Bioprofarma S.A.			BIO PROFARMA
Producto: Oxaltie (frente)	Arte: Bagó	Código: **117-PRIB/1**	Programa: Quark X Press — Escala: 1:1
Presentación: Prospecto	Destino/s: Asia - Europa		Tipografía/s: Helvética - Symbol
Producto/s Relacionado/s: ----		Fecha Revisión: 29 / 06 / 09	Tintas: ■ Negro
Fecha Vigencia: / /	Fecha Caducidad: / /		Dimensiones:
Dir. Técnica: Marina P. de Henrich	Fecha Aprobación: / /	Firma:	Ancho: 267 MM - Alto: 380 MM
Observaciones: Se actualiza versión en código, se elimina Dirección Técnica y se corrigen espacios en los títulos. Se modifica el texto de “Storage”.			

HOW SUPPLIED
OXALTIE® is supplied in amber glass, single-use vials with gray elastomeric stoppers and aluminum flip-off seals containing 50 mg or 100 mg of oxaliplatin as a sterile, preservative-free lyophilized powder for reconstitution. Lactose monohydrate is also present as an inactive ingredient.

STORAGE
Should be stored under normal lighting conditions between 15 °C - 25 °C (59 °F - 77 °F).

HANDLING AND DISPOSAL
As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions prepared from **OXALTIE®**. The use of gloves is recommended. If a solution of **OXALTIE®** contacts the skin, wash the skin immediately and thoroughly with soap and water. If **OXALTIE®** contacts the mucous membranes, flush thoroughly with water. Procedures for the handling and disposal of anticancer drugs should be considered. Several guidelines on the subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

THIS MEDICATION MUST BE USED EXCLUSIVELY UNDER MEDICAL PRESCRIPTION AND SURVEILLANCE AND CANNOT REPEATED WITHOUT A NEW MEDICAL PRESCRIPTION

DO NOT USE AFTER EXPIRATION DATE

MEDICINE: KEEP OUT OF CHILDREN'S REACH

Medicinal specialty authorized by the Argentinean Ministry of Health Certificate Nº **48330**
Manufactured by: Bioprofarma S.A. Argentina Bagó Group Member
Terrada 1270 - C1416ARD - C.A. de Buenos Aires - Argentina

Laboratorios Bagó S.A.
Current at April 2002
Package Insert Code: 117-PRIB/1

OXALTIE ®
OXALIPLATIN

Lyophilized powder for injection

Prescription Only
Made in Argentina

WARNING
OXALTIE® (oxaliplatin for injection) should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.
Anaphylactic-like reactions to **OXALTIE®** have been reported, and may occur within minutes of **OXALTIE®** administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms.

DESCRIPTION
ATC Code: L01XA03
OXALTIE® (oxaliplatin for injection) is an antineoplastic agent with the molecular formula $C_8H_{14}N_2O_4Pt$ and the chemical name of:
cis-[(1R,2R)-1,2-cyclohexanediamine-N,N'] [oxalate(2-)-O,O'] platinum.
Oxaliplatin is an organoplatinum complex in which the platinum atom is complexed with 1,2- diaminocyclohexane (DACH) and with an oxalate ligand as a leaving group.
The molecular weight is 397.3. Oxaliplatin is slightly soluble in water at 6 mg/mL, very slightly soluble in methanol, and practically insoluble in ethanol and acetone.
OXALTIE® is supplied in vials containing 50 mg or 100 mg of oxaliplatin as a sterile, preservative-free lyophilized powder for reconstitution. Lactose monohydrate is present as an inactive ingredient at 450 mg and 900 mg in the 50 mg and 100 mg dosage strengths, respectively.

CLINICAL PHARMACOLOGY
Mechanism of Action
Oxaliplatin undergoes non-enzymatic conversion in physiologic solutions to active derivatives via displacement of the labile oxalate ligand. Several transient reactive species are formed, including monoaquo and diaquo DACH platinum, which covalently bind with macromo-lecules. Both inter- and intra-strand Pt-DNA cross-links are formed. Cross-links are formed between the N7 positions of two adjacent guanines (GG), adjacent adenine-guanines (AG), and guanines separated by an intervening nucleotide (GNG). These cross-links inhibit DNA replication and transcription. Cytotoxicity is cell-cycle nonspecific.
Pharmacology
In vivo studies have shown antitumor activity of oxaliplatin against colon carcinoma. In combination with 5-fluorouracil (5-FU), oxaliplatin exhibits in vitro and in vivo antiproliferative activity greater than either compound alone in several tumor models [HT29 (colon), GR (mammary), and L1210 (leukemia)]
Human Pharmacokinetics
The reactive oxaliplatin derivatives are present as a fraction of the unbound platinum in plasma ultra filtrate. The decline of ultra filterable platinum levels following oxaliplatin administration is triphasic, characterized by two relatively short distribution phases (t 1/2 α; 0.43 hours and t 1/2 β; 16.8 hours) and a long terminal elimination phase (t 1/2 γ; 391 hours). Pharmacokinetics parameters obtained after a single 2-hour IV infusion of oxaliplatin at a dose of 85 mg/m² expressed as ultra filterable platinum were C_{maxs} of 0.814 mg/mL and volume of distribution of 440 L.
Interpatient and intrapatient variability in ultra filterable platinum exposure (AUC_{0-48}) assessed over 3 cycles was moderate to low (23% and 6%, respectively). A pharmacodynamics relationship between platinum ultra filtrate levels and clinical safety and effectiveness has not been established.
Distribution
At the end of a 2-hour infusion of oxaliplatin, approximately 15% of the administered platinum is present in the systemic circulation. The remaining 85% is rapidly distributed into tissues or eliminated in the urine. In patients, plasma protein binding of platinum is irreversible and is greater than 90%. The main binding proteins are albumin and gamma-globulins. Platinum also binds irreversibly and accumulates (approximately 2-fold) in erythrocytes, where it appears to have no relevant activity. No platinum accumulation was observed in plasma ultra filtrate following 85 mg/m² every two weeks.
Metabolism
Oxaliplatin undergoes rapid and extensive nonenzymatic biotransformation. There is no evidence of cytochrome P450-mediated metabolism in vitro.
Up to 17 platinum-containing derivatives have been observed in plasma ultra filtrate samples from patients, including several cytotoxic species (monochloro DACH platinum, dichloro DACH platinum, and monoaquo and diaquo DACH platinum) and a number of non-cytotoxic, conjugated species.
Elimination
The major route of platinum elimination is renal excretion. At five days after a single 2-hour infusion of oxaliplatin, urinary elimination accounted for about 54% of the platinum eliminated, with fecal excretion accounting for only about 2%. Platinum was cleared from plasma at a rate (10 - 17 L/h) that was similar to or exceeded the average human glomerular filtration rate (GFR; 7.5 L/h). There was no significant effect of gender on the clearance of ultra filterable platinum. The renal clearance of ultra filterable platinum is significantly correlated with GFR.

Pharmacokinetics in Special Populations
Renal Impairment
The AUC_{0-48hr} of platinum in the plasma ultra filtrate increa-ses as renal function decreases. The AUC_{0-48hr} of platinum in patients with mild (creatinine clearance, CL_{cr} 50 to 80 mL/min), moderate (CL_{cr} 30 to <50 mL/min) and severe renal (CL_{cr} <30 mL/min) impairment is increased by about 60, 140 and 190%, respectively, compared to patients with normal renal function (CL_{cr} >80 mL/min)].
Drug - Drug Interactions
No pharmacokinetics interaction between 85 mg/m² of oxaliplatin and infusional 5-FU has been observed in patients treated every 2 weeks, but increases of 5-FU plasma concentrations by approximately 20% have been observed with doses of 130 mg / m² of oxaliplatin administered every 3 weeks. In vitro, platinum was not displaced from plasma proteins by the following medications: erythromycin, salicylate, sodium valproate, granisetron, and paclitaxel. In vitro, oxaliplatin is not metabolized by, nor does it inhibit, human cytochrome P450 isoenzymes. No P450-mediated drug-drug interactions are therefore anticipated in patients.
Since platinum containing species are eliminated primarily through the kidney, clearance of these products may be decreased by co-administration of potentially nephrotoxic compounds, although this has not been specifically studied.

CLINICAL STUDIES
Combination therapy with Oxaliplatin and infusional 5-FU/LV in previously treated patients with advanced colorectal cancer.
A multicenter, randomized, three arm controlled study was conducted in the US and Canada comparing the efficacy and safety of oxaliplatin in combination with an infusional schedule of 5-FU/LV to the same dose and schedule of 5-FU/LV alone and to single agent oxaliplatin in patients with advanced colorectal cancer who had relapsed/progressed during or within t months of first line therapy with bolus 5-FU/LV and Irinotecan. The study was intended to be analyzed for response rate after 450 patients were enrolled. Survival will be subsequently assessed in all patients enrolled. Patients in the study had to be al least years of age, have unresectable, measurable, histologically proven colorectaladenocarcinoma, with a Karnofsky performance status > 50%. Patients had to have SGOT (AST) and SGPT (ALT) ≤ 2x the institution's upper limit of normal (ULN), unless liver metastases were present and documented at baseline by Ct or MRI scan, in which case ≤ 5x ULN was permitted. Patients had to have alkaline phosphatase ≤ 2x the institution's ULN, unless liver metastases were present and documented al baseline by CT or MRI scan, in which cases ≤ 5x ULN was permitted. Prior radiotherapy was permitted if it had been completed at least 3 weeks before randomization.
The dosing regimens of the three arms of the study are presented in the table below.

Dosing regimens in refractory and relapsed colorectal Cancer clinical trial

Treatment arm	Dose	Regimen
Oxaliplatin + 5-FU/LV (N=152)	Day 1: oxaliplatin: 85 mg/m² (2-hour infusion) + LV 200 mg/m² (2-hour infusion), followed by 5-FU: 400 mg/m² (bolus), 600 mg/m² (22-hour infusion) Day 2: LV 200 mg/m² (2-hour infusion), followed by 5-FU: 400 mg/m² (bolus), 600 mg/m² (22-hour infusion)	q2w
5-FU/LV (N =151)	Day 1: LV 200 mg/m² (2-hour infusion), followed by 5-FU: 400 mg/m² (bolus), 600 mg/m² (22-hour infusion) Day 2: LV 200 mg/m² (2-hour infusion), followed by 5-FU: 400 mg/m² (bolus), 600 mg/m² (22-hour infusion)	q2w
Oxaliplatin (N=156)	Day 1: oxaliplatin: 85 mg/m² (2-hour infusion)	q2w

Patients entered into the study for evaluation of response must have had at least one unidimensional lesion measuring ≥ 20mm using conventional CT or MRI scans, or ≥ 10mm using a spiral CT scan. Tumor response and progression were assessed every 3 cycles (6 weeks) using the Response Evaluation Criteria in Solid Tumors (RECIST) until radiological documentation of progression or for 13 months following the first dose of study drug(s), whichever came first. Confirmed responses were based on two tumor assessments separated by at least 4 weeks.
The demographics of the patient population entered into this study are shown in the table below.

Patient Demographics in Refractory and Relapsed Colorectal Cancer Clinical Trial

	5FU/LV N=151	OXALIPLATIN N=156	OXALIPLATIN+ 5FU/LV N=152
Sex: Male (%)	54.3	60.9	57.2
Female (%)	45.7	39.1	42.8
Median age	60.0	61.0	59.0
Range21 - 80	27 - 79	22 - 88	
Race (%)			
Caucasian	87.4	84.6	88.8
Black 7.9	7.1	5.9	
Asian 1.3	2.6	2.6	
Other 3.3	5.8	2.6	
KPS (%)			
70 - 10094.7	92.3	95.4	
50 - 602.6	4.5	2.0	
Not reported	2.6	4.5	2.0
Prior radiotherapy (%)	25.2	19.2	25.0
Prior pelvic radiation (%)	18.5	13.5	21.1
Number of metastatic sites (%)			
1 27.2	31.4	25.7	
≥ 2 72.2	67.9	74.3	
Liver involvement (%)			
Liver only	22.5	25.6	18.4
Liver + other	60.3	59.0	53.3

The median number of cycles administered per patient was 6 for the oxaliplatin and infusional 5-FU/LV combination and 3 each for infusional 5-FU/LV alone and oxaliplatin alone. Patients treated with the combination of oxaliplatin and infusional 5-FU/LV had an increased response rate compared to patients given infusional 5-FU/LV or oxaliplatin alone. The efficacy results are summarized in the tables below.

Response Rates (ITT Analysis)

Best response	5FU/LV (N=151)	OXALIPLATIN (N=156)	OXALIPLATIN+ 5FU/LV N=152
CR	0	0	0
PR	0	2(1%)	13 (9%)
p-value	0.0002 for 5FU/LV vs. OXALIPLATIN + 5FU/LV		
95% CI	0 - 2.4 %	0.2 - 4.6 %	4.6 - 14.2 %

Summary of Radiographic Time to Progression*

ARM	5FU/LV (N=151)	OXALIPLATIN (N=156)	OXALIPLATIN+ 5FU/LV N=152
No. of progressors	74	101	50
No. of patients with no radiological evaluation beyond baseline	22 (15%)	16 (10%)	17 (11%)
Median TTP (months)	2.7	1.6	4.6
95% CI	1.8 - 3.0	1.4 - 2.7	4.2 - 6.1

**This is not an ITT analysis. Events were limited to radiographic disease progression documented 161 by independent review of radiographs. Clinical progression was not included in this analysis, and 18% of patients were excluded from the analysis based on unavailability of the radiographs for independent review.*

At the time of the interim analysis 49% of the radiographic progression events had occurred. In this interim analysis an estimated 2-month increase in median time to radiographic progression was observed compared to infusional 5-FU/LV alone. Of the 13 patients who had tumor response to the combination of oxaliplatin and infusional 5-FU/LV, 5 were female and 8 were male, and included patients <65 years old and 65 years old. The small number of non-Caucasian participants made efficacy analyses in these populations uninterpretable.

INDICATIONS AND USAGE
OXALTIE®, used in combination with infusional 5-FU/LV, is indicated for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed during or within 6 months of completion of first line therapy with the combination of bolus 5-FU/LV and Irinotecan.

Bioprofarma S.A.			
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CONTRAINDICATIONS
OXALTIE® should not be administered to patients with a history of known allergy to oxaliplatin or other platinum compounds.

WARNINGS
As in the case for other platinum compounds, hypersensitivity and anaphylactic/anaphylactoid reactions to oxaliplatin have been reported. These allergic reactions were similar in nature and severity to those reported with other platinum-containing compounds, i.e., rash, urticaria, erythema, pruritus, and, rarely, bronchospasm and hypotension. These reactions occur within minutes of administration and should be managed with appropriate supportive therapy. Drug-related deaths associated with platinum compounds from this reaction have been reported.

Pregnancy Category D
Positive evidence of human fetal risk based on adverse reaction from investigational or marketing experiences, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.
Oxaliplatin may cause fetal harm when administered to a pregnant woman. Pregnant rats were administered 1 mg/kg/day oxaliplatin (less than one-tenth the recommen-ded human dose based on body surface area) during gestation days 1-5 (pre-implantation), 6-10, or 11-16 (during organogenesis). Oxaliplatin caused developmental morta-lity (increased early resorptions) when administered on days 6-10 and 11-16 and adversely affected fetal growth (decreased fetal weight, delayed ossification) when administered on days 6-10. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with oxaliplatin.

PRECAUTIONS
General
Oxaliplatin should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.
Neuropathy
Neuropathy was graded using a study-specific neurotoxicity scale, which was different than the National Cancer Institute Common Toxicity Criteria, Version 2.0 (NCI CTC)
Oxaliplatin is associated with two types of neuropathy:
• An acute, reversible primarily peripheral sensory neuropathy that is of early onset, occurring within hours or one to two days of dosing, that resolves within 14 days, and that frequently recurs with further dosing. The symptoms may be precipitated or exacerbated by exposure to cold temperature or cold objects and they usually present as transient paresthesia, dysesthesia and hypoesthesia in the hands, feet, perioral area, or throat. Jaw spasm, abnormal tongue sensation, dysarthria, eye pain, and a feeling of chest pressure have also been observed. The acute, reversible pattern of sensory neuropathy was observed in about 56% of study patients who received oxaliplatin with infusional 5-FU/LV. In any individual cycle acute neuroto-xicity was observed in approximately 30% of patients. Ice (mucositis prophylaxis) should be avoided during the infusion of oxaliplatin because cold temperature can exacerbate acute neurological symptoms.
An acute syndrome of pharyngolaryngeal dysesthesia seen in 1-2% of patients is characterized by subjective sensations of dysphagia or dyspnea, without any laryngospasm or bronchospasm (no stridor or wheezing).
• A persistent (>14 days), primarily peripheral, sensory neuropathy that is usually characterized by paresthesias, dysethesias, hypoesthesias, but may also include deficits in proprioception that can interfere with daily activities (e.g., writing, buttoning, swallowing, and difficulty walking from impaired proprioception). These forms of neuropathy occurred in 48% of the study patients receiving oxaliplatin with infusional 5-FU/LV. Persistent neuropathy can occur without any prior acute neuropathy event. The majority of the patients (80%) who developed grade 3 persistent neuropathy progressed from prior Grade 1 or 2 events. These symptoms may improve in some patients upon discontinuation of oxaliplatin.

Neurotoxicity scale
The grading scale for paresthesias/dysesthesias was:
Grade 1, resolved and did not interfere with functioning; **Grade 2**, interfered with function but not daily activities; **Grade 3**, pain or functional impairment that interfered with daily activities; **Grade 4**, persistent impairment that is disabling or life-threatening.

Pulmonary Toxicity
Oxaliplatin has been associated with pulmonary fibrosis (0.7% of study patients), which may be fatal. In case of unexplained respiratory symptoms such as non-productive cough, dyspnea, crackles, or radiological pulmonary infiltrates, oxaliplatin should be discontinued until further pulmonary investigation excludes interstitial lung disease or pulmonary fibrosis.

Information for Patients
Patients and patient’s caregivers should be informed of the expected side effects of oxaliplatin, particularly its neurologic effects, both the acute, reversible effects, and the persistent neurosensory toxicity. Patients should be informed that the acute neurosensory toxicity might be precipitated or exacerbated by exposure to cold or cold objects. Patients should be instructed to avoid cold drinks, use of ice, and should cover exposed skin prior to exposure to cold temperature or cold objects.
Patients must be adequately informed of the risk of low blood cell counts and instructed to contact their physician immediately should fever, particularly if associated with persistent diarrhea, or evidence of infection develop.
Patients should be instructed to contact their physician if persistent vomiting, diarrhea, signs of dehydration, cough or breathing difficulties occur, or signs of allergic reaction appear.

Laboratory Tests
Standard monitoring of the white blood cell count with differential, hemoglobin, platelet count, and blood chemistries (including ALT, AST, bilirubin and creatinine) is recommended before each **OXALTIE®** cycle.

Laboratory Test Interactions
None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies have not been performed to evaluate the carcinogenic potential of oxaliplatin. Oxaliplatin was not mutagenic to bacteria (Ames test) but was mutagenic to mammalian cells in vitro (L5178Y mouse lymphoma assay). Oxaliplatin was clastogenic both in vitro (chromosome aberration in human lymphocytes) and in vivo (mouse bone marrow micronucleus assay).
In a fertility study, male rats were given oxaliplatin at 0, 0.5, 1 or 2 mg/kg/day for five days every 21 days for a total of three cycles prior to mating with females that received two cycles of oxaliplatin on the same schedule. A dose of 2 mg/kg/day (less than one-seventh the recommended human dose on a body surface area basis) did not affect pregnancy rate, but caused developmental mortality (increased early resorptions, decreased live fetuses, decreased live births) and delayed growth (decreased fetal weight).
Testicular damage, characterized by degeneration, hypoplasia, and atrophy, was observed in dogs administered oxaliplatin at 0.75 mg/kg/day x 5 days every 28 days for three cycles. A no effect level was not identified. This daily dose is approximately one-sixth of the recommended human dose on a body surface area basis.

Pregnancy Category D
Nursing Mothers
It is not known whether oxaliplatin or its derivatives are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from oxaliplatin, a decision should be made whether to discontinue nursing or delay the use of the drug, taking into account theimportance of the drug to the mother.

Pediatric Use
The safety and effectiveness of oxaliplatin in pediatric patients have not been established.

Patients with Renal Impairment
The safety and effectiveness of the combination of oxaliplatin and infusional 5-FU/LV in patients with renal impairment has not been evaluated.
The combination of oxaliplatin and infusional 5-FU/LV should be used with caution in patients with preexisting renal impairment since the primary route of platinum elimination is renal. Clearance of ultra filterable platinum is decreased in patients with mild, moderate, and severe renal impairment. A pharmacodynamics relationship between platinum ultra filtrate levels and clinical safety and effectiveness has not been established.

Geriatric Use
No significant effect of age on the clearance of ultra filterable platinum has been observed. In the randomized clinical trial of oxaliplatin, 95 patients treated with oxaliplatin and infusional 5-FU/LV were < 65 years and 55 patients were ≥ 65 years. The rates of overall adverse events, including grade 3 and 4 events, were similar across and within arms in the different age groups. The incidence of diarrhea, dehydration, hypokalemia, and fatigue were higher in patients ≥ 65 years old.

Drug Interactions
No specific cytochrome P-450-based drug interaction studies have been conducted. No pharmacokinetics interaction between 85 mg/m² oxaliplatin and infusional 5-FU has been observed in patients treated every 2 weeks. Increases of 5-FU plasma concentrations by approximately 20% have been observed with doses of 130 mg/m² oxaliplatin dosed every 3 weeks. Since platinum containing species are eliminated primarily through the kidney, clearance of these products may be decreased by co administration of potentially nephrotoxic compounds; although, this has not been specifically studied.

ADVERSE REACTIONS
More than 1,500 patients with advanced colorectal cancer have been treated in clinical studies with oxaliplatin either as a single agent or in combination with other medications. The most common adverse reactions were peripheral sensory neuropathies, neutropenia, nausea, emesis, and diarrhea. Four hundred and fifty patients (about 150 receiving the combination of oxaliplatin and 5-FU/LV) were studied in a randomized trial in patients with refractory and relapsed colorectal cancer. The adverse event profile in this study was similar to that seen in other studies and the adverse reactions in this trial are shown in the tables below.
Thirteen per cent of patients in the oxaliplatin and infusio-nal 5-FU/LV-combination arm and 18% in the infusional 5-FU/LV arm had to discontinue treatment because of adverse effects related to gastrointestinal or hematologic adverse events, or neuropathies. Both 5-FU and oxaliplatin are associated with gastrointestinal and hematologic adverse events. When oxaliplatin is administered in combination with infusional 5-FU, the incidence of these events is increased.
The incidence of death within 30 days of treatment, regardless of causality, was 5% with the oxaliplatin and infusional 5-FU/LV combinations, 8% with oxaliplatin alone, and 7% with infusional 5-FU/LV. Of the 7 deaths that occurred on the oxaliplatin and infusional 5-FU/LV combination arm within 30 days of stopping treatment, 3 may have been treatment-related, associated with gastrointestinal bleeding or dehydration.
The following table provides adverse events reported in the study in decreasing order of frequency in the oxaliplatin and infusional 5-FU/LV combination arm for events with overall incidences ≥ 5% and for grade 3/4 events with incidences ≥ 1%. This table does not include hematologic and blood chemistry abnormalities; these are shown separately below.

Adverse Experience Reported In Colorectal Cancer Clinical Trial
(≥ 5% of all patients and with ≥ 1% NCI Grade 3/4 events)

Adverse event (WHO / Preferred)	5FU/LV (N=142)		OXALIPLATIN (N=153)		OXALIPLATIN + 5FU/LV (N=150)	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Any event	98	41	100	46	99	73
Fatigue	52	6	61	9	68	7
Diarrhea	44	3	46	4	67	11
Nausea	59	4	64	4	65	11
Neuropathy	17	0	76	7	73	7
Acute	10	0	65	5	56	2
Persistent	9	0	43	3	48	6
Vomiting	27	4	37	4	40	9
Stomatitis	32	3	14	4	40	9
Abdominal pain	31	5	31	7	33	4
Fever	23	1	25	1	29	1
Anorexia	20	1	20	2	29	3
Dyspnea	11	2	13	7	20	4
Back pain	16	4	11	0	19	3
Coughing	9	0	11	0	19	1
Edema	13	1	10	1	15	1
Pain	9	3	14	3	15	2
Injection site reaction	5	1	6	0	10	3
Thrombo-embolism	4	2	2	1	9	8
Hypokalemia	3	1	3	2	9	4
Dehydration	6	4	5	3	8	3
Chest pain	4	1	5	1	8	1
Febrile Neutropenia	1	1	0	0	6	6
Gastroeso-phageal reflux	3	0	1	0	5	2
Peripheral edema	11	5			10	
Allergic reaction	1	3			10	
Arthralgia	10	7			10	
Upper resp. tract infection	4	7			10	
Pharyngitis	10	2			9	
Rash	5	5			9	
Insomnia	4	11			9	
Epistaxis	1	2			9	
Mucosistis	10	2			7	
Alopecia	3	3			7	
Abnormal lacrimation	6	1			7	
Rigors	6	9			7	
Hematuria	4	0			6	
Dysuria	1	1			6	
Hiccup	0	2			5	
Flatulence	6	3			5	

The following table provides adverse events reported in the study in decreasing order of frequency in the oxaliplatin and infusional 5-FU/LV combination arm for events with overall incidences ≥ 5% but with incidences <1% NCI Grade 3/4 events.

Adverse Experience Reported In Colorectal Cancer Clinical Trial
(≥ 5% of all patients but with <1% NCI Grade 3/4 events)

Adverse event (WHO / Preferred)	5FU/LV (N=142) All grades	OXALIPLATIN (N=153) All grades	OXALIPLATIN + 5FU/LV (N=150) All grades
Constipation	23	31	32
Headache	8	13	17
Rhinitis	4	6	15
Dyspepsis	10	7	14
Taste perversion	1	5	13
Dizziness	8	7	13
Hand-foot syndrome	13	1	11
Flushing	2	3	10

Adverse events were similar in men and women and in patients < 65 and ≥ 65 years, but older patients may have been more susceptible to dehydration, diarrhea, hypokalemia and fatigue. The following additional adverse events, at least possibly related to treatment and potentially important, were reported in ≥ 2% and <5% of the patients in the oxaliplatin and infusional 5-FU/LV combination arm (listed in decreasing order of frequency): anxiety, myalgia, erythematous rash, increased sweating, conjunctivitis, weight decrease, dry mouth, rectal hemorrhage, depression, ataxia, ascites, hemorrhoids, muscle weakness, nervousness, tachycardia, abnormal micturition frequency, dry skin, pruritis, hemoptysis, purpura, vaginal hemorrhage, melena, somnolence, pneumonia, proctitis, involuntary muscle contractions, intestinal obstruction, gingivitis, tenesmus, hot flashes, enlarged abdomen, urinary incontinence.
Hematologic
The following table lists the hematologic changes occurring in ≥ 5% of patients, based on laboratory values and NCI grade.

Adverse Hematologic Experiences
(≥ 5% of patients)

Hematology parameter	5FU/LV (N=142)		OXALIPLATIN (N=153)		OXALIPLATIN + 5FU/LV (N=150)	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Anemia	68	2	64	1	81	2
Leukopenia	34	1	13	0	76	19
Neutropenia	25	5	7	0	73	44
Thrombo-cytopenia	20	0	30	3	64	4

Thrombocytopenia
Thrombocytopenia was frequently reported with the combination of oxaliplatin and infusional 5-FU/LV. The incidence of Grade 3/4 thrombocytopenia was 4%. Grade 3/4 hemorrhagic events were reported at low frequency and the incidence of these events was similar for the combination of oxaliplatin and infusional 5-FU/LV and the infusional 5-FU/LV control group. The incidence of all hemorrhagic events, however, was higher on the oxaliplatin combination arm compared to the 5-FU/LV arm. These events included gastrointestinal bleeding, hematuria and epistaxis.
Neutropenia
Neutropenia was frequently observed with the combination of oxaliplatin and infusional 5-FU/LV, with Grade 3 and 4 events reported in 27% and 17% of previously treated patients, respectively. The incidence of febrile neutropenia was 1% in the infusional 5-FU/LV arm and 6% (less than 1% of cycles) in the oxaliplatin and infusional 5-FU/LV combination arm.
Gastrointestinal
In patients receiving the combination of oxaliplatin and infusional 5-FU/LV, the incidence of Grade 3 and 4 nausea, vomiting, diarrhea, and mucositis/stomatitis increased compared to infusional 5-FU/LV controls.
The incidence of gastrointestinal adverse events appears to be similar across cycles.
Premedication with anti emetics, including 5-HT3 blockers, is recommended. Diarrhea and mucositis may be exacerbated by the addition of oxaliplatin to infusional 5-FU/LV, and should be managed with appropriate supportive care. Since cold temperature can exacerbate acute neurological symptoms, ice (mucositis prophylaxis) should be avoided during the infusion of oxaliplatin.
Dermatology
Oxaliplatin did not increase the incidence of alopecia compared to infusional 5-FU/LV alone. No complete alopecia was reported. The incidence of hand-foot syndrome was 13% in the infusional 5-FU/LV arm and 11% in the oxaliplatin and infusional 5-FU/LV combination arm.
Care of Intravenous Site
Extravasation may result in local pain and inflammation that may be severe and lead to complications, including necrosis. Injection site reaction, including redness, swelling, and pain have been reported.
Neurologic
Oxaliplatin is consistently associated with two types of peripheral neuropathy. Seventy-four percent of patients experienced neuropathy. The incidence of overall and Grade 3/4 persistent peripheral neuropathy was 48% and 6%, respectively, in the study. These events can occur without any prior acute event. The majority of the patients (80%) that developed grade 3 persistent neuropathy progressed from prior Grade 1 or 2 events. The median number of cycles administered on the oxaliplatin with infusional 5- FU/LV combination arm was 6 cycles. In clinical trials that have studied similar administration schedules of this combination regimen, (median cycles ranged 10-12), a higher incidence (17%) of Grade 3/4 persistent neurotoxicity was observed.
Allergic reactions
Hypersensitivity to oxaliplatin has been observed (<1% Grade 3/4) in clinical studies. These allergic reactions, which can be fatal, were similar in nature and severity to those reported with other platinum-containing compounds - i.e., rash, urticaria, erythema, pruritis, and, rarely, bronchospasm and hypotension. These reactions are usually managed with standard epinephrine, corticosteroid, and antihistamine therapy, anaphylactic/anaphylactoid reactions.)
Renal
About 10% of patients in all groups had some degree of elevation of serum creatinine. The incidence of Grade 3/4 elevations in serum creatinine in the oxaliplatin and infusional 5-FU/LV combination arm was 1%.
Hepatic
The following table lists the clinical chemistry changes associated with hepatic toxicity occurring in ≥ 5% of patients, based on laboratory values and NCI CTC grade.

Adverse Hepatic – Clinical Chemistry Experience
(≥ 5% of patients)

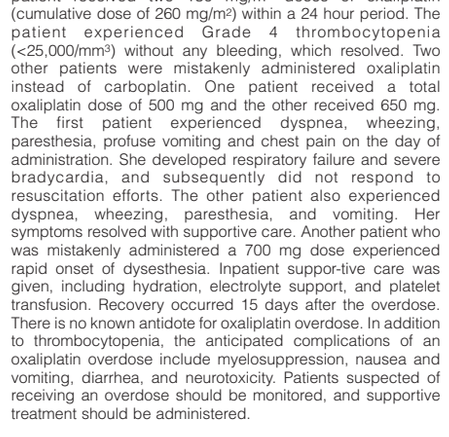
Clinical Chemistry	5FU/LV (N=142)		OXALIPLATIN (N=153)		OXALIPLATIN + 5FU/LV (N=150)	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
ALT (SGPT - ALAT)	28	3	36	1	31	0
AST (SGOT - ASAT)	39	2	54	4	47	0
Total bilirubin	22	6	13	5	13	1

Thromboembolism
The incidence of thromboembolic events was 4% in the infusional 5-FU/LV arm, and 9% in the oxaliplatin and infusional 5-FU/LV combination arm.

Postmarketing Experience
Body as a whole: angioedema, anaphylactic shock.
Central and peripheral nervous system disorders: loss of deep tendon reflexes, dysarthria, Lhermittes’ sign, cranial nerve palsies, fasciculations .
Gastrointestinal system disorders: severe diarrhea/vomiting resulting in hypokalemia, metabolic acidosis; ileus; intestinal obstruction, pancreatitis.
Hearing and vestibular system disorders: deafness.
Platelet, bleeding, and clotting disorders: immuno-allergic thrombocytopenia.
Red Blood Cell disorders: hemolytic uremic syndrome patients.
Respiratory system disorders: pulmonary fibrosis, and other interstitial lung diseases.
Vision disorders: decrease of visual acuity, visual field disturbance, and optic neuritis.

OVERDOSAGE
There have been four oxaliplatin overdoses reported. One patient received two 130 mg/m² doses of oxaliplatin (cumulative dose of 260 mg/m²) within a 24 hour period. The patient experienced Grade 4 thrombocytopenia (<25,000/mm³) without any bleeding, which resolved. Two other patients were mistakenly administered oxaliplatin instead of carboplatin. One patient received a total oxaliplatin dose of 500 mg and the other received 650 mg. The first patient experienced dyspnea, wheezing, paresthesia, profuse vomiting and chest pain on the day of administration. She developed respiratory failure and severe bradycardia, and subsequently did not respond to resuscitation efforts. The other patient also experienced dyspnea, wheezing, paresthesia, and vomiting. Her symptoms resolved with supportive care. Another patient who was mistakenly administered a 700 mg dose experienced rapid onset of dysesthesia. Inpatient suppor-tive care was given, including hydration, electrolyte support, and platelet transfusion. Recovery occurred 15 days after the overdose. There is no known antidote for oxaliplatin overdose. In addition to thrombocytopenia, the anticipated complications of an oxaliplatin overdose include myelosuppression, nausea and vomiting, diarrhea, and neurotoxicity. Patients suspected of receiving an overdose should be monitored, and supportive treatment should be administered.

DOSAGE AND ADMINISTRATION
The recommended dose schedule given every two weeks is as follows:
Day 1:
OXALTIE® 85 mg/m² IV infusion in 250-500 mL D5W and leucovorin 200 mg/m² IV infusion in D5W both given over 120 minutes at the same time in separate bags using a Y-line, followed by 5-FU 400 mg/m² IV bolus given over 2-4 minutes, followed by 5-FU 600 mg/m² IV infusion in 500 mL D5W (recommended) as a 22-hour continuous infusion.
Day 2:
Leucovorin 200 mg/m² IV infusion over 120 minutes, followed by 5-FU 400 mg/m² 2 IV bolus given over 2-4 minutes, followed by 5-FU 600 mg/m² IV infusion in 500 mL D5W (recommended) as a 22-hour continuous infusion.
Repeat cycle every 2 weeks.
The administration of **OXALTIE®** does not require prehydration.
Premedication with antiemetics, including 5-HT3 blockers with or without dexamethasone, is recommended.



Dose Modification Recommendations
Prior to subsequent therapy cycles, patients should be evaluated for clinical toxicities and laboratory tests. Neuropathy was graded using a study-specific neurotoxicity scale; other toxicities were graded by the NCI CTC, Version 2.0. Prolongation of infusion time for oxaliplatin from 2 hours to 6 hours decreases the C_{max} by an estimated 32% and may mitigate acute toxicities. The infusion time for infusional 5-FU and leucovorin do not need to be changed.
For patients who experience persistent Grade 2 neurosensory events that do not resolve, a dose reduction of **OXALTIE®** to 65 mg/m² should be considered. For patients with persistent Grade 3 neurosensory events, discontinuing therapy should be considered. The infusional 5-FU/LV regimens need not be altered.
A dose reduction of **OXALTIE®** to 65 mg/m² and infusional 5-FU by 20% (300 mg/m² bolus and 500 mg/m² 22 hour infusion) is recommended for patients after recovery from grade 3/4 gastrointestinal (despite prophylactic treatment) or grade 3/4 hematologic toxicity (neutrophils <1.5 x 10^9 /L, platelets <100 x 10^9 /L)

Preparation of Infusion Solution
Reconstitution or final dilution must never be performed with a sodium chloride solution or other chloride-containing solutions.
The lyophilized powder is reconstituted by adding 10 mL (for the 50 mg vial) or 20 mL (for the 100 mg vial) of Water for Injection, USP or 5% Dextrose Injection, USP.
Do not administer the reconstituted solution without further dilution. The reconstituted solution must be further diluted in an infusion solution of 250-500 mL of 5% Dextrose Injection, USP.
After reconstitution in the original vial, the solution may be stored up to 24 hours under refrigeration 2°C-8°C (36°F-46°F).
After final dilution with 250-500 mL of 5% Dextrose Injection, USP, the shelf life is **6 hours at room temperature 20°C-25°C (68°F-77°F) or up to 24 hours under refrigeration 2°C-8°C (36°F-46°F). OXALTIE®** is not light sensitive under normal room condition.
Oxaliplatin is incompatible in solution with alkaline medications or media (such as basic solutions of 5-FU) and must not be mixed with these or administered simulta-neously through the same infusion line. **The infusion line should be flushed with D5W prior to administration of any concomitant medication.**
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and discarded if present.
Needles or intravenous administration sets containing aluminum parts that may come in contact with oxaliplatin should not be used for the preparation or mixing of the drug. Aluminum has been reported to cause degradation of platinum compounds.