of individual active compounds have not been determined. The pharmacokinetics of ultrafiltrable platinum, representing a mixture of all unbound, active and inactive platinum species, following a 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/m^2 Every Two Weeks or at 130 mg/m^2 Every Three Weeks

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

Mean AUC_{0-48}, and C_{max} values were determined on Cycle 3 (85 mg/m^2) or cycle 5 (130 mg/m^2).

Mean AUC, 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 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/m^2 every two weeks or 130 mg/m^2 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 active substance was detectable in plasma ultrafiltrate at the end of a 2 h-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.

A significant decrease in clearance from 17.6 ± 2.18 l/h to 9.95 ± 1.91 l/h in renal impairment was observed together with a statistically significant decrease in distribution volume from 330 ± 40.9 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 preclinical species (mice, rats, dogs, and/or monkeys) in single- and multiple-dose studies included the bone marrow, the gastrointestinal system, the kidney, the testes, the nervous system, and the heart. The target organ toxicities observed in animals are consistent with those produced by other platinum-containing medicinal products and DNA-damaging, cytotoxic medicinal products

used in the treatment of human cancers with the exception of the effects produced on the heart. Effects on the heart were observed only in the dog and included electrophysiological disturbances with lethal ventricular fibrillation. Cardiotoxicity is considered specific to the dog not only because it was observed in the dog alone but also because doses similar to those producing lethal cardiotoxicity in dogs (150 mg/m^2) were well-tolerated by humans. Preclinical studies using rat sensory neurons suggest that the acute neurosensory symptoms related to Oxaliplatin may involve an interaction with voltage-gated Na^+ channels.

Oxaliplatin was mutagenic and clastogenic in mammalian test systems and produced embryo-fetal toxicity in rats. Oxaliplatin is considered a probable carcinogen, although carcinogenic studies have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient(s)

Succinic acid, sodium hydroxide and water for injections

6.2 Incompatibilities

The diluted medicinal product should not be mixed with other medicinal products in the same infusion bag or infusion line. Under instructions for use described in section 6.6, oxaliplatin can be co-administered with folinic acid (FA) via a Y-line.

- DO NOT mix with alkaline medicinal products or solutions, in particular 5-fluorouracil, folinic acid 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 (see section 6.6).

- DO NOT dilute oxaliplatin with saline or other solutions containing chloride ions (including calcium, potassium or sodium chlorides).

- DO NOT mix with other medicinal products in the same infusion bag or infusion line (see Section 6.6 for instructions concerning simultaneous administration with folinic acid).

- DO NOT use injection equipment containing aluminium.

6.3 Shelf life

3 years

After dilution in glucose 5% solution, chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C to 8 °C and 6 hours at 15 °C to 25 °C. From a microbiological point of view, the solution for infusion should be used immediately.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C and 6 hours at 15 °C to 25 °C unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

10 ml concentrate in a vial (Type I clear glass) with chlorobutyl elastomer stopper

20 ml concentrate in a vial (Type I clear glass) with chlorobutyl elastomer stopper

Pack size: 1 vial per unit dose carton.

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

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

Excreta and vomit must be handled with care.

Pregnant women must be warned to avoid handling cytotoxic agents.

Any broken container must be treated with the same precautions and considered as contaminated waste. Contaminated waste should be incinerated in suitably labelled rigid containers. See below chapter “Disposal”.

If oxaliplatin concentrate or solution for infusion, should come into contact with skin, wash immediately and thoroughly with water.

If oxaliplatin concentrate or solution for infusion, should come into contact with mucous membranes, wash immediately and thoroughly with water.

Special precautions for administration

- DO NOT use injection equipment containing aluminium.
- DO NOT administer undiluted.
- Only glucose 5% infusion solution is to be used as a diluent. DO NOT dilute for infusion with sodium chloride or chloride containing solutions.
- DO NOT mix with any other medicinal products in the same infusion bag or administer simultaneously by the same infusion line
- DO NOT mix with alkaline medicinal products or solutions, in particular 5-fluorouracil, folinic acid 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 (as calcium folinate or disodium folinate)

Oxaliplatin 85 mg/m² intravenous infusion in 250 ml to 500 ml of glucose 5% solution is given at the same time as folinic acid intravenous infusion in glucose 5% 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 must not contain trometamol as an excipient and must only be diluted using isotonic glucose 5% solution, never in alkaline solutions or sodium chloride or chloride containing solutions.

Instruction for use with 5-fluorouracil

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

After oxaliplatin administration, flush the line and then administer 5-fluorouracil.

For additional information on medicinal products combined with oxaliplatin, see the corresponding manufacturer's summary of product characteristics.

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 (see disposal below).

Dilution for intravenous infusion

Withdraw the required amount of concentrate from the vial(s) and then dilute with 250 ml to 500 ml of a glucose 5% solution to give an oxaliplatin concentration between not less than 0.20 mg/ml and 0.70 mg/ml. The concentration range over which the physico-chemical stability of oxaliplatin has been demonstrated is 0.20 mg/ml to 2.0 mg/ml.

Administer by intravenous infusion.

After dilution in glucose 5% solution, chemical and physical in-use stability has been demonstrated for 24 hours at +2 °C to +8 °C, and 6 hours at 15 °C to 25 °C.

From a microbiological point of view, this infusion preparation should be used **immediately**.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C and 6 hours at 15 °C to 25 °C unless dilution has taken place in controlled and validated aseptic conditions.

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 (see chapter “disposal” below).

NEVER use sodium chloride or chloride containing solutions for dilution.

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

Infusion

The administration of oxaliplatin does not require prehydration.

Oxaliplatin diluted in 250 ml to 500 ml of a glucose 5% solution to give a concentration not less than 0.20 mg/ml must be infused via a central venous line or a peripheral vein over 2 to 6 hours. When oxaliplatin is administered with 5-fluorouracil, the oxaliplatin infusion must precede the administration of 5-fluorouracil.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

Fresenius Kabi Oncology Plc.

FRESENIUS KABI
caring for life

Lion Court, Farnham Road
Bordon, Hampshire
GU35 0NF, United Kingdom

8. MARKETING AUTHORISATION NUMBER (S)

PL 18727/0012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

-

10. DATE OF REVISION OF THE TEXT

February 2009