Public Assessment Report

Decentralised

Oxaliplatin Hospira 5mg/ml Concentrate for Solution for Infusion

UK/H/971/01/DC

Hospira UK Ltd

(formerly Mayne Pharma Ltd)

Lay Summary

The Medicines and healthcare products regulatory Agency (MHRA) granted Hospira UK ltd (formerly Mayne Pharma Ltd) a Marketing Authorisation (licence) for the medicinal product Oxaliplatin Hospira 5mg/ml concentrate for solution for infusion. This is a prescription only medicine.

This medicinal product contains the active ingredient oxaliplatin an is used, after complete surgical removal of the bowel tumour, to treat cancer of the large bowel (colon) that has spread beyond the bowel wall to nearby lymph glands but not to other tissues, such as the liver or lungs. In addition, this medicine can be used on combination with other anti-cancer medicinal products cald 5-fluorouaracil and folinic acid, with or without prior surgery to remove the cancer.

The data submitted in support of the application for Oxaliplatin Hospira 5mg/ml, concentrate for solution for infusion raised no clinically significant safety concerns and it was therefore, judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation was granted.

TABLE OF CONTENTS

Module 1

Product Name	Oxaplatin Hospira 5mg/ml Concentrate for Solution for Infusion
Type of Application	Decentralised
Active Substance (INN)	Oxaliplatin
Pharmacotherapeutic Classification (ATC)	L01XA03
Pharmaceuctical Form and Strength	Concentrate for Solution for Infusion, 5mg/ml
Procedure Numbers	UK/H/971/01/DC
RMS	UK
CMS	AT, BE, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, NL, NO, PL, PT, SE, SK
Start Date	15/09/2006
End Date	12/09/2007
MA Number	PL 04515/0215
Name and address of MA holder	Hospira UK Ltd, Queensway, Royal Leamington Spa, Warwickshire, CV31 3RW, UK

Module 2

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Oxaplatin Hospira 5mg/ml Concentrate for Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One 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 solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- Adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of primary tumour

- Treatment of metastatic colorectal cancer.

4.2 Posology and method of administration

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 2 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.

Oxaliplatin is administered as a 2- to 6-hour intravenous infusion in 250 to 500 ml of glucose 5% solution (50 mg/ml) to give a concentration between 0.2 mg/ml and 0.70 mg/ml; 0.70 mg/ml is the highest concentration in clinical practice for 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 impairment:

In a phase I study including patients with several levels of hepatic impairment, frequency and severity of hepatobiliary disorders appeared to be related to progressive disease and impaired liver function tests at baseline. No specific dose adjustment for patients with abnormal liver function tests was performed during clinical development.

- 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 (50 mg/ml) to give a concentration not less than 0.2 mg/ml must be infused either via a peripheral vein or central venous line 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 5% glucose diluent is to be used to dilute the concentrate for solution for infusion product. (See section 6.6).

4.3 Contraindications

Oxaliplatin is contraindicated in patients who

- have hypersensitivity to oxaliplatin or to the excipient.

- are breast feeding.

- have myelosuppression prior to starting first course, as evidenced by baseline neutrophils $<2x10^9$/l and/or platelet count of $<100x10^9$l.

- have a peripheral sensory neuropathy with functional impairment prior to first course.

- have a severely impaired renal function (creatinine clearance less than 30 ml/min).

4.4 Special warnings and precautions for use

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

Due to limited information on safety in patients with moderately impaired renal function, administration should only be considered after suitable appraisal of the benefit/risk for the patient. In this situation, renal function should be closely monitored and dose adjusted according to toxicity.

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

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

Neurological toxicity of oxaliplatin should be carefully monitored, especially if co-administered with other medicinal products with specific neurological toxicity. A neurological examination should be performed before each administration and periodically thereafter.

For patients who develop acute laryngopharyngeal dysaesthesia (see section 4.8), during or within the hours following the 2-hour infusion, the next oxaliplatin infusion should be administered over 6 hours.

If neurological symptoms (paraesthesia, dysaesthesia) occur, the following recommended oxaliplatin dosage adjustment should be based on the duration and severity of these symptoms:

- If symptoms last longer than seven days and are troublesome, the subsequent oxaliplatin dose should be reduced from 85 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 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 possibilities of persistent symptoms of peripheral sensory neuropathy after the end of the treatment. Localised moderate parasthesias or parasthesias 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 < 1.5x10^9/l or platelets < 50x10^9/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 and ⁄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 ≥ 1.5 x 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 3-4 thrombocytopenia (platelets < 50x10^9/l) occur, the dose of oxaliplatin should be reduced from 85 to 65 mg/m² (metastatic setting) or 75 mg/m² (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 cases of abnormal test results of liver function or portal hypertension, which does not obviously result from liver metastases, very rare cases of drug induced hepatic vascular disorder 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 preformed. However, oxaliplatin treatment resulting in an increased risk of dizziness, nausea and

vomiting, and other neurological 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 (5-FU/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 5-FU/FA combination than with 5-FU/FA alone.

The frequencies reported in the table below are derived from clinical trials in the metastatic and adjuvant settings (having included 416 and 1108 patients respectively in the oxaliplatin + 5-FU/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 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10000 to < 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 Class	Very common	Common	Uncommon	Rare
Infections and infestations*	- Infection	- Rhinitis - Upper respiratory tract infection - Neutropenic sepsis - Febrile neutropenia		
Blood and lymphatic system disorders*	- Anaemia - Neutropenia - Thrombocytopenia - Leukopenia - Lymphopenia			- Autoimmune thrombocytopenia - Haemolytic anaemia
Immune system disorders*	- Allergy/allergic reaction+			
Metabolism and nutrition disorders	- Anorexia - Glycaemia alterations - Hypokalaemia - Natremia alterations	- Dehydration	- Metabolic acidosis	
Psychiatric disorders		- Depression - Insomnia	- Nervousness	
Nervous system disorders*	- Peripheral sensory neuropathy - Sensory disturbance - Dysgeusia - Headache	- Dizziness - Motor neuritis - Meningism		- Dysarthria
Eye disorders		- Conjunctivitis - Visual disturbances		- Visual acuity reduced transiently - Visual field disturbance - Optic neuritis
Ear and labyrinth disorders			- Ototoxicity	- Deafness
Vascular	- Epistaxis	- Haemorrhage		

disorders		- Flushing - Deep vein thrombosis - Pulmonary embolism		
Respiratory, thoracic and medistinal disorders	- Dyspnoea - Coughing	- Hiccups		- Interstitial lung disease - Pulmonary fibrosis**
Gastointestinal disorders*	- Nausea - Diarrhoea - Vomiting - Stomatitis/ mucositis - Abdominal pain - Constipation	- Dyspepsia - Gastroesophageal reflux - Rectal haemorrhage	- Ileus - Intestinal obstruction	- Colitis including *Clostridium difficile* diarrhoea
Skin and subcutaneous tissue disorders	- Skin disorder - Alopecia	- Skin exfolation (i.e Hand and Foot syndrome) - Rash erythematous - Rash - Hyperhidrosis - Nail disorder		
Musculo-skeletal, connective tissue disorders	- Back pain	- Arthralgia - Bone pain		
Renal and urinary disorders		- Dysuria - Micturition 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 4.4).

Hepatobiliary disorders

Very rare (≤1/10,000):
Liver sinusoidal obstruction syndrome, also known as veno-occlusive liver disease or pathological manifestations related to such liver disorders, including peliosis hepatis, nodular regenerative hyperplasia, perisinusoidal fibrosis. Clinical manifestations may be portal hypertension and/or elevation of transaminases.

Renal and urinary disorders

Very rare (≤1/10000):
Acute tubulo-interstitial nephropathy leading to acute renal failure.

Haematological toxicity:

Incidence by patient (%), by grade

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

Digestive toxicity:

Incidence by patient (%), by grade

Oxaliplatin and 5FU/FA 85 mg/m^2	**Metastatic Setting**			**Adjuvant Setting**		
Every 2 weeks	**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 parasthesia 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 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 localised paraesthesias of moderate intesity (2.3%) or with paraesthesias 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 paresthesia, dysesthesia and hypoesthesia. An acute syndrome of pharyngolaryngeal dysesthesia occurs in 1% and 2% of 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 and 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 : L01XA 03

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 (85mg/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 randomized patients either to 5-fluorouracil/folinic acid alone (LV5FU2, N=210) or the combination of oxaliplatin with 5-fluorouracil/folinic (FOLFOX4, N=210)

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

- Finally, the uncontrolled 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 EFC 4584 performed in refractory pretreated patients, the difference in median overall survival (OS) between the combination of oxaliplatin and 5-FU/FA did not reach statistical significance.

Response rate under FOLFOX4 versus LV5FU2

Response rate % (95% 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 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)** **ITT analysis with independent radiological examination**	**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 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**
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 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/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 MOSAIC comparative 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 tumour of colon cancer either to 5-FU/FA alone (LV5FU2) or to combination of oxaliplatin and 5-FU/FA (FOLFOX4).

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 5-FU/FA combination (FOLFOX4) over 5-FU/FA alone (LV5FU2).

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

Patient stage	*Stage II* **(Duke's B2)**		**Stage III** **Duke's C**	
Treatment arm	LV5FU2	FOLFOX4	LV5FU2	FOLFOX4
Percent 3-year disease free survival (95% 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 favour of the FOLFOX4 not reaching statistical significance (hazard ratio = 0.90). The figures were 92.2% versus 92.4% in the stage II (Duke's B2) sub-population (hazard ratio = 1.01) and 80.4% versus 78.1% in the stage III (Duke's C) sub-population (hazard ratio = 0.87), for FOLFOX4 and LV5FU2, respectively.

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	Cmax	AUC0-48	AUC	$t_{1/2\alpha}$	$t_{1/2\beta}$	$t_{1/2\gamma}$	Vss	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, Vss, CL, and CL_{R0-48} values were determined on Cycle 1.
C_{end}, C_{max}, AUC, AUC_{0-48}, Vss and CL values were determined y 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 130mg/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 drug was detectable in plasma ultrafiltrate at the end of a 2h-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 drugs and DNA-damaging, cytotoxic drugs used in the treatment of human cancers with the exception of the effects produced on the heart. Effects on the heart were observed only in the dog and included electrophysiological disturbances with lethal ventricular fibrillation. Cardiotoxicity is considered specific to the dog not only because it was observed in the dog alone but also because doses similar to those producing lethal cardiotoxicity in dogs (150 mg/m^2) were well-tolerated by humans. Preclinical studies using rat sensory neurons suggest that the acute neurosensory symptoms related to Oxaliplatin may involve an interaction with voltage-gated Na+ channels.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient(s)

Water for Injections
Tartaric acid
Sodium Hydroxide (for pH adjustment)

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 excipients and trometamol salts of other medicinal products. 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 line (see section 6.6 to check instructions related to co-administration with folinic acid)

6.3 Shelf-life

Medicinal product as packaged for sale: 2 years

After dilution in 5% glucose, chemical and physical in-use stability has been demonstrated for 24 hours at +2°C - +8°C and for 6 hours at +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 unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Medicinal product as packaged for sale: Keep the vial in the outer carton in order to protect from light. Do not freeze.

For storage conditions of the diluted medicinal product see section 6.3.

6.5 Nature and contents of container

1 vial with 10 ml concentrate (Type I clear glass vial with or without Onco-Tain sleeve) with elastomeric stopper and flip-off cap.

1 vial with 20 ml concentrate (Type I clear glass vial with or without Onco-Tain sleeve) with elastomeric stopper and flip-off cap.

Pack size: 1 vial per box. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

As with other potentially toxic compounds, caution should be exercised when handling and preparing oxaliplatin 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 material 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 excipients and trometamol salts of other drugs. Alkaline drugs or solutions will adversely effect the stability of oxaliplatin.

<u>Instruction for use with folinic acid (FA) (as calcium folinate or disodium folinate)</u>

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 medical 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.

Intructions 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 drugs 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.

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 1.3 mg/ml.

Administer by intravenous infusion.

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

7. MARKETING AUTHORISATION HOLDER

Hospira UK Ltd

8. MARKETING AUTHORISATION NUMBER(S)

PL 04515/0215

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/09/2007

10. DATE OF REVISION OF THE TEXT

Module 3

Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Oxaliplatin Hospira 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 HOSPIRA 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 HOSPIRA

Do not use Oxaliplatin Hospira**:**
- if you are hypersensitive (allergic) to oxaliplatin or any of the other ingredients of Oxaliplatin Hospira
- if you are breast feeding,
- 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 Hospira**:**

- 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 neurological symptoms that affect gait and balance. If this happens, you should not drive or operate machinery.

3. HOW OXALIPLATIN HOSPIRA IS USED

For adults only.

Oxaliplatin Hospira 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 Hospira 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 Hospira **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 HOSPIRA

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 use after the expiry date, the last day of the month, which is stated on the carton and label.

Once diluted the infusion preparation should be used immediately. Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C and 6 hours at 25°C. If not used immediately, in-use storage times and conditions are the responsibility of the user and would not normally be longer than 24 hours at 2°C to 8°C.

6. FURTHER INFORMATION

What Oxaliplatin** Hospira **contains

- The active substance is oxaliplatin.
  One 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.
- The other ingredients are tartaric acid, sodium hydroxide and water for injections

What Oxaliplatin Hospira **looks like and contents of the pack**
Oxaliplatin Hospira 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 wrapped in a protective plastic to reduce the risk of spillage if the vials break - these are referred to as ONCO-TAIN®. The vials are available in single packs.

The solution is then diluted in glucose 5% solution and can be given as an infusion via a drip.

Marketing Authorisation Holder and Manufacturer
Hospira UK Ltd, Queensway, Royal Leamington Spa, Warwickshire, CV31 3RW, UK

This leaflet was last approved in September 2007
----------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 1.3 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 for 6 hours at 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 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.

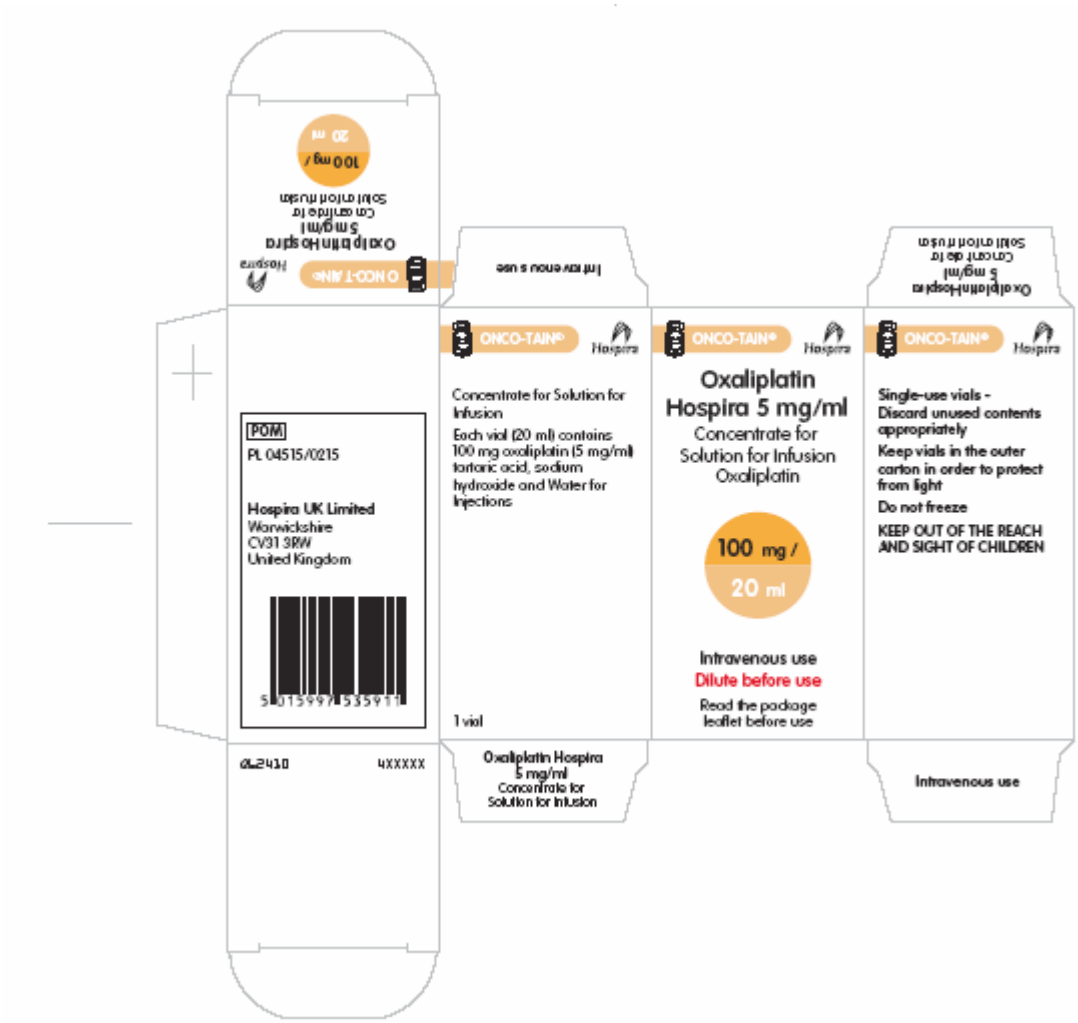
Oxaliplatin diluted in 250 to 500 ml of a glucose 5% solution to give a concentration not less than 0.2 mg/ml must be infused either by peripheral vein or central venous line over 2 to 6 hours. When oxaliplatin is administered with 5-fluorouracil, the oxaliplatin infusion must precede the administration of 5-fluorouracil.

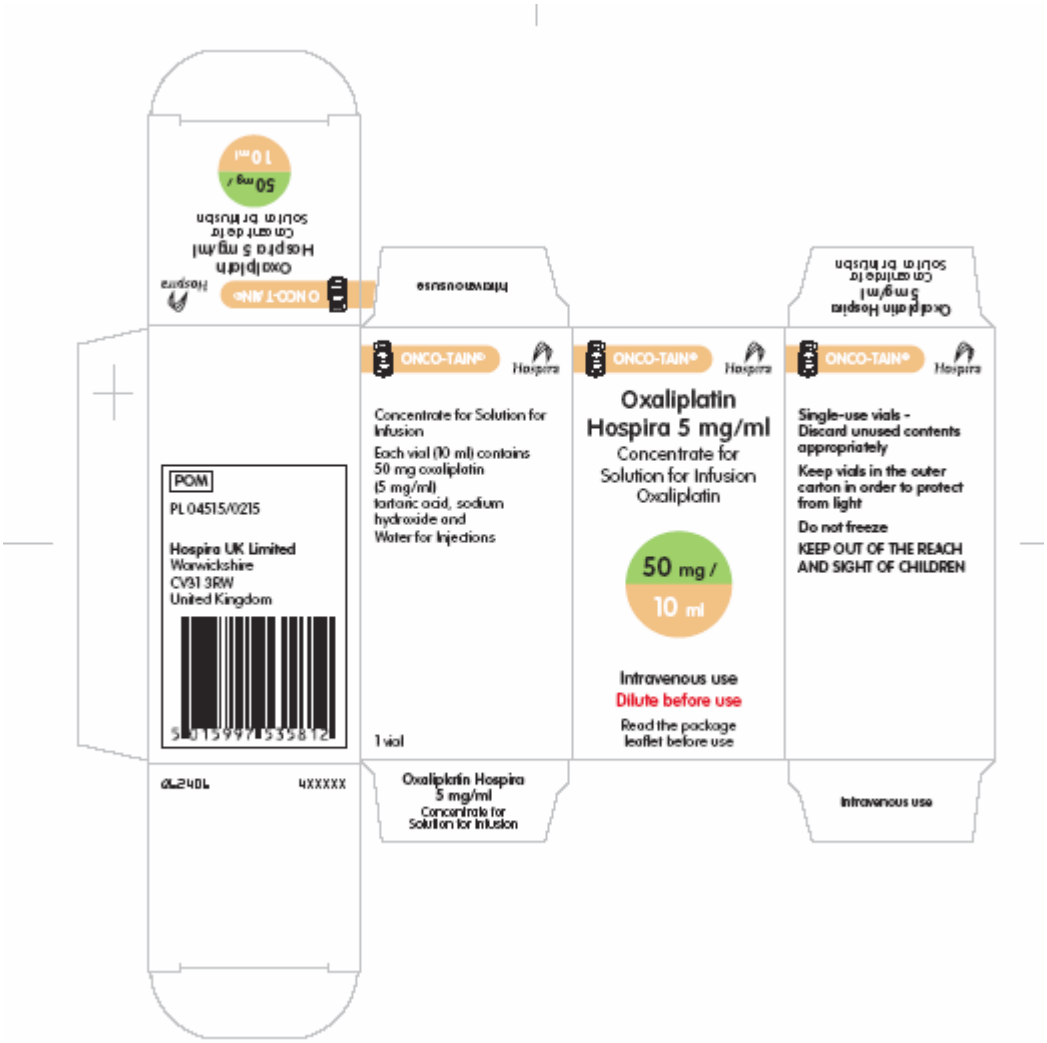
Disposal

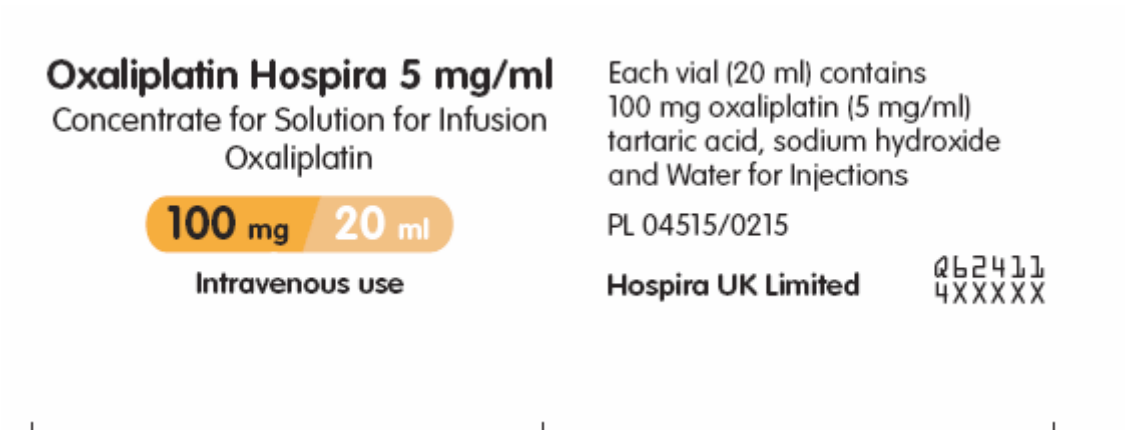
Remnants of the medicinal product as well as all materials that have been used for dilution and administration must be destroyed according to hospital standard procedures applicable to cytotoxic agents in accordance with local requirements related to the disposal of hazardous waste.

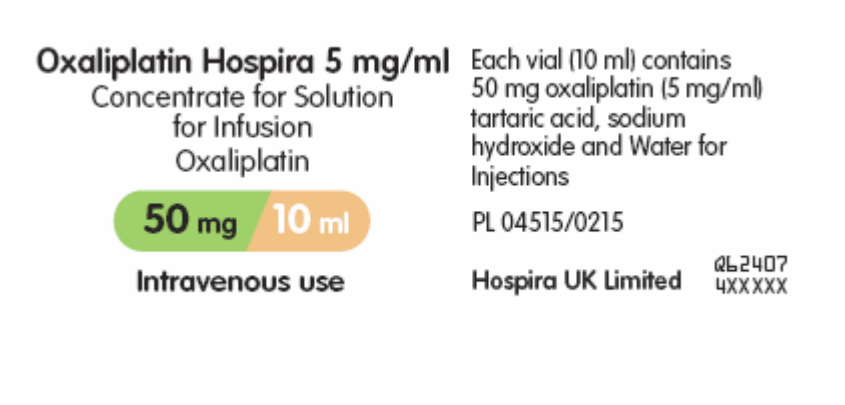
Module 4

Labelling




ONCO-TAIN®
Hospira
Concentrate for Solution for Infusion
Each vial (10 ml) contains
50 mg oxaliplatin
(5 mg/ml)
tartaric acid, sodium hydroxide and
Water for Injections
1 vial
POM
PL 04515/0215
Hospira UK Limited
Warwickshire
CV31 3RW
United Kingdom
Oxaliplatin Hospira 5 mg/ml
Concentrate for Solution for Infusion
Oxaliplatin
50 mg / 10 ml
Intravenous use
Dilute before use
Read the package leaflet before use
Single-use vials - Discard unused contents appropriately
Keep vials in the outer carton in order to protect from light
Do not freeze
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
Intravenous use


Oxaliplatin Hospira 5 mg/ml
Concentrate for Solution for Infusion
Oxaliplatin
100 mg 20 ml
Intravenous use
Each vial (20 ml) contains
100 mg oxaliplatin (5 mg/ml)
tartaric acid, sodium hydroxide
and Water for Injections
PL 04515/0215
Hospira UK Limited
Q62411
4XXXXX


Oxaliplatin Hospira 5 mg/ml
Concentrate for Solution
for Infusion
Oxaliplatin
50 mg 10 ml
Intravenous use
Each vial (10 ml) contains
50 mg oxaliplatin (5 mg/ml)
tartaric acid, sodium
hydroxide and Water for
Injections
PL 04515/0215
Hospira UK Limited
Q62407
4XXXXX

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 applications for oxaliplatin 5mg/ml concemtrate for solution for infusion, in the treatment of metastatic colorectal cancer, is approvable.

EXECUTIVE SUMMARY
Problem statement

This abridged decentralised application concerns a generic version of oxaliplatin submitted under Article 10.1. The reference product is Eloxatin Solution for Infusion 5mg/ml (PL11723/0423), authorised on 15 December 2005 as a line extension to Eloxatin 5mgml Powder for Solution for Infusion (PL11723/0288), authorised on 23 August 1999 to Sanofi-Synthelabo in the UK. Both of these licences are part of the MRP FR/H/0144/01 from the original global marketing authorisation for Eloxatin Powder for solution for infusion in France, grant dated 4 December 1996. The legal basis is satisfactory.

Originally the application was submitted by Mayne Pharma PLC, however the company has now changed its name to Hospira UK Ltd and the marketing authorisation has been altered by variation. In addition the name of the product has been changed by variation from Oxaliplatin Mayne 5mg/ml Concentrate for Solution for Infusion to Oxaliplatin Hopsira 5mg/ml Concentrate for Solution for Infusion.

With the UK as the Reference Member State in this Decentralised Procedure, Hospira UK appled for the Marketing Authorisations for oxaliplatin 5mg/ml solution for infusion in AT, BE, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, SE and SK.

About the product

Oxaliplatin belongs to the platinium compounds group. Anastrozole is a platinium based compound used in combination with fluorouracil and folinic acid, for the treatment of metastatic colorectal cancer and as adjuvant treatment of colon cancer after resection of the primary tumour.

General comments on the submitted dossier

The submitted dossier is of adequate standard.

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. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

SCIENTIFIC OVERVIEW AND DISCUSSION
Quality aspects

Drug substance

The chemical-pharmaceutical documentation and Expert Report in relation to oxaliplatin 5mg/ml solution for infusion are of sufficient quality in view of the present European regulatory requirements. The active substance oxaliplatin is described in the European Pharmacopoeia and a certificate of suitability has been submitted. The drug substance specification for drug substance is generally acceptable. Stability studies have been performed with the drug substance. No significant changes in any parameters were observed.

Drug Product

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. Batch analysis has been performed on two 30 litre batches of the 50mg presentation and one 50 litres batch and 30 litres batch of the 100mg presentation. The batch analysis results show that the finished products meet the specifications proposed. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. The proposed shelf-life of 24 months without the requirement of any special storage conditions is acceptable.

Non clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of oxaliplatin are well known. As oxaliplatin is a well known active substance, no further new non-clinical data are required and the applicant has not provided any.

Clinical aspects

Pharmacokinetics

No novel PK data are supplied. The PK claims within the SPC are appropriately consistent with the innovator label.

Pharmacodynamics

No novel efficacy or safety data are supplied or required for this application. The PD claims within the SPC are appropriately consistent with the innovator label.

Clinical efficacy

No novel efficacy data are supplied or required for this generic application, thus the efficacy claims within the SPC are appropriately consistent with the innovator label.

Clinical safety

No new safety data have been submitted and none are required for this application, hence the SPC claims are appropriate.

Overall Conclusion

Quality
The important quality characteristics of Oxaliplatin Hospira 5mg/ml concentrate for solution for infusion are well defined can controlled. The specification 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 preclinical data is needed for these applications.

Efficacy
Clinical studies have demonstrated the efficacy of Oxaliplatin 5mg/ml concentrate for solution for infusion in the treatment of metastatic colorectal cancer and adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of primary tumour.

The product literature is satisfactory and consistent with that for the innovator product.

BENEFIT RISK ASSESSMENT

Overall the risk:benefit for the Oxaliplatin Hopsira 5mg/ml concentrate for solution for infusion 5 mg/ml is considered favourable and approval is recommended.

Module 6

Steps taken after procedure

Variations to change the Marketing Authorisation holder from Mayne Pharma PLC to Hospira UK Ltd and to change the name of the product from Oxaliplatin Mayne 5mg/ml Concentrate for Solution for Infusion to Oxaliplatin Hopsira 5mg/ml Concentrate for Solution for Infusion was granted on 25/01/2008.