Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Oxaliplatin Ebewe 5 mg/ml powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial with powder for solution for infusion contains 50 mg or 100 mg or 150 mg oxaliplatin.

One ml of reconstituted concentrate solution contains 5 mg oxaliplatin.

50 mg vial : Each vial contains 50 mg oxaliplatin for reconstitution in 10 ml of solvent .
100 mg vial : Each vial contains 100 mg oxaliplatin for reconstitution in 20 ml of solvent.
150 mg vial: Each vial contains 150 mg oxaliplatin for reconstitution in 30 ml of solvent.

Excipient(s) with known effect:
One 50 mg vial contains 450 mg of lactose monohydrate.
One 100 mg vial contains 900 mg of lactose monohydrate.
One 150 mg vial contains 1350 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion

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 tumour
- Treatment of metastatic colorectal cancer.

4.2 Posology and method of administration

Posology

FOR ADULTS ONLY

Paediatric population
There is no relevant use of Oxaliplatin in the paediatric population for the claimed indications.

The recommended dose for oxaliplatin in adjuvant setting is 85 mg/m² intravenously repeated every two weeks for 12 cycles (6 months).

The recommended dose for oxaliplatin in treatment of metastatic colorectal cancer is 85 mg/m² intravenously repeated every 2 weeks.

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

Oxaliplatin should always be administered before fluoropyrimidines.

Oxaliplatin is administered as a 2- to 6-hour intravenous infusion in 250 to 500 ml of 5% glucose solution to give a concentration between 0.2 mg/ml and 0.70 mg/ml; 0.70 mg/ml is the highest concentration in clinical practice for an oxaliplatin dose of 85 mg/m².
Oxaliplatin was mainly used in combination with continuous infusion 5-fluorouracil based regimens. For the two-weekly treatment schedule 5-fluorouracil regimens combining bolus and continuous infusion were used.

Special Populations

- Renal impairment

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

- Hepatic 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 patients

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

Method of administration

Oxaliplatin is administered by intravenous infusion.

The administration of oxaliplatin does not require hyperhydration.

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

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

The preparation of injectable solution of cytotoxic agents must be carried out by trained specialist personnel with knowledge of the medicinal products used, in condition that guarantee the integrity of medical product, the protection of the environment and in the 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.

Instructions for use:
See section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Breast feeding
- 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
- Peripheral sensory neuropathy with functional impairment prior to first course
- 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.

Renal impairment
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.

Hypersensitivity reactions
Special surveillance should be ensured for patients with a history of allergic manifestations to other products containing platinum. In case of anaphylactic manifestations the infusion should be interrupted immediately and an appropriate symptomatic treatment started. Re-administration of oxaliplatin to such patients is contraindicated. Cross reactions, sometimes fatal, have been reported with all platinum compounds.

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

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

For patients who develop acute laryngopharyngeal dysaesthesia (see section 4.8) during or within several hours after a 2-hour infusion, the subsequent oxaliplatin infusion must be administered over 6 hours.

Peripheral neuropathy
If neurological symptoms (paraesthesia, dysaesthesia) occur, the following recommended oxaliplatin dosage should be adjusted based on duration and severity of existing 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 about the possibility of persistent symptoms of peripheral sensory neuropathy after the end of the treatment. Localised moderate paraesthesia or paraesthesia that may interfere with functional activities can persist after up to 3 years following treatment cessation in the adjuvant setting.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
Cases of Reversible Posterior Leukoencephalopathy Syndrome (RPLS, also known as PRES, Posterior Reversible Encephalopathy Syndrome) have been reported in patients receiving oxaliplatin in combination chemotherapy. RPLS is a rare, reversible, rapidly evolving neurological condition, which can include seizure, hypertension, headache, confusion, blindness, and other visual and neurological disturbances (see section 4.8 Undesirable effects).
Diagnosis of RPLS is based upon confirmation by brain imaging, preferably MRI (Magnetic Resonance Imaging).

Nausea, vomiting, diarrhoea, dehydration, and hematologic changes
Gastrointestinal toxicity of oxaliplatin, i.e. symptoms such as nausea and vomiting, requires prophylactic and/or therapeutic use of antiemetics (see section 4.8 Undesirable effects).

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 therapy and before each subsequent course.

Patients must be adequately informed about the risk of diarrhoea/emesis, mucositis/stomatitis and neutropenia following oxaliplatin and 5-fluorouracil (5-FU) administration so 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 I or less and/or until the neutrophil count is ≥ 1.5 x 10^9/l.

For oxaliplatin combined with 5-fluorouracil (5-FU) (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 < 1.0 x 10^9/l), 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.

Pulmonary
In cases 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 Undesirable effects).

Hepatic
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.

Pregnancy
For use in pregnant women, see section 4.6 Pregnancy and lactation.

Fertility
Genotoxic effects were observed with oxaliplatin in 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..Effective contraception must be used throughout the treatment and following the treatment for 4 months. (see section 4.6).

Immunosuppressant Effects/Increased Susceptibility to Infections/live or live-attenuated vaccines
Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including oxaliplatin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving oxaliplatin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Paediatric population
There is no relevant indication for use of oxaliplatin in children. The safety and efficacy of Oxaliplatin in children has not been established.

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 plasma levels of 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: erythromycin, salicylates, granisetron, paclitaxel, and sodium valproate.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
To date there is no available information on safety of use in pregnant women. In animal studies, reproductive toxicity was observed. Consequently, oxaliplatin is not recommended during pregnancy and in women of childbearing potential not using contraceptive measures.

The use of oxaliplatin should only be considered after suitably appraising the patient of the risk to the foetus and with the patient's consent.

Appropriate contraceptive measures must be taken during and after cessation of therapy during 4 months for women and 6 months for men.

Breast feeding
Excretion in breast milk has not been studied. Breast-feeding is contraindicated during oxaliplatin therapy.

Fertility
Oxaliplatin may have an anti-fertility effect (see section 4.4 Special warnings and precautions for use).

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. Vision abnormalities, in particular transient vision loss (reversible following therapy discontinuation), may affect patients' ability to drive and use machines. Therefore, patients should be warned of the potential effect of these events on the ability to drive or use machines.

4.8 Undesirable effects

The most frequent adverse events of oxaliplatin in combination with 5-fluorouracil and folinic acid (5-FU and FA) were of gastrointestinal (diarrhoea, nausea, vomiting and mucositis), haematological (neutropenia, thrombocytopenia) and neurological (acute and dose cumulative peripheral sensory neuropathy) nature.
Overall, these adverse events were more frequent and severe when 5-FU/FA was administered in combination with oxaliplatin compared to 5-FU/FA alone.
The frequency data reported in the table below are derived from clinical trials on the treatment of metastases and adjuvant treatment (including 416 and 1,108 patients, respectively, in the oxaliplatin + 5-fluorouracil (5-FU)/folinic acid (FA) treatment arm) and from post marketing surveillance.

Frequencies in this table are defined using the following convention: 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).
Further details are given following this table.

MedDRA classification	Very common	Common	Uncommon	Rare	Very rare
Infections and infestations*	-Infection	-Rhinitis -Upper respiratory tract infection -Neutropenic sepsis			
Blood and lymphatic system disorders*	-Anemia -Neutropenia -Thrombocytopenia -Leukopenia	-Febrile neutropenia		-Haemolytic anemia -Immunoallergic thrombocytopenia	

	-Lymphopenia				
Immune system disorders*	-Allergy/allergic reaction+				
Metabolism and nutrition disorders	-Anorexia -Hyperglycemia -Hypokalaemia -Hypematraemia	-Dehydration	-Metabolic acidosis		
Psychiatric disorders		-Depression -Insomnia	-Nervousness		
Nervous system disorders*	-Peripheral sensory neuropathy -Headache -Sensory disturbance -Dysgeusia	-Dizziness -Motor neuritis -Meningism		-Dysarthria -Reversible Posterior Leukoencephalopathy syndrome (RPLS) -also known as PRES)**	
Eye disorders		-Conjunctivitis -Visual disturbance		-Visual acuity reduced transiently -Visual field disturbance, optic neuritis, -Transient vision loss (reversible following therapy discontinuation)	
Ear and labyrinth			-Ototoxicity	-Deafness	
Vascular disorders		-Haemorrhage -Flushing -Deep vein thrombosis -Hypertension			
Respiratory, thoracic and mediastinal disorders	-Dyspnoea -Cough -Epistaxis	-Hiccups -Pulmonary embolism		-Interstitial lung disease, sometimes fatal -Pulmonary fibrosis**	
Gastrointestinal disorders	-Diarrhea -Nausea -Vomiting -Stomatitis / Mucositis -Abdominal pain -Constipation	-Dyspepsia -Gastroesophageal reflux -Gastrointestinal haemorrhage	-Ileus -Intestinal obstruction	-Colitis including Clostridium difficile diarrhea -Pancreatitis	
Hepatobiliary disorders					Liver sinusoidal obstruction syndrome (see below)
Skin and subcutaneous tissue disorders	-Skin disorder -Alopecia	-Skin exfoliation (i.e. hand foot syndrome) -Rash erythematous, -Rash -Hyperhidrosis -Nail disorder			
Musculoskeletal system, connective tissue and bone disorders	-Back pain	-Arthralgia -Bone pain			
Renal and urinary disorders		-Haematuria -Dysuria -Micturition frequency abnormal			-Acute tubular necrosis -Acute interstitial nephritiis -Acute renal failure
General disorders and administration site conditions	-Fever++ -Injection site reaction+++ -Fatigue -Asthenia -Pain				
Investigations	-Blood alkaline phosphatase increase -Blood bilirubin increase -Blood lactate dehydrogenase (LDH) increase -Hepatic enzymes	-Creatinine increases, loss of weight (metastatic setting)			

	increase -Weight increase (adjuvant setting)				

* See detailed information in the section below
** See section 4.4.
\+ Very common: frequent allergy/allergic reactions, occurring mainly during perfusion, sometimes fatal (frequent allergic reactions such as skin rash, in particularly urticaria, conjunctivitis, rhinitis.
Common anaphylactic or anaphylactoid reactions, include bronchospasm, angioedema, hypotension, sensation of chest pain, and anaphylactic shock.
++ Very commonly fever, rigors (tremor), either from infection (with or without febrile neutropenia) or possibly from immunological mechanism.
+++ Injection site reactions including local pain, reddening, swelling and thrombosis have been reported. Extravasation may result in local pain and inflammation, which may be severe and lead to complications including necrosis, especially when oxaliplatin is infused through a peripheral vein (see. 4.4).

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

Blood and lymphatic system disorders

Incidence by patient (%) and by grade

Oxaliplatin/5 FU/FA, 85 mg/m^2 every 2 weeks	Treatment of metastases			Adjuvant therapy		
	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

Postmarketing experience with frequency unknown:
Hemolytic uremic syndrome

Gastrointestinal disorders

Incidence by patient (%) and by grade

Oxaliplatin/5 FU/FA, 85 mg/m^2 every 2 weeks	Treatment of metastases			Adjuvant therapy		
	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/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 (5-FU) (see section 4.4).

Nervous system disorders:

Oxaliplatin shows dose limiting neurological toxicity. 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 functional disorders is an indication for dose adjustments or even treatment discontinuation, depending on the duration of these symptoms (see section 4.4).
These functional disorders include difficulties in executing delicate movements and are 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 improved or totally recovered when treatment was 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 persistent localised paraesthesia of moderate intensity (2.3%) or with paraesthesia with functional impairment (0.5%).
Acute neurosensory manifestations (see section 5.3) have been reported, appearing within hours of administration and often related to exposure to the cold. They may present as transient paraesthesia, dysaesthesia and hypoaesthesia or as an acute syndrome of pharyngolaryngeal dysaesthesia. This acute syndrome of pharyngolaryngeal dysaesthesia, with an incidence between 1% and 2%, is characterised by subjective sensations of dysphagia or dyspnoea, 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 were rapidly reversible even in the absence of treatment. Prolongation of the infusion helps to reduce the incidence of this syndrome (see section 4.4). In addition, the following symptoms were occasionally observed: Jaw spasms, muscle spasms, involuntary muscle contractions, muscle twitching, myoclonus, impaired coordination, abnormal gait, ataxia, balance disorders, throat or chest tightness, feeling of pressure, discomfort, pain. In addition, cranial nerve dysfunctions may be associated with the above mentioned events, or also occur as an isolated event such as ptosis, diplopia, aphonia, dysphonia, hoarseness, sometimes described as vocal cord paralysis, abnormal tongue sensation or dysarthria, sometimes described as aphasia, trigeminal neuralgia, facial pain, eye pain, decrease in visual acuity, visual field disorders.
Other neurological symptoms such as dysarthria, loss of deep tendon reflex and Lhermitte's sign were reported during treatment with oxaliplatin. Isolated cases of optic neuritis have been reported.

Postmarketing experience with frequency unknown:
Convulsion

Immune system disorders:

Incidence by patient (%) and by grade

Oxaliplatin/5 FU/FA, 85mg/m^2 every 2 weeks	Treatment of metastases			Adjuvant therapy		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 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: 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 (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 phase III study (de Gramont, A et al., 2000) randomised 420 patients either to 5-FU/FA alone (LV5FU2, N=210) or the combination of oxaliplatin with 5-FU/FA (FOLFOX4, N=210).

- In pretreated patients, a comparative three arms phase III study (Rothenberg, ML et al., 2003) randomised 821 patients refractory to an irinotecan (CPT-11) + 5-FU/FA combination either to 5-FU/FA alone (LV5FU2, N=275), oxaliplatin single agent (N=275), or combination of oxaliplatin with 5-FU/FA (FOLFOX4, N=271).

- Finally, an uncontrolled phase II study (André, T et al., 1999) included patients refractory to 5-FU/FA alone, that were treated with the oxaliplatin and 5-FU/FA combination (FOLFOX4, N=57)

The two randomised clinical trials in front-line therapy (de Gramont, A et al.) and in pretreated patients (Rothenberg ML et al.), demonstrated a significantly higher response rate and a prolonged progression free survival (PFS) / time to progression (TTP) as compared to treatment with 5-FU/FA alone. In the study of Rothenberg et al. performed in refractory pretreated patients, the difference in median overall survival (OS) between the combination of oxaliplatin and 5-FU/FA versus 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 (de Gramont, A et al., 2000) *Response assessment every 8 weeks*	22 (16-27)	49 (42-46)	NA*
	P value = 0.0001		
Pretreated patients (Rothenberg, ML et al., 2003) (refractory to CPT-11 + 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		

Pretreated patients (André, T et al., 1999) (refractory to 5-FU/FA) *Response assessment every 12 weeks*	NA*	23 (13-36)	NA*

* NA: Not applicable.

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

Median PFS/TTP, Months (95% CI) independent radiological review ITT analysis	**LV5FU2**	**FOLFOX4**	**Oxaliplatin Single agent**
Front-line treatment (de Gramont, A et al., 2000) (PFS)	6.0 (5.5-6.5)	8.2 (7.2-8.8)	NA*
	Log-rank P value = 0.0003		
Pretreated patients (Rothenberg, ML et al., 2003) (TTP) (refractory to CPT-11 + 5-FU/FA)	2.6 (1.8-2.9)	5.3 (4.7-6.1)	2.1 (1.6-2.7)
	Log-rank P value < 0.0001		
(Pretreated patients (André, T et al., 1999) (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 (de Gramont, A et al., 2000)	14.7 (13.0-18.2)	16.2 (14.7-18.2)	NA*
	Log-rank P value = 0.12		
Pretreated patients (Rothenberg, ML et al., 2003) (TTP) (refractory to CPT-11 + 5-FU/FA)	8.8 (7.3-9.3)	9.9 (9.1-10.5)	8.1 (7.2-8.7)
	Log-rank P value = 0.09		
Pretreated patients (André, T et al., 1999) (refractory to 5-FU/FA)	NA*	10.8 (9.3-12.8)	NA*

* NA: Not applicable.

In pretreated patients (Rothenberg, ML et al., 2003), who were symptomatic at baseline, a higher proportion of those treated with oxaliplatin and 5-FU/FA experienced a significant improvement of their disease-related symptoms compared to those treated with 5-FU/FA alone (27.7 % vs 14.6 %, p = 0.0033).

In non pretreated patients (de Gramont, A et al., 2000), 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 tumour of colon cancer either to 5-FU/FA alone (LV5FU2, N=1123 (B2 / C = 448 / 675) or to combination of oxaliplatin and 5-FU/FA (FOLFOX4, N=1123 (B2 / C) = 451 / 672).

MOSAIC-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 (70.6-75.6)	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).

MOSAIC-3-year Disease Free Survival (ITT analysis)* according to Stage of Disease

Patient stage	**Stage II (Duke's B2)**		**Stage III (Duke's C)**	
Treatment arm	LV5FU2	FOLFOX4	LV5FU2	FOLFOX4
Percent 3-year disease free survival (95% CI)	84.3 (80.9-87.7)	87.4 (84.3-90.5)	65.8 (62.1-69.5)	72.8 (69.4-76.2)
Hazard ratio (95% CI)	0.79 (0.57-1.09)		0.75 (0.62-0.90)	
Stratified log rank test	P = 0.151		P = 0.002	

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

Overall Survival (ITT analysis):

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

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:

Table 10: Summary of Platinum Pharmacokinetic Parameter Estimates in Ultrafiltrate following Multiple Doses of Oxaliplatin at 85 mg/m^2 Every Two Weeks or at 130 mg/m^2 Every Three Weeks

Dose	**C_{max}**	**AUC_{0-48}**	**AUC**	**$t_{1/2\alpha}$**	**$t_{1/2\beta}$**	**$t_{1/2\gamma}$**	**V_{ss}**	**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}, V_{ss} and CL values were determined by non-compartmental analysis.
$t_{1/2\alpha}$, $t_{1/2\beta}$, $t_{1/2\gamma}$ 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 non-clinical 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. Non-clinical 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 diluted medicinal product should not be mixed with other medications in the same infusion bag or infusion line. Under instructions for use described in section 6.6, oxaliplatin can be co-administered with folinic acid via a Y-line.

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

6.3 Shelf life

Medicinal product as packaged for sale:
3 years

Reconstituted concentrate solution in the original vial:
The reconstituted concentrate solution should be diluted immediately.

Solution for infusion after dilution:
After dilution of the reconstituted solution in 5 % glucose solution, chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C.

From a microbiological point of view, the solution for infusion should be used immediately.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C.

6.4 Special precautions for storage

Medicinal product as packaged for sale:
This medicinal product does not require any special storage conditions.
For storage conditions of the reconstituted and diluted product, see section 6.3.

6.5 Nature and contents of container

Type I glass vials with stoppers of chlorobutyl elastomer.
Supplied in packs of 1 vial containing oxaliplatin 50 mg, 100 mg or 150 mg.
Glass vialswith/without transparent plastic container (ONKO-Safe)

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 in accordance with the hospital policy. It requires a preparation area reserved for this purpose. It is forbidden to smoke, eat or drink in this area.

Personnel must be provided with appropriate handling materials, notably long sleeved gowns, protection masks, caps, protective goggles, sterile single-use gloves, protective covers for the work area, containers and collection bags for waste.

Excreta and vomit must be handled with care.

Pregnant women must be warned to avoid handling cytotoxic agents.

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

If oxaliplatin 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 glucose 5% infusion solution (50 mg/ml) is to be used as a diluent.
- DO NOT reconstitute or dilute for infusion with sodium chloride or chloride containing solutions.
- DO NOT administer extravascularly.
- DO NOT mix with any other medication in the same infusion bag or administer simultaneously by the same infusion line.
- DO NOT mix with alkaline drugs or solutions, in particular 5-fluorouracil, folinic acid preparations containing trometamol as an excipient and trometamol salts of other drugs. Alkaline drugs or solutions will adversely affect the stability of oxaliplatin.

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

Oxaliplatin 85mg/m² IV infusion in 250 to 500 ml of 5% glucose solution (50 mg/ml) is given at the same time as folinic acid IV infusion in 5% glucose solution, over 2 to 6 hours, using a Y-line placed immediately before the site of infusion.
These two drugs should **not** be combined in the same infusion bag. Folinic acid must not contain trometamol as an excipient and must only be diluted using isotonic 5% glucose solution, never in alkaline solutions or sodium chloride or chloride containing solutions.

Instruction for use with 5-fluorouracil

Oxaliplatin should always be administered before fluoropyrimidines – i.e. 5-fluorouracil.
After oxaliplatin administration, flush the line and then administer 5-fluorouracil.
For additional information on drugs combined with oxaliplatin, see the corresponding manufacturer's summary of product characteristics.

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 powder
- Water for injections or 5 % glucose solution (50 mg/ml) should be used to reconstitute the solution.
- 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.
- For a vial of 150 mg: add 30 ml of solvent to obtain a concentration of 5 mg oxaliplatin/ml.

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 (see below “Disposal”).

Dilution before infusion

Withdraw the required amount of reconstituted concentrate 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, concentration range for which the physico-chemical stability of oxaliplatin has been demonstrated.
Administer by IV infusion.
After dilution in 5% glucose, chemical and physical in-use stability has been demonstrated for 24 hours 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.
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 solution for either reconstitution or dilution.

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

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

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

7 MARKETING AUTHORISATION HOLDER

Ebewe Pharma Ges.m.b.H. Nfg. KG
Mondseestrasse 11
4866 Unterach
Austria

8 MARKETING AUTHORISATION NUMBER

PA0789/016/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12th December 2008

Date of last renewal: 19th March 2012

10 DATE OF REVISION OF THE TEXT

October 2013