IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0937/007/002
Case No: 2049393

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

Pharmachemie BV

Swensweg 5, **P.O Box 552**, **Haarlem**, **2003 RN**, **Netherlands**

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 **01/09/2008** until **08/06/2013**.

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

20 mg vial: each vial contains 20 mg of Oxaliplatin for reconstitution in 4 ml of solvent
50 mg vial: each vial contains 50 mg of Oxaliplatin for reconstitution in 10 ml of solvent
100 mg vial: each vial contains 100 mg of Oxaliplatin for reconstitution in 20 ml of solvent

1ml of reconstituted solution contains 5 mg oxaliplatin

Excipient: lactose monohydrate.
A 20 mg vial contains 180 mg lactose monohydrate.
A 50 mg vial contains 450 mg lactose monohydrate.
A 100 mg vial contains 900 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion.
White or almost white, caked powdery mass.

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 medical product used, in conditions that guarantee the integrity of the medical product, the protection of the environment and in particular the protection of the personnel handling the medicinal products, in accordance with the hospital policy. It requires a preparation area reserved for this purpose. It is forbidden to smoke, eat or drink in this area.

Posology

Oxaliplatin is used in adults only.

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

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

Dosage given should be adjusted according to tolerability (see section 4.4).

Oxaliplatin should always be administered before fluoropyrimidines.

Oxaliplatin is administered as a 2- to 6-hour intravenous infusion in 250 to 500 ml of 5% glucose solution to give a concentration between 0.2 mg/ml and 0.70 mg/ml; 0.70 mg/ml is the highest concentration in clinical practice for an oxaliplatin dose of 85 mg/m².

Oxaliplatin is mainly used in combination with continuous infusion 5-fluorouracil (5-FU) based regimens. For the two-weekly treatment schedule 5-fluorouracil (5-FU) regimens combining bolus and continuous infusion are 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 hepato-biliary disorders appeared to be related to progressive disease and impaired liver function tests at baseline. During clinical development no specific dose adjustments for patients with abnormal liver function were performed.

Elderly patients
No increase in severe toxicities was observed when oxaliplatin was used as a single agent or in combination with 5-fluorouracil (5-FU) in patients over the age of 65. Therefore, no specific dose adjustments are required for elderly.

Method of administration

Oxaliplatin is administered by intravenous infusion.

The administration does not require hyperhydratation.

After reconstitution, Oxaliplatin diluted in 250 to 500 ml of 5% glucose solution to give a concentration not less than 0.2 mg/ml must be infused via a central venous line or peripheral vein over 2 to 6 hours. Oxaliplatin infusion should always precede that of 5-fluorouracil (5-FU).
(See section 6.6).

In case of extravasation, administration must be discontinued immediately.

Instructions for use

Oxaliplatin must be reconstituted and diluted before use. Water for injections or a 5% glucose solution should be used to reconstitute the powder for solution for infusion. Only a 5% glucose solution should be used to dilute the reconstituted solution (see section 6.6).

4.3 Contraindications

Oxaliplatin is contra-indicated in patients who:
- are hypersensitive to oxaliplatin or to any of the excipients
- are breastfeeding
- have a peripheral sensitive neuropathy with functional impairment prior to first course
- have myelosuppression prior to starting first course, as evidenced by baseline neutrophils < 2 x 10^9/l and/or platelet count of < 100 x 10^9 l
- have a severely impaired renal function (creatinine clearance less than 30 ml/min)

4.4 Special warnings and precautions for use

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

Due to limited information on safety in patient 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 re-challenge is contra-indicated in this situation.

In case of extravasation, the infusion should be stopped immediately and usual local symptomatic treatment has to be initiated.

Neurologic toxicity should be carefully monitored, especially if co-administered with other medications with specific neurological toxicity. A neurological examination should be performed before each administration and periodically thereafter.

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

If neurological symptoms (paraesthesia, dysaesthesia) occur, the following recommended oxaliplatin dose should be based on the duration and severity of these symptoms:
- If symptoms last longer than 7 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 dose should be reduced from 85 to 65 mg/m^2 (metastatic setting) or 75 mg/m^2 (adjuvant setting).
- If paraesthesia with functional impairment persists until the next cycle, oxaliplatin should be discontinued.
- If these symptoms improve following discontinuation of oxaliplatin therapy, resumption of therapy may be considered.

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

Gastrointestinal toxicity, which manifests as nausea and vomiting, warrants prophylactic and/or therapeutic anti-emetic therapy (see section 4.8).

Dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis particularly when combining oxaliplatin with 5-fluorouracil (5-FU).

If haematological toxicity occurs (neutrophils < 1.5 x 10^9/l or platelets < 50 x 10^9/l), administration of the next course of therapy should be postponed until haematological values return to acceptable levels. A full blood count with white cell differential should be performed prior to start of therapy and before each subsequent course.

Patient should be adequately informed of the risk of diarrhoea/emesis, mucositis/stomatitis and neutropenia after oxaliplatin and 5-fluorouracil (5-FU) 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.

If oxaliplatin is combined with 5-fluorouracil (5-FU) (with or without folinic acid (FA)), the usual dose adjustments for 5-fluorouracil (5-FU) associated toxicities should apply.

If WHO grade 4 diarrhoea, grade 3 - 4 neutropenia (neutrophils < 1.0 x 10^9/l) or grade 3 - 4 thrombocytopenia (platelets < 50 x 10^9/l) occur, the dose of oxaliplatin should be reduced from 85 mg/m^2 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 case of unexplained respiratory symptoms such as non-productive cough, dyspnoea, crackles or radiological pulmonary infiltrates, oxaliplatin should be discontinued until further pulmonary investigations exclude an interstitial lung disease or pulmonary fibrosis (see section 4.8).

In case of abnormal liver function test results or portal hypertension which does not obviously result from liver metastases, very rare cases of drug-induced hepatic vascular disorders should be considered.

For use in pregnant women see section 4.6.

In pre-clinical studies genotoxic effects were seen. Therefore, male patients which are treated with oxaliplatin are advised not to conceive a child during and until 6 months after the end of oxaliplatin therapy. The patient has to be consulted about sperm preservation, because oxaliplatin can cause infertility which may be permanent.
Women should not to become pregnant during oxaliplatin therapy and until 4 months after therapy, therefore contraceptive measures have to be taken (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 (5-FU), no change in the level of exposure to 5-fluorouracil (5-FU) has been observed.

In vitro, no significant displacement of oxaliplatin binding to plasma proteins has been observed with the following agents: salicylates, paclitaxel, erythromycin, granisetron, and sodium valproate.

4.6 Pregnancy and lactation

Women of childbearing potential/Contraception
In pre-clinical studies genotoxic effects were seen. Therefore, male patients which 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 to become pregnant during oxaliplatin therapy and until 4 months after therapy, therefore contraceptive measures have to be taken.

Pregnancy
To date, there are no data available on the safety of use of oxaliplatin in pregnant women (see section 5.3). In animal studies, reproductive toxicity was observed (see section 5.3). Based on the results of animal studies and the pharmacological action of the compound, the use of oxaliplatin during pregnancy is advised against, in particular during the first trimester. Oxaliplatin therapy should only be considered after suitable appraising the patient of the risk to the foetus and with the patient’s consent.

Lactation
Excretion in breast milk has not been studied. Oxaliplatin is contra-indicated in breast-feeding women.

Fertility
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 effect on the ability to drive and to use machines have been performed. Treatment with oxaliplatin however, can cause dizziness, nausea and vomiting and other neurological symptoms which can influence gait and balance. This can lead to minor to moderate influence on the ability to drive or to 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). In general, these adverse events were more frequent and severe with oxaliplatin and 5-fluorouracil/folinic acid (5-FU/FA) combination than with 5-fluorouracil/folinic acid (5-FU/FA) alone.

The frequencies below are derived from clinical trials in the metastatic and adjuvant setting (having included 416 and 1108 patients respectively in the oxaliplatin + 5-fluorouracil/folinic acid (5-FU/FA) treatment arms) and from post-marketing experience.

Frequencies through the text use the following convention:

Very Common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000), not known (cannot be estimated from the available data)

Infections and infestations
Very common
Infection.
Common
Rhinitis, upper respiratory tract infection, febrile neutropenia, neutropenic sepsis.

Blood and lymphatic system disorders
Very common
Anaemia, neutropenia, thrombocytopenia, leukopenia, lymphopenia.
Rare
Immunoallergic thrombocytopenia, hemolytic anaemia.

Incidence per patient (%), by grade

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

Immune system disorders
Very common
Allergy/allergic reaction.
Common
Skin rash (particularly urticaria), conjuctivitis, rhinitis, anaphylactic reactions, including bronchospasm, sensation of chest pain, angiooedema, hypotension and anaphylactic shock.

Incidence by patient (%), by grade

Oxaliplatin 85 mg/m^2 and 5-FU/FA every 2 weeks	Metastatic setting			Adjuvant setting		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Allergic reaction/allergy	9.1	1	< 1	10.3	2.3	0.6

Metabolism and nutrition disorders
Very common
Anorexia, glycaemic abnormalities, hypokalaemia, natraemia abnormalities.
Common
Dehydration.
Uncommon
Metabolic acidosis.

Psychiatric disorders
Common
Depression, insomnia.
Uncommon
Nervousness.

Nervous system disorders
Very common
Peripheral sensory neuropathy, sensory disturbance, dysgeusia, headache.

Common
Dizziness, neuritis motor, meningism.
Rare
Dysarthria.

The dose limiting toxicity is neurological. It involves a sensory peripheral neuropathy characterised by dysaesthesia and/or paraesthesia of the extremities with or without cramps, often triggered by the cold. These symptoms occur in up to 95% of patients treated. The duration of these symptoms, which usually regress between courses of treatment, increases with the number of treatment cycles.

The onset of pain and/or a functional disorder are indications, depending on the duration of the symptoms, for dose adjustment, or even treatment discontinuation (see section 4.4).
This functional disorder includes difficulties in executing delicate movements and is a possible consequence of sensory impairment. The risk of occurrence of persistent symptoms for a cumulative dose of 850 mg/m^2 (10 cycles) is approximately 10% and 20% for a cumulative dose of 1020 mg/m^2 (12 cycles).
In the majority of the cases, the neurological signs and symptoms improve or totally recover when treatment is discontinued. In the adjuvant setting of colon cancer, 6 months after treatment cessation, 87% of patients had no or mild symptoms. After up to 3 years of follow up, about 3% of patients presented either with persisting localized 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 paraesthesia, dysaesthesia and hypoaesthesia. An acute syndrome of pharyngolaryngeal dysaesthesia occurs in 1% - 2% of patients and is characterized by subjective sensations of dysphagia or dyspnoea/feeling of suffocation, without any objective evidence of respiratory distress (no cyanosis or hypoxia) or 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 symptom(see section 4.4). Occasionally

other symptoms that have been observed include jaw spasm/muscle spasms/muscle contractions-involuntary/muscle twitching/myoclonus, coordination abnormal/gait abnormal/ ataxia/ balance disorders, throat or chest tightness/ pressure/ discomfort/pain.
In addition, cranial nerve dysfunctions may be associated, or also occur as an isolated event such as ptosis, diplopia, aphonia/ dysphonia/ hoarseness, sometimes described as vocal cord paralysis, abnormal tongue sensation or dysarthria, sometimes described as aphasia, trigeminal neuralgia/ facial pain/ eye pain, decrease in visual acuity, visual field disorders.
Other neurological symptoms such as dysarthria, loss of deep tendon reflex and Lhermitte's sign were reported during treatment with oxaliplatin. Isolated cases of optic neuritis have been reported.

Eye disorders
Common
Conjunctivitis, visual disturbance.
Rare
Transiently reduced visual acuity, visual field disturbances, optical neuritis.

Ear and labyrinth disorders
Uncommon
Ototoxicity.
Rare
Deafness.

Vascular disorders
Very common
Epistaxis.
Common
Haemorrhage NOS (Not Otherwise Specified), flushing, deep vein thrombosis, pulmonary embolism.

Respiratory, thoracic and mediastinal disorders
Very common
Dyspnoea, coughing.
Common
Hiccups.
Rare
Interstitial lung disease, pulmonary fibrosis (see also section 4.4).

Gastrointestinal disorders
Very common
Diarrhoea, nausea, vomiting, stomatitis/mucositis, abdominal pain, constipation.
Common
Dyspepsia, gastroesophageal reflux, rectum haemorrhage.
Uncommon
Ileus, intestinal obstruction.
Rare
Colitis including *Clostridium difficile* diarrhoea.

Incidence per patient (%), by grade

Oxaliplatin 85 mg/m^2 and 5-FU/FA every 2 weeks	Metastatic setting			Adjuvant setting		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 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 treatment with potent antiemetics is highly recommended**.**

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) (see section 4.4).

Skin and subcutaneous tissue disorders
Very common
Skin disorder, alopecia.
Common
Skin exfoliation (i.e. Hand & Foot syndrome), rash erythematous, rash, hyperhidrosis, nail disorder.

Musculoskeletal and connective tissue disorders
Very common)
Back pain.
Common
Arthralgia, bone pain.

Hepato-biliary disorders
Very rare
Liver sinusoidal obstruction syndrome, also known as veno-occlusive disease of liver, or pathological manifestations related to such liver disorder, including peliosis hepatis, nodular regenerative hyperplasia, perisinusoidal fibrosis. Clinical manifestations may be portal hypertension and/or increased transaminases.

Renal and urinary disorders
Common
Haematuria, dysuria, abnormal micturition frequency.
Very rare
Acute tubulo-interstitial nephropathy leading to acute renal failure.

General disorders and administration site conditions
Very common
Fever[+], fatigue, asthenia, pain, injection site reaction[++].

[+] *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 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).*

Investigations
Very common
Hepatic enzymes increase, alkaline phosphatase increase, bilirubin increase, lactate dehydrogenase (LDH) increase, weight increase (adjuvant setting).
Common
Increased blood creatinine level, weight decrease (metastatic setting).

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- [oxalate (trans-I-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 demonstrated *in vitro* and *in vivo* activity in various cisplatin resistant models.

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

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

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

- In front-line treatment, a 2-arm comparative three arms phase III study randomised 420 patients either to 5-FU/FA alone (LV5FU2, n=210) or the combination of oxaliplatin with 5-FU/FA (FOLFOX4, n=210).

- In pre-treated patients, a comparative three arms phase III study randomised 821 patients refractory to an irinotecan + 5-FU/FA combination either to 5-FU/FA alone (LV5FU2, n=275), oxaliplatin single agent (n=275), or combination of oxaliplatin with 5-FU/FA (FOLFOX4, n=271).

- Finally, a uncontrolled phase II study included patients refractory to 5-FU/FA alone (LV5FU2), that were treated with the oxaliplatin and 5-FU/FA combination (FOLFOX4, n=57).

The two randomised clinical trials, in front-line therapy and in pre-treated patients, demonstrated a significantly higher response rate and a prolonged progression free survival (PFS)/time to progression (TTP) as compared to treatment with 5-FU/FA alone (LV5FU2). In the trial preformed in refractory pre-treated patients, the difference in median overall survival (OS) between the combination of oxaliplatin and 5-FU/FA (FOLFOX4) did not reach statistical significance.

Response rate oxaliplatin + 5-FU/FA (FOLFOX4) versus 5-FU/FA alone (LV5FU2)

Response ratio, % (95% Cl) independent radiological review ITT analysis	5-FU/FA (LV5FU2)	oxaliplatin + 5-FU/FA (FOLFOX4)	Oxaliplatin monotherapy
Frontline treatment Response assessment every 8 weeks	22 (16-27)	49 (42-46)	NA*
	P value = 0.0001		
Pre-treated patients (refractory to irinotecan + 5-FU/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		
Pre-treated patients	NA*	23 (13-36)	NA*

(refractory to 5-FU/FA) Response assessment every 12 weeks			

CI Confidence interval
5FU 5-fluorouracil
FA folinic acid
ITT Intention to treat
**NA Not applicable*

Median progression free survival (PFS) / median time to progression (TTP) oxaliplatin + 5-FU/FA (FOLFOX4) versus 5-FU/FA alone(LV5FU2)

Median PFS/TTP, months (95% Cl) independent radiological review ITT analysis	5-FU/FA (LV5FU2)	oxaliplatin + 5-FU/FA (FOLFOX4)	Oxaliplatin monotherapy
Frontline treatment (PFS)	6.0 (5.5-6.5)	8.2 (7.2-8.8)	NA*
	Log-rank P value = 0.0003		
Pre-treated patients (TTP) (refractory to irinotecan + 5-FU/FA)	2.6 (1.8-2.9)	5.3 (4.7-6.1)	2.1 (1.6-2.7)
	Log-rank P value < 0.0001		
Pre-treated patients (refractory to 5-FU/FA)	NA*	5.1 (3.1-5.7)	NA*

CI Confidence interval
5FU 5-fluorouracil
FA folinic acid
ITT Intention to treat
**NA Not applicable*

Median overall survival (OS) under oxaliplatin + 5-FU/FA (FOLFOX4) versus 5-FU/LFa alone (LV5FU2)

Median OS; months (95% Cl) ITT analysis	5-FU/FA (LV5FU2)	oxaliplatin + 5-FU/FA (FOLFOX4)	Oxaliplatin monotherapy
Frontline treatment	14.7 (13.0-18.2)	16.2 (14.7-18.2)	NA*
	Log-rank P value = 0.12		
Pre-treated patients (refractory to irinotecan + 5-FU/FA)	8.8 (7.3-9.3)	9.9 (9.1-10.5)	8.1 (7.2-8.7)
	Log-rank P value = 0.09		
Pre-treated patients (refractory to 5-FU/FA)	NA*	10.8 (9.3-12.8)	NA*

CI Confidence interval
5FU 5-fluorouracil
FA folinic acid
ITT Intention to treat
**NA Not applicable*

In pre-treated patients, who were symptomatic at baseline, a higher proportion of those treated with oxaliplatin and 5-FU/FA (FOLFOX4) experienced a significant improvement of their disease-related symptoms compared to those treated with 5-FU/FA alone (LV5FU2) (27.7% vs 14.6%, p = 0.0033).

In non-pre-treated patients, no statistically significant difference between the two treatment groups was found for any of the quality of life dimensions. However, the quality of life scores were generally better in the control arm for measurement of global health status and pain and worse in the oxaliplatin arm for nausea and vomiting.

In the adjuvant setting, the MOSAIC comparative phase III study 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 (FOLFOX4, n=1123 (B2/C = 451/672).

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

Treatment arm	5-FU/FA (LV5FU2)	oxaliplatin + 5-FU/FA (FOLFOX4)
Percent 3-year disease free survival (95% CI)	73.3 (70.6-75.9)	78.7 (76.2-81.1)
Hazard ratio (95% CI)	0.76 (0.64-0.89)	
Stratified log rank test	P= 0.0008	

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

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

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

Patient stage	Stage II (Duke's B2)		Stage III (Duke's C)	
Treatment arm	5-FU/FA (LV5FU2)	oxaliplatin + 5-FU/FA (FOLFOX4)	5-FU/FA (LV5FU2)	oxaliplatin + 5-FU/FA (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 oxaliplatin + 5-FU/FA (FOLFOX4) arm versus 83.8% in the 5-FU/FA (LV5FU2) arm. This translated into an overall reduction in mortality risk of 10% in favour of oxaliplatin + 5-FU/FA (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 oxaliplatin + 5-FU/FA (FOLFOX4) and 5-FU/FA (LV5FU2), respectively.

5.2 Pharmacokinetic properties

The pharmacokinetics of individual active compounds have not been determined. The pharmacokinetics of ultrafiltrable platinum, representing a mixture of all unbound, active and inactive platinum species, following a two-hour infusion of oxaliplatin at 130 mg/m^2 every three weeks for 1 to 5 cycles and oxaliplatin at 85 mg/m^2 every two weeks for 1 to 3 cycles are as follows:

Summary of platinum pharmacokinetic parameter estimates in ultrafiltrate following multiple doses of oxaliplatin 85 mg/m^2 every two weeks or 130 mg/m^2 every three weeks

Dose	C^{max} µg/ml	AUC_{0-48} µg.h/ml	AUC µg.h/ml	$T_{1/2\alpha}$ h	$T_{1/2\beta}$ h	$T_{1/2\gamma}$ h	V_{ss} l	CL 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, V_{ss}, CL, and CL_{RO-48} values were determined on cycle 1.
C_{end}, C_{max}, AUC, AUC_{0-48}, V_{ss} 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. No teratogenicity was observed in rats and rabbits; however, this was only studied up to 1/20 of the maximum recommended clinical dose, based on body surface area. 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 diluted medication should not be mixed with other medicinal products in the same infusion bag or the same infusion line. In section 6.6 the instructions are described for co-administration of oxaliplatin and folinic acid (FA) using a Y-line.

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

6.3 Shelf Life

Vial before opening:
3 years

Stability in-use:
After reconstitution in water for injection or 5% glucose, chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C.

From a microbiological and chemical point of view, the reconstituted solution should be diluted immediately with 5% glucose solution.

After dilution in 5% glucose, chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C and for 6 hours at 25°C.

From a microbiological point of view, this infusion preparation should be used immediately.
If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
Infusion preparation: for storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

1 colourless, type I glass vial with chlorobutyl rubber stopper, aluminium seal and polypropylene snap-cap, containing 20 mg of oxaliplatin.
1 colourless, type I glass vial with chlorobutyl rubber stopper, aluminium seal and polypropylene snap-cap, containing 50 mg of oxaliplatin.
1 colourless, type I glass vial with chlorobutyl rubber stopper, aluminium seal and polypropylene snap-cap, containing 100 mg of oxaliplatin.

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 to avoid handling cytotoxic agents.

Any broken container must be treated with the same precautions and considered as contaminated waste. Contaminated waste should be incinerated in suitably labelled rigid containers. See below section “Disposal”.

If oxaliplatin powder, reconstituted solution or infusion solution should come into contact with skin, wash immediately and thoroughly with water.
If oxaliplatin powder, reconstituted solution or infusion solution, should come into contact with mucous membranes, wash immediately and thoroughly with water.

Special precautions for administration

- DO NOT use injection material containing aluminium.
- DO NOT administer undiluted.
- ONLY dilute with 5% glucose solution. DO NOT dilute for infusion with saline or chloride containing solution.
- DO NOT mix with any other medication in the same infusion bag or administer simultaneously by the same infusion line.
- DO NOT mix with alkaline medical products or solutions, in particular 5-fluorouracil, (5-FU), folinic acid (FA) products containing trometamol as an excipient and trometamol salts of other active substances. The alkaline medicinal products or solutions will adversely affect the stability of oxaliplatin.

Instructions for use with folinic acid (FA) (calcium folinate or sodium folinate)

Oxaliplatin 85 mg/m^2 IV in 250 to 500 ml of 5% glucose solution can be co-administered with folinic acid (FA) IV infusion in 5% glucose solution during 2 to 6 hours, using a Y-line, which is placed immediately before the site of injection. These two medical products should not be combined in the same infusion bag. Folinic acid (FA) must not contain trometamol as an excipinet and must only be diluted using isotonic infusion solutions such as 5% glucose solution but NOT sodium chloride solutions, chloride containing solutions or alkaline solutions.

Instruction for use with 5-fluorouracil (5-FU)

Oxaliplatin should always be administered before fluoropyrimidines (eg. 5-fluorouracil (5-FU)).
Always flush the line following oxaliplatin administration and only after that can 5-fluorouracil (5-FU) be administered.

Reconstitution of the solution

Water for injections or 5% glucose solution should be used to reconstitute the powder.
- For a vial of 20 mg: add 4 ml of solvent to obtain a concentration of 5 mg oxaliplatin/ml.
- For a vial of 50 mg: add 10 ml of solvent to obtain a concentration of 5 mg oxaliplatin/ml.
- 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 solution should be discarded.

Dilution for intravenous infusion

Withdraw the required amount of 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 0.2 mg/ml and 0.7 mg/ml. The concentration range over which the physico-chemical stability of oxaliplatin has been demonstrated is 0.2 mg/ml to 1.25 mg/ml.

Administer by intravenous infusion.

After dilution in 5% glucose, chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C and for 6 hours at 25°C.

From a microbiological point of view, this infusion prepared 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 2-8°C unless dilution has taken place in controlled and validated aseptic conditions.

Inspect visually prior to use. Only clear solutions without particles should be used.

The medicinal product is for single use only. Any unused solution should be discarded.

NEVER use sodium chloride or chloride containing solutions for dilution.

The compatibility of oxaliplatin 5 mg/ml, powder for solution for infusion has been tested with PVC free administration sets.

Infusion

The administration of oxaliplatin does not require prehydration.

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

Disposal

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

7 MARKETING AUTHORISATION HOLDER

Pharmachemie B.V.
Swensweg 5
P.O. Box 552
2003 RN Haarlem
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 937/7/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9 June 2008

10 DATE OF REVISION OF THE TEXT