IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0585/030/001
Case No: 2038422

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Pliva Pharma Limited

Vision House, **Bedford Road**, **Petersfield**, **Hampshire GU32 3QB**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Oxaliplatin 5 mg/ml Powder for Solution for Infusion

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **15/02/2008** until **14/02/2013**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

OXALIPLATIN 5 mg/ml
Powder for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

50mg vial: Each 26 ml vial contains 50 mg oxaliplatin for reconstitution in 10ml of solvent
100mg vial: Each 60 ml vial contains 100 mg oxaliplatin for reconstitution in 20ml of solvent

1 ml of reconstituted solution contains 5 mg oxaliplatin

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion
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 tumour.
- Treatment of metastatic colorectal cancer.

4.2 Posology and method of administration

The preparation of injectable solutions of cytotoxic agents must be carried out by trained specialist personnel with knowledge of the medicines used, in conditions that guarantee the protection of the environment and in particular the protection of the personnel handling the medicines, in compliance with the hospital regulations. 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/m^2 intravenously repeated every 2 weeks for 12 cycles (6 months).

The recommended dose of oxaliplatin in the treatment of metastatic colorectal cancer is 85 mg/ m^2 intravenously, repeated every 2 weeks.

It is necessary to adjust the indicated dose depending on individual tolerance (see section 4.4).

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

Oxaliplatin is administered in the form of an intravenous infusion lasting 2-6 hours in 250 to 500ml of 5% glucose solution to give a concentration between 0.2 mg/ml and 0.70mg/ml; 0.70mg/ml is the highest concentration in clinical practice for oxaliplatin in doses of 85 mg/m^2.

Oxaliplatin is used mainly in combination with continuous infusion 5-fluorouracil (5-FU) based regimens.
In the two-week schedule, bolus and continuous infusion of 5-fluorouracil (5-FU) regimens are combined.

Special population groups

- 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 started with the normal recommended dose (see section 4.4). It is not necessary to adjust the dose 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 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 persons:
No increase in severe toxicities was observed during the administration of oxaliplatin alone or in combination with 5-fluorouracil (5-FU) to patients over 65 years; therefore, it is not necessary to adjust the posology in these patients specially.

Method of administration
Oxaliplatin is administered by intravenous infusion. Its administration does not require hyper hydration.

Oxaliplatin must be administered by infusion into a peripheral vein or through a central venous catheter for a period of 2-6 hours, diluted into 250-500ml 5% of glucose solution to a concentration of at least 0.2 mg/ml. The infusion of oxaliplatin must always precede the administration of 5-fluorouracil (5-FU).

In case of extravasation of oxaliplatin, the administration must be discontinued immediately.

Instruction for use:
Before use, oxaliplatin must be reconstituted and further diluted. Only 5% glucose solution should be used for reconstitution and the subsequent dilution of the lyophilizate (see section 6.6).

4.3 Contraindications

Hypersensitivity to oxaliplatin or to excipients contained in the preparation;
Breast-feeding;
Myelosuppression determined before the start of the first treatment cycle, which is evident from a neutrophil count < 2 $\times 10^9$/l and/or platelet count < 100 x 10^9/l;
Peripheral sensory neuropathy with function impairment before the start of the first treatment cycle;
Severe impairment of renal function (creatinine clearance below 30ml/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.

Considering the limited amount of information regarding the safety of administration to patients with moderate impairment of renal function, the benefit/risk ratio for the patient should be assessed before the preparation administration. In this case, renal function should be thoroughly monitored and the dose should be adjusted depending on toxicity.

Patients with a history of allergic reactions to other compounds of platinum should be thoroughly monitored for timely detection of symptoms of an allergic reaction. In case of an anaphylactic type reaction following the oxaliplatin administration, the infusion must be discontinued immediately and appropriate symptomatic treatment started. In this case, the repeated administration of oxaliplatin is contraindicated.

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

Neurotoxicity of oxaliplatin should be carefully monitored, especially in case of combined treatment with other medicinal products showing specific neurological toxicity. The patient should be neurologically examined before the treatment initiation, before every subsequent cycle, and regularly following the administration.

If acute laryngopharyngeal dysaesthesia occurs in the patient (see section 4.8) in the course of a 2-hour infusion or within several hours following its completion, subsequent doses of oxaliplatin should be administered in the form of a 6-hour infusion.

If neurological symptoms occur (paraesthesia, dysaesthesia), the adjustment of subsequent doses is recommended depending on the duration, as well as on the severity of neurological symptoms:
- If the symptoms persist for more than 7 days and are inconvenient, the next dose should be reduced from 85 to 65 mg/ m^2 (metastatic setting) or 75 mg/ m^2 (adjuvant setting).
- In the case of paraesthesia without functional impairment, persisting until the next treatment cycle, the next 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, the treatment should be discontinued.
- If the symptoms abate following the treatment discontinuation, its resumption may be considered.

Patients should be informed about the possibility of persistent symptoms of peripheral sensory neuropathy after the end of treatment. Localized moderate paresthesias or paresthesias that may interfere with functional activities can persist after up to 3 years following treatment cessation in the adjuvant setting.

Toxic effects of oxaliplatin on the gastrointestinal system, manifesting by nausea or vomiting, justify preventative and/or therapeutic administration of antiemetics (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 (5 FU).

If manifestations of haematological toxicity (neutrophil count < 1.5 x 10^9/l and/or platelet count < 50 x 10^9/l) occur, the subsequent treatment cycle should be postponed until the blood count improves to acceptable levels. A complete blood count including white cell differential calculation should be performed at the beginning of the treatment and then before every cycle.

Patients must be informed appropriately about the risk of diarrhoea/vomiting, mucositis/stomatitis and neutropenia following the administration of oxaliplatin/5-fluorouracil (5-FU), so that they can contact their treating physicians for appropriate treatment. If mucositis/stomatitis occurs with or without neutropenia, subsequent treatment should be suspended until mucositis/stomatitis recovers to grade 1 or less and/or until neutrophil count is ≥ 1.5 x 10^9/l.

If oxaliplatin is administered in combination with 5-fluorouracil (5-FU) (together with folinic acid (FA) or without), the dose of 5-fluorouracil (5-FU) should be adjusted according to its toxic effect.

In the case of WHO grade 4 diarrhoea, grade 3-4 neutropenia (neutrophil count < 1 x 10^9/l), grade 3-4 thrombocytopenia (thrombocyte count < 50 x 10^9/l), the dose of oxaliplatin should be reduced from 85 to 65 mg/ m^2 (metastatic setting) or 75 mg/ m^2 (adjuvant setting) in addition to any 5-fluorouracil (5-FU) dose reductions required.

In the case of unexplained respiratory symptoms for example. nonproductive cough, dyspnoea, crackles or radiologically detected pulmonary infiltrates, the administration of oxaliplatin should be discontinued, until the following pulmonary examinations exclude interstitial pulmonary 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 during pregnancy see section 4.6.

Genotoxic effects of oxaliplatin were observed in preclinical studies. Therefore, male patients treated with oxaliplatin are advised not to father a child during and up to 6 months after treatment. It is recommended to seek information on possible sperm conservation before the treatment, because oxaliplatin can have an anti-fertility effect, which is potentially irreversible.
Women should not conceive during treatment with oxaliplatin and should use effective contraception (see section 4.6). Effective contraception must be used throughout the treatment and following the treatment for 4 months in women and 6 months in men.

4.5 Interaction with other medicinal products and other forms of interaction

In patients receiving a single 85 mg/ m^2 dose of oxaliplatin immediately before administration of 5-fluorouracil (5-FU), no change in the level of exposure to 5-fluorouracil (5-FU) has been observed.

In vitro, no significant displacement of oxaliplatin was observed from binding to plasma proteins by the following substances: erythromycin, salicylates, granisetron, paclitaxel, and sodium valproate.

4.6 Pregnancy and lactation

Women of childbearing potential/Contraception
In pre-clinical studies genotoxic effects were seen. Therefore, male patients who are treated with oxaliplatin are advised not to conceive a child during and until 6 months after the end of oxaliplatin therapy.
Women should not become pregnant during oxaliplatin therapy and until 4 months after therapy, therefore contraceptive measures have to be taken.

Pregnancy
Currently, no data are available regarding the safety of the product in administration during pregnancy. Reproduction toxicity was observed in animal studies (see section 5.3). Based on the results of animal studies and the pharmacological action of the compound, it is not recommended to use oxaliplatin during pregnancy, especially during the first trimester. Administration of oxaliplatin can be considered only after the assessment of benefit/risk ratio for the foetus and with the previous consent of the patient.

Lactation
Release of oxaliplatin into breast milk has not been studied. Breast-feeding is contraindicated during oxaliplatin therapy.

Fertility
Oxaliplatin may have anti-fertility effects (see section 4.4).
Testicular damage was observed in dogs at doses lower than the human therapeutic dose based on body surface area. Based on the pharmacological action of the compound, oxaliplatin may cause infertility. Male patients have to be consulted about sperm preservation.

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 increased risk of dizziness, nausea and vomiting, and other neurologic symptoms that affect gait and balance, may lead to minor or moderate influence on the ability to drive and use machines.

4.8 Undesirable effects

The most frequent undesirable effects of oxaliplatin in combination with 5-fluorouracil (5-FU)/folinic acid (FA) are gastrointestinal (diarrhoea, nausea, vomiting, and mucositis), haematological (neutropenia, thrombocytopenia) and neurological effects (acute and dose cumulative peripheral sensory neuropathy).
Overall, these adverse events were more frequent and more severe with oxaliplatin and 5-fluorouracil (5-FU)/folinic acid combination than with 5-fluorouracil (5-FU) / folinic acid alone.
The incidence of the reported undesirable effects listed in the table is based on clinical trials in the metastatic and adjuvant setting (having included 416 and 1108 patients respectively in the oxaliplatin + 5-fluorouracil (5-FU)/folinic acid (FA) treatment arms) and from post-marketing experience.

The incidences in this table are defined by the following method: very common (≥1/10); common (≥1/100. <1/10); uncommon (≥1/1 000. <1/100); rare (≥1/10 000. <1/1 000); very rare (<1/10 000), not known (cannot be estimated from the available data).
Detailed data are summarized in the table.

MedDRA organ classification	Very common (≥1/10)	Common (≥1/100.<1/10)	Uncommon (≥1/1000. <1/100)	Rare (≥1/10 000. <1/1000)	Very rare (<1/10000)
Infections and infestations*	Infection	rhinitis, upper respiratory tract infection, febrile neutropenia/ neutropenic sepsis			
Blood and lymphatic system disorders*	anaemia, neutropenia, thrombocytopenia, leucopenia, lymphopenia			immunoallergic thrombo-cytopenia, haemolytic anaemia	
Immune system disorders*	Allergy/ allergic reactions+				
Metabolism and nutrition disorders	Anorexia, glycaemic 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		transient decrease of visual acuity, visual field disturbances optic neuritis	
Ear and labyrinth disorders			ototoxicity	deafness	
Vascular disorders	Epistaxis	haemorrhage (NOS), flushing, deep vein thrombosis, pulmonary embolism			
Respiratory, thoracic, and mediastinal disorders	dyspnoea, cough	hiccup		interstitial pulmonary disease, pulmonary fibrosis**	
Gastrointestinal disorders*	nausea, diarrhoea, vomiting, stomatitis /mucositis, abdominal pain, constipation	dyspepsia, gastroesophageal reflux, rectal haemorrhage	ileus, intestinal obstruction	colitis incl. diarrhoea caused by *Clostridium difficile*	
Skin and subcutaneous tissue disorders	skin disorders, alopecia	skin exfoliation (e.g. Hand and Foot syndrome), erythematous rash, rash, hyperhidrosis, nail disorder			
Musculoskeletal and connective tissue disorders	back pain	arthralgia, bone pain			
Renal and urinary tract disorders		dysuria, haematuria, abnormal micturition frequency			Acute tubulo-interstitial nephropathy leading to acute renal

					failure
General disorders and administration site conditions	fatigue, fever++, asthenia, pain, injection site reaction +++				
Investigations	- increase of blood alkaline phosphatases - increase of blood bilirubin - increase of lactate dehydrogenase (LDH) - increase of weight (adjuvant setting)	- increase of blood creatinine - weight reduction (metastatic setting)			
Hepatobiliary disorders	- increase of hepatic enzymes				Liver sinusoidal obstruction syndrome (see below)

* see the detailed paragraph below
** see section 4.4
+ Common allergic reactions, such as skin rash (particularly urticaria), conjunctivitis, rhinitis. Common anaphylactic reactions, including bronchospasm, sensation of chest pain, angioedema, hypotension, and anaphylactic shock.
++ Very common fever, rigors (tremors), either from infection (with or without febrile neutropenia) or possibly from immunological mechanism.
+++ Injection site 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 section 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.

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

Therapeutic or preventative administration of antiemetics is recommended.

Dehydration, paralytic ileus, intestinal obstruction, hypokalaemia, metabolic acidosis and renal impairment can be caused by severe diarrhoea/vomiting, especially with combination of oxaliplatin with 5-fluorouracil (5-FU) (see section 4.4).

Nervous system:
The dose limiting toxicity is neurological. It includes sensory peripheral neuropathy characterized by dysaesthesia and/or paraesthesia in the extremities, which may be accompanied by cramps, often triggered by the cold. These symptoms occur in up to 95% of treated patients. The duration of such symptoms, which usually disappear in the period between individual treatment cycles, extends with the number of cycles.

The occurrence of pain and/or dysfunction are reason for an adjustment of dose or even treatment discontinuation, depending on the duration of symptoms (see section 4.4).

This dysfunction includes difficulties with delicate motor functions and is probably a consequence of sensory impairment. The risk of occurrence of persistent difficulties with cumulative dosage of approximately 850mg/m^2 (i.e. 10 cycles) is approximately 10% and 20% with cumulative dosage of 1020mg/ m^2 (i.e. 12 cycles). Symptoms of neurological toxicity improve following the treatment discontinuation in most cases. 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 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 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). 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 were reported during oxaliplatin treatment, such as dysarthria, loss of deep tendon reflexes and Lhermitte's symptom. Isolated cases of optic neuritis were 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

An antidote to oxaliplatin is not available. In cases of overdose, worsening of undesirable effects may be expected. It is necessary to start monitoring haematological parameters and give relevant symptomatic treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:Other antineoplastic agents, Platinum compounds
ATC code: L01XA03

Oxaliplatin is an antineoplastic medicinal substance belonging among the platinum derivatives, where an atom of platinum is bonded in complex with 1.2-diaminocyclohexane ("DACH") and an oxalate group. Oxaliplatin is a single enantiomer, the Cis -[oxalato (trans-l-1,2- DACH) platinum].

Oxaliplatin demonstrates a broad spectrum of cytotoxicity *in vitro*, as well as anti-tumour activity *in vivo* on different tumour model systems, including models of colorectal carcinoma in men. Oxaliplatin also acts *in vitro* and *in vivo* in various model systems resistant to cisplatin.

Synergic cytotoxic effects were observed in combination with 5-fluorouracil (5-FU) both *in vitro* and *in vivo*.
Studies of the mechanism of oxaliplatin activity, which is not yet fully clarified, support a hypothesis that the hydrated metabolite of oxaliplatin enters into interaction with DNA and thus forms intra- and inter- bridges between DNA threads, which leads to the termination of DNA synthesis. The result is a cytotoxic and anti-tumour effect.

In patients with metastatic colorectal cancer, the effectiveness of oxaliplatin (85 mg/ m^2 repeated every two weeks) in combination with 5-fluorouracil (5-FU)/folinic acid (FA) was proved in three clinical studies:

- In the first line of treatment, a double-arm randomized study Phase III EFC2962 randomized patients as follows: 5-fluorouracil (5-FU)/folinic acid (FA) alone (LV5FU2, N=210) or combination of oxaliplatin + 5-fluorouracil (5-FU)/folinic acid (FA) (FOLFOX4, N=210).
- In previously treated patients, a three-arm head to head trial Phase III EFC4584 randomized patients refractory to irinotecan (CPT-11) + 5-fluorouracil (5-FU)/folinic acid (FA) combination into either 5-fluorouracil (5-FU)/folinic acid (FA) alone (LV5FU2, N=275), oxaliplatin in monotherapy (N=275) or combination of oxaliplatin with 5-fluorouracil (5-FU)/folinic acid (FA) (FOLFOX4, N=271).
- Finally, a non controlled study Phase II EFC2964 included patients refractory to 5-fluorouracil (5-FU)/folinic acid (FA) alone. Patients were treated with oxaliplatin with 5-fluorouracil (5-FU)/folinic acid (FA) (FOLFOX4, N=57).

The two aforementioned randomized clinical trials, EFC2962 in the first line treatment and EFC4584 in previously treated patients, demonstrated significantly higher response to treatment and extension of progression free survival (PFS)/time to progression (TTP), compared with treatment with 5-fluorouracil (5-FU)/folinic acid (FA) alone. In EFC4584 study, conducted in previously treated refractory patients, no statistical difference was determined in median of the overall survival (OS) between oxaliplatin and 5-fluorouracil (5-FU)/folinic acid (FA).

Response to treatment in FOLFOX4 versus LV5FU2

Response to treatment, % (95% CI) independent radiological assessment by ITT analysis	**LV5FU2**	**FOLFOX4**	**Oxaliplatin alone**
First line EFC2962	22 (16-27)	49 (42-46)	NA
Review of the response to treatment every 8 weeks	p value =0.0001		
Previously treated patients EFC4584 (refractory to CPT-11 + 5-FU/LV)	0.7 (0.0-2.7)	11.1 (7.6-15.5)	1.1 (0.2-3.2)
Review of the response to treatment every 6 weeks	p value < 0.0001		
Previously treated patients EFC2964 (refractory to 5-FU/LV) Review of the response to treatment 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 assessment by ITT analysis	**LV5FU2**	**FOLFOX4**	**Oxaliplatin alone**
First line EFC2962 (PFS)	6.0 (5.5-6.5)	8.2 (7.2-8.8)	NA
	Log-rank level p = 0.0003		
Previously treated patients			

EFC4584 (TTP) (refractory to CPT-11 + 5-FU/LV)	2.6 (1.8-2.9)	5.3 (4.7-6.1)	2.1 (1.6-2.7)
	Log-rank level p < 0.0001		
Previously treated patients EFC2964 (refractory to 5-FU/LV)	NA	5.1 (3.1-5.7)	NA

NA = not applicable

Median of overall survival (OS) in FOLFOX4 versus LV5FU2

Median OS, Months (95% CI) ITT analysis	**LV5FU2**	**FOLFOX4**	**Oxaliplatin alone**
First line EFC2962	14.7 (13-18.2)	16.2 (14.7-18.2)	NA
	Log-rank p value = 0.12		
Previously treated patients EFC4584* (refractory to CPT-11 + 5-FU/LV)	8.8 (7.3-9.3)	9.9 (9.1-10.5)	1.3 (0.1-4.6)
	Log-rank p value = 0.09		
Previously treated patients EFC2964 (refractory to 5-FU/LV)	NA	10.8 (9.3-12.8)	NA

NA = not applicable
* survival data from 90% of reported events (deaths)

In previously treated patients (EFC4584), which were symptomatic in the beginning of the trial, the majority of patients treated with oxaliplatin/5-fluorouracil (5-FU)/folinic acid (FA) showed significant improvement of symptoms, compared to patients treated with 5-fluorouracil (5-FU)/folinic acid (FA) alone (27.7% vs. 14.6%, p<0.0033). In so far untreated patients (EFC2962), no statistical difference was found between the two treated groups in the assessment of all aspects of quality of life. Nevertheless score of the quality of life was generally better in the control arm in the assessment of the overall measurement of health status and pain, and worse for nausea and vomiting in the oxaliplatin arm.

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 platinum compounds have not been determined.
The pharmacokinetics of ultrafiltrable platinum, represented by the mixture of all active and inactive derivatives of platinum following the 2-hour infusion of oxaliplatin at the 130 mg/ m^2 dose every three weeks from one to five cycles and in the 85 mg/ m^2 dose of oxaliplatin every two weeks from one to three cycles, is demonstrated in the following table:

The summary of pharmacokinetic parameters of platinum evaluated in the ultra filtrate following several repeated doses of oxaliplatin 85 mg/ m^2 every two weeks or 130 mg/ m^2 every three weeks

Dose	**C_{max}**	**AUC_{0-48}**	**AUC**	**$t_{1/2}\alpha$**	**$t_{1/2}\beta$**	**$t_{1/2}\gamma$**	**V_{ss}**	**CL**
	µg/ml	**µg.hour/ml**	**µg.hour/ml**	**hour**	**hour**	**hour**	**l**	**l/hour**
85 mg/ m^2 Mean level	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 level	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 level AUC_{0-48} and C_{max} levels were established in the 3rd cycle (85 mg/ m^2) or in the 5th cycle (130 mg/ m^2).
Mean levels of AUC, Vss, Cl and CL_{R0-48} were established in the 1st cycle.
C_{end}, C_{max}, AUC, AUC_{0-48}, Vss, Cl levels were established by non-compartment analysis.
$T_{1/2}\alpha$, $t_{1/2}\beta$ and $t_{1/2}\gamma$ levels were established by compartment analysis (combined from cycles 1-3).

At the end of the 2-hour infusion, 15% of platinum administered is present in the systemic circulation, the remaining 85% is rapidly distributed into tissues or excreted in urine. Irreversible binding of platinum to red blood cells and plasma proteins means that the platinum half-time in blood approaches the natural turnover of red blood cells and serum albumin. No accumulation of oxaliplatin was observed in plasma ultra filtrate following the administration of 85 mg/ m^2 every two weeks or 130 mg/ m^2 every three weeks and steady state was achieved in cycle 1, when the variability between patients was low.

Bio transformation *in vitro* is considered to be the result of non-enzymatic degradation and there is no evidence that the P450 cytochrome is involved in the metabolism of the diaminocyclohexane (DACH) cycle.
In vivo, oxaliplatin is subject to extensive bio transformation and is not detectable in the plasmatic ultra filtrate at the end of a 2-hour infusion. Some cytotoxic metabolites, including monochloro-, dichloro- and dihydro- DACH platin, have been identified in the circulation system together with other inactive conjugates at later time points.

Predominantly, platinum is excreted in urine within the first 48 hours following administration.
Approximately 54% of totally administered dosage is excreted in urine and < 3% in faeces within 5 days.

In the case of renal impairment, a significant decrease of oxaliplatin clearance from 17.6 +- 2.18 l/hour to 9.95 +- 1.91 l/hour, together with statistically significant decrease in distribution volume from 330 +- 40.9 l to 241 +- 36.1 l was seen. The influence of severe renal impairment on platinum clearance has not yet been assessed.

5.3 Preclinical safety data

The target organs identified in non-clinical species (mouse, rat, dog, and/or monkey) included the bone marrow, GIT, kidney, testicles, nervous system and heart in studies with both single and repeated doses.
The target organ toxicities observed in animals correspond to the apparent toxicity following the administration of other platinum containing medicinal products and other DNA damaging cytotoxic medicinal products used in the treatment of cancer, except for effects on the heart. The impact on the heart was observed in dogs only, and was demonstrated by electro-physiologic disorders with lethal chamber fibrillation. Cardiotoxicity is assumed only in dogs not only because it was observed in dogs only, but also because the lethal cardiotoxic dose in dogs (150mg/ m^2) was well tolerated by human. Preclinical studies using sensory neurons of rats show that the acute neurosensory symptoms related to administration of oxaliplatin may indicate the interaction with voltage controlled sodium channels.

Oxaliplatin was mutagenic and clastogenic in mammalian test systems and showed embryotoxicity and foetotoxicity in rats. Oxaliplatin is considered possibly carcinogenic, although carcinogenicity studies with oxaliplatin have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

6.2 Incompatibilities

The reconstituted medicinal product should not be mixed with other medicinal products in the same infusion bag or infusion line. According to section 6.6 instructions for use, oxaliplatin can be administered together with folinic acid (FA) by means of Y line.
- DO NOT MIX with alkaline medicinal products or solutions, especially with 5-fluorouacil (5-FU), with folinic acid (FA) preparations containing trometamol as an excipient, and with trometamol salts of other active substances. Alkaline medicinal products or solutions will negatively affect the oxaliplatin stability (see section 6.6).
- DO NOT RECONSTITUTE OR DILUTE oxaliplatin with saline or other solutions containing chloride ions (including calcium chloride, potassium chloride, or sodium chloride).
- DO NOT MIX with any other medicinal products in the same infusion bag or infusion line (see section 6.6 for the instructions regarding concomitant administration with folinic acid (FA)).
- DO NOT USE aluminium containing equipment.

6.3 Shelf Life

2 years

Reconstituted solution:
Chemical and physical in-use stability following reconstitution with water for injections or 5% glucose solution has been demonstrated for 24 hours at 2°C - 8°C. From a microbiological point of view, the reconstituted solution should be diluted immediately.

Solution for infusion:
Chemical and physical in-use stability following dilution in 5% glucose solution has been demonstrated for 24 hours at 2°C - 8°C. From a microbiological point of view, the diluted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and normally shouldn’t exceed 24 hours at 2°C - 8°C.

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

Powder (containing 50 mg oxaliplatin) in 26 ml colourless glass vial (type I) with bromobutyl rubber stopper, aluminium closure and polypropylene flip-off cover.

Pack size: 1 vial.
Powder (containing 100 mg oxaliplatin) in 60 ml colourless glass vial (type I) with bromobutyl rubber stopper, aluminium closure and polypropylene flip-off cover.

Pack size : 1 vial.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Instructions for handling
The handling of this cytotoxic agent by 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 protection of the environment and in particular the protection of the personnel handling the medicines. 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 substances.
Any broken container should be handled as contaminated waste. The waste should be incinerated in suitably labelled rigid containers (see Section “Disposal” below).
If the oxaliplatin powder, reconstituted solution or solution for infusion should come into contact with skin, the affected area should be immediately and thoroughly washed with water. If the oxaliplatin powder, reconstituted solution or solution for infusion should come into contact with mucous membranes, the affected area should be immediately and thoroughly washed with water.

Special precautions for use:
- DO NOT use injection equipment containing aluminium.
- DO NOT administer undiluted preparation.
- ONLY dilute with 5% glucose solution.
- DO NOT reconstitute or 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 in the same infusion line.
- DO NOT mix with alkaline medicinal products or solutions, especially 5-fluorouracil (5-FU), folinic acid (FA) preparations containing trometamol as an excipient, and trometamol salts of other active substances. Alkaline medicinal products or solutions will negatively affect the oxaliplatin stability.

Instruction for use with folinic acid (as calcium folinate or sodium folinate):
Oxaliplatin 85 mg/m^2 infusion in 250-500ml of 5% glucose solution can be co-administered with folinic acid infusion in 5% glucose solution during 2-6 hours, using a Y line which is placed immediately in front of the infusion site. These two medicinal products must not be combined in the same infusion bag. The folinic acid must not contain trometamol as an excipient and can only be diluted with isotonic 5% glucose solution, NEVER with alkaline solutions or sodium chloride solution or chloride containing solutions.

Instruction for use with 5-fluorouracil (5-FU):
Oxaliplatin must always be administered before fluoropyrimidines – i.e. 5-fluorouracil (5-FU). Always flush the line following oxaliplatin administration and only after that can 5- fluorouracil (5-FU) be administered.

For further information on medicinal products combined with oxaliplatin refer to the relevant Summary of Product Characteristics.

Any reconstituted solution showing the presence of precipitates must not be used and must be disposed of according to the precautions for handling hazardous waste (see below).

Reconstitution of the solution:
- Water for injections or 5% glucose solution should be used to reconstitute the solution.
- 50mg vial: for 5mg/ml oxaliplatin concentration, add 10ml of solvent.
- 100mg vial: for 5mg/ml oxaliplatin concentration, add 20ml of solvent.

Inspect the solution visually before use – only clear solution, free from particles, can be used.

Dilution of the solution for intravenous infusion:
Withdraw the required amount of the reconstituted solution from the vial and dilute in 250-500ml of 5% glucose solution to give an oxaliplatin concentration between 0.2mg/ml to 0.7mg/ml.

Inspect the solution visually before use – only clear solution, free from particles, can be used.

The product is for single use only. Any unused solution must be discarded (see the Section "Disposal" below).

NEVER use sodium chloride or chloride containing solutions for reconstitution or dilution.

Infusion
Administer by intravenous infusion. The administration of oxaliplatin does not require pre hydration.
Oxaliplatin diluted in 250-500 ml of 5% glucose solution to a concentration of not less than 0.2 mg/ml must be infused either by peripheral vein or central venous line over 2-6 hours. If the oxaliplatin is administered in combination with 5-fluorouracil (5-FU), the oxaliplatin infusion must precede the 5-fluorouracil (5-FU) infusion.

Disposal
Any unused solution, remaining medicinal product as well as any other material used for the reconstitution, dilution, and infusion, must be disposed of according to standard procedures specified for the disposal of cytotoxic agents, in accordance with local requirement for the disposal of hazardous waste.

7 MARKETING AUTHORISATION HOLDER

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