1. NAME OF THE MEDICINAL PRODUCT

Oxaliplatin Ebewe 5 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml concentrate for solution for infusion contains 5 mg oxaliplatin.

10 ml of concentrate for solution for infusion contains 50 mg of oxaliplatin

20 ml of concentrate for solution for infusion contains 100 mg of oxaliplatin

30 ml of concentrate for solution for infusion contains 150 mg of oxaliplatin

40 ml of concentrate for solution for infusion contains 200 mg of oxaliplatin

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion

Clear, colourless liquid

pH: 4.0 – 6.0

Osmolarity: 140 mOsmol/kg

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 (see section 6.6 for detailed information).

Posology

FOR ADULTS ONLY

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

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

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

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

Oxaliplatin is administered as a 2- to 6-hour intravenous infusion in 250 to 500 ml of 5% glucose solution (50mg/ml) to give a concentration between 0.2 mg/ml and 0.70 mg/ml; 0.7 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.

- Pediatric patients:

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

Method of administration

Oxaliplatin is administered by intravenous infusion.

The administration of oxaliplatin does not require hyperhydration.

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

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

Instructions for use

Oxaliplatin must be further diluted before use. Only 5% glucose diluent is to be used to dilute the concentrate for solution for infusion. (see section 6.6).

4.3 Contraindications

Oxaliplatin is contraindicated in patients who

- have a known history of hypersensitivity to oxaliplatin or to any of the excipients.
- are breast feeding.
- 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 peripheral sensory neuropathy with functional impairment prior to first course.
- have a severely impaired renal function (creatinine clearance less than 30 ml/min).

4.4 Special warnings and special precautions for use

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

For use in pregnant women, see section 4.6.

Due to limited information on safety in patients with moderately impaired renal function, administration should only be considered after suitable appraisal of the benefit/risk for the patient.

In this situation, renal function should be closely monitored and dose adjusted according to toxicity.

Patients with a history of allergic reaction to platinum compounds should be monitored for allergic symptoms. In case of an anaphylactic-like reaction to oxaliplatin, the infusion should be immediately discontinued and appropriate symptomatic treatment initiated. Oxaliplatin rechallenge is contraindicated.

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

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

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

If neurological symptoms (paraesthesia, dysaesthesia) occur, the following recommended oxaliplatin dosage adjustment should be based on the duration and severity of these symptoms:

- If symptoms last longer than seven days and are troublesome, the subsequent oxaliplatin dose should be reduced from 85 to 65 mg/m² (metastatic setting) or 75 mg/m² (adjuvant setting).
- If paraesthesia without functional impairment persists until the next cycle, the subsequent oxaliplatin dose should be reduced from 85 to 65 mg/m² (metastatic setting) or 75 mg/m² (adjuvant setting).
- If paraesthesia with functional impairment persists until the next cycle, oxaliplatin should be discontinued.
- If these symptoms improve following discontinuation of oxaliplatin therapy, resumption of therapy may be considered.

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

Gastrointestinal toxicity, which manifests as nausea and vomiting, warrants prophylactic and/or therapeutic

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

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

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

Patients must be adequately informed of the risk of diarrhoea/emesis, mucositis/stomatitis and neutropenia after oxaliplatin and 5-fluorouracil administration so that they can urgently contact their treating physician for appropriate management.

If mucositis/stomatitis occurs with or without neutropenia, the next treatment should be delayed until recovery from mucositis/stomatitis to grade 1 or less and/or until the neutrophil count is > 1.5 x 10^9/l.

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

If grade 4 diarrhoea, grade 3-4 neutropenia (neutrophils < 1.0 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/m² to 65 mg/m² (metastatic setting) or 75 mg/m² (adjuvant setting), in addition to any 5-fluorouracil dose reductions required.

In the case of unexplained respiratory symptoms such as non-productive cough, dyspnoea, crackles or radiological pulmonary infiltrates, oxaliplatin should be discontinued until further pulmonary investigations exclude an interstitial lung disease (see section 4.8).

In 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.

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

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

Immunosuppressant Effects/Increased Susceptibility to Infections: 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.

4.5 Interactions with other medicinal products and other forms of interaction

In patients who have received a single dose of 85 mg/m² of oxaliplatin, immediately before administration of 5-fluorouracil, no change in the level of exposure to 5-fluorouracil has been observed.

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

4.6 Fertility, Pregnancy and lactation

To date there is no available information on safety of use in pregnant women.

In animal studies, reproductive toxicity was observed (see section 5.3). Consequently, oxaliplatin is not recommended during pregnancy and in women of childbearing potential not using contraceptive measures.

The use of oxaliplatin should only be considered after suitably apprising 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.

Oxaliplatin may have an anti-fertility effect (see section 4.4).

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

4.7 Effects on ability to drive and use machines

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

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

4.8 Undesirable effects

The most frequent adverse events of oxaliplatin in combination with 5-fluorouracil/folinic acid (5-FU/FA) were gastrointestinal (diarrhea, nausea, vomiting and mucositis), haematological (neutropenia, thrombocytopenia) and neurological (acute and dose cumulative peripheral sensory neuropathy). Overall, these adverse events were more frequent and severe with oxaliplatin and 5-FU/FA combination than with 5-FU/FA alone.

The frequencies reported in the table below are derived from clinical trials in the metastatic and adjuvant settings (having included 416 and 1108 patients respectively in the oxaliplatin +

5-FU/FA treatment arms) and from post marketing experience.

The frequency of undesirable effects listed below is defined using 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)

Further details are given after the table.

Table 1: Adverse effects by system organ class

MedDRA Organ System Class	Very common	Common	Uncommon	Rare
Infections and infestations*	- Infection	- Rhinitis - Upper respiratory tract infection - Febrile neutropenia / neutropenic sepsis		
Blood and lymphatic system disorders*	- Anemia - Neutropenia - Thrombocytopenia - Leukopenia - Lymphopenia			- Haemolytic anemia - Immunoallergic thrombocytopenia
Immune system disorders*	- Allergy/allergic reaction+			
Metabolism and nutrition disorders	- Anorexia - Glycemia abnormalities - Hypokalaemia - Natraemia abnormalities	- Dehydration	- Metabolic acidosis	
Psychiatric disorders		- Depression - Insomnia	- Nervousness	
Nervous system disorders*	- Peripheral sensory neuropathy - Headache - Sensory disturbance - Dysgeusia	- Dizziness - Motor neuritis - Meningism		- Dysarthria
Eye disorders		- Conjunctivitis - Visual disturbance		- Transient reduction in visual acuity - Visual field disturbances - Optic neuritis - Transient vision loss, reversible following therapy discontinuation
Ear and labyrinth disorders			- Ototoxicity	- Deafness

disorders				
Vascular disorders	- Epistaxis	- Haemorrhage NOS - Flushing - Deep vein thrombosis - Pulmonary embolism - Hypertension		
Respiratory, thoracic and mediastinal disorders	- Dyspnoea - Cough	- Hiccups		- Interstitial lung disease, sometimes fatal - Pulmonary fibrosis**
Gastrointestinal disorders *	- Diarrhea - Nausea - Vomiting - Stomatitis / Mucositis - Abdominal pain - Constipation	- Dyspepsia - gastroesophageal reflux - Gastrointestinal haemorrhage - Rectal haemorrhage	- Ileus - intestinal obstruction	- Colitis including Clostridium difficile diarrhea
Skin and subcutaneous tissue disorders	- Skin disorder - Alopecia	- Skin exfoliation (i.e. hand and foot syndrome) - Rash erythematous, - Rash - Hyperhidrosis - Nail disorder		
Musculoskeletal and connective tissue disorders	- Back pain	- Arthralgia - Bone pain		
Renal and urinary disorders		- Haematuria - Dysuria - micturition frequency abnormal		
General disorders and administration site conditions+	- Fever++ - Injection site reaction+++ - Fatigue - Asthenia - Pain			
Investigations	- Alkaline phosphatase increase - Bilirubin increase - LDH increase - Hepatic enzymes (SGPT/ALAT, SGOT/ ASAT) increase - Weight increase (adjuvant setting)	- Creatinine increase - Weight decrease (metastatic setting)		

* See detailed section below

** See section 4.4

+ Common allergic reactions such as skin rash (particularly urticaria), conjunctivitis, rhinitis.

Common anaphylactic reactions, including bronchospasm, sensation of chest pain, angioedema, hypotension and anaphylactic shock

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

Hepato-biliary disorders

Very rare (1/10,000):

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

Very rare (1/10,000):

Acute tubular necrosis, acute interstitial nephritis and acute renal failure.

Blood and lymphatic system disorders

Table 2: Incidence by patient (%), by grade

Oxaliplatin and 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
Anemia	82.2	3	< 1	75.6	0.7	0.1
Neutropenia	71.4	28	14	78.9	28.8	12.3
Thrombocytopenia	71.6	4	< 1	77.4	1.5	0.2
Febrile neutropenia	5.0	3.6	1.4	0.7	0.7	0.0
Neutropenic sepsis	1.1	0.7	0.4	1.1	0.6	0.4

Postmarketing experience with frequency unknown
Hemolytic uremic syndrome

Gastrointestinal disorders

Table 3: Incidence by patient (%), by grade

Oxaliplatin and 5-FU/FA 85 mg/m² every 2 weeks	**Metastatic Setting**			**Adjuvant Setting**		
	All grades	Gr 3	Gr 4	All grades	Gr 3	Gr 4
Nausea	69.9	8	< 1	73.7	4.8	0.3
Diarrhoea	60.8	9	2	56.3	8.3	2.5
Vomiting	49.0	6	1	47.2	5.3	0.5
Mucositis / Stomatitis	39.9	4	< 1	42.1	2.8	0.1

Prophylaxis and/or treatment with potent antiemetic agents is indicated.

Dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis particularly when combining oxaliplatin with 5-fluorouracil (see section 4.4).

Nervous system:

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

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

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

In the majority of the cases, the neurological signs and symptoms improve or totally recover when treatment is discontinued. In the adjuvant setting of colon cancer, 6 months after treatment cessation, 87 % of patients had no or mild symptoms. After up to 3 years of follow up, about 3 % of patients presented either with persisting localised paraesthesias of moderate intensity (2.3 %) or with paraesthesias that may interfere with functional activities (0.5 %).

Acute neurosensory manifestations (see section 5.3) have been reported. They start within hours of administration and often occur on exposure to cold. They may present as transient paraesthesia, dysaesthesia and hypoesthesia or as an acute syndrome of pharyngolaryngeal dysaesthesia. This acute syndrome of

pharyngolaryngeal dysaesthesia, with an incidence estimated between 1 % and 2 %, is characterised by subjective sensations of dysphagia or dyspnoea/feeling of suffocation, without any objective evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm (no stridor or wheezing). Although antihistamines and bronchodilators have been administered in such cases, the symptoms are rapidly reversible even in the absence of treatment. Prolongation of the infusion helps to reduce the incidence of this syndrome (see section 4.4). Occasionally other symptoms that have been observed include jaw spasm/muscle

spasms/muscle contractions-involuntary/muscle twitching/myoclonus, coordination abnormal/gait abnormal/ ataxia/ balance disorders, throat or chest tightness/pressure/discomfort/pain.

In addition, cranial nerve dysfunctions may be associated, or also occur as an isolated event such as ptosis, diplopia, aphonia/dysphonia/hoarseness, sometimes described as vocal cord paralysis, abnormal tongue sensation or dysarthria, sometimes described as aphasia, trigeminal neuralgia/ facial pain/ eye pain, decrease in visual acuity, visual field disorders.

Other neurological symptoms such as dysarthria, loss of deep tendon reflex and Lhermitte's sign were reported during treatment with oxaliplatin. Isolated cases of optic neuritis have been reported.

Postmarketing experience with frequency unknown

Convulsion

Allergic reactions:

Table 4: Incidence by patient (%), by grade

Oxaliplatin and 5-FU/FA 85 mg/m² every 2 weeks	Metastatic Setting			Adjuvant Setting		
	All grades	Gr 3	Gr 4	All grades	Gr 3	Gr 4
Allergic reactions / Allergy	9.1	1	< 1	10.3	2.3	0.6

4.9 Overdose

There is no known antidote to oxaliplatin. In cases of overdose, exacerbation of adverse events can be expected. Monitoring of haematological parameters should be initiated and symptomatic treatment given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antineoplastic agents, platinum compounds
ATC-Code: L01XA03

Oxaliplatin is an antineoplastic active substance belonging to a new class of platinum-based compounds in which the platinum atom is complexed with 1,2-diaminocyclohexane ("DACH") and an oxalate group.

Oxaliplatin is a single enantiomer, the Cis-[oxalato(trans-l-1,2- DACH) platinum].

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

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

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

In patients with metastatic colorectal cancer, the efficacy of oxaliplatin (85mg/m² 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.

Table 5: 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.

Table 6: 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.

Table 7: 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.

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).

Table 8: 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 (70.6-75.9)	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).

Table 9: 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 (62.2-69.5)	72.8 (69.4-76.2)
Hazard ratio (95% CI)	0.79 (0.57-1.09)		0.75 (0.62-0.90)	
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.

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

5.2 Pharmacokinetic properties

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

Table 10: Summary of Platinum Pharmacokinetic Parameter Estimates in Ultrafiltrate Following Multiple Doses of Oxaliplatin at 85 mg/m² Every Two Weeks or at 130 mg/m² 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/m² 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/m² Mean	1.21	8.20	11.9	0.28	16.3	273	582	10.1
SD	0.10	2.40	4.60	0.06	2.90	19.0	261	3.07

Mean AUC_{0-48} and C_{max} values were determined on Cycle 3 (85 mg/m²) or Cycle 5 (130 mg/m²).

Mean AUC, V_{ss}, CL, and CLR_{0-48} 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/m² every two weeks or 130 mg/m² 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 active substance 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 medicinal products and DNA-damaging, cytotoxic medicinal products 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/m²) were well-tolerated by humans. Preclinical studies using rat sensory neurons suggest that the acute neurosensory symptoms related to Oxaliplatin may involve an interaction with voltage-gated Na+ channels.

Oxaliplatin was mutagenic and clastogenic in mammalian test systems and produced embryo-fetal toxicity in rats. Oxaliplatin is considered a probable carcinogen, although carcinogenic studies have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Water for injections

6.2 Incompatibilities

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

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

6.3 Shelf-life

Medicinal product as packaged for sale: 18 months

In-use stability after dilution

From a microbiological point of view, the product 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 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

Chemical and physical in-use stability has been demonstrated for 7 days at 2 to 8 °C with protection from light when diluted to the concentrations of 0.2 mg/ml and 2.0 mg/ml with glucose 5% as well as for 7 days at 20-25 °C with or without protection from light when diluted to the concentration of 2.0 mg/ml with glucose 5%.

6.4 Special precautions for storage

Keep the vial in the outer carton in order to protect from light.
Do not freeze.
Do not store above 25°C.
For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Colourless glass vials with grey Halobutyl rubber stoppers and aluminium seals with plastic flip-off caps.
Pack sizes:
50 mg/10 ml: 1 vial
100 mg/20 ml: 1 vial
150 mg/30 ml: 1 vial
200 mg/40 ml: 1 vial

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

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

Excreta and vomit must be handled with care.

Pregnant women must be warned to avoid handling cytotoxic agents.

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

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

Special precautions for administration

- DO NOT use injection material containing aluminium.
- DO NOT administer undiluted.
- Only glucose 5% infusion solution is to be used as a diluent. DO NOT dilute for infusion with sodium chloride or chloride containing solutions.
- DO NOT mix with any other medicinal products in the same infusion bag or administer simultaneously by the same infusion line.
- DO NOT mix with alkaline medicinal products or solutions, in particular 5-fluorouracil, folinic acid products containing trometamol as an excipient and trometamol salts of other products. Alkaline medicinal products or solution will adversely affect the stability of oxaliplatin.

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

Oxaliplatin 85mg/m² IV infusion in 250 to 500 ml of 5% glucose solution is given at the same time as folinic acid IV infusion in 5% glucose solution, over 2 to 6 hours, using a Y-line placed immediately before the site of infusion. These two medicinal products 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 medicinal products combined with oxaliplatin, see the corresponding manufacturer's summary of product characteristics.

Concentrate for solution for infusion

Inspect visually prior to use. Only clear solutions free from visible particles should be used.

This medicinal product is for single use only. Any unused concentrate should be discarded.

Dilution for intravenous infusion

Withdraw the required amount of concentrate from the vial(s) and then dilute with 250 ml to 500 ml of a 5 % glucose solution to give an oxaliplatin concentration not less than 0.2 mg/ml.

Administer by IV infusion.

From a microbiological point of view, the product 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.

Chemical and physical in-use stability has been demonstrated for 7 days at 2 to 8 °C with protection from light when diluted to the concentrations of 0.2 mg/ml and 2.0 mg/ml with glucose 5% as well as for 7 days at 20-25 °C with or without protection from light when diluted to the concentration of 2.0 mg/ml with glucose 5%.

Inspect visually prior to use. Only clear solutions free from visible particles should be used.

The medicinal product is for single use only. Any unused infusion solution should be discarded (see chapter "disposal" below).

NEVER use sodium chloride solution for either reconstitution or dilution.

Infusion

The administration of oxaliplatin does not require prehydration.

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

Disposal

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

7. MARKETING AUTHORISATION HOLDER

EBEWE Pharma Ges.m.b.H. Nfg.KG
A-4866 Unterach, AUSTRIA

8. DATE OF REVISION OF THE TEXT

December 2010