Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion

(Oxaliplatin)

UK/H/2713/001/DC

UK licence numbers: PL 15413/0024

Hikma Farmacêutica (Portugal), S.A.

LAY SUMMARY

On 29th January 2010, the MHRA granted Hikma Farmacêutica (Portugal), S.A. a Marketing Authorisation (licence) for the medicinal product, Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion (PL 15413/0024, UK/H/2713/001/DC). This is a prescription-only medicine (POM) used in the treatment of cancer of the large bowel.

Oxaliplatin belongs to the therapeutic group of anti-neoplastic or anti-cancer agents that contain platinum in their chemical structure. Oxaliplatin 5mg/ml is used to treat metastatic (advanced) cancer of the colon (large bowel) and rectum (back passage); or for treatment of stage III colon cancer following surgery to remove a tumour (growth) in the colon. It is used in combination with other anticancer agents, 5-fluorouracil and folinic acid. Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion has to be diluted before it can be injected into a vein.

This application is based on a reference product with a valid UK licence. No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion outweigh the risks; hence a Marketing Authorisation has been granted.

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Module 1

Information about Initial Procedure

Product Name	Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion
Type of Application	Generic, Article 10.1
Active Substance	Oxaliplatin
Form	Concentrate for solution for infusion
Strength	5 mg / ml
MA Holder	Hikma Farmacêutica (Portugal), S.A. Estrada do Rio da Mó n^{os} 8, 8A e 8B -Fervença 2705-906 Terrugem SNT Portugal
Reference Member State (RMS)	UK
Concerned Member State / s (CMS)	AT, DE, NL, PT and SK
Procedure Number	UK/H/2712/001/DC
Timetable	Day 210; 26th November 2009

Module 2

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 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
40 ml of concentrate for solution for infusion contains 200 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 (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

FOR ADULTS ONLY

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 (see section 6.6).

The recommended dose for oxaliplatin in adjuvant setting is 85 mg/m² intravenously repeated every two weeks for 12 cycles (6 months). The recommended dose for oxaliplatin in treatment of metastatic colorectal cancer is 85 mg/m² intravenously repeated every 2 weeks. Dosage given should be adjusted according to tolerability (see section 4.4). Oxaliplatin should always be administered **before** fluoropyrimidines – i.e. 5-fluorouracil. Oxaliplatin is administered as a 2- to 6-hour intravenous infusion in 250 to 500 ml of 5% glucose solution 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/m².

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

Special populations

Renal impairment:
Oxaliplatin has not been studied in patients with severe renal impairment (see section 4.3). In patients with moderate renal impairment, treatment may be initiated at the normally recommended dose (see section 4.4). There is no need for dose adjustment in patients with mild renal dysfunction.

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

Elderly patients:
No increase in severe toxicities was observed when oxaliplatin was used as a single agent or in combination with 5-fluorouracil in patients over the age of 65. In consequence no specific dose adaptation is required for elderly patients.

Paediatric patients:
There is no relevant indication for use of oxaliplatin in children. The effectiveness of oxaliplatin single agent in the paediatric populations with solid tumours has not been established (see sections 5.1).

Method of administration
Oxaliplatin is administered by intravenous infusion.

The administration of oxaliplatin does not require hyperhydration.

Oxaliplatin diluted in 250 to 500 ml of 5% glucose solution to give a concentration not less than 0.2 mg/ml must be infused via a central venous line or 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 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 a known history of hypersensitivity to oxaliplatin or any of the excipients.
- are breast feeding.
- have myelosuppression prior to starting first course, as evidenced by baseline neutrophils $<2x10^9$/l and/or platelet count of $<100x10^9$/l.
- have a peripheral sensitive 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 medications 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 possibility of persistent symptoms of peripheral sensory neuropathy after the end of the treatment. Localised moderate paraesthesias or paraesthesias 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 75mg/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 case of abnormal liver function test results or portal hypertension which does not obviously result from liver metastases, very rare cases of drug induced hepatic vascular disorders should be considered.

For use in pregnant women, see section 4.6.

Genotoxic effects were observed with oxaliplatin in the preclinical studies. Therefore male patients treated with oxaliplatin are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment because oxaliplatin may have an anti-fertility effect which could be irreversible.

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

4.5 Interaction with other medicinal products and other forms of interaction

In patients who have received a single dose of 85 mg/m^2 of oxaliplatin, immediately before administration of 5-fluorouracil, no change in the level of exposure to 5-fluorouracil has been observed. *In vitro*, no significant displacement of oxaliplatin binding to plasma proteins has been observed with the following agents: erythromycin, salicylates, granisetron, paclitaxel, and sodium valproate.

4.6 Pregnancy and lactation

To date there is no available information on safety of use in pregnant women. In animal studies, reproductive toxicity was observed (see section 5.3). 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. Vision abnormalities, in particular transient vision loss (reversible following therapy discontinuation), may affect patients' ability to drive and use machines. Therefore, patients should be warned of the potential effect of these events on the ability to drive or 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 neurophathy). 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, < 1/10), uncommon (≥ 1/1000, < 1/100), rare (≥ 1/10000, ≤ 1/1000), very rare (< 1/10000), not known (cannot be estimated from the available data).

Further details are given after the table.

MedDRA Organ system classes	Very common	Common	Uncommon	Rare
Infections and Infestations*	- Infection	- Rhinitis - Upper respiratory tract infection - Febrile neutropenia /neutropenic sepsis		
Blood and the lymphatic system disorders*	- Anaemia - Neutropenia - Thrombocytopenia - Leukopenia - Lymphopenia			- Immunoallergic thrombocytopenia - Haemolytic anaemia
Immune system disorders*	- Allergy / allergic reaction+			
Metabolism and nutrition disorders	- Anorexia - Glycaemia abnormalities - Hypokalaemia - Natraemia abnormalities	- Dehydration	- Metabolic acidosis	
Psychiatric disorders		- Depression - Insomnia	- Nervousness	

Nervous system disorders*	- Peripheral sensory neuropathy - Sensory disturbance - Dysgeusia - Headache	- Dizziness - Motor neuritis - Meningism		- Dysarthria
Eye disorders		- Conjunctivitis - Visual disturbance		- Visual acuity reduced transiently - Visual field disturbances - Optic neuritis - transient vision loss, reversible following therapy discontinuation
Ear and labyrinth disorders			- Ototoxicity	- Deafness
Vascular disorders	- Epistaxis	- Haemorrhage - Flushing - Deep vein thrombosis - Pulmonary embolism - Hypertension		
Respiratory, thoracic and mediastinal disorders	- Dyspnoea - Cough	- Hiccups		- Interstitial lung disease, sometimes fatal - Pulmonary fibrosis**
Gastro-intestinal disorders*	- Nausea - Diarrhoea - Vomiting - Stomatitis / Mucositis - Abdominal pain - Constipation	- Dyspepsia - Gastroesophageal reflux - Rectal haemorrhage - Gastrointestinal haemorrhage	- Ileus - Intestinal obstruction	- Colitis including Clostridium difficile diarrhoea
Skin and subcutaneous tissue disorders	- Skin disorder - Alopecia	- Skin exfoliation (i.e. Hand and Foot syndrome) - Rash erythematous - Rash - Hyperhidrosis - Nail disorder		
Musculo-skeletal, connective tissue and bone disorders	- Back pain	- Arthralgia - Bone pain		
Renal and urinary disorders		- Dysuria - Micturition frequency abnormal - Haematuria		
General disorders and administration site conditions	- Fatigue - Fever^{++} - Asthenia - Pain - Injection site reaction^{+++}			
Investi-gations	- Hepatic enzyme increase - Blood alkaline phosphatase increase - Blood bilirubin	- Blood creatinine increase - Weight decrease (metastatic setting)		

	increase - Blood lactate dehydro-genase increase - Weight increase (adjuvant 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, angiooedema, hypotension and anaphylactic shock.

++ Very common fever, rigors (tremors), either from infection (with or without febrile neutropenia) or possibly from immunological mechanism.

+++ Injection site reactions including local pain, redness, swelling and thrombosis have been reported. Extravasation may also result in local pain and inflammation which may be severe and lead to complications, including necrosis, especially when oxaliplatin is infused through a peripheral vein (see 4.4).

Hepatobiliary disorders:

Very rare (< 1/10 000):
Liver sinusoidal obstruction syndrome, known also as veno-oclusive liver disease, or pathological manifestations related with such liver disorders, including peliosis hepatis, nodular regenerative hyperplasia, perisinusoidal fibrosis. Clinical manifestations may include portal hypertension and/or increase of transaminase.

Renal and urinary disorders
Very rare (<1/10000):
Acute tubulo-interstitial nephropathy leading to acute renal failure

Blood and Lymphatic system disorders

Incidence by patient (%), by grade

Oxaliplatin and 5-FU/FA 85 mg/m²	Metastatic Setting			Adjuvant Setting		
every 2 weeks	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

Postmarketing experience with frequency unknown
Hemolytic uremic syndrome

Gastrointestinal disorders

Incidence by patient (%), by grade

Oxaliplatin and 5-FU/FA 85 mg/m²	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 paraesthesia of the extremities with or without cramps, often triggered by the cold. These symptoms occur in up to 95% of patients treated. The duration of these symptoms, which usually regress between courses of treatment, increases with the number of treatment cycles.

The onset of pain and/or a functional disorder are indications, depending on the duration of the symptoms, for dose adjustment, or even treatment discontinuation (see section 4.4).

This functional disorder includes difficulties in executing delicate movements and is a possible consequence of sensory impairment. The risk of occurrence of persistent symptoms for a cumulative dose of 850 mg/m² (10 cycles) is approximately 10% and 20% for a cumulative dose of 1020 mg/m² (12 cycles).

In the majority of the cases, the neurological signs and symptoms improve or totally recover when treatment is discontinued. In the adjuvant setting of colon cancer, 6 months after treatment cessation, 87 % of patients had no or mild symptoms. After up to 3 years of follow up, about 3 % of patients presented either with persisting localised paraesthesias of moderate intensity (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 may present as transient paraesthesia, dysaesthesia and hypoesthesia. An acute syndrome of pharyngolaryngeal dysaesthesia occurs in 1% to 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 spasms/muscle contractions – involuntary/muscle twitching/myoclonus, coordination abnormal / gait abnormal/ataxia/balance disorders, throat or chest tightness/pressure/discomfort/pain. In addition, cranial nerve dysfunctions 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.

Postmarketing experience with frequency unknown
Convulsion

Immune system disorders

Incidence of allergic reactions by patient (%), by grade

Oxaliplatin and 5-FU/FA 85 mg/m²	Metastatic Setting			Adjuvant Setting		
every 2 weeks	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, (*SP*-4-2)-[(1*R*,2*R*)-Cyclohexane-1,2-diamine-k*N*, k*N*′] [ethanedioato(2-)-kO^1, kO^2] platinum.

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

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

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

In patients with metastatic colorectal cancer, the efficacy of oxaliplatin (85mg/m^2 repeated every two weeks) combined with 5-fluorouracil/folinic acid (5-FU/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 three arms phase III study EFC4584 randomised 821 patients refractory to an irinotecan (CPT-11) + 5-FU/FA combination either to 5-FU/FA alone (LV5FU2, N=275), oxaliplatin single agent (N=275), or combination of oxaliplatin with 5-FU/FA (FOLFOX4, N=271).
- Finally, the uncontrolled phase II EFC2964 study included patients refractory to 5-FU/FA alone, that were treated with the oxaliplatin and 5-FU/FA combination (FOLFOX4, N=57)

The two randomised 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-FU/FA alone. In EFC4584 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	22 (16 - 27)	49 (42 - 46)	NA*
Response assessment every 8 weeks	P value = 0.0001		
Pretreated patients EFC4584 (refractory to CPT-11 + 5-FU/FA)	0.7 (0.0 - 2.7)	11.1 (7.6 - 15.5)	1.1 (0.2-3.2)
Response assessment every 6 weeks	P value < 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) independent radiological review ITT analysis	LV5FU2	FOLFOX4	Oxaliplatin Single agent
Front-line treatment EFC2962 (PFS)	6.0 (5.5 - 6.5)	8.2 (7.2 - 8.8)	NA*
	Log-rank P value = 0.0003		
Pretreated patients EFC4584 (TTP) (refractory to CPT-11 + 5-FU/FA)	2.6 (1.8 - 2.9)	5.3 (4.7 - 6.1)	2.1 (1.6 - 2.7)
	Log-rank P value < 0.0001		
Pretreated patients EFC2964 (refractory to 5-FU/FA)	NA*	5.1 (3.1 - 5.7)	NA*

*NA = not applicable

Median Overall Survival (OS) 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 + 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		
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 and 5-FU/FA experienced a significant improvement of their disease-related symptoms compared to those treated with 5-FU/FA alone (27.7% vs 14.6% p = 0.0033).

In non-pretreated patients (EFC2962), no statistically significant 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 MOSAÏC 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, N=1123 (B2/C = 448/675) or to combination of oxaliplatin and 5-FU/FA (FOLFOX4, 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 over 44.2 months (all patients 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 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.

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

5.2 Pharmacokinetic properties

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

Summary of Platinum Pharmacokinetic Parameter Estimates in Ultrafiltrate Following Multiple Doses of Oxaliplatin at 85 mg/m^2 Every Two Weeks or at 130 mg/m^2 Every Three Weeks

Dose	C_{max} µg/ml	AUC_{0-48} µg·h/ml	AUC µg·h/ml	$t_{1/2}\alpha$ h	$t_{1/2}\beta$ h	$t_{1/2}\gamma$ h	Vss L	CI 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/m²) or cycle 5 (130 mg/m²).

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 by non-compartmental analysis.

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

At the end of a 2-hour infusion, 15% of the administered platinum is present in the systemic circulation, the remaining 85% being rapidly distributed into tissues or eliminated in the urine. Irreversible binding to red blood cells and plasma, results in half-lives in these matrices that are close to the natural turnover of red blood cells and serum albumin. No accumulation was observed in plasma ultrafiltrate following 85 mg/m^2 every two weeks or 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 dihydro-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 excipients

Water for injections
gluconolactone

6.2 Incompatibilities

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

This medicinal product should not be mixed with other medicinal products except those mentioned in section 6.6

- DO NOT mix with alkaline drugs or solutions, in particular 5-fluorouracil, folinic acid preparations containing trometamol as an excipient and trometamol salts of other drugs. 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 mix with other drugs in the same infusion bag or infusion line (see section 6.6 for instructions concerning simultaneous administration with folinic acid).
- DO NOT use injection equipment containing aluminium.

6.3 Shelf life

2 years

After dilution in 5% glucose, chemical and physical in-use stability has been demonstrated for 48 hours at +2°C to +8°C and for 24 hours at +25°C.

From a microbiological point of view, the 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.

6.4 Special precautions for storage

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 10ml concentrate, 20ml concentrate or 40ml concentrate.

Type I clear glass vial with bromobutyl stopper, Aluminium cap and polypropylene cover.

Not all pack sizes may be marketed

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 nursing or medical 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 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 section “Disposal”.

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

If oxaliplatin concentrate or infusion solution 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 medication in the same infusion bag or administer simultaneously by the same infusion line.

- DO NOT mix with alkaline drugs or solutions, in particular 5 fluorouracil, folinic acid preparations containing trometamol as an excipient and trometamol salts of other drugs. Alkaline drugs or solutions will adversely affect the stability of oxaliplatin.

Instruction for use with folinic acid (as calcium folinate or disodium folinate)
Oxaliplatin 85mg/m² IV infusion in 250 to 500 ml of 5% glucose solution is given at the same time as folinic acid IV infusion in 5% glucose solution, over 2 to 6 hours, using a Y-line placed immediately before the site of infusion.

These two drugs 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 5% glucose 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 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 before infusion
Withdraw the required amount of concentrate from the vial(s) and then dilute with 250 ml to 500 ml of a 5% glucose solution to give an oxaliplatin concentration between 0.2 mg/ml and 0.70mg/ml. The concentration range for which the physico-chemical stability of oxaliplatin has been demonstrated is 0.2 mg/ml to 2.0mg/ml.

Administer by IV infusion.

After dilution in 5% glucose, chemical and physical in-use stability has been demonstrated for 48 hours at +2°C to +8°C and for 24 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 5% glucose 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 and with due regard to current laws related to the disposal of hazardous waste.

7 MARKETING AUTHORISATION HOLDER

Hikma Farmacêutica (Portugal), S.A.
Estrada do Rio da Mó n^{os} 8, 8A e 8B -Fervença
2705-906 Terrugem SNT Portugal
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e-mail: geral@hikma.pt

8 MARKETING AUTHORISATION NUMBER(S)

PL 15413/0024

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/01/2010

10 DATE OF REVISION OF THE TEXT

29/01/2010

Module 3

Product Information Leaflet

Text version

PACKAGE LEAFLET: INFORMATION FOR THE USER

Oxaliplatin Hikma, 5mg/ml Concentrate for solution for infusion

Oxaliplatin

Read all of this leaflet carefully before you start taking this medicine.
1. Keep this leaflet. You may need to read it again.
2. If you have any further questions, ask your doctor or pharmacist.
3. 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 HIKMA, 5MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION, IS AND WHAT IT IS USED FOR

The active ingredient of Oxaliplatin Hikma, 5mg/ml Concentrate for solution for infusion, is oxaliplatin.

It is used to treat cancer of the large bowel (metastatic cancer of colon and rectum). Oxaliplatin is used in combination with other anticancer medicines called 5-fluorouracil and folinic acid.

Oxaliplatin Hikma, 5mg/ml Concentrate for solution for infusion, has to be diluted before it can be injected into a vein.

Oxaliplatin is an antineoplastic or anticancer drug and contains platinum.

2. BEFORE YOU ARE GIVEN OXALIPLATIN HIKMA, 5MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

Do not use Oxaliplatin Hikma, 5mg/ml Concentrate for solution for infusion
- if you are allergic (hypersensitive) to oxaliplatin or any of the other ingredients of the product
- 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 or lacing up shoes
- if you have severe kidney problems (creatinine clearance below 30 ml/min)
- If any of these apply to you and you have not already discussed this with your doctor or nurse, you should do so as soon as possible and before the first administration of the preparation.

Take special care with Oxaliplatin Hikma, 5mg/ml Concentrate for solution for infusion if you
- are pregnant or planning to become pregnant
- have ever suffered an allergic reaction to platinum-containing medicines such as carboplatin or cisplatin
- have moderate kidney problems
- have any liver problems
- experience numbness or tingling in your fingers or toes or difficulty in swallowing.

If any of these apply to you and you have not already discussed this with your doctor or nurse, you should do so as soon as possible and before the first administration of the product.

Your doctor or nurse will administer this medicine and will carefully and frequently monitor you during and after the treatment, including taking blood tests before each administration of the product. Before and after treatment you will be given a neurological examination. This monitoring is necessary to see how your body is responding to the medicine and to prevent possible unwanted side effects that can occur. On the basis of the test results, your doctor may decide to discontinue your medication or to change your treatment accordingly.

If you experience swelling or pain around the area where your infusion has been given, inform your doctor or nurse immediately.

If you experience breathing problems or a cough inform your doctor or nurse immediately.

If you experience sore lips or mouth ulcers inform your doctor or nurse immediately.

Oxaliplatin should not come into contact with the eyes or skin. If there is any accidental spillage, tell the doctor or nurse immediately.

During oxaliplatin treatment, feeling or being sick can occur. Therefore, your doctor can administer sickness reducing preparations, to stop this happening or to treat it.

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

Pregnancy and breast-feeding
Currently, no information is available on the safety of this medicine during its administration in the course of pregnancy. In animal studies, a negative effect was seen on the foetus. You must not use oxaliplatin during pregnancy unless clearly indicated by your doctor.

You must not become pregnant during treatment with oxaliplatin and must use an effective method of contraception. If you get pregnant 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.

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.

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

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

Driving and using machines
Oxaliplatin may result in an increased risk of dizziness, feeling or being sick and other neurological symptoms that affect your gait and balance. Do not drive or use machines if you are suffering from these side-effects.

3. HOW YOU ARE GIVEN OXALIPLATIN HIKMA, 5MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

Oxaliplatin Hikma, 5mg/ml Concentrate for solution for infusion, is intended only for adults.

Dosage:
The dose of oxaliplatin is based on your body surface area. This is calculated from your height and weight.

The usual dose for adults including the elderly is 85 mg/m^2 of body surface area. The dose you receive will also depend on results of blood tests and whether you have previously experienced side effects with oxaliplatin.

Method and route of administration:
Oxaliplatin will be prescribed for you by a specialist in cancer treatment.

You will be treated by a healthcare professional, who will have made up the required dose of oxaliplatin. It is administered by slow injection into a vein (as an intravenous infusion) over a 2 to 6 hour period.

The injection is made by diluting the solution in 5% glucose solution.

Oxaliplatin Hikma, 5mg/ml Concentrate for solution for infusion, will be given to you at the same time as folinic acid and before the infusion of 5-fluorouracil.

Frequency of administration:
Oxaliplatin Hikma, 5mg/ml Concentrate for solution for infusion, will be administered once every 2 weeks.

Duration of treatment:
The duration of the treatment will be determined by your doctor.

If you receive more Oxaliplatin Hikma, 5mg/ml Concentrate for solution for infusion, than you should
As this medicine is administered by a healthcare professional it is highly unlikely that you will receive too much oxaliplatin. Your doctor will ensure that the correct dose for your condition is given. In case of overdose, you may experience increased side effects. Your doctor may give you appropriate treatment for these side effects. If

you are worried that too much has been administered or you have any questions about the dose being given, ask your nurse or doctor administering your medicine.

If you miss a dose of Oxaliplatin Hikma, 5mg/ml Concentrate for solution for infusion
If you think you have missed a dose please talk to your nurse or doctor in charge.

If you have any further questions on the use of this product ask your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Oxaliplatin Hikma, 5mg/ml Concentrate for solution for infusion, can cause side effects, although not everybody gets them.

Tell your doctor or go to the nearest hospital 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 dry cough, difficulties in breathing or crackles.
- Swelling of hands, feet, ankles, face, lips, mouth or throat (which may cause difficulties in swallowing or breathing and are symptoms of angioedema).
- Sensation of discomfort close to or at the injection site during infusion.

Very common side effects (affecting a least 1 in 10 people treated)
- Allergic reactions such as skin rash (particularly raised lumps), inflammation of the conjunctiva, swelling of hands, feet, ankles, face, mouth, lips or throat which may cause difficulties in swallowing or breathing, sudden wheeziness or tightness of chest, which can make you feel like fainting.
- Reduction of red blood cells (anaemia), which makes the skin pale and causes weakness or breathlessness
- Reduction in blood platelets, which increases the risk of abnormal bleeding or bruising
- Reduction in white blood cells, which increases the risk of infections
- Fever, tremors, tiredness, lack or loss of strength or energy.
- Low potassium in blood (this can be recognized by muscle cramps, muscle weakness or fatigue).
- Abnormal sodium blood level (this can be recognized by tiredness and confusion).
- Changes in blood glucose level (this can be recognized by great thirst, dry mouth or a need to urinate more often).
- Alteration in blood tests including those relating to abnormalities in liver function.
- Increase in liver enzymes, increase in alkaline phosphatase in the blood, increase in bilirubin in the blood, increase in lactate dehydrogenase in the blood.
- Skin disorder.
- Oxaliplatin may affect the nerves (peripheral sensory neuropathy). You may experience tingling and/or numbness in the fingers, toes, around the mouth or in the throat, which may sometimes occur in association with cramps. These side effects are often triggered by the cold, e.g. at opening the refrigerator or holding a cold drink. Additionally, you can have difficulties performing delicate tasks like buttoning clothes. Although in most cases, these symptoms resolve themselves completely there is a possibility of persistent symptoms of peripheral sensory neuropathy after the end of the treatment.
- Some people have experienced a tingling, shock-like sensation passing down the arms or trunk when the neck is flexed (Lhermitte's sign).
- 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.
- Headache.
- Diarrhoea.
- Nausea and vomiting (feeling or being sick). Medication to prevent the sickness is usually given to you by your doctor before treatment and may be continued after treatment.
- Ulcers in mouth, sore lips or gums.
- Abdominal pain, constipation, lack or loss of appetite.
- Weight gain.
- Back pain.
- Bleeding from nose.
- Coughing, difficulty breathing.
- Loss of hair (alopecia).
- Taste alteration.

Common side effects (affecting at least 1 in 100 people treated)
- Flushing.

- Chest pain.
- Dizziness, stiff neck, inflammation of the nerves associated with muscle weakness, difficulty with specific movements and sometimes muscle cramps (motor neuritis).
- Digestion disorders and heartburn, hiccups.
- Skin rash including red, itching, and peeling skin.
- Dehydration (lack of body liquids).
- Joint and bone pain.
- Blood in urine/faeces, vein swelling, clots in lungs.
- Depression, inability to sleep.
- Blocked or stuffy nose.
- Increased sweating, nail disorders.
- Pain when passing urine, changes in frequency of passing urine.
- Changes in kidney function (increase in blood creatinine).
- Conjunctivitis, visual disturbances.
- Weight loss.
- Infection of the respiratory tract.
- Serious condition (with fever or blood poisoning) caused by a decrease of white blood cells associated with an increased susceptibility for infections (febrile neutropenia, neutropenic sepsis).

Uncommon side effects (affecting at least 1 in 1000 people treated)
- Blockage or swelling of the bowel (usually demonstrated by abdominal pain and failure to pass wind). If you suspect a blockage or swelling of the bowel, inform the doctor immediately.
- Nervousness.
- Hearing problems (ototoxicity).
- Blood tests which show an increase in acidity (metabolic acidosis).

Rare side effects (affecting at least 1 in 10,000 people treated)
- Serious lung condition associated with shortness of breath, difficulties in breathing and/or scarring of the lungs (interstitial lung disease, pulmonary fibrosis).
- Deafness.
- Transient decrease of visual definition, abnormal visual field, decrease in eyesight caused by inflammation of the optical nerve (optical neuritis).
- Blood abnormality (short of platelets) caused by an allergic reaction associated with bruises and abnormal bleeding (immunoallergic thrombocytopenia).
- Reduction of red blood cells (anaemia) caused by too much degradation of blood (haemolytic anaemia).
- Difficulty speaking.

Very rare side effects (affecting less than 1 in 10,000 people treated)
- Liver disease that your doctor will monitor for you.
- Changes in kidney function leading to kidney failure.

Your doctor will take blood to check that you have a sufficient blood cell count before you start treatment and before each subsequent course.

If you experience any side effects, it is important to inform your doctor before the next treatment.

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 nurse.

5. HOW TO STORE OXALIPLATIN HIKMA, 5MG/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 use Oxaliplatin Hikma, 5mg/ml Concentrate for solution for infusion, after the expiry date which is stated on the carton and vial after: EXP. The expiry date refers to the last day of that month.

After dilution in 5% glucose the product should be used immediately or can be stored for 48 hours at 2°C to 8°C or for 24 hours at 25°C.

Do not use Oxaliplatin Hikma, 5mg/ml Concentrate for solution for infusion, if you notice any changes in colour or unusual particles.

Medicines should not be disposed of via wastewater or household waste. Your doctor, nurse, or pharmacist will dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Oxaliplatin Hikma, 5mg/ml Concentrate for solution for infusion, contains

- The active substance is oxaliplatin. 1ml of concentrate contains 5mg of oxaliplatin.

50mg vial: Each vial contains 50mg of oxaliplatin in 10ml.
100mg vial: Each vial contains 100mg of oxaliplatin in 20ml.
200mg vial: Each vial contains 200mg of oxaliplatin in 40ml.

- The other ingredients are water for injections and gluconolactone.

What Oxaliplatin Hikma, 5mg/ml Concentrate for solution for infusion, looks like and contents of the pack

Concentrate for solution for infusion
Oxaliplatin Hikma, 5mg/ml Concentrate for solution for infusion, is a clear, colourless liquid.
Pack sizes: 1 vial containing 50mg, 100mg or 200mg of oxaliplatin in 10ml, 20ml or 40ml.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

Hikma Farmacêutica (Portugal), S.A.
Estrada do Rio da Mó nºs 8, 8A e 8B -Fervença
2705-906 Terrugem SNT Portugal
Tel.: 21-960 84 10
Fax: 21-961 51 02
e-mail: geral@hikma.pt

Manufacturer:
PLIVA – Lachema a.s., Brno, Czech Republic

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria:	Oxaliplatin Hikma, 5 mg/ml Konzentrat zur Herstellung einer Infusionslösung
Germany:	Riboxatin-L, 5 mg/ml Konzentrat zur Herstellung einer Infusionslösung
Portugal:	Oxaliplatina Hikma, 5mg/ml Concentrado para solução para perfusão
Slovakia:	Oxaliplatin Hikma, 5mg/ml Infuzny Koncentrát
The Netherlands:	Oxaliplatine Hikma, 5 mg/ml Concentraat voor oplossing voor infusie
United Kingdom:	Oxaliplatin Hikma, 5mg/ml Concentrate for solution for infusion

This leaflet was last approved in {MM/YYYY}.

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

GUIDELINES FOR THE PREPARATION AND USE OF OXALIPLATIN HIKMA, 5MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

It is important to read all of the contents of these guidelines before the preparation and use of the medicinal product Oxaliplatin Hikma, 5mg/ml Concentrate for solution for infusion.

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 nursing or medical 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 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 not to handle 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 section "Disposal".

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

If oxaliplatin concentrate or infusion solution 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 5% glucose 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, especially 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 (as calcium folinate or sodium folinate)

Oxaliplatin 85 mg/m^2 IV infusion in 250 to 500ml of 5% glucose solution is given at the same time as folinic acid IV infusion in 5% glucose 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 can only be diluted using isotonic 5% glucose 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.
This medicinal product is for single use only. Any unused concentrate should be discarded.

Dilution before infusion

Withdraw the required amount of concentrate from the vial(s) and dilute with 250 to 500ml of a 5% glucose solution to give an oxaliplatin concentration between 0.2mg/ml and 0.7mg/ml.

Administer by IV 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.

NEVER use sodium chloride or chloride containing solutions for dilution.

Infusion

The administration of oxaliplatin does not require prehydration.

Oxaliplatin diluted in 250 to 500 ml of a 5% glucose 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 and with due regard to current laws related to the disposal of hazardous waste.

Storage

Unopened vial:
Keep the vial in the outer carton in order to protect from light.
Do not freeze.

Diluted product:
After dilution in 5% glucose, chemical and physical in-use stability has been demonstrated for 48 hours at +2°C to +8°C and for 24 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.

Module 4

Labelling

Text version

Initial Proposed label plus proposed revisions (using track-changes function) CARTON; VIALS 20ml and 40ml
1. NAME OF THE MEDICINAL PRODUCT Oxaliplatin 5mg/ml Concentrate for solution for infusion Oxaliplatin
2. STATEMENT OF ACTIVE SUBSTANCE(S) 1ml contains 5mg of oxaliplatin One vial of 10 ml of concentrate for solution for infusion contains 50 mg of oxaliplatin. One vial of 20 ml of concentrate for solution for infusion contains 100 mg of oxaliplatin. One vial of 40 ml of concentrate for solution for infusion contains 200 mg of oxaliplatin
3. LIST OF EXCIPIENTS Excipients: water for injections, gluconolactone
4. PHARMACEUTICAL FORM AND CONTENTS Concentrate for solution for infusion 1 vial, 50mg/10ml 1vial, 100mg/20ml 1 vial, 200mg/40ml
5. METHOD AND ROUTE(S) OF ADMINISTRATION For intravenous use only. Must be diluted before use. Read the package leaflet before use.
6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN Keep out of the reach and sight of children.
7. OTHER SPECIAL WARNING(S), IF NECESSARY Cytostatic agent
8. EXPIRY DATE EXP Read the leaflet for the shelf-life after dilution.
9. SPECIAL STORAGE CONDITIONS Keep the vial in the outer carton in order to protect from light. Do not freeze
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE Any unused product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER Hikma Farmacêutica (Portugal), S.A. Estrada do Rio da Mó n^{os} 8, 8A e 8B -Fervença 2705-906 Terrugem SNT Portugal
12. MARKETING AUTHORISATION NUMBER(S) PL 15413/0024
13. BATCH NUMBER Lot
14. GENERAL CLASSIFICATION FOR SUPPLY Medicinal product subject to medical prescription.
15. INSTRUCTIONS ON USE
16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS VIAL – 10ml
1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION Oxaliplatin 5mg/ml Concentrate for solution for infusion Oxaliplatin For IV use only
2 METHOD OF ADMINISTRATION
3. EXPIRY DATE EXP
4. BATCH NUMBER Lot
5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT 50mg/10ml
6. OTHER Cytostatic agent

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Hikma Farmacêutica (Portugal), S.A. a Marketing Authorisation for the medicinal product, Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion (PL 15413/0024, UK/H/2713/001/DC) on 29th January 2010. The product is a prescription-only medicine.

This is an abridged application for Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion, submitted under Article 10.1 of Directive 2001/83 EC, as amended. The application refers to the reference medicinal product Eloxatin 5 mg/ml powder for solution for infusion (Eloxatine 5 mg/ml, Poudre pour solution pour perfus), which has been registered to Sanofi Aventis, France, since 1996. The reference product has been authorised in the EEA for more than 10 years, hence the period of data exclusivity has expired.

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

Oxaliplatin is an alkylating agent and platinum analogue consisting of platinum bound to oxalate and diaminocyclohexane (DACH) complex. Oxaliplatin forms interstrand and intrastrand cross links with DNA, inhibiting DNA synthesis and resulting in cell death. The use of Oxaliplatin has been investigated in a number of malignancies including colorectal cancer, ovarian cancer, mesothelioma, breast cancer, non-Hodgkin's lymphoma, glioblastoma and pancreatic cancer. In patients with colorectal cancer, a synergistic combination of Fluorouracil/Leucovorin/Oxaliplatin (FOLFOX) has emerged as a standard treatment regimen. The pharmacokinetics of individual active compounds have not been determined. Common adverse reactions associated with Oxaliplatin include neurotoxicity, gastrointestinal disturbances, ototoxicity and myelosuppression.

The drug product is presented as a clear colourless concentrate for solution for infusion. The solution is intended for administration by intravenous infusion after dilution in 5 % glucose between 0.20 mg/ml and 0.70 mg/ml. The product is not for self-administration; it will be administered to the patient by a healthcare professional.

No new preclinical or clinical studies were conducted, which is acceptable given that this is a generic application cross-referring to a product that has been licensed for over 10 years. Bioequivalence studies are not necessary to support this application for a parenteral product.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. 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.

The RMS considers that the pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation holder (MAH) has provided adequate justification for not submitting a Risk Management Plan (RMP) and Environmental Risk Assessment (ERA). The lack of an Environmental Risk Assessment is justified since the application is for a generic version of an approved product and it is not likely to change the total market of oxaliplatin.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion
Name(s) of the active substance(s) (INN)	Oxaliplatin
Pharmacotherapeutic classification (ATC code)	Other antineoplastic agents, platinum compounds (L01X A03)
Pharmaceutical form and strength(s)	Concentrate for solution for infusion 5 mg / ml
Reference numbers for the Mutual Recognition Procedure	UK/H/2713/001/DC
Reference Member State	United Kingdom
Member States concerned	AT, DE, NL, PT and SK
Marketing Authorisation Number(s)	PL 15413/0024
Name and address of the authorisation holder	Hikma Farmacêutica (Portugal), S.A. Estrada do Rio da Mó n^{os} 8, 8A e 8B - Fervença 2705-906 Terrugem SNT Portugal

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

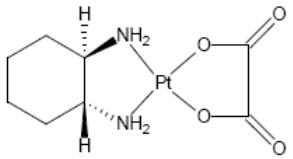
ACTIVE SUBSTANCE

Oxaliplatin

Nomenclature:

INN:	Oxaliplatin
Chemical name:	[(1*R*,2*R*)-1,2-cyclohexanediamine-*N*,*N'*][oxalato(2-)-*O*,*O'*]-platinum(II)Cis-oxalato(*trans-L*-1,2-cyclohexanediammine)Pt(II) complex

Structure:



Molecular formula:	$C_8H_{14}N_2O_4Pt$
Molecular weight:	397.29 g/mol
CAS No:	61825-94-3
Physical form:	A white or almost white crystalline powder
Solubility:	Slightly soluble in water, poorly soluble in common solvents (alcohol, acetone, ether)

The active substance, oxaliplatin, is the subject of a European Pharmacopeia (Ph. Eur.) monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

An appropriate specification has been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided for 3 batches and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in brown Type III glass bottles (1000 ml) with screw cap and polyethylene fixing inset. Relevant specifications and satisfactory Certificates of Analysis are provided for the packaging components. Appropriate declarations have been provided stating that the primary packaging components comply with the food contact requirements of Directive 2002/72/EC, (as amended).

Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and support the retest period of 24 months, when stored below 25 °C and protected from light.

DRUG PRODUCT

Description & Composition

The drug product is presented as a clear colourless concentrate for solution for infusion. Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion is available in three proportionally formulated strengths: 50 mg/10 ml, 100 mg/20 ml, and 200 mg/40 ml. All strengths contain 5 mg of oxaliplatin per ml.

Other ingredients consist of the pharmaceutical excipients, water for injections and gluconolactone. Appropriate justification for the inclusion of these excipients has been provided. Water for injections complies with its European Pharmacopoeia monograph and gluconolactone complies with its US Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

The MAH has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product. Satisfactory TSE declarations have been provided for Gluconolactone.

There were no novel excipients used and no overages.

Impurity profiles

Comparative impurity profiles were provided for test and reference products. The impurity profiles were found to be similar, with all impurities within the specification limits.

Pharmaceutical development

Details of the pharmaceutical development of the drug product have been supplied and are satisfactory. The physiochemical properties of the drug product were compared with the originator product and found to be comparable.

Manufacture

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

In-process controls are appropriate considering the nature of the product and the method of manufacture.

Process validation data are provided for two commercial scale batches of each presentation for the main steps of the manufacturing process. All results are consistent and well within the acceptable limits. The MAH has committed to perform the validation of the full manufacturing process on full scale production batches prior to commercialization of Oxaliplatin 5 mg/ml product. This is acceptable.

Finished product specification

The finished product specifications are provided for both release and shelf life and are satisfactory; they provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory Certificates of Analysis have been provided for two full-scale batches of each of the product presentations. All parameters are well within specification and comparable. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The drug product is presented in clear, colourless Type I glass vials, closed with bromobutyl rubber stoppers aluminium caps and flip-off polypropylene covers. The vials contain 10ml, 20ml, or 40ml of concentrate for solution for infusion containing 50mg, 100mg, or 200mg of oxaliplatin respectively, to give a concentration of 5mg / ml.

The vials are packaged individually with the Product Information Leaflet (PIL) into cardboard outer cartons. The MA Holder has stated that not all pack sizes may be marketed. The vials satisfy Directive 2002/72/EC (as amended), and are suitable for contact with parenteral preparations. Specifications and Certificates of Analysis for all packaging components used have been provided, and are satisfactory.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. Storage instructions are “Keep the vial in the outer carton in order to protect from light. Do not freeze”.

For storage conditions and advice for use and handling of the diluted medicinal product, refer to the SmPC. Acceptable in-use stability studies were conducted and the results provided to support the statements made in the SmPC. The SmPC also contains information on disposal of the product and contaminated materials.

Bioequivalence Study

Bioequivalence studies are not necessary to support this application for a parenteral product.

Expert Report

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Product Information

The approved SmPC, and leaflet and labelling texts are satisfactory.

Conclusion

The proposed product, Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion, has been shown to be a generic version of the reference product, Eloxatin 5 mg/ml powder for solution for infusion (Sanofi Aventis, France), because both products contain the same quantitative and qualitative composition of the active ingredient, oxaliplatin, and at the time of administration, the test and reference solutions are identical. The test product is pharmaceutically equivalent to the reference product, which has been licensed in the UK for over 10 years. Given the route of administration it is not necessary to demonstrate bioequivalence of the proposed product to the reference product.

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. A Marketing Authorisation was therefore granted.

III.2 PRE-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable for this application for a generic version of a product that has been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic, and toxicological properties of oxaliplatin, which is a widely used and well-known active substance. The CV of the pre-clinical expert has been supplied.

III.3 CLINICAL ASPECTS

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

The indications are consistent with those for the reference product and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

Full details concerning the posology are provided in the SmPC. The posology is consistent with that for the reference product and is satisfactory.

TOXICOLOGY

No new data have been submitted and none are required for these types of application.

CLINICAL PHARMACOLOGY

The clinical pharmacology of oxaliplatin is well known. No novel pharmacodynamic or pharmacokinetic data are supplied or required for this application.

Clinical efficacy

No new data are submitted and none are required for these types of application. Efficacy is reviewed in the clinical expert report. Satisfactory evidence to support combination and adjuvant therapy has been provided. The efficacy of oxaliplatin is well-established from its extensive use in clinical practice.

Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion is to be administered as an aqueous intravenous solution and contains the same active substance, in the same concentration, as the currently authorised reference product Eloxatin 5 mg/ml powder for solution for infusion (Sanofi Aventis, France). At the time of administration, the test and reference solutions are identical. Thus, in accordance with the "Note for Guidance on the Investigation of Bioavailability and Bioequivalence", (CPMP/EWP/QWP/1401/98), the applicant was not required to submit a bioequivalence study.

Clinical safety

Oxaliplatin has an acceptable adverse events profile. No novel safety data are supplied or required for this generic application. Oxaliplatin has a well established side-effect profile and is generally well-tolerated. The MAH has provided a review of clinical trials published in the literature confirming the safety of oxaliplatin.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPC is consistent with that for the reference product and is acceptable.

Product Information Leaflet (PIL)

The final PIL text is in line with the approved SmPC and is satisfactory.

Labelling

The labelling text is satisfactory.

Expert report

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Periodic Safety Update Report (PSUR)

The RMS recommends PSUR submissions to be aligned with the EU Harmonised Birthday and related Data Lock Points as published on the HMA website and recommends submission of three yearly PSURs.

CONCLUSIONS

The grounds for establishing the proposed product, Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion, as a generic version of the reference product, Eloxatin 5 mg/ml powder for solution for infusion (Sanofi Aventis, France), are considered adequate. The product literature is approved.

Sufficient clinical information has been submitted to support this application. All issues have been adequately addressed by the MAH. When used as indicated, Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion has a favourable benefit-to-risk ratio. The granting of a Marketing Authorisation was therefore recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Oxaliplatin 5 mg/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

The applicant's Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion has been demonstrated to be a generic version of the reference product Eloxatin 5 mg/ml powder for solution for infusion (Sanofi Aventis, France). At the time of administration, the test and reference solutions are identical.

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE

The text of the approved SmPC is satisfactory and consistent with that of the reference product.

The final PIL and labelling texts are satisfactory and consistent with those for the reference product and with the approved SmPC.

A user consultation with target patient groups on the package information leaflet (PIL) text has been performed on the basis of a bridging report making reference to Oxaliplatin Pliva 5 mg/ml Powder for solution for infusion, CZ/H/0146/MR. The bridging report submitted by the applicant has been found acceptable.

The Marketing Authorisation Holder (MAH) has committed to submitting mock-ups for all packaging for assessment before packs are commercially marketed.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant's Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion is a generic version of the reference product, Eloxatin 5 mg/ml powder for solution for infusion (Sanofi Aventis, France). Extensive clinical experience with oxaliplatin is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit ratio is therefore considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

There have been no variation applications submitted after approval of the initial procedure.

Date submitted	Application type	Scope	Outcome