

**OXALIPLATIN 5MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION  
PL 18727/0012**

**UKPAR**

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**OXALIPLATIN 5MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION  
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**LAY SUMMARY**

On 25<sup>th</sup> February 2009, the MHRA granted Fresenius Kabi Oncology Plc a Marketing Authorisation (licence) for Oxaliplatin 5mg/ml Concentrate for Solution for Infusion (PL 18727/0012). 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).

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Oxaliplatin 5mg/ml Concentrate for Solution for Infusion outweigh the risks; hence a Marketing Authorisation has been granted.

**OXALIPLATIN 5MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION  
PL 18727/0012**

**SCIENTIFIC DISCUSSION**

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## INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Oxaliplatin 5mg/ml Concentrate for Solution for Infusion (PL 18727/0012) to Fresenius Kabi Oncology Plc on 25<sup>th</sup> February 2009. This prescription only medicine is used in combination with 5-fluorouracil (5FU) and folinic acid (FA) for the following indications:

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

This application for Oxaliplatin 5mg/ml Concentrate for Solution for Infusion is submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product to Eloxatin Concentrate for Solution for Infusion 5mg/ml, first authorised to Sanofi-Synthelabo Limited in December 2005.

The product contains the active substance oxaliplatin, an antineoplastic active substance, a third-generation cisplatin analogue (a class of platinum-based compounds) with important difference in the molecule, and hence in the DNA adducts formed, confers a different spectrum of activity compared with cisplatin.

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.

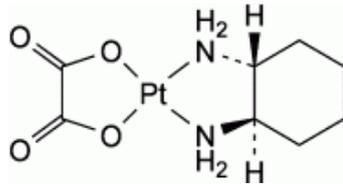
## PHARMACEUTICAL ASSESSMENT

## DRUG SUBSTANCE

**Oxaliplatin**

INN: Oxaliplatin  
 Chemical name: (SP-4-2)-[(1R,2R)-Cyclohexane-1,2-diamine-κN,κN']  
 [ethanedioato(2)-κO<sup>1</sup>,κO<sup>2</sup>]platinum.

Structure:



Physical form: white or almost white, crystalline powder.  
 Solubility: slightly soluble in water, very slightly soluble in methanol, practically insoluble in ethanol.

Molecular formula: C<sub>8</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>Pt  
 Molecular weight: 397.3

Oxaliplatin is the subject of a European Pharmacopoeia monograph. An Active Substance Master File (ASMF) has been provided covering the manufacture and control of the active substance oxaliplatin.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient.

An appropriate specification is provided for the active substance oxaliplatin. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer.

The specifications and typical analytical test reports are provided and are satisfactory.

Satisfactory specifications and certificates of analysis have been provided all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

An appropriate retest period has been proposed based on stability data submitted for the active substance oxaliplatin.

## **DRUG PRODUCT**

### **Other ingredients**

Other ingredients consist of pharmaceutical excipients sodium hydroxide, succinic acid and water for injection. Sodium hydroxide and water for injection comply with their relevant European Pharmacopoeia monographs. Succinic acid complies with in-house specifications.

None of the excipients used contain material of animal or human origin.

### **Product development**

The objective of the development programme was to produce a product that could be considered a generic medicinal product of Eloxatin Concentrate for Solution for Infusion 5mg/ml (Sanofi-Synthelabo Limited, December 2005.)

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative impurity profiles have been provided for the finished product versus the reference product Eloxatin Concentrate for Solution for Infusion 5mg/ml (Sanofi-Synthelabo Limited).

### **Manufacture**

A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on commercial size batches of the finished product.

### **Finished product specification**

The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis for all working standards used have been provided and are satisfactory.

### **Container-Closure System**

The product is packaged in clear, type I, glass vials sealed with chlorobutyl elastomer stopper.

Specifications and certificates of analysis for the packaging types used have been provided. All primary product packaging complies with European Pharmacopoeia monograph 3.2.1 (glass containers for pharmaceutical use).

The product is packaged in sizes of 1 vial of 10ml or 20ml.

### **Stability**

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years for an opened product has been set with the storage precautions 'Do not freeze' and 'Keep the vial in the outer carton in order to protect from light.'

After dilution of the product, the solution for infusion should be used immediately, otherwise in-use storage time should be no 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.'

## **ADMINISTRATIVE**

### **Expert Report**

A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

### **Summary of Product Characteristics (SPC)**

This is pharmaceutically satisfactory.

### **Labelling**

These are pharmaceutically satisfactory.

### **Patient Information Leaflet (PIL)**

This is pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

### **MAA Form**

This is pharmaceutically satisfactory.

### **Conclusion**

It is recommended that a Marketing Authorisation is granted for this application.

**PRECLINICAL ASSESSMENT**

This application for Oxaliplatin 5mg/ml Concentrate for Solution for Infusion was submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal products of Eloxatin Concentrate for Solution for Infusion 5mg/ml, first authorised to Sanofi-Synthelabo Limited in December 2005.

No new preclinical data have been supplied with this application and none are required for applications of this type.

## CLINICAL ASSESSMENT

### **CLINICAL PHARMACOLOGY**

No bioequivalence studies have been performed and none are required for this application, as the product is administered as a parenteral aqueous solution, distributed rapidly *in vivo*.

### **EFFICACY**

No new data has been provided.

### **SAFETY**

No new data has been provided.

### **EXPERT REPORTS**

The clinical expert report has been written by a suitably qualified person and is satisfactory.

### **PATIENT INFORMATION LEAFLET (PIL)**

This is consistent with that for the reference product and is satisfactory.

### **LABELLING**

These are satisfactory.

### **APPLICATION FORM (MAA)**

This is satisfactory.

### **SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**

This is consistent with that for the reference product and is satisfactory.

### **DISCUSSION**

A bioequivalence study with the reference product is not required for this product and can be justified as a generic medicinal product considering the quantitative and qualitative composition of the product and the route of administration.

### **MEDICAL CONCLUSION**

The grant of a marketing authorisation is recommended for this application.

**OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT****QUALITY**

The important quality characteristics of Oxaliplatin 5mg/ml Concentrate for Solution for Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

**PRECLINICAL**

No new preclinical data were submitted and none are required for applications of this type.

**EFFICACY**

Oxaliplatin is a well-known drug and has been used for many years.

Bioequivalence has been demonstrated between the applicant's Oxaliplatin 5mg/ml Concentrate for Solution for Infusion and the reference product Eloxatin Concentrate for Solution for Infusion 5mg/ml (Sanofi-Synthelabo Limited).

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference product Eloxatin Concentrate for Solution for Infusion 5mg/ml.

**RISK BENEFIT ASSESSMENT**

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The data submitted supports the claim that the applicant's product and the reference product are interchangeable. Extensive clinical experience with oxaliplatin is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

**OXALIPLATIN 5MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION  
PL 18727/0012****STEPS TAKEN FOR ASSESMENT**

1	The MHRA received the marketing authorisation application on 28 <sup>th</sup> June 2007.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 3 <sup>rd</sup> December 2007.
3	Following assessment of the application, the MHRA requested further information relating to the quality dossier on 14 <sup>th</sup> December 2007, 1 <sup>st</sup> May 2008 and 6 <sup>th</sup> August 2008. The MHRA requested further information relating to the clinical dossier on 24 <sup>th</sup> January 2008.
4	The applicant responded to the MHRA's requests, providing further information on 18 <sup>th</sup> March 2008, 9 <sup>th</sup> July 2008 and 12 <sup>th</sup> November 2008 for the quality section. The applicant provided further information on 31 <sup>st</sup> March 2008 for the clinical section.
5	The application was determined on 25 <sup>th</sup> February 2009.

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**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

<b>Date submitted</b>	<b>Application type</b>	<b>Scope</b>	<b>Outcome</b>

**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**Posology**FOR ADULTS ONLY**

The recommended dose for oxaliplatin in adjuvant setting is 85 mg/m<sup>2</sup> intravenously repeated every two weeks for 12 cycles (6 months).

The recommended dose for oxaliplatin in treatment of metastatic colorectal cancer is 85 mg/m<sup>2</sup> 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<sup>2</sup>.

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  $<2 \times 10^9/l$  and/or platelet count of  $<100 \times 10^9/l$ .
- have a peripheral sensory neuropathy with functional impairment prior to first 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 contraindicated.

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<sup>2</sup> to 65 mg/m<sup>2</sup> (metastatic setting) or 75 mg/m<sup>2</sup> (adjuvant setting).
- If paraesthesia without functional impairment persists until the next cycle, the subsequent oxaliplatin dose should be reduced from 85 mg/m<sup>2</sup> to 65 mg/m<sup>2</sup> (metastatic setting) or 75 mg/m<sup>2</sup> (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  $< 1.0 \times 10^9/l$ ), grade 3 to 4 thrombocytopenia (platelets  $< 50 \times 10^9/l$ ) occur, the dose of oxaliplatin should be reduced from 85 mg/m<sup>2</sup> to 65 mg/m<sup>2</sup> (metastatic setting) or 75 mg/m<sup>2</sup> (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

##### **Interaction with other medicinal products and other forms of Interaction**

In patients who have received a single dose of 85 mg/m<sup>2</sup> 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.

<b>MedDRA Organ system classes</b>	<b>Very common</b>	<b>Common</b>	<b>Uncommon</b>	<b>Rare</b>
<b>Infections and infestations *</b>	- Infection	- Rhinitis - Upper respiratory tract infection - Febrile neutropenia /Neutropenic sepsis		
<b>Blood and the lymphatic system disorders*</b>	- Anaemia - Neutropenia - Thrombocytopenia - Leucopenia - Lymphopenia			- Autoimmune thrombocytopenia - Haemolytic anaemia
<b>Immune system disorders*</b>	- Allergy/ allergic reaction+			
<b>Metabolism and nutrition disorders</b>	- Anorexia - Glycaemia abnormalities - Hypokalaemia - Natraemia abnormalities	- Dehydration	- Metabolic acidosis	
<b>Psychiatric disorders</b>		- Depression - Insomnia	- Nervousness	
<b>Nervous system disorders*</b>	- Peripheral sensory neuropathy - Sensory disturbance - Dysgeusia - Headache	- Dizziness - Motor neuritis - Meningism		- Dysarthria
<b>Eye disorders</b>		- Conjunctivitis - Visual disturbance		- Visual acuity reduced transiently - Visual field disturbances - Optic neuritis
<b>Ear and labyrinth disorders</b>			- Ototoxicity	- Deafness
<b>Vascular disorders</b>	- Epistaxis	- Haemorrhage - Flushing - Haematuria		

		- Deep vein thrombosis - Pulmonary embolism - Rectal haemorrhage		
<b>Respiratory, thoracic and mediastinal disorders</b>	- Dyspnoea - Cough	- Hiccups - Chest pain		- Interstitial lung disease - Pulmonary fibrosis**
<b>Gastrointestinal disorders*</b>	- Nausea - Diarrhoea - Vomiting - Stomatitis /Mucositis - Abdominal pain - Constipation	- Dyspepsia - Gastro-esophageal reflux	- Ileus - Intestinal obstruction	- Colitis including clostridium difficile diarrhoea
<b>Skin and subcutaneous tissue disorders</b>	- Skin disorder - Alopecia	- Skin exfoliation (i.e. Hand & Foot syndrome) - Rash erythematous - Rash - Hyperhidrosis - Nail disorder		
<b>Musculo-skeletal, connective tissue and bone disorders</b>	- Back pain	- Arthralgia - Bone pain		
<b>Renal and urinary disorders</b>		- Dysuria - Micturition frequency abnormal		
<b>General disorders and administration site conditions</b>	- Fatigue - Fever++ - Asthenia - Pain - Injection site reaction+++			
<b>Investigations</b>	- 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 ( $\leq 1/10000$ ):

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 ( $\leq 1/10000$ ):

Acute tubulo-interstitial nephropathy leading to acute renal failure

Haematological toxicity:**Incidence by patient (%), by grade**

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

Digestive toxicity:**Incidence by patient (%), by grade**

Oxaliplatin and 5-FU/FA 85 mg/m <sup>2</sup> 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/m<sup>2</sup> (10 cycles) is approximately 10 % and 20 % for a cumulative dose of 1020 mg/m<sup>2</sup> (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 and 5-FU/FA 85 mg/m <sup>2</sup> 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-*kN*, *kN'*][ethanedioato(2-)-*kO*<sup>1</sup>, *kO*<sup>2</sup>] 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<sup>2</sup> 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
<b>Front-line treatment</b> EFC2962	22 (16-27)	49 (42-46)	NA*
Response assessment every 8 weeks	P value = 0.0001		
<b>Pretreated patients</b> EFC4584 (refractory to CPT-11 + 5-FU/FA)	0.7 (0.0-2.7)	11.1 (7.6-15.5)	1.1 (0.2-3.2)
Response assessment every 6 weeks	P value <0.0001		
<b>Pretreated patients</b> EFC2964 (refractory to 5-FU/FA) Response assessment every 12 weeks	NA*	23 (13-36)	NA*

NA: Not Applicable

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

##### FOLFOX4 versus LV5FU2

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

NA: Not Applicable

#### Median Overall Survival (OS) under FOLFOX4 versus LV5FU2

Median OS, months (95% CI) ITT analysis	LV5FU2	FOLFOX4	Oxaliplatin Single agent
<b>Front-line treatment</b> EFC2962	14.7 (13.0-18.2)	16.2 (14.7-18.2)	NA*
	Log-rank P value = 0.12		
<b>Pretreated patients</b> EFC4584 (refractory to CPT-11 + 5-FU/FA)	8.8 (7.3 - 9.3)	9.9 (9.1-10.5)	8.1 (7.2-8.7)
	Log-rank P value = 0.09		
<b>Pretreated patients</b> EFC2964 (refractory to 5-FU/FA)	NA*	10.8 (9.3-12.8)	NA*

NA: Not Applicable

In pretreated patients (EFC4584), who were symptomatic at baseline, a higher proportion of those treated with oxaliplatin and 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)	
	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)	
<u>Log-rank test</u>	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/m<sup>2</sup> every three weeks for 1 to 5 cycles and oxaliplatin at 85 mg/m<sup>2</sup> 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<sup>2</sup> Every Two Weeks or at 130 mg/m<sup>2</sup> Every Three Weeks**

Dose	C <sub>max</sub>	AUC <sub>0-48</sub>	AUC	t <sub>1/2α</sub>	t <sub>1/2β</sub>	t <sub>1/2γ</sub>	V <sub>ss</sub>	CL
	μg/mL	μg.h/mL	μg.h/mL	h	h	h	L	L/h
85 mg/m <sup>2</sup> 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 <sup>2</sup> 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<sub>0-48</sub>, and C<sub>max</sub> values were determined on Cycle 3 (85 mg/m<sup>2</sup>) or cycle 5 (130 mg/m<sup>2</sup>).

Mean AUC, V<sub>ss</sub>, CL, and CL<sub>R0-48</sub> values were determined on Cycle 1.

C<sub>end</sub>, C<sub>max</sub>, AUC, AUC<sub>0-48</sub>, V<sub>ss</sub> and CL values were determined by non-compartmental analysis.

t<sub>1/2α</sub>, t<sub>1/2β</sub>, and t<sub>1/2γ</sub>, 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<sup>2</sup> every two weeks or 130 mg/m<sup>2</sup> 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<sup>2</sup>) 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<sup>+</sup> 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 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 folic acid (FA) via a Y-line.

- DO NOT mix with alkaline medicinal products or solutions, in particular 5-fluorouracil, folic 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 folic 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

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/m<sup>2</sup> 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.**

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**  
25/02/2009
- 10**     **DATE OF REVISION OF THE TEXT**  
25/02/2009
- 11**     **DOSIMETRY (IF APPLICABLE)**
- 12**     **INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)**

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
2. Before you use Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion
3. How to use Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion
4. Possible side effects
5. How to store Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion
6. Further Information.

**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.

**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 TO USE 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<sup>2</sup>) 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<sup>2</sup> 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.

**Very common (affects more than 1 in 10 people):**

- 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).

**Common (affects more than 1 in 100 but less than 1 in 10 people):**

- 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**

#### **Fresenius Kabi Oncology Plc.**

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

**This leaflet is prepared in February 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, folic 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 folic acid (FA) (as calcium folinate or disodium folinate)**

Oxaliplatin 85 mg/m<sup>2</sup> intravenous infusion in 250 to 500 ml of glucose 5 % solution is given at the same time as folic 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. Folic 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 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.

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.

Each 10 ml vial contains oxaliplatin 50 mg.

Other ingredients: Succinic acid, sodium hydroxide and water for injections.

**For intravenous use only.**

For use as directed by the clinician.

To be administered by I.V. infusion over 2 to 6 hours.

Keep out of the reach and sight of children.

Do not inject without first diluting the concentrate.

**50 mg/10 ml**

**Oxaliplatin**

**5 mg/ml**

concentrate for solution for infusion



**Cytotoxic Agent**

Oxaliplatin

1 Vial



**Must be diluted before use.**

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

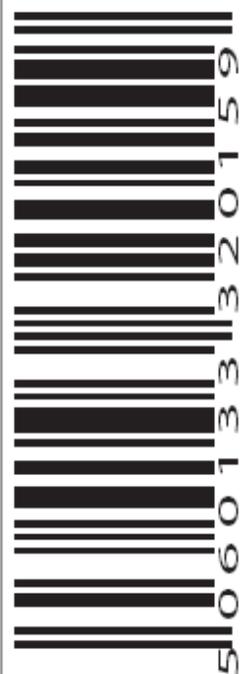
Do not freeze.

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United Kingdom

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**POM**

Batch No.:  
Exp:



Each 20 ml vial contains oxaliplatin 100 mg.  
 Other ingredients: Succinic acid, sodium hydroxide and water for injections.  
**For intravenous use only.**  
 For use as directed by the clinician.  
 To be administered by I.V. infusion over 2 to 6 hours.  
 Keep out of the reach and sight of children.  
 Do not inject without first diluting the concentrate.

**100 mg/20 ml**

**Oxaliplatin  
5 mg/ml**

concentrate for solution  
for infusion

Oxaliplatin

**Cytotoxic Agent**

1 Vial



**Must be diluted before use.**  
 Keep the vial in the outer carton in order to protect from light.  
 Do not freeze.

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**POM**

Batch No.:

Exp:

Oxaliplatin  
concentrate for solution  
for infusion

**Oxaliplatin**  
**5 mg/ml**

**50 mg/10 ml**

**Oxaliplatin**  
**5 mg/ml**  
concentrate for solution  
for infusion

Oxaliplatin

Cytotoxic Agent

1 Vial




Each 10 ml vial contains oxaliplatin 50 mg.  
Other ingredients:  
Succinic acid, sodium hydroxide and water for injections.  
**For intravenous use only.**  
For use as directed by the clinician.  
To be administered by I.V. infusion over 2 to 6 hours.

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5 0 6 0 1 3 3 1 3 2 0 1 4 2

**50 mg/10 ml**

**Oxaliplatin**  
**5 mg/ml**  
concentrate for solution  
for infusion

Oxaliplatin

Cytotoxic Agent

1 Vial




Keep out of the reach and sight of children.  
**Do not inject without first diluting the concentrate. Must be diluted before use.**  
Keep the vial in the outer carton in order to protect from light. Do not freeze.

Handling and destruction:  
Pregnant women must not handle oxaliplatin. This product must be handled, diluted and disposed of in accordance with hospital and other local policies to avoid risk to staff and other people, the environment, and facilities used. Any unused product or waste materials must be disposed of as above: see insert.

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POM

Pantone 304 C

Pantone 685 C

Pantone 300 C

Black

Batch No.:

Exp:

Oxaliplatin  
concentrate for solution  
for infusion

**Oxaliplatin**  
**5 mg/ml**

**100 mg/20 ml**

**Oxaliplatin**  
**5 mg/ml**

concentrate for solution  
for infusion

Oxaliplatin

**Cytotoxic Agent**

1 Vial




Each 20 ml vial contains oxaliplatin 100 mg.

Other ingredients:  
Succinic acid, sodium hydroxide and water for injections.

**For intravenous use only.**  
For use as directed by the clinician.  
To be administered by I.V. infusion over 2 to 6 hours.

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**100 mg/20 ml**

**Oxaliplatin**  
**5 mg/ml**

concentrate for solution  
for infusion

Oxaliplatin

**Cytotoxic Agent**

1 Vial




Keep out of the reach and sight of children.  
**Do not inject without first diluting the concentrate. Must be diluted before use.**  
Keep the vial in the outer carton in order to protect from light. Do not freeze.

**Handling and destruction:**  
Pregnant women must not handle oxaliplatin. This product must be handled, diluted and disposed of in accordance with hospital and other local policies to avoid risk to staff and other people, the environment, and facilities used. Any unused product or waste materials must be disposed of as above: see insert.

R 02/09  
PL18727/0012 **POM**

Batch No.:

Exp:

Pantone 685 C

Pantone 285 C

Pantone 300 C

Black

