Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Oxaliplatin 5mg/ml, Powder for Solution for Infusion

UK/H/1308/01/DC
UK licence no: PL 20075/0096

Accord Healthcare Limited

LAY SUMMARY

The Medicines Healthcare products Regulatory Agency granted Accord Healthcare Limited a Marketing Authorisation (licence) for the medicinal product Oxaliplatin 5mg/ml Powder for Solution for Infusion. This is a prescription-only medicine for the treatment of advanced cancer of the colon or rectum, or as additional treatment following surgery to remove a tumour in the colon.

The active ingredient, oxaliplatin, is an anticancer drug. It works by preventing further abnormal cell growth.

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

TABLE OF CONTENTS

Module 1: Information about initial procedure		Page 4
Module 2: Summary of Product Characteristics		Page 5
Module 3: Product Information Leaflet		Page 19
Module 4: Labelling		Page 23
Module 5: Scientific Discussion		Page 24
	1 Introduction	Page 24
	2 Quality aspects	Page 26
	3 Pre-clinical aspects	Page 27
	4 Clinical aspects	Page 27
	5 Overall conclusions	Page 29
Module 6	Steps taken after initial procedure	Page 30

Module 1

Product Name	Oxaliplatin 5mg/ml Powder for Solution for Infusion
Type of Application	Generic, Article 10.1
Active Substance	Oxaliplatin
Form	Powder for solution for infusion,
Strength	5mg/ml
MA Holder	Accord Healthcare Limited
RMS	UK
CMS	Germany, Denmark, Italy, The Netherlands, Poland, Portugal, Romania, Sweden and Spain.
Procedure Number	UK/H/1308/001/DC
Timetable	Day 210 – 15th July 2008

Module 2
Summary of Product Characteristics

The UK Summary of Product Characteristics (SPC) for Oxaliplatin 5mg/ml Powder for Solution for Infusion are as follows:

1 NAME OF THE MEDICINAL PRODUCT

Oxaliplatin 5 mg /ml, Powder for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of reconstituted solution contains oxaliplatin 5 mg.
Each vial contains 100 mg oxaliplatin.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion.
A white to off-white powder

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 tumor
- Treatment of metastatic colorectal cancer.

4.2 Posology and method of administration

The preparation of injectable solutions of cytotoxic agents must be carried out by trained specialist personnel with knowledge of the medicinal product used, in conditions that guarantee the integrity of the medicinal product, the protection of the environment and in particular the protection of the personnel handling the medicinal products, in accordance with hospital policy. It requires a preparation area reserved for this purpose. It is forbidden to smoke, eat or drink in this area.

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 (5 FU).
Oxaliplatin powder for solution for infusion 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 powder for solution for infusion 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 powder for solution for infusion is administered by intravenous infusion.
The administration of Oxaliplatin powder for solution for infusion does not require hyperhydration.

Oxaliplatin powder for solution for infusion is 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 the administration of 5-fluorouracil.
In the event of extravasation, administration must be discontinued immediately.
Instructions for use:
Oxaliplatin powder for solution for infusion must be reconstituted and further diluted before use. Only glucose 5% (50 mg/ml) diluent is to be used to reconstitute and then dilute the freeze-dried medicinal product. (See section 6.6).

4.3 Contraindications

Oxaliplatin is contraindicated in patients who
- have a 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 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 for Injection 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 (see section 4.8).
In cases of abnormal liver function test results or portal hypertension, which does not obviously result from liver metastases, very rare cases of drug induced hepatic vascular disorders should be considered.
For use in pregnant women see section 4.6.
Genotoxic effects were observed with oxaliplatin in the preclinical studies. Therefore male patients treated with oxaliplatin are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment, because oxaliplatin may have an anti-fertility effect which could be irreversible.
Women should not become pregnant during treatment with oxaliplatin and should use an effective method of contraception (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Pregnancy and lactation

To date there is no available information on safety of use in pregnant women. In animal studies, reproductive toxicity was observed. Consequently Oxaliplatin for Injection is not recommended during pregnancy and in women of childbearing potential not using contraceptive measures. The use of Oxaliplatin for Injection 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 for Injection therapy.
Oxaliplatin may have an anti-fertility effect (see section 4.4).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machinery have been performed. However, oxaliplatin treatment resulting in an increased risk of dizziness, nausea and vomiting, and other neurologic symptoms that affect gait and balance may lead to a minor or moderate influence on the ability to drive and use machines.

4.8 Undesirable effects

The most frequent adverse events of oxaliplatin in combination with 5-fluorouracil/folinic acid (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 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 Class	Very common	Common	Uncommon	Rare
Infections and infestations*	- Infection	- Rhinitis - Upper respiratory tract infection - Neutropenic sepsis		
Blood and lymphatic system disorders*	- Anaemia - Neutropenia - Thrombocytopenia - Leukopenia - Lymphopenia	-Febrile neutropenia		Immunoallergic thrombocytopenia - Haemolytic anaemia
Immune system disorders*	- Allergy/allergic reaction+			
Metabolism and nutrition disorders	- Anorexia Glycemia 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
SEye disorders		- Conjunctivitis - Vision _disturbance		- Visual acuity reduced transiently - Visual field disturbances - Optic neuritis
Ear and labyrinth disorders			- Ototoxicity	- Deafness
Vascular disorders	- Epistaxis	- Haemorrhage - Flushing - Deep vein thrombosis - Pulmonary embolism		

MedDRA Organ System Class	Very common	Common	Uncommon	Rare
Respiratory, thoracic and mediastinal disorders	- Dyspnoea - Coughing	- Hiccups		- Interstitial lung disease - Pulmonary fibrosis**
Gastointestinal disorders*	- Nausea - Diarrhoea - Vomiting - Stomatitis/ mucositis - Abdominal pain - Constipation	- Rectal haemorrhage - Dyspepsia - Gastroesophageal reflux	- 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		
Musculoskeletal, 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	- Blood Creatinine increase - Weight decrease (metastatic setting)		

MedDRA Organ System Class	Very common	Common	Uncommon	Rare
	- Weight increase (adjuvant setting)			

* See detailed section below
** See section 4.4 'Special warnings and precaution for use'
+ Common allergic reactions such as skin rash (particularly urticaria), conjunctivitis, rhinitis. Common anaphylactic reactions, including broncospasm, 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 side reaction including local pain, redness, swelling and thrombosis has 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 section 4.4).
-

Hepatobiliar disorders
Very common (≥1/10): Increase of hepatic enzymes
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 (<1/10,000*):*
Acute tubulo-interstitial nephropathy leading to acute renal failure.
Haematological toxicity:
Incidence by patient (%), by grade

Oxaliplatin / 5 FU/FA 85 mg/m² every 2 weeks	**Metastatic setting**			**Adjuvant setting**		
	All grades	**gr 3**	**gr 4**	**All** grades	**gr 3**	**gr4**
Anaemia	82.2	3	<1	75.6	0.7	0.1
Neutropenia	71.4	28	14	78.9	28.8	12.3
Thrombocyto-penia	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/ 5 FU/FA **85 mg/m² every 2 weeks**	**Metastatic setting**			**Adjuvant setting**		
	All grades	**gr 3**	**gr 4**	All grades	**gr 3**	**gr 4**
Nausea	69.9	8	<1	73.7	4.8	0.3
Diarrhoea	60.8	9	2	56.3	8.3	2.5
Vomiting	49.0	6	1	47.2	5.3	0.5
Mucositis/ Stomatitis	39.9	4	<1	42.1	2.8	0.1

Prophylaxis and/or treatment with potent antiemetic agents is indicated.
Dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis particularly when combining oxaliplatin with 5-fluorouracil (see section 4.4).
Nervous system:
The dose limiting toxicity of oxaliplatin is neurological. It involves a sensory peripheral neuropathy characterised by dysaesthesia and/or 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 localized paresthesias of moderate intensity (2.3%) or with paresthesias that may interfere with functional activities (0.5%).
Acute neurosensory manifestations (see section 5.3) have been reported. They start within hours of administration and often occur on exposure to cold. They usually present as transient paresthesia, dysesthesia and hypoesthesia. An acute syndrome of pharyngolaryngeal dysesthesia occurs in 1% - 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).
Occassionally 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.

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

Oxaliplatin / 5 FU/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 randomized 420 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 three arms phase III study EFC4584 study randomized 821 patients refractory to an irinotecan (CPT-11) + 5-fluorouracil/folinic combination either to 5-fluorouracil/folinic acid alone (LV5FU2, N=275), oxaliplatin single agent, or combination of oxaliplatin with 5-fluorouracil/folinic (FOLFOX4, N=271)
- Finally, the non controlled phase II EFC2964 study included patients refractory to 5-fluorouracil/folinic acid alone, that were treated with the oxaliplatin and 5-fluorouracil/folinic acid combination (FOLFOX4, N=57)

The two randomized clinical trials, EFC2962 in front-line therapy and EFC4584 in pretreated patients, demonstrated a significantly higher response rate and a prolonged progression free survival (PFS)/time to progression (TTP) as compared to treatment with 5-fluorouracil/folinic acid alone. IN 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	22 (16-27)	49 (42-46)	NA*

Response rate % (95% CI) **Independent radiological review ITT analysis**	LV5FU2	FOLFOX4	**Oxaliplatin** **Single agent**
Response assessment every 8 weeks	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*

Median Progression Free Survival (PFS) / Median Time to Progression (TTP) FOLFOX4 versus LV5FU2

Median PFS/TTP, **Months (95% CI)** **Independent radiological review ITT analysis**	LV5FU2	**FOLFOX4**	**Oxaliplatin** **Single agent**
Front-line treatment EFC2962 (PFS)	6.0 (5.5-6.5)	8.2 (7.2-8.8)	NA*
	Log-rank P value = 0.0003		
Pretreated patients EFC4584 (TTP) (refractory to CPT-11 + 5FU/FA)	2.6 (1.8-2.9)	5.3 (4.7-6.1)	2.1 (1.6-2.7)
	Log-rank P value < 0.0001		
Pretreated patients EFC2964 (refractory to 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, no statistical 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 comparative MOSAIC phase III study (EFC3313) randomised 2246 patients (899 stage II/ Duke's B2 and 1347 stage III/ Duke's C) further to complete resection of the primary tumor of colon cancer either to 5-FU/FA alone (LV5FU2 N=1123, B2/C = 448/675) or to combination of oxaliplatin and 5-FU/FA (FOLFOX 4 N =1123, B2/C = 451/672)

EFC 3313 3-year disease free survival (ITT analysis)* for the overall population.

Treatment arm	**LV5FU2**	**FOLFOX4**
Percent 3-year disease free survival (95 % CI)	73.3 (70.6-75.9)	78.7 (76.2-81.1)
Hazard ratio (95 % CI)	0.76 (0.64-0.89)	
Stratified log rank test	P=0.0008	

* median follow up 44.2 months (all patients followed for at least 3 years)

The study demonstrated an overall significant advantage in 3-year disease free survival for the oxaliplatin and 5 FU/FA combination (FOLFOX4) over 5 FU/FA alone (LV5FU2).

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

Patient stage	**Stage II (Duke's B2)**		**Stage III (Duke's C)**	
Treatment arm	LV5FU2	FOLFOX4	LV5FU2	FOLFOX4
Percent 3-year disease free survival (95 % CI)	84.3 (80.9-87.7)	87.4 (84.3-90.5)	65.8 (62.2-69.5)	72.8 (69.4-76.2)
Hazard ratio (95 % CI)	0.79 (0.57-1.09)		0.75 (0.62-0.90)	
Log-rank test	P=0.151		P=0.002	

* median follow up 44.2 months (all patients followed for at least 3 years)

Overall Survival (ITT analysis)
At time of the analysis of the 3-year disease free survival, which was the primary endpoint of the MOSAIC trial, 85.1 % of the patients were still alive in the FOLFOX4 arm versus 83.8 % in the LV5FU2 arm. This translated into an overall reduction in mortality risk of 10 % in favor of FOLFOX4 not reaching statistical significance (hazard ratio = 0.90).
The figures were 92.2 % versus 92.4 % in the Stage II (Duke's B2) sub-population (hazard ratio = 1.01) and 80.4 % versus 78.1 % in the Stage III (Duke's C) sub-population (hazard ratio = 0.87), for FOLFOX4 and LV5FU2, respectively.

5.2 Pharmacokinetic properties

The pharmacokinetics of individual active compounds have not been determined. The pharmacokinetics of ultrafiltrable platinum, representing a mixture of all unbound, active and inactive platinum species, following a two-hour infusion of oxaliplatin at 130 mg/m² every three weeks for 1 to 5 cycles and oxaliplatin at 85 mg/m² every two weeks for 1 to 3 cycles are as follows :
Summary of Platinum Pharmacokinetic Parameter Estimates in Ultrafiltrate
Following Multiple Doses of Oxaliplatin at 85 mg/m^2 every two weeks or at 130 mg/m^2 every three weeks

Dose	Cmax	AUC0-48	AUC	$t_{1/2\alpha}$	$t_{1/2\beta}$	$t_{1/2\gamma}$	Vss	CL
	µg/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 by non-compartmental analysis. $t_{1/2\alpha}$, $t_{1/2\beta}$, and $t_{1/2\gamma}$, were determined by compartmental analysis (Cycles 1-3 combined).

At the end of a 2-hour infusion, 15% of the administered platinum is present in the systemic circulation, the remaining 85% being rapidly distributed into tissues or eliminated in the urine. Irreversible binding to red blood cells and plasma, results in half-lives in these matrices that are close to the natural turnover of red blood cells and serum albumin. No accumulation was observed in plasma ultrafiltrate following 85 mg/m^2 every two weeks or 130 mg/m^2 every three weeks and steady state was attained by cycle one in this matrix. Inter- and intra-subject variability is generally low.
Biotransformation *in vitro* is considered to be the result of non-enzymatic degradation and there is no evidence of cytochrome P450-mediated metabolism of the diaminocyclohexane (DACH) ring.
Oxaliplatin undergoes extensive biotransformation in patients, and no intact 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 excipients

Lactose monohydrate

6.2 Incompatibilities

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

- DO NOT mix with alkaline medicinal products or solutions, in particular 5-fluorouracil, folinic acid preparations containing trometamol as an excipient and trometamol salts of other active substances. Alkaline medicinal products or solutions will adversely affect the stability of oxaliplatin (see section 6.6).
- DO NOT reconstitute or dilute oxaliplatin with saline or other solutions containing chloride ions (including calcium, potassium or sodium chloride).
- DO NOT mix with other medicinal products in the same infusion bag or infusion line (see section 6.6 for instructions concerning simultaneous administration with folinic acid).
- DO NOT use injection equipment containing aluminium

6.3 Shelf life

Medicinal product as packaged for sale : 2 years.
Reconstituted solution in the original vial : From a microbiological and chemical point of view, the reconstituted solution should be diluted immediately.
Infusion preparation : Store at 2ºC to 8ºC for not longer than 24 hours. 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

Medicinal product as packaged for sale: This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

50 ml glass vial closed with chlorobutyl rubber stopper and sealed with 20 mm aluminium flip off lavender seal, containing 100 mg of oxaliplatin.
Pack size: 1 vial per carton

6.6 Special precautions for disposal

As with other potentially toxic compounds, caution should be exercised when handling and preparing oxaliplatin solutions.

Instructions for Handling

The handling of this cytotoxic agent by healthcare personnel requires every precaution to guarantee the protection of the handler and his surroundings.
The preparation of injectable solutions of cytotoxic agents must be carried out by trained specialist personnel with knowledge of the medicines used, in conditions that guarantee the integrity of the medicinal product, the protection of the environment and in particular the protection of the personnel handling the medicines, in accordance with the hospital policy. It requires a preparation area reserved for this purpose. It is forbidden to smoke, eat or drink in this area.
Personnel must be provided with appropriate handling materials, notably long sleeved gowns, protection masks, caps, protective goggles, sterile single-use gloves, protective covers for the work area, containers and collection bags for waste.
Excreta and vomit must be handled with care.
Pregnant women must be warned to avoid handling cytotoxic agents.
Any broken container must be treated with the same precautions and considered as contaminated waste. Contaminated waste should be incinerated in suitably labelled rigid containers. See below chapter “Disposal”.
If Oxaliplatin powder, reconstituted solution or solution for infusion, should come into contact with skin, wash immediately and thoroughly with water.
If Oxaliplatin powder, reconstituted solution 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 % (50 mg/ml) infusion solution is to be used as a diluent. DO NOT reconstitute or dilute for infusion with sodium chloride or chloride containing solutions.
- DO NOT mix with any other medicinal products in the same infusion bag or administer simultaneously by the same infusion line
- DO NOT mix with alkaline medicinal products or solutions, in particular 5 fluorouracil, folinic acid preparations containing trometamol as an excipient and trometamol salts of others active substances. Alkaline medicinal products or solutions will adversely affect the stability of oxaliplatin

Instruction for use with folinic acid (FA) (as calcium folinate or disodium folinate)

Oxaliplatin 85 mg/m² intravenous infusion in 250 to 500 ml of glucose 5 % (50 mg/ml) solution is given at the same time as folinic acid (FA) intravenous infusion in glucose 5 % (50 mg/ml) 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 % (50 mg/ml) 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 reconstituted solution 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).

Reconstitution of the solution

Water for injections or 5% glucose solution should be used to reconstitute the solution.

- For a vial of 100 mg: add 20 ml of solvent to obtain a concentration of 5 mg oxaliplatin/ml.

From a microbiological and chemical point of view, the reconstituted solution should be diluted immediately with 5% glucose solution.
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 reconstituted solution from the vial(s) and then dilute with 250 ml to 500 ml of a 5% glucose solution to give an oxaliplatin concentration between not less than 0.2 mg/ml and 0.7 mg/ml. The concentration range over which the physico-chemical stability of oxaliplatin has been demonstrated is 0.2 mg/ml to 2 mg/ml.

Administer by intravenous infusion.

After dilution in glucose 5 % (50 mg/ml) solution, chemical and physical in-use stability has been demonstrated at 2°C to 8°C. From a microbiological point of view, this infusion preparation should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C unless dilution has taken place in controlled and validated aseptic conditions.

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

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 solution or chloride containing solutions for either reconstitution or 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 reconstitution, 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

Accord Healthcare Limited
Sage House
319, Pinner Road
North Harrow
Middlesex, HA1 4HF
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0096

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/09/2008

10 DATE OF REVISION OF THE TEXT

11/09/2008

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Module 3
PATIENT INFORMATION LEAFLET

accord

PACKAGE LEAFLET: INFORMATION FOR THE USER

Oxaliplatin 5 mg/ml powder for solution for infusion

Oxaliplatin

Read all of this leaflet carefully before you start using this medicine
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- 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 powder for solution for infusion is and what it is used for
2. Before you are given Oxaliplatin powder for solution for infusion
3. How Oxaliplatin powder for solution for infusion is given
4. Possible side effects
5. How to store Oxaliplatin powder for solution for infusion
6. Further information

1. What Oxaliplatin Powder for solution for infusion is and what it is used for

Oxaliplatin is an anti-cancer drug and is used to treat metastatic (advanced) cancer of the colon (large bowel) or rectum (back passage), or as additional treatment following surgery to remove a tumour (growth) in the colon.

It is used in combination with other anti-cancer medicines called 5-fluorouracil (5-FU) and folinic acid (FA).

2. Before you are given Oxaliplatin for solution for infusion

You should not be given Oxaliplatin powder for solution for infusion
- if you are allergic (hypersensitive) to Oxaliplatin or any of the other ingredients of the Oxaliplatin powder for solution for infusion including lactose monohydrate
- if you already have a reduced number of blood cells
- if you breast feeding
- 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 severe kidney problems

Take Special care with Oxaliplatin powder for solution for infusion
- if you have ever suffered an allergic reaction to platinum-containing medicines such as carboplatin, cisplatin
- if you have moderate kidney problems
- if you have any liver problems
- if blood cell counts are too low after previous oxaliplatin treatment. Your doctor will perform tests to check that you have sufficient blood cells before treatment.
- if you have symptoms of nerve damage such as weakness, numbness, disturbances of feeling or taste 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 carry out neurological examinations, before and regularly during treatment, especially if you are given other drugs which may cause nerve damage. Symptoms of nerve damage can persist after the end of the treatment.
- if you also receive 5-fluorouracil, because the risk of diarrhoea, vomiting, sore mouth and blood abnormalities is increased.

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.

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

Pregnancy and breast-feeding:
Pregnancy
You must not be treated with oxaliplatin unless clearly indicated by your doctor. 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.

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

Driving and using machines
Oxaliplatin treatment results in an increased risk of dizziness, nausea and vomiting, and other neurologic symptoms that affect gait and balance which may lead to a minor or moderate influence on the ability to drive and use machines.
Do not drive or use machines until you are sure of how Oxaliplatin affects you.

3. How Oxaliplatin powder for solution for infusion is given

Oxaliplatin powder for solution for infusion should only be used in specialised departments of cancer treatment and should be administered under the supervision of an experienced specialist in cancer treatment.

Oxaliplatin for powder for solution for infusion is only to be given to adults.

Oxaliplatin is given by injection into a vein (an intravenous infusion) over a 2 to 6 hour period. The injection is first made by mixing the powder with a small amount of water or glucose solution. This is then diluted further in approximately 250 to 500 ml of glucose solution.
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**.

Oxaliplatin for infusion will be made up in a special area before the doctor or nurse gives it to you.
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 once every 2 weeks before the infusion of the other anticancer medicines.

The dose you receive will also depend on results of blood tests and whether you have previously experienced side effects with Oxaliplatin for powder for solution for infusion.

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 powder for solution for infusion than you should
Your doctor will ensure that the correct dose for your condition is given. In case of an overdose, you may experience increased side effects. Your doctor will monitor your blood counts carefully and will treat your symptoms.

If you missed a dose of Oxaliplatin powder for solution for infusion
Oxaliplatin needs to be given on a fixed schedule. Be sure to keep all appointments. If you miss a dose, you should discuss this with your doctor. Your doctor will decide when you should be given your next dose of Oxaliplatin.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Oxaliplatin powder for solution for infusion can cause side effects, although not everybody gets them.
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)

The following information is intended for medical or healthcare professionals only

Instructions for use

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.

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

Oxaliplatin powder for solution for infusion 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/m².

Oxaliplatin powder for solution for infusion 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.
- In patients with moderate renal impairment, treatment may be initiated at the normally recommended dose. 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 for Injection 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 powder for solution for infusion is administered by intravenous infusion.

The administration of Oxaliplatin powder for solution for infusion does not require hyperhydration.

Oxaliplatin powder for solution for infusion is 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 the administration of 5-fluorouracil.

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

As with other potentially toxic compounds, caution should be exercised when handling and preparing Oxaliplatin solutions.

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 % (50 ml) solution is given at the same time as folinic acid (FA) intravenous infusion in glucose 5 % (50 ml) 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 % (50 ml) solution, never in alkaline solutions or sodium chloride or chloride containing solutions.

Instruction for use with 5 fluorouracil (5 FU)

Oxaliplatin for Injection 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).

- 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, problems with balance, 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
- Abnormal blood tests which show worsening in the way the kidney is working
- 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
- 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 listed in this leaflet, please tell your doctor or pharmacist

5. How to store Oxaliplatin powder for solution for infusion

Do not use Oxaliplatin powder for solution for infusion after the expiry date on the vial or carton. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions when the vial is unopened.
The reconstituted solution should be diluted immediately with 5% glucose solution to give an oxaliplatin concentration between not less than 0.2 mg/ml and 0.7 mg/ml. 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further information

What Oxaliplatin powder for solution for infusion contains:
Oxaliplatin powder for solution for infusion contains the active ingredient Oxaliplatin 100 mg, with lactose monohydrate as inactive ingredient.

What Oxaliplatin powder for solution for infusion looks like and contents of the pack:
Oxaliplatin powder for solution for infusion is a white to off white lyophilized powder in a clear glass vial.
Each glass vial is packed in individual carton.

Marketing Authorisation Holder and manufacturer:
Accord Healthcare Limited,
Sage House, 319 Pinner Road,
North Harrow HA1 4HF, UK

The leaflet was last approved in 07/2008

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 reconstituted solution 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).

Reconstitution of the solution
Water for injections or 5% glucose solution should be used to reconstitute the solution.
For a vial of 100 mg: add 20 ml of solvent to obtain a concentration of 5 mg Oxaliplatin/ml.
From a microbiological and chemical point of view, the reconstituted solution should be diluted immediately with 5% glucose solution.
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 reconstituted solution from the vial(s) and then dilute with 250 ml to 500 ml of a 5% glucose solution to give an Oxaliplatin concentration between not less than 0.2 mg/ml and 0.7 mg/ml. The concentration range over which the physico-chemical stability of Oxaliplatin has been demonstrated is 0.2 mg/ml to 2 mg/ml.

Administer by intravenous infusion.
After dilution in glucose 5 % (50 mg/ml) solution, chemical and physical in-use stability has been demonstrated at 2°C to 8°C. From a microbiological point of view, this infusion preparation should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C unless dilution has taken place in controlled and validated aseptic conditions.
NEVER use sodium chloride solution or chloride containing solutions for either reconstitution or dilution.

Infusion
The administration of Oxaliplatin for Injection does not require prehydration.
Oxaliplatin for Injection 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.

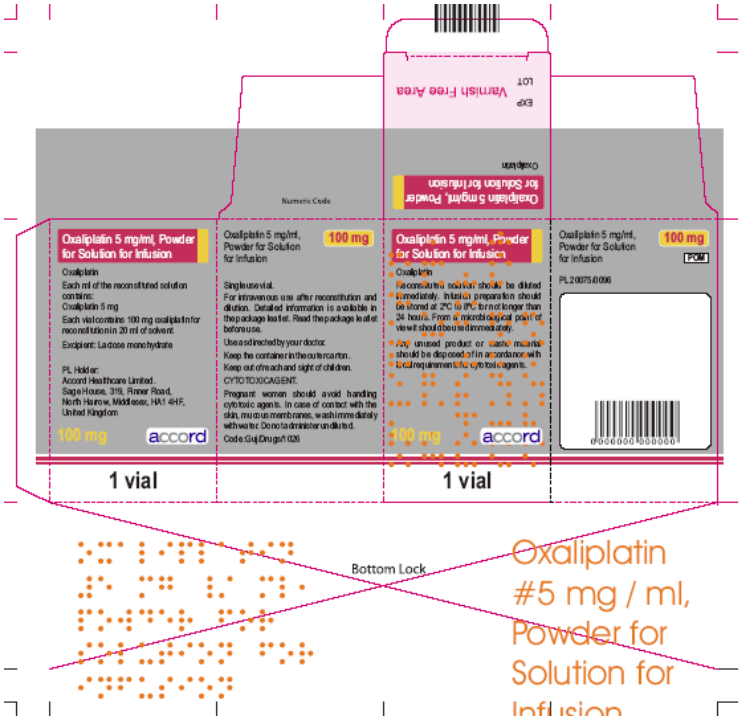
Disposal
Remnants of the medicinal product as well as all materials that have been used for reconstitution, for dilution and administration must be destroyed according to hospital standard procedures applicable to cytotoxic agents in accordance with local requirements related to the disposal of hazardous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

Incompatibilities:
This medicinal product should not be mixed with other medicinal products in the same infusion bag or infusion line, except for those mentioned in this leaflet. Oxaliplatin can be co-administered with folinic acid (FA) via a Y-line.
- DO NOT mix with alkaline medicinal products or solutions, in particular 5-fluorouracil, folinic acid preparations containing trometamol as an excipient and trometamol salts of other active substances. Alkaline medicinal products or solutions will adversely affect the stability of Oxaliplatin.
- DO NOT reconstitute or dilute oxaliplatin with saline or other solutions containing chloride ions (including calcium, potassium or sodium chloride).
- DO NOT mix with other medicinal products in the same infusion bag or infusion line.
- DO NOT use injection equipment containing aluminium.

Shelf-life
Reconstituted solution in the original vial: From a microbiological and chemical point of view, the reconstituted solution should be diluted immediately.
Infusion preparation: Store at 2ºC to 8ºC for not longer than 24 hours. From a microbiological point of view, the infusion preparation should be used immediately.

Module 4
Labelling

Carton- Pack size 50ml vial



Label

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Oxaliplatin, in the treatment of metastatic colorectal cancer and as an adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of primary tumor, is approvable.

This decentralised procedure concerns a generic version of Oxaliplatin 5 mg/ml powder for solution for infusion (UK/H/1308/01/DC). This application refers to the reference medicinal product Eloxatine 5 mg/ml powder for solution for infusion which has been authorised for 10 years in at least a Member state or in the Community. The originator product Eloxatine (5 mg/ml, powder for solution for infusion) by Sanofi Aventis France has been registered in France since the 12th of April, 1996.

The application is submitted under Article 10(1) of Directive 2001/83/EC (as amended), as a so-called 'generic application.' Concerned Member States are Denmark, Germany, Italy, The Netherlands, Poland, Portugal, Romania, Spain and Sweden.

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

The application is submitted in accordance with Article 10(1) of Directive 2001/83/EC (as amended). The submitted documentation in relation to the proposed product is of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory quality, non-clinical and clinical overviews have been submitted.

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

A Risk Management Plan has not been provided and one is not required for this generic application.

Consultation with Target Patient Groups: The applicant has carried out face to face interviews with a total of 20 test participants and readability of the package leaflet was demonstrated.

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.

No GCP certificate is required for this type of application.

No new non-clinical studies have been submitted for this application.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Oxaliplatin 5mg/ml Powder for solution for infusion
Name(s) of the active substance(s) (INN)	Oxaliplatin
Pharmacotherapeutic classification (ATC code)	L01XA03, Antineoplastic Agents
Pharmaceutical form and strength(s)	Powder for solution for infusion, 5mg/ml
Reference numbers for the Mutual Recognition Procedure	UK/H/1308/001/DC
Reference Member State	United Kingdom
Member States concerned	Denmark, Germany, Italy, The Netherlands, Poland, Portugal, Romania, Spain and Sweden.
Marketing Authorisation Number(s)	PL 20075/0096
Name and address of the authorisation holder	Accord Healthcare Limited Sage House, 319 Pinner Road, North Harrow, Middlesex, HA1 4HF, UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

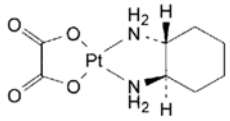
S. Active substance

General Information

Nomenclature

INN: Oxaliplatin

Structure:



Description: White to almost white, crystalline powder

Molecular formula: $C_8H_{14}N_2O_4Pt$

RMS: 397.29

Solubility: Slightly soluble in water, very slightly soluble in methanol and practically insoluble in ethanol.

Oxaliplatin is the subject of a European Pharmacopoeia monograph.

Manufacture

An Active Substance Master File (ASMF) has been provided covering the manufacture and control of the drug substance oxaliplatin. The drug substance specification complies with the Ph.Eur. monograph.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active oxaliplatin is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data have been provided and comply with the proposed specification.

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

Appropriate stability data have been generated supporting a re-test period of 48 months.

P Medicinal Product

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate which complies with its Ph. Eur monograph. A satisfactory certificate of analysis has been provided for lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

The development of the product has been described, the choice of excipient has been justified and its function explained.

Impurity profiles
Impurity profiles of the drug product were found to be similar to those for the reference product.

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. Validations of the analytical methods have been presented. Process validation has been carried out on three 16 litre batches which are within the specifications proposed; this is satisfactory. Certificates of analysis have been provided for any working standards used.

Container Closure System
The product is intended to be packed in clear 50ml type I glass vials and sealed with chlorobutyl rubber stoppers and aluminium flip-off caps. Satisfactory specifications and certificates of analysis are provided. Pack size; 1 vial per carton.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 24 months has been set with specific storage conditions, which is satisfactory.

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

The proposed product has met the requirements of a generic medicinal product with respect to qualitative and quantitative content of the active substance, and pharmaceutical form.

III.2 Non clinical aspects

The pharmacological, pharmacokinetic and toxicological properties of oxaliplatin are well known. As oxaliplatin is a well known active substance, no further studies are required and the applicant has provided none. An overview based on a literature review is thus appropriate.

The non-clinical overview has been written by a suitably qualified person with experience in clinical research and pharmacology. The overview cites 32 references from the published literature which are dated from 1979 to 2006. The overview is adequate.

Conclusions

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

III.3 Clinical aspects

Introduction

Oxaliplatin 5 mg/ml powder for solution for infusion is the generic version of Eloxatine (5 mg/ml powder for solution for infusion, Sanofi Aventis France). The use of the reference product is well-established in the EU. Both products contain the same quantitative and qualitative composition of the active ingredient, Oxaliplatin.

No new data have been submitted and none are required for this application. In keeping with CPMP guidelines, the applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product (*CPMP/EWP/1401/98, subpoint 5.1.6, Parenteral solutions*).

The clinical overview has been written by a suitably qualified person and is satisfactory. The report refers to 35 publications up to year 2006.

The indications, poslogy and method of administration stated for the product in the proposed SPC section 4.1 and 4.2 are in line with the innovator product (Eloxatin) and are satisfactory.

Clinical Pharmacology

No novel pharmacodynamic or pharmacokinetic data are supplied or required for this application. The pharmacodynamic and pharmacokinetic claims in the SPC are appropriately consistent with the innovator product. The pharmacodynamic and pharmacokinetic properties of this combination have been extensively studied in the past.

Clinical efficacy

The clinical overview describes several clinical studies which have established Oxaliplatin as an active drug, with 5-FU/FA (FOLFOX), in the treatment of colorectal cancer. Oxaliplatin has shown antitumoral activity, in vitro and in vivo, against several human colon cancer lines, including some with primary or acquired resistance to 5-FU. The use of FOLFOX as an adjuvant therapy has been shown to decrease recurrence in patients who have undergone curative surgery. The FOLFOX regimen has also been demonstrated to improve survival in patients with advanced colorectal cancer.

Clinical safety

No novel safety data are supplied or required for this generic application. However, the applicant has provided a review of clinical trials published in the literature confirming the safety of Oxaliplatin. Oxaliplatin is generally well tolerated and the toxicity associated with its use (gastrointestinal disturbance, myelosuppression, neurotoxicity) is not usually treatment limiting. No new safety data have been identified.

BENEFIT RISK ASSESSMENT

The use of Oxaliplatin is well established. It has recognised efficacy and acceptable safety. With regards to the current application, sufficient clinical information has been submitted which includes adequate review of published clinical data. The claim that this is a generic product of the brand leader can be accepted. Overall the benefit: risk analysis for Oxaliplatin is considered favourable and approval is recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The important quality characteristics of Oxaliplatin 5mg/ml Powder for Solution for Infusion is 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.

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

No bioequivalence data were submitted and none are required for an application of this type.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with oxaliplatin is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome