Safeguarding public health

MHRA

Public Assessment Report

Decentralised

Oxaliplatin 5mg/ml concentrate for solution for infusion

Oxaliplatin

UK/H/1282/01

PL 18727/0016
(formerly 19156/0038)

Fresenius Kabi Oncology PLC

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Module 1

Product Name	Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion
Type of Application	Complex Abridged Decentralised (Article 10.1)
Active Substance (INN)	Oxaliplatin Ph.Eur
Pharmacotherapeutic Classification (ATC)	Anti-cancer drugs – immunosuppressive agents – platinum ATC code L01XA 03
Pharmaceuctical Form and Strength	Concentrate for Solution for Infusion, 5 mg/ml
Procedure Numbers	UK/H/1282/01/DC
RMS	UK
CMS	CZ, DE, DK, EL, ES, FI, HU, IE, IT, NL, NO, PL, PT and SK
Start Date	17/08/2007
End Date	10/06/2009
MA Number	PL 18727/0016
Name and address of MA holder	Fresenius Kabi Oncology Plc

Module 2

Summary of Product Characteristics

SUMMARY OF PRODUCT CHARACTERISTICS

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

The preparation of injectable solutions of cytotoxic agents must be carried out by trained specialist personnel with knowledge of the medicinal product 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 hospital policy. It requires a preparation area reserved for this purpose. It is forbidden to smoke, eat or drink in this area (see section 6.6).

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

Special Populations

- *Renal impairment:*

Oxaliplatin 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.

- *Paediatric patients:*

There is no relevant indication for use of oxaliplatin in children (see section 5.1).

Method of administration

Oxaliplatin is administered by intravenous infusion.

The administration of oxaliplatin does not require hyperhydration.

Oxaliplatin diluted in 250 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 that 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 concentrate for solution for infusion (see section 6.6).

4.3 Contraindications

Oxaliplatin is contraindicated in patients who

- have a hypersensitivity to oxaliplatin or to the excipients.
- 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 the 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 machinery 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 adverse 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 arms) and from post marketing experience.

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

Further details are given after the table.

MedDRA Organ system classes	**Very common**	**Common**	**Uncommon**	**Rare**
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			- Immunoallergic thrombocyto-penia - Haemolytic anaemia
Immune system disorders*	- Allergy/ allergic reaction+			
Metabolism and nutrition disorders	- Anorexia - Glycaemia alterations - Hypokalaemia	- Dehydration	- Metabolic acidosis	

	- Natraemia alterations			
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 - Deep vein thrombosis - Pulmonary embolism		
Respiratory, thoracic and mediastinal disorders	- Dyspnoea - Coughing	- Hiccups - Chest pain		- Interstitial lung disease - Pulmonary fibrosis**
Gastrointestinal disorders*	- Nausea - Diarrhoea - Vomiting - Stomatitis /Mucositis - Abdominal pain - Constipation	- Dyspepsia - Gastro-esophageal reflux - Rectal haemorrhage	- 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		- Dysuria - Micturition		

disorders		frequency abnormal - Haematuria		
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, sensation 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 reaction including local pain, redness, swelling and thrombosis have been reported. Extravasation may result in local pain and inflammation which may be severe and lead to complications including necrosis, especially when oxaliplatin is infused through a peripheral vein (see section 4.4).

Hepato-biliary disorders

Very rare (≤1/10000):

Liver sinusoidal obstruction syndrome, also known as veno-occlusive liver disease , 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

Gastrointestinal toxicity

Incidence by patient (%), by grade

Oxaliplatin/5FU/FA 85 mg/m² every 2 weeks	Metastatic Setting			*Adjuvant Setting*		
	All grade	**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.An acute syndrome of pharyngolaryngeal dysaesthesia occurs in 1% to 2% of the patients and is characterised by subjective sensations of dysphagia or dyspnoea/feeling of suffocation, without any objective evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm (no stridor or wheezing). Although antihistamines and bronchodilators have been administered in such cases, the symptoms are rapidly reversible even in the absence of treatment. Prolongation of the infusion helps to reduce the incidence of this syndrome (see section 4.4).
Occasionally other symptoms that have been observed include jaw spasm/muscle spasm/muscle contractions-involuntary/muscle twitching/myoclonus, coordination abnormal/gait abnormal/ataxia/balance disorders, throat or chest tightness/pressure/ discomfort /pain. In addition, cranial nerve dysfunction may be associated, or also occur as an isolated event such as ptosis, diplopia, aphonia/dysphonia, hoarseness, sometimes described as vocal cord paralysis, abnormal tongue sensation or dysarthria, sometimes described as aphasia, trigeminal neuralgia/facial pain/eye pain, decrease in visual acuity, visual field disorders.

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

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

Oxaliplatin is a single enantiomer, the Cis -[oxalato (trans-l-1,2- DACH) platinum].

Oxaliplatin exhibits a wide spectrum of both *in vitro* cytotoxicity and *in vivo* antitumour activity in a variety of tumour model systems including human colorectal cancer models. Oxaliplatin also demonstrates *in vitro* and *in vivo* activity in various cisplatin resistant models.

A synergistic cytotoxic action has been observed in combination with 5-fluorouracil both *in vitro* and *in vivo*.

Studies on the mechanism of action of oxaliplatin, although not completely elucidated, show that the aqua-derivatives resulting from the biotransformation of oxaliplatin, interact with DNA to form both inter and intra-strand cross-links, resulting in the disruption of DNA synthesis leading to cytotoxic and antitumour effects.

In patients with metastatic colorectal cancer, the efficacy of oxaliplatin (85 mg/m^2 repeated every two weeks) combined with 5-fluorouracil/folinic acid is reported in three clinical studies:

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

- In pretreated patients the comparative 3-arm EFC4584 study randomised patients refractory to an irinotecan (CPT-11) + 5-fluorouracil/folinic acid combination either to 5-fluorouracil/folinic acid alone (LV5FU2, N = 275), oxaliplatin single agent (N = 275), or combination of oxaliplatin with 5-fluorouracil/folinic acid (FOLFOX4, N = 271)

- Finally, the non controlled phase II EFC2964 study included patients refractory to 5-fluorouracil/folinic acid alone, that were treated with the oxaliplatin and 5-fluorouracil/folinic acid 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 5-fluorouracil/folinic acid 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 5-fluorouracil/folinic acid experienced a significant improvement of their disease-related symptoms compared to those treated with 5-fluorouracil/folinic acid 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) or to combination of oxaliplatin and 5FU/FA (FOLFOX 4)

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.

Paediatric patients

Oxaliplatin single agent has been evaluated in paediatric population in 2 Phase I (69 patients) and 2 Phase II (90 patients) studies. A total of 159 paediatric patients (7 months-22 years of age) with solid tumors have been treated. The effectiveness of oxaliplatin single agent in the paediatric populations treated has not been established. Accrual in both Phase II studies was stopped for lack of tumor response.

5.2 Pharmacokinetic properties

The pharmacokinetics of individual active compounds have not been determined. The pharmacokinetics of 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 excipients

Succinic acid
Sodium hydroxide
Water for injections

6.2 Incompatibilities

This medicinal product should not be mixed with other medicinal products except for those mentioned in section 6.6. Oxaliplatin can be co-administered with folinic acid 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 drugs 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 use injection equipment containing aluminium.

- DO NOT mix with other medicinal products in the same infusion bag or infusion line (see section 6.6 to check instructions related to co-administration with folinic acid)

6.3 Shelf life

2 years

After dilution in glucose 5% solution, chemical and physical in-use stability has been demonstrated for 24 hours at room temperature (15°-25°C) and at refrigerated condition (2°-8°C).

From a microbiological point of view, the solution for infusion should be used immediately.
If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not freeze. Store below 30°C.

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

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 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 drugs or solutions, in particular 5-fluorouracil, folinic acid preparations containing trometamol as an excipient and trometamol salts of others active substances. Alkaline drugs or solutions will adversely affect the stability of oxaliplatin

Instruction for use with folinic acid (FA) (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 (FA) 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 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 room temperature (15°-25°C) and at refrigerated condition (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 °C to 8 °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.
Lion Court, Farnham Road, Bordon
Hamsphire, GU35 0NF
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 18727/0016

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/06/2009

10 DATE OF REVISION OF THE TEXT

10/06/2009

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Module 3

Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion (Oxaliplatin)

Read all of this leaflet carefully before you start taking this medicine
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT OXALIPLATIN 5 MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION IS AND WHAT IT IS USED FOR

Oxaliplatin is an anti-cancer drug and is used to treat metastatic (advanced) cancer of the colon (large bowel) or rectum (back passage), or as additional treatment following surgery to remove a tumour (growth) in the colon. It is used in combination with other anti-cancer medicines called 5-fluorouracil (5-FU) and folinic acid (FA).

2. BEFORE YOU USE OXALIPLATIN 5 MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

Do not use Oxaliplatin 5 mg/ml:
- If you are hypersensitive (allergic) to oxaliplatin or any of the other ingredients of Oxaliplatin 5 mg/ml
- If you are breastfeeding
- If you already have a reduced number of blood cells.
- If you already have tingling and numbness in the fingers and/or toes, and have difficulty performing delicate tasks, such as buttoning clothes
- If you have a severe kidney problem.

Take special care with Oxaliplatin 5 mg/ml:
- If you have moderate kidney problems.
- If you have ever suffered an allergic reaction to other platinum-containing medicines such as carboplatin or cisplatin.
- If you have symptoms of nerve damage such as weakness, numbness, disturbance of feeling after previous oxaliplatin treatment. These effects are often triggered by exposure to cold. If you notice such symptoms tell your doctor, especially if they are troublesome and/or last longer than 7 days. Your doctor will regularly carry out neurological examinations, before and regularly during treatment, especially if you are given other drugs which may cause nerve damage.
- If you have any liver problems.
- If your blood cell counts are too low after previous infusions of oxaliplatin. Your doctor will regularly take blood to check you have sufficient blood cells.

Before and/or during treatment with oxaliplatin you may be given special medicinal products to prevent and/or treat vomiting.

Oxaliplatin may have an anti-fertility effect, which could be irreversible. Male patients are therefore 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.

Taking other medicines:

Please tell your doctor if you are taking or have recently taken, any other medicines, including medicines obtained without a prescription.

Pregnancy

Ask your doctor or pharmacist for advice before taking any medicine.

You must not become pregnant during treatment with oxaliplatin and must use an effective method of contraception. If pregnancy occurs during your treatment, you must immediately inform your doctor. You should take appropriate contraceptive measures during and after cessation of therapy continuing for 4 months for women and 6 months for men.

Breast-feeding

You must not breast-feed while you are treated with oxaliplatin.

Driving and using machines:

Oxaliplatin treatment may result in an increased risk of dizziness, nausea and vomiting, and other neurologic symptoms that affect gait and balance. If this happens, you should not drive or operate machinery.

3. HOW TO USE OXALIPLATIN 5 MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

For adults only

Oxaliplatin 5 mg/ml should only be used in specialised departments of cancer treatment and should be administered under the supervision of an experienced specialist in cancer treatment.

Dosage

The dose depends on your body surface area (calculated by m^2) and your state of health. It also depends on other medicines that are used in your cancer treatment. The usual dose for adults, including the elderly, is 85 mg/m^2 of body surface area once every 2 weeks, before the infusion of the other anti-cancer medicines. The dose you receive will depend on results of blood tests and whether you have previously experienced side effects with oxaliplatin.

Method and route of administration

Oxaliplatin 5 mg/ml is diluted before being given by injection into a vein (an intravenous infusion) over a 2-6 hour period. The needle must remain in the vein while the drug is being given. If the needle comes out or becomes loose, or the solution is going into the tissue outside the vein (you may feel discomfort or pain) - **tell the doctor or nurse immediately.**

Frequency of administration

You should usually receive your infusion once every 2 weeks.

Duration of treatment

The duration of treatment will be determined by your doctor. Treatment for 6 months is recommended when Oxaliplatin is used after surgery to remove your cancer.

If you are given more Oxaliplatin 5 mg/ml than you should:

As this medicine is administered by a healthcare professional, it is highly unlikely that you will be given too little or too much. In case of overdose, you may experience increased side effects. Your doctor may give you appropriate treatment for these side effects.

If you have any questions about your treatment, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, oxaliplatin can cause side effects, although not everybody gets them. If you experience any side effect it is important that you inform your doctor before your next treatment.

Tell your doctor immediately if you notice any of the following:
- Abnormal bruising, bleeding or signs of infection such as a sore throat and high temperature.
- Persistent or severe diarrhoea or vomiting.
- Stomatitis/mucositis (sore lips or mouth ulcers).
- Unexplained respiratory symptoms such as a dry cough, difficulty in breathing or crackles.
- Swelling of the face, lips, mouth or throat (which may cause difficulty in swallowing or breathing).
- Sensation of pain or discomfort close to or at the injection site during the infusion.

<u>Very common (affects more than 1 in 10 people):</u>
- A disorder of the nerves which can cause weakness, tingling or numbness in the fingers, toes, around the mouth or in the throat that may sometimes occur in association with cramps. This is often triggered by exposure to cold e.g. opening a refrigerator or holding a cold drink. You may also have difficulty in performing delicate tasks, such as buttoning clothes. Although in the majority of cases these symptoms resolve completely there is a possibility of persistent symptoms after the end of the treatment.
- Oxaliplatin can sometimes cause an unpleasant sensation in the throat, in particular when swallowing, and give the sensation of shortness of breath. This sensation, if it happens, usually occurs during or within hours of the infusion and may be triggered by exposure to the cold. Although unpleasant, it will not last long and goes away without the need for any treatment. Your doctor may decide to alter your treatment as a result.
- Signs of infection such as a sore throat and high temperature.
- Reduction in the number of white blood cells, which make infections more likely
- Reduction in blood platelets, which increases risk of bleeding or bruising.
- Reduction in red blood cells, which can make the skin pale and cause weakness or breathlessness. Your doctor will take blood to check that you have sufficient blood cells before you start treatment and before each subsequent course.
- Allergic reactions - skin rash including red itchy skin, swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing) and you may feel you are going to faint.
- Loss or lack of appetite.
- Too high levels of glucose (sugar) in your blood which may cause a great thirst, dry mouth or a need to urinate more often.
- Low blood levels of potassium which can cause abnormal heart rhythm.
- Low blood levels of sodium which can cause tiredness and confusion, muscle twitching, fits or coma.
- Taste disorder.
- Headache.
- Nosebleeds.
- Shortness of breath.
- Coughing.
- Nausea, vomiting - medication to prevent sickness is usually given to you by your doctor before treatment and may be continued after treatment.
- Diarrhoea, if you suffer from persistent or severe diarrhoea or vomiting contact your doctor immediately for advice.
- Sore mouth or lips, mouth ulcers.
- Stomach pain, constipation.
- Skin disorder.
- Hair loss.
- Back pain.
- Tiredness, loss of strength/weakness, body pain.
- Pain or redness close to or at the injection site during the infusion.
- Fever.
- Blood tests which show changes in the way the liver is working.
- Weight gain (when oxaliplatin is used after surgery to remove the tumour).

<u>Common (affects more than 1 in 100 but less than 1 in 10 people):</u>
- Runny nose.
- Nose and throat infection.
- Dehydration.
- Dizziness.
- Inflammation of the nerves accompanied by pain, disturbances of feeling, reduced action of the nerve. Other symptoms of nerve disorders which have been reported include jaw or muscle spasms, twitching, muscle contractions, coordination and balance problems, staggering, double or abnormal/decreased vision, drooping of eyelids, voice problems (hoarseness or loss of voice), speech problems, abnormal tongue sensation, facial or eye pain.
- Neck stiffness, intolerance/dislike of bright light and headache.
- Conjunctivitis, visual problems.
- Abnormal bleeding, blood in the urine and stools.
- Blood clot, usually in a leg, which causes pain swelling or redness.
- Blood clot in the lungs which causes chest pain and breathlessness.

- Flushing.
- Chest pain.
- Hiccups.
- Indigestion and heartburn.
- Flaking skin, skin rash, increased sweating and nail disorder.
- Joint pain and bone pain.
- Pain on passing urine or a change in frequency when passing urine.
- Abnormal blood tests which show worsening in the way the kidney is working.
- Weight loss (when oxaliplatin is used in the treatment of advanced disease that has spread beyond the bowel to other tissues).
- Depression.
- Difficulty sleeping.
- Reduction in the number of a special form of white blood cells accompanied by fever and/or generalized infection.
- Throat or chest tightness.

Uncommon (affects more than 1 in 1,000 but less than 1 in 100 people):

- Hearing problems.
- Blockage or swelling of the bowel.
- Feeling anxious or nervous.
- Blood tests which show an increase in the body's acidity.

Rare (affects more than 1 in 10,000 but less than 1 in 1,000 people):

- Slurred speech.
- Deafness.
- Scarring of the lungs which may cause shortness of breath and/or cough.
- Bowel inflammation which causes abdominal pain and/or diarrhoea which may be bloody.
- Inflammation of the optic nerve, visual field disturbances.
- Reduction in red blood cells caused by cell destruction, and reduction in blood platelets due to an allergic reaction.

Very rare (affects less than 1 in 10,000 people):

- Liver disease.
- Kidney inflammation and kidney failure.

If any of the side effects gets serious, or if you notice any side effects not mentioned in this leaflet, please inform your doctor.

5. HOW TO STORE OXALIPLATIN 5 MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

Keep out of the reach and sight of children.

Keep the vial in the outer carton in order to protect from light. Do not freeze. Do not store above 30 °C.

Do not use Oxaliplatin 5 mg/ml after the expiry date which is stated on the carton and the vial after the words "Do not use after" or "exp". The first two numbers indicate the month, the last numbers indicate the year. The expiry date refers to the last day of the month.

6. FURTHER INFORMATION

- The active ingredient of Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion is oxaliplatin. Each vial contains a concentrate for solution for infusion containing 50 mg or 100 mg of oxaliplatin. The vials are supplied in cartons each containing one vial.
- The other ingredients are succinic acid, sodium hydroxide and water for injections

Oxaliplatin 5 mg/ml is in the form of a concentrate solution for infusion (a concentrated solution which is diluted to make a solution which can be given as a slow infusion via a drip). Each millilitre (ml) of solution contains 5 milligrams (mg) of oxaliplatin. It is a clear, colourless solution contained in glass containers called vials, containing 50 mg (10 ml) and 100 mg (20 ml) of oxaliplatin. The vials are available in single packs. The concentrate for solution for infusion must be diluted before it can be injected into a vein, as an infusion via a drip.

Marketing Authorisation Holder and Manufacture

Fresenius Kabi Oncology Plc.

Lion Court, Farnham Road, Bordon

Hampshire, GU35 0NF

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This medicines is authorised in Member States of the EEA under the following names

Czech Republic	Oxaliplatin Kabi 5 mg/ml koncentrát pro přípravu infuzního roztoku
Denmark	Oxaliplatin Fresenius Kabi
Finland	Oxaliplatin Kabi 5 mg/ml infuusiokonsentraatti, liuosta varten
Germany	Oxaliplatin Kabi 5 mg/ml Konzentrat zur Herstellung einer Infusionslösung
Greece	Oxaliplatin Kabi 5 mg/ml πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση
Hungary	Oxaliplatin Kabi 5 mg/ml koncentrátum oldatos infúzióhoz
Italy	Oxaliplatino Kabi 5 mg/ml concentrato per soluzione per infusione
Ireland	Oxaliplatin 5 mg/ml concentrate for solution for infusion
Netherlands	Oxaliplatine Kabi 5 mg/ml concentraat voor oplossing voor infusie
Norway	Oxaliplatin Fresenius Kabi 5 mg/ml konsentrat til infusjonsvæske
Poland	Oxaliplatin Kabi
Portugal	Oxaliplatina Kabi 5 mg/ml concentrado para solução para perfusão
Slovak Republic	Oxaliplatin Kabi 5 mg/ml infúzny koncentrát
Spain	Oxaliplatino Kabi 5 mg/ml concentrado para solución para perfusión
UK	Oxaliplatin 5 mg/ml concentrate for solution for infusion

This leaflet is prepared in May 2009

The following information is intended for medical or healthcare professionals only:

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 preparations 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.

Faeces 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 other 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)

Oxaliplatin 85 mg/m² intravenous infusion in 250 to 500 ml of glucose 5 % solution is given at the same time as folinic acid (FA) 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 (FA) 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 (5 FU)

Oxaliplatin should always be administered before fluoropyrimidines – i.e. 5 fluorouracil (5 FU). After oxaliplatin administration, flush the line and then administer 5 fluorouracil (5 FU).

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

- USE ONLY the recommended solvents (see below).
- Any concentrate that shows evidence of precipitation should not be used and should be destroyed with due regard to legal requirements for disposal of hazardous waste (see below).

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 infusion solution should be discarded.

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 0.2 mg/ml and 0.7 mg/ml. The concentration range over which the physico-chemical stability of oxaliplatin has been demonstrated is 0.2 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 room temperature (15°-25°C) and at refrigerated condition (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° C to 8°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.

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 to 500 ml of a glucose 5% solution to give a concentration not less than 0.2 mg/ml must be infused either by peripheral vein or central venous line over 2 to 6 hours. When oxaliplatin is administered with 5-fluorouracil, the oxaliplatin infusion must precede the administration of 5-fluorouracil.

Disposal

Remnants of the medicinal product as well as all materials that have been used for 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.

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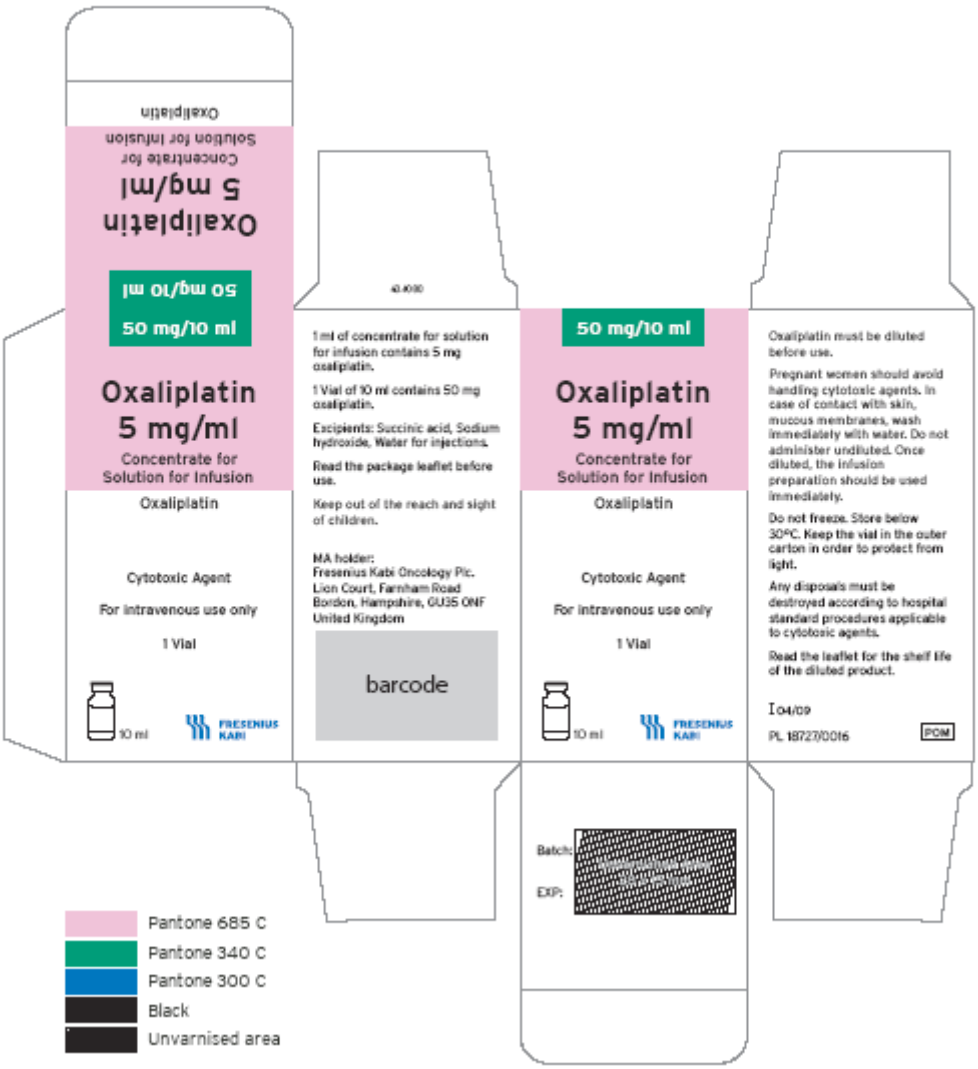
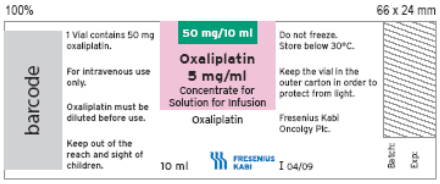
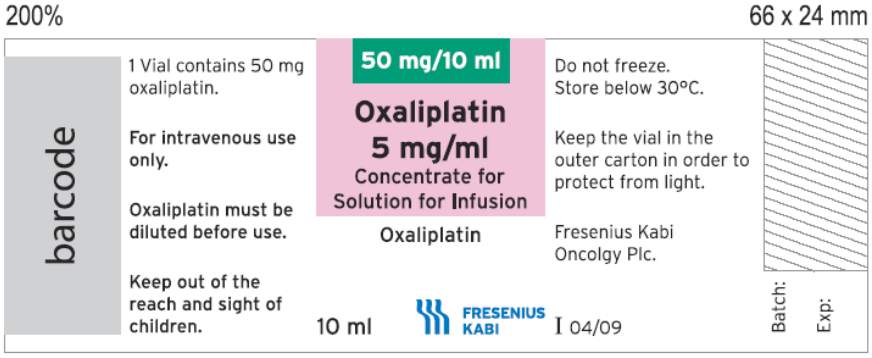
Module 4

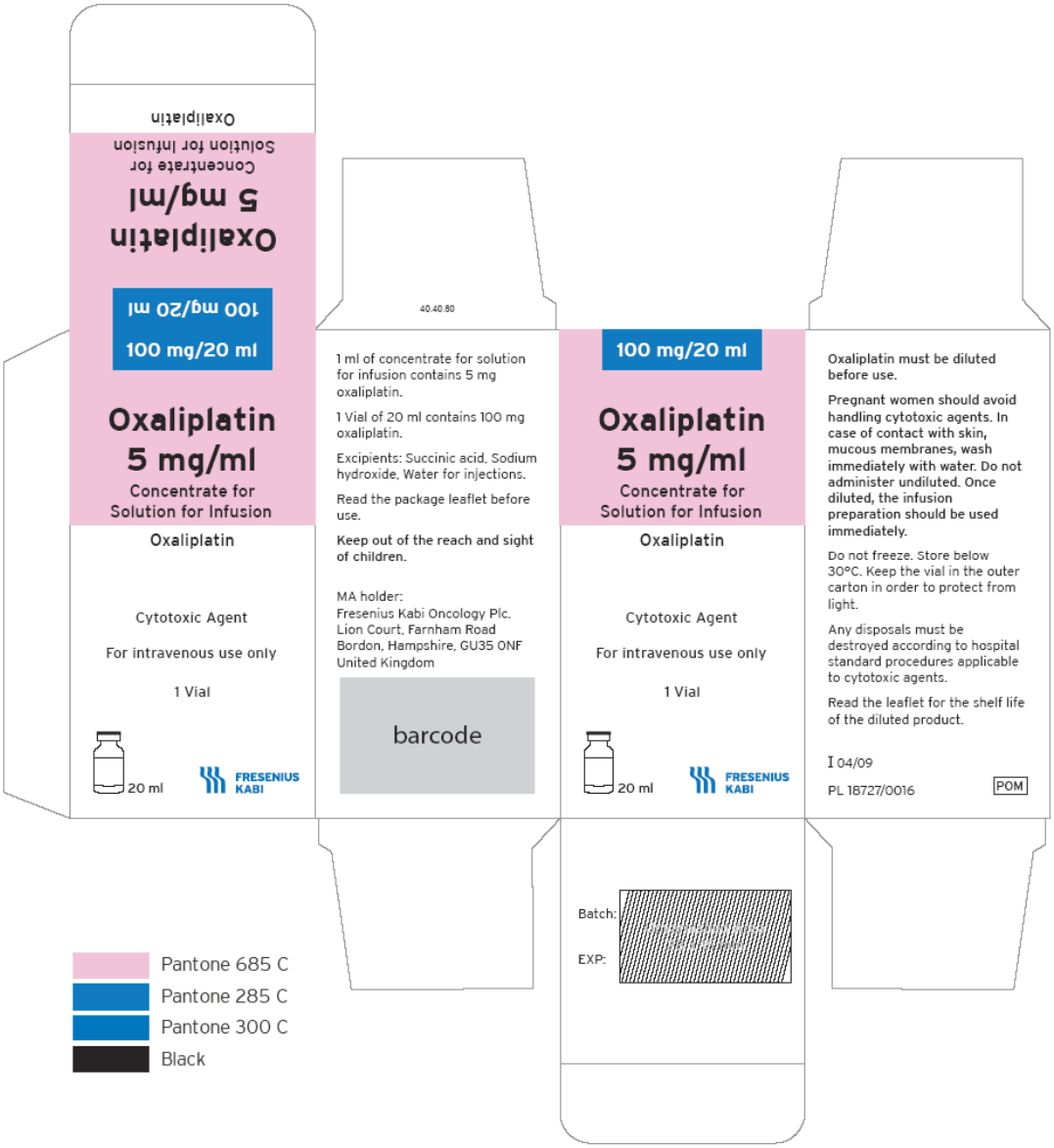
Labelling

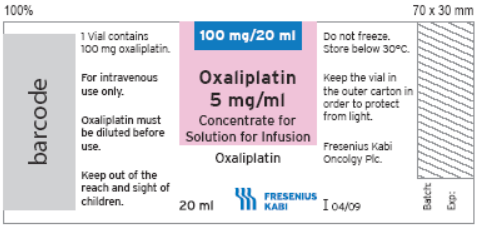
Oxaliplatin 50 mg Carton - UK

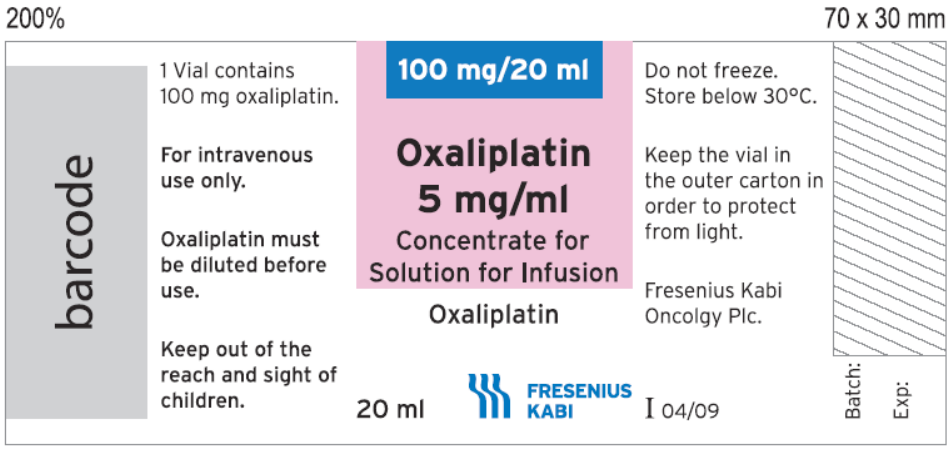



100%
66 x 24 mm
barcode
1 Vial contains 50 mg oxaliplatin.
For intravenous use only.
Oxaliplatin must be diluted before use.
Keep out of the reach and sight of children.
50 mg/10 ml
Oxaliplatin
5 mg/ml
Concentrate for Solution for Infusion
Oxaliplatin
10 ml
FRESENIUS KABI
I 04/09
Do not freeze.
Store below 30°C.
Keep the vial in the outer carton in order to protect from light.
Fresenius Kabi Oncolgy Plc.
Batch:
Exp:


200%
66 x 24 mm
barcode
1 Vial contains 50 mg oxaliplatin.
For intravenous use only.
Oxaliplatin must be diluted before use.
Keep out of the reach and sight of children.
50 mg/10 ml
Oxaliplatin
5 mg/ml
Concentrate for Solution for Infusion
Oxaliplatin
10 ml
FRESENIUS KABI
I 04/09
Do not freeze.
Store below 30°C.
Keep the vial in the outer carton in order to protect from light.
Fresenius Kabi Oncolgy Plc.
Batch:
Exp:


Oxaliplatin
Concentrate for Solution for Infusion
Oxaliplatin 5 mg/ml
100 mg/20 ml
100 mg/20 ml
Oxaliplatin 5 mg/ml
Concentrate for Solution for Infusion
Oxaliplatin
Cytotoxic Agent
For intravenous use only
1 Vial
20 ml
FRESENIUS KABI
40.40.80
1 ml of concentrate for solution for infusion contains 5 mg oxaliplatin.
1 Vial of 20 ml contains 100 mg oxaliplatin.
Excipients: Succinic acid, Sodium hydroxide, Water for injections.
Read the package leaflet before use.
Keep out of the reach and sight of children.
MA holder:
Fresenius Kabi Oncology Plc.
Lion Court, Farnham Road
Bordon, Hampshire, GU35 0NF
United Kingdom
barcode
100 mg/20 ml
Oxaliplatin 5 mg/ml
Concentrate for Solution for Infusion
Oxaliplatin
Cytotoxic Agent
For intravenous use only
1 Vial
20 ml
FRESENIUS KABI
Batch:
EXP:
Oxaliplatin must be diluted before use.
Pregnant women should avoid handling cytotoxic agents. In case of contact with skin, mucous membranes, wash immediately with water. Do not administer undiluted. Once diluted, the infusion preparation should be used immediately.
Do not freeze. Store below 30°C. Keep the vial in the outer carton in order to protect from light.
Any disposals must be destroyed according to hospital standard procedures applicable to cytotoxic agents.
Read the leaflet for the shelf life of the diluted product.
I 04/09
PL 18727/0016
POM
Pantone 685 C
Pantone 285 C
Pantone 300 C
Black


100%
70 x 30 mm
barcode
1 Vial contains 100 mg oxaliplatin.
For intravenous use only.
Oxaliplatin must be diluted before use.
Keep out of the reach and sight of children.
100 mg/20 ml
Oxaliplatin 5 mg/ml
Concentrate for Solution for Infusion
Oxaliplatin
20 ml
FRESENIUS KABI
I 04/09
Do not freeze. Store below 30°C.
Keep the vial in the outer carton in order to protect from light.
Fresenius Kabi Oncolgy Plc.
Batch:
Exp:


200%
70 x 30 mm
barcode
1 Vial contains 100 mg oxaliplatin.
For intravenous use only.
Oxaliplatin must be diluted before use.
Keep out of the reach and sight of children.
100 mg/20 ml
Oxaliplatin 5 mg/ml
Concentrate for Solution for Infusion
Oxaliplatin
20 ml
FRESENIUS KABI
I 04/09
Do not freeze. Store below 30°C.
Keep the vial in the outer carton in order to protect from light.
Fresenius Kabi Oncolgy Plc.
Batch:
Exp:

Module 5

Scientific discussion during initial procedure

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Oxaliplatin, in the treatment of metastatic colorectal cancer and as an adjuvant treatment of stage III (Duke's C) surgically resected colon cancer, approval was recommended. This product was originally granted a Marketing Authorisation as PL 19156/0038 with the licence holder being Jubilant Pharmaceuticals nv on 10/06/2009. A Change of Ownership application to Fresenius Kabi Oncology PLC (18727/0016) was approved on 06/07/2009.

EXECUTIVE SUMMARY
Problem statement
This decentralised procedure concerns a generic version of Oxaliplatin, under the proposed trade name Oxaliplatin 5mg/ml concentrate for solution for infusion. In this Assessment Report, the name Oxaliplatin is used. This application refers to the reference medicinal product Eloxatin 5 mg/ml powder for solution for infusion which has been authorised for 10 years in at least a Member state or in the Community (Sanofi, France, registered since April 1996). Oxaliplatin 5 mg/ml concentrate for solution for infusion is considered to be a generic version of the reference product (powder for solution for infusion) because both products contain the same quantitative and qualitative composition of the active ingredient, Oxaliplatin, and at the time of administration, the test and reference solutions are identical.

With the UK as the Reference Member State in this Decentralised Procedure, Jubilant Pharmaceuticals nv is applying for Marketing Authorisations for Oxaliplatin in the following CMS's:

CZ, DE, DK, EL, ES, FI, HU, IE, IT, NL, NO, PL, PT and SK.

About the product
Oxaliplatin is an alkylating agent and platinum analogue consisting of platinum bound to oxalate and diaminocyclohexane (DACH) complex. Oxaliplatin forms interstrand and intrastrand cross links with DNA, inhibiting DNA synthesis and resulting in cell death. The use of Oxaliplatin has been investigated in a number of malignancies including colorectal cancer, ovarian cancer, mesothelioma, breast cancer, non-Hodgkin's lymphoma, glioblastoma and pancreatic cancer. In patients with colorectal cancer, a synergistic combination of Fluorouracil/Leucovorin/Oxaliplatin (FOLFOX) has emerged as a standard treatment regimen. Common adverse reactions associated with Oxaliplatin include neurotoxicity, gastrointestinal disturbances, ototoxicity and myelosuppression.

General comments on the submitted dossier
This application is submitted in accordance with Article 10(1) of Directive 2001/83/EC (as amended). The submitted documentation in relation to the proposed product is of sufficient quality and is consistent with the current EU regulatory requirements.

A formal Environmental Risk Assessment has not been performed as the product is intended for generic substitution. Hence no increase in environmental risk is to be expected compared to that of the reference product.

The Applicant has provided a justification for not submitting a European Risk Management Plan. Other documentation relating to Pharmacovigilance systems has been provided.

Consultation with Target Patient Groups: The Applicant has submitted the results of a user testing study.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

No GCP certificate is required for this type of application.

SCIENTIFIC OVERVIEW AND DISCUSSION

Quality aspects

Drug substance
The active substance Oxaliplatin is described in the European Pharmacopoeia.. The proposed retest period is two years with no special temperature storage conditions. A Certificate of Suitability to support the quality of the API was provided .

Drug Product
The chemical-pharmaceutical documentation and Expert Report in relation to Oxaliplatin 5 mg/ml concentrate for solution for infusion are of sufficient quality in view of the present European regulatory requirements. The development of the product has been described, the choice of excipients is justified and their functions explained. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Process validation data have been provided for two batches of 50 mg/10 ml (30.0 litres) and two validation batches of 100 mg/20 ml (45.0 litres). The control tests are adequate. A shelf life of two years when stored below 30 °C is supported by stability data.

Non clinical aspects

Critical evaluation of the Non-Clinical Overview and Summary
Introduction
The pharmacological, pharmacokinetic and toxicological properties of oxaliplatin are well known. The overview cites 31 references from the published literature which are dated from 1993 to 2006. The overview was adequate.

The proposed formulation of the finished product (Oxaliplatin) has been shown to have the same qualitative and quantitative composition in active substances, and the same pharmaceutical form as the reference medicinal product (powder for solution for infusion). The applicant states that the lyophilised product at the point of injection, when reconstituted and diluted as required, is similar to the ready-to-use formulation. However the reference product being used is the powder for solution as the ready-to-use formulation has only been approved in the UK since 2005.

The Applicant has adequately discussed the potential presence of impurities due to the different excipient (succinic acid) and the formation of new platinum complexes. The Applicant has provided a probable pathway for the formation of succiniplatin. Succiniplatin has been adequately qualified by the GLP 14-day toxicity study in rats.

Conclusions
There are no non-clinical points outstanding. There are no objections to approval of Oxaliplatin 5mg/mL, concentrate for solution for infusion from a non-clinical point of view.

Clinical aspects
Introduction
Oxaliplatin 5 mg/ml concentrate for solution for infusion is the generic version of Eloxatin 5 mg/ml powder for solution for infusion, Sanofi, France. The use of the reference product is well-established in the EU. The product is essentially similar to Eloxatin 5 mg/ml, powder for solution for infusion as both products contain the same quantitative and qualitative composition of the active ingredient, Oxaliplatin. Oxaliplatin 5mg/ml concentrate for solution for infusion is considered to be a generic version of the reference product (powder for solution for infusion) because at the time of administration, the test and reference solutions are identical.

According to CPMP guidelines, the applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product (CPMP/EWP/1401/98, subpoint 5.1.6, Parenteral solutions).

Clinical Pharmacology
No new data have been submitted and none are required for this generic application.

The pharmacodynamic and pharmacokinetic claims in the SPC are consistent with the innovator product. The pharmacodynamic and pharmacokinetic properties have been extensively studied in the past.

Clinical efficacy
No new clinical studies have been submitted and none are required for this application.

Oxaliplatin is indicated in combination with 5-fluorouracil (5-FU) and folinic acid (FA) for treatment of metastatic colorectal cancer and as an adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of primary tumour.

- Evidence to support combination therapy includes de Gramont et al., 2000, Hospers et al, Grothey et al., 2006, Levi et al., 1994, Levi et al., 1997

- Evidence to support adjuvant therapy includes Andre et al., 2004 and de Gramont et al., 2005.

Clinical safety
Oxaliplatin has an acceptable adverse events profile. No novel safety data are supplied or required for this generic application. Oxaliplatin has a well established side-effect profile and is generally well-tolerated. The applicant has provided a review of clinical trials published in the literature confirming the safety of Oxaliplatin (Extra et al., 1998 and Cassidy and Misset., 2002).

Pharmacovigilance system
The RMS considers that the Pharmacovigilance system as described by the Applicant fulfils the requirements and provides adequate evidence that the Applicant has the services of a

qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The Applicant has provided an acceptable justification for not submitting a European Risk Management Plan.

BENEFIT RISK ASSESSMENT

The use of oxaliplatin is well established. It has recognised efficacy and acceptable safety. With regards to the current application, sufficient clinical information has been submitted which includes adequate review of published clinical data. Overall the risk: benefit analysis for Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion is considered favourable and a Marketing Authorisation was granted.

Module 6

Steps taken after procedure

This product was originally granted a Marketing Authorisation as PL 19156/0038 with the licence holder being Jubilant Pharmaceuticals. A Change of Ownership application to Fresenius Kabi Oncology Plc (18727/0016) was approved on 06/07/2009.