Summary of Product Characteristics for Pharmaceutical Products

1. Name of the Medicinal Product

OXITAN INJECTION CONCENTRATE (50 MG & 100 MG)

2. Qualitative And Quantitative Composition

Each mL contains 5 mg of Oxaliplatin USP

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Sterile Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Oxaliplatin used in combination with infusional 5-fluorouracil/leucovorin is indicated for:

• Adjuvant treatment of stage III colon cancer in patients who have undergone complete resection of the primary tumor.

• Treatment of advanced colorectal cancer.

4.2 Posology and Method of Administration

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.

Dosage

Administer oxaliplatin in combination with 5-fluorouracil (5-FU)/leucovorin (LV) every 2 weeks. For advanced disease, treatment is recommended until disease progression or unacceptable toxicity. For adjuvant use, treatment is recommended for a total of 6 months (12 cycles):

Day 1:	Oxaliplatin 85 mg/m^2 IV infusion in 250-500 ml 5 % Dextrose injection, USP and leucovorin 200 mg/m^2 IV infusion in 5 % Dextrose injection, USP both given over 120 minutes at the same time in separate bags using a Y-line, followed by 5-FU 400 mg/m^2 IV bolus given over 2-4 minutes, followed by 5-FU 600 mg/m^2 IV infusion in 500 ml 5 % Dextrose injection, USP (recommended) as a 22-hour continuous infusion.
Day 2:	Leucovorin 200 mg/m^2 IV infusion over 120 minutes, followed by 5-FU 400 mg/m^2 IV bolus given over 2-4 minutes, followed by 5-FU 600 mg/m^2 IV infusion in 500 ml 5 % Dextrose injection, USP (recommended) as a 22-hour continuous infusion.

Day 1	5-FU bolus 400 mg/m^2 over 2 minutes to 4 minutes ↓	Day 2	5-FU bolus 400 mg/m^2 over 2 minutes to 4 minutes ↓
Leucovorin 200 mg/m^2	5-FU infusion 600 mg/m^2	Leucovorin 200 mg/m^2	5-FU infusion 600 mg/m^2
Oxaliplatin Injection 85 mg/m^2			
O h	2 h ⟵ 22 hrs ⟶	O h	2 h ⟵ 22 hrs ⟶

← 2 hrs →		← 2 hrs →	

The administration of oxaliplatin does not require prehydration. Premedication with antiemetics, including 5-HT3 blockers with or without dexamethasone, is recommended.
For information on 5-fluorouracil and leucovorin, see the respective package inserts.

Dose Modification Recommendations

Prior to subsequent therapy cycles, patients should be evaluated for clinical toxicities and laboratory tests. Prolongation of infusion time for oxaliplatin from 2 hours to 6 hours may mitigate acute toxicities. The infusion times for 5-FU and leucovorin do not need to be changed.

Adjuvant Therapy in Patients with Stage III Colon Cancer

Neuropathy and other toxicities were graded using the NCI CTC scale version 1.
For patients who experience persistent grade 2 neurosensory events that do not resolve, a dose reduction of oxaliplatin to 75 mg/m^2 should be considered. For patients with persistent grade 3 neurosensory events, discontinuing therapy should be considered. The infusional 5-FU/LV regimen need not be altered.
A dose reduction of oxaliplatin to 75 mg/m^2 and infusional 5-fluorouracil to 300 mg/m^2 bolus and 500 mg/m^2 22-hour infusion is recommended for patients after recovery from grade 3/4 gastrointestinal (despite prophylactic treatment) or grade 4 neutropenia or febrile neutropenia or grade 3/4 thrombocytopenia. The next dose should be delayed until: neutrophils ≥1.5×109/L and platelets ≥75×109/L.

Dose Modifications in Therapy in Previously Untreated and Previously Treated Patients with Advanced Colorectal Cancer

Neuropathy was graded using a study-specific neurotoxicity scale. Other toxicities were graded by the NCI CTC, version 2.0.
For patients who experience persistent Grade 2 neurosensory events that do not resolve, a dose reduction of oxaliplatin to 65 mg/m^2 should be considered. For patients with persistent grade 3 neurosensory events, discontinuing therapy should be considered. The 5-FU/LV regimen need not be altered.
A dose reduction of oxaliplatin to 65 mg/m2 and 5-FU by 20 % (300 mg/m^2 bolus and 500 mg/m^2 22-hour infusion) is recommended for patients after recovery from grade 3/4 gastrointestinal (despite prophylactic treatment) or grade 4 neutropenia or grade 3/4 thrombocytopenia. The next dose should be delayed until: neutrophils >1.5 x 109/L and platelets >75 x 109/L.

Dose Modifications in Therapy for Patients with Renal Impairment

In patients with normal renal function or mild to moderate renal impairment, the recommended dose of oxaliplatin is 85 mg/m2. In

patients with severe renal impairment, the initial recommended oxaliplatin dose should be reduced to 65 mg/m^2.

4.3 Contraindications

OXITAN (Oxaliplatin Injection) should not be administered to patients with a history of known allergy to oxaliplatin or other platinum compounds.

4.4 Special Warnings and Precautions for Use

Allergic Reactions

Grade 3/4 hypersensitivity, including anaphylactic/anaphylactoid reactions, to oxaliplatin has been observed in 2-3 % of colon cancer patients. These allergic reactions which can be fatal, can occur within minutes of administration and at any cycle, and were similar in nature and severity to those reported with other platinum-containing compounds, such as rash, urticaria, erythema, pruritus, and, rarely, bronchospasm and hypotension. The symptoms associated with hypersensitivity reactions reported in the previously untreated patients were urticaria, pruritus, flushing of the face, diarrhea associated with oxaliplatin infusion, shortness of breath, bronchospasm, diaphoresis, chest pains, hypotension, disorientation and syncope. These reactions are usually managed with standard epinephrine, corticosteroid, antihistamine therapy, and require discontinuation of therapy. Rechallenge is contraindicated in these. Drug-related deaths associated with platinum compounds from anaphylaxis have been reported.

Neurologic Toxicity

Neuropathy

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 5-FU/LV. In any individual cycle acute neurotoxicity was observed in approximately 30 % of patients. In adjuvant patients the median cycle of onset for grade 3 peripheral sensory neuropathy was 9 in the previously treated patients the median number of cycles administered on the oxaliplatin with 5 FU/LV combination arm was 6.

An acute syndrome of pharyngolaryngeal dysesthesia seen in 1-2 % (grade 3/4) of patients previously untreated for advanced colorectal cancer, and the previously treated patients, is characterized by subjective sensations of dysphagia or dyspnea, without any laryngospasm or bronchospasm (no stridor or wheezing). Ice (mucositis prophylaxis)

should be avoided during the infusion of oxaliplatin because cold temperature can exacerbate acute neurological symptoms.

A persistent (>14 days), primarily peripheral, sensory neuropathy that is usually characterized by paresthesias, dysesthesias, 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 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.

In the adjuvant colon cancer trial, neuropathy was graded using a prelisted module derived from the Neuro-Sensory section of the National Cancer Institute Common Toxicity Criteria (NCI CTC) scale, Version 1, as follows:

Table 1: NCI CTC Grading for Neuropathy in Adjuvant Patients

NCI Grade	Definition
Grade 0	No change or none
Grade 1	Mild paresthesias, loss of deep tendon reflexes
Grade 2	Mild or moderate objective sensory loss, moderate paresthesias
Grade 3	Severe objective sensory loss or paresthesias that interfere with function
Grade 4	Not applicable

Peripheral sensory neuropathy was reported in adjuvant patients treated with the oxaliplatin combination with a frequency of 92 % (all grades) and 13 % (grade 3). At the 28-day follow-up after the last treatment cycle, 60 % of all patients had any grade (Grade 1=40 %, Grade 2=16 %, Grade 3=5 %) peripheral sensory neuropathy decreasing to 39 % at 6 months follow-up (Grade 1=31 %, Grade 2=7 %, Grade 3=1 %) and 21 % at 18 months of follow-up (Grade 1=17 %, Grade 2=3 %, Grade 3=1 %).

In the advanced colorectal cancer studies, neuropathy was graded using a study-specific neurotoxicity scale, which was different from the NCI CTC scale, Version 2.0.

Table 2: Grading Scale for Paresthesias/Dysesthesias in Advanced Colorectal Cancer Patients

Grade	Definition
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

Overall, neuropathy was reported in patients previously untreated for advanced colorectal cancer in 82 % (all grades) and 19 % (grade 3/4), and in the previously treated patients in 74 % (all grades) and 7 % (grade 3/4) events. Information regarding reversibility of neuropathy was not available from the trial for patients who had not been previously treated for colorectal cancer.

Reversible Posterior Leukoencephalopathy Syndrome

Reversible Posterior Leukoencephalopathy Syndrome (RPLS, also known as PRES, Posterior Reversible Encephalopathy Syndrome) has been observed in clinical trials (< 0.1 %) and postmarketing experience. Signs and symptoms of RPLS could be headache, altered mental functioning, seizures, abnormal vision from blurriness to blindness, associated or not with hypertension. Diagnosis of RPLS is based upon confirmation by brain imaging.

Severe Neutropenia

Grade 3 or 4 neutropenia occurred in 41–44% of patients with colorectal cancer treated with oxaliplatin in combination with 5-flurouracil (5-FU) and leucovorin compared to 5% with 5-FU plus leucovorin alone. Sepsis, neutropenic sepsis and septic shock have been reported in patients treated with oxaliplatin, including fatal outcomes.

Delay oxaliplatin until neutrophils are ≥ 1.5 × 109/L. Withhold oxaliplatin for sepsis or septic shock. Dose reduce oxaliplatin after recovery from Grade 4 neutropenia or febrile neutropenia.

Pulmonary Toxicity

Oxaliplatin has been associated with pulmonary fibrosis (<1 % of study patients), which may be fatal. The combined incidence of cough and dyspnea was 7.4 % (any grade) and <1 % (grade 3) with no grade 4 events in the oxaliplatin plus infusional 5-FU/LV arm compared to 4.5 % (any grade) and no grade 3 and 0.1 % grade 4 events in the infusional 5-FU/LV alone arm in adjuvant colon cancer patients. In the study, one patient died from eosinophilic pneumonia in the oxaliplatin combination arm. The combined incidence of cough, dyspnea, and hypoxia was 43 % (any grade) and 7 % (grade 3 and 4) in the oxaliplatin plus 5-FU/LV arm compared to 32 % (any grade) and 5 % (grade 3 and 4) in the Irinotecan plus 5-FU/LV arm of unknown duration for patients with previously untreated colorectal cancer. 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.

Hepatotoxicity

Hepatotoxicity as evidenced in the adjuvant study, by increase in transaminases (57 % vs. 34 %) and alkaline phosphatase (42 % vs. 20 %) was observed more commonly in the oxaliplatin combination arm. The incidence of increased bilirubin was similar on both arms. Changes

noted on liver biopsies include: peliosis, nodular regenerative hyperplasia or sinusoidal alterations, perisinusoidal fibrosis, and veno-occlusive lesions. Hepatic vascular disorders should be considered and if appropriate, should be investigated in case of abnormal liver function test results or portal hypertension, which cannot be explained by liver metastases.

Cardiovascular Toxicity

QT prolongation and ventricular arrhythmias including fatal Torsade de Pointes have been observed following oxaliplatin administration. ECG monitoring is recommended if therapy is initiated in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics, and electrolyte abnormalities. Correct hypokalemia or hypomagnesemia prior to initiating oxaliplatin and monitor these electrolytes periodically during therapy. Avoid oxaliplatin in patients with congenital long QT syndrome.

Rhabdomyolysis

Rhabdomyolysis, including fatal cases, has been observed in patients treated with oxaliplatin. Discontinue oxaliplatin if any signs or symptoms of rhabdomyolysis occur.

Recommended 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 oxaliplatin cycle. There have been reports while on study and from post-marketing surveillance of prolonged prothrombin time and INR occasionally associated with hemorrhage in patients who received oxaliplatin plus 5-fluorouracil/leucovorin while on anticoagulants. Patients receiving oxaliplatin plus 5-fluorouracil/leucovorin and requiring oral anticoagulants may require closer monitoring.

Use in Specific Populations

Pediatric Use

The effectiveness of oxaliplatin in children has not been established. Oxaliplatin has been tested in 2 Phase I and 2 Phase II trials in 235 patients ages 7 months to 22 years with solid tumors (see below) and no significant activity observed. In a Phase I/II study, oxaliplatin was administered as a 2-hour intravenous infusion on days 1, 8 and 15 every 4 weeks (1 cycle), for a maximum of 6 cycles, to 43 patients with refractory or relapsed malignant solid tumors, mainly neuroblastoma and osteosarcoma. Twenty-eight pediatric patients in the Phase I study received oxaliplatin at 6 dose levels starting at 40 mg/m² with escalation to 110 mg/m². The dose limiting toxicity (DLT) was sensory neuropathy at the 110 mg/m² dose. Fifteen patients received oxaliplatin at a dose of 90 mg/m² intravenous in the Phase II portion of the study. At this dose, paresthesia (60%, G3/4: 7%), fever (40%, G3/4: 7%) and thrombocytopenia (40%, G3/4: 27%) were the main adverse reactions. No responses were observed.

In a second Phase I study, oxaliplatin was administered to 26 pediatric patients as a 2-hour intravenous infusion on day 1 every 3 weeks (1 cycle) at 5 dose levels starting at 100 mg/m² with escalation to 160 mg/m², for a maximum of 6 cycles. In a separate cohort, oxaliplatin 85 mg/m² was administered on day 1 every 2 weeks, for a maximum of 9 doses. Patients had metastatic or unresectable solid tumors mainly neuroblastoma and ganglioneuroblastoma. No responses were observed. The DLT was sensory neuropathy at the 160 mg/m² dose. Based on these studies, oxaliplatin 130 mg/m² as a 2-hour intravenous infusion on day 1 every 3 weeks (1 cycle) was used in subsequent Phase II studies. A dose of 85 mg/m2 on day 1 every 2 weeks was also found to be tolerable.

In one Phase II study, 43 pediatric patients with recurrent or refractory embryonal CNS tumors received oxaliplatin 130 mg/m2 every 3 weeks for a maximum of 12 months in absence of progressive disease or unacceptable toxicity. In patients < 10 kg the oxaliplatin dose used was 4.3 mg/kg. The most common adverse reactions reported were leukopenia (67%, G3/4: 12%), anemia (65%, G3/4: 5%), thrombocytopenia (65%, G3/4: 26%), vomiting (65%, G3/4: 7%), neutropenia (58%, G3/4: 16%) and sensory neuropathy (40%, G3/4: 5%). One partial response was observed.

In a second Phase II study, 123 pediatric patients with recurrent solid tumors, including neuroblastoma, osteosarcoma, Ewing sarcoma or peripheral PNET, ependymoma, rhabdomyosarcoma, hepatoblastoma, high grade astrocytoma, Brain stem glioma, low grade astrocytoma, malignant germ cell tumor and other tumors of interest received oxaliplatin 130 mg/m2 every 3 weeks for a maximum of 12 months or 17 cycles. In patients ≤ 12 months old the oxaliplatin dose used was 4.3 mg/kg. The most common adverse reactions reported were sensory neuropathy (52%, G3/4: 12%), thrombocytopenia (37%, G3/4: 17%), anemia (37%, G3/4: 9%), vomiting (26%, G3/4:4%), ALT increased (24%, G3/4: 6%), AST increased (24%, G3/4: 2%), and nausea (23%, G3/:4 3%). Two partial responses were observed. The pharmacokinetic parameters of ultrafiltrable platinum have been evaluated in 105 pediatric patients during the first cycle. The mean clearance in pediatric patients estimated by the population pharmacokinetic analysis was 4.7 L/h. The inter-patient variability of platinum clearance in pediatric cancer patients was 41%. Mean platinum pharmacokinetic parameters in ultrafiltrate were Cmax of 0.75 + 0.24 mcg/mL, AUC0-48 of 7.52 + 5.07 mcg.h/mL and AUCinf of 8.83 + 1.57 mcg.h/mL at 85 mg/m² of oxaliplatin and Cmax of 1.10 + 0.43 mcg/mL, AUC0-48 of 9.74 + 2.52 mcg.h/mL and AUCinf of 17.3 + 5.34 mcg.h/mL at 130 mg/m² of oxaliplatin.

Geriatric Use

No significant effect of age on the clearance of ultrafilterable platinum has been observed.

In the adjuvant therapy colon cancer randomized clinical trial, 723 patients treated with Oxaliplatin and infusional 5-fluorouracil/leucovorin were <65 years and 400 patients were ≥65 years.
A descriptive subgroup analysis demonstrated that the improvement in DFS for the Oxaliplatin combination arm compared to the infusional 5-fluorouracil/leucovorin alone arm appeared to be maintained across genders. The effect of Oxaliplatin in patients ≥65 years of age was not conclusive. Insufficient subgroup sizes prevented analysis by race. Patients ≥ 65 years of age receiving the combination therapy experienced more grade 3-4 granulocytopenia than patients < 65 years of age (45% versus 39%).
In the previously untreated for advanced colorectal cancer randomized clinical trial of Oxaliplatin, 160 patients treated with Oxaliplatin and 5-fluorouracil/leucovorin were < 65 years and 99 patients were ≥65 years. The same efficacy improvements in response rate, time to tumor progression, and overall survival were observed in the ≥65-year-old patients as in the overall study population. In the previously treated for advanced colorectal cancer randomized clinical trial of Oxaliplatin, 95 patients treated with Oxaliplatin and 5-fluorouracil/leucovorin were <65 years and 55 patients were ≥65 years. The rates of overall adverse reactions, including grade 3 and 4 events, were similar across and within arms in the different age groups in all studies. The incidence of diarrhea, dehydration, hypokalemia, leukopenia, fatigue and syncope were higher in patients ≥65 years old. No adjustment to starting dose was required in patients ≥65 years old.
Patients with Renal Impairment
The exposure (AUC) of unbound platinum in plasma ultrafiltrate tends to increase in renally impaired patients. Caution and close monitoring should be exercised when oxaliplatin is administered to patients with renal impairment. The starting oxaliplatin dose does not need to be reduced in patients with mild (creatinine clearance=50-80 ml/min) or moderate (creatinine clearance=30-49 ml/min) renal impairment. However, the starting dose of oxaliplatin should be reduced in patients with severe renal impairment (creatinine clearance < 30 ml/min).

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

No pharmacokinetic interaction between 85 mg/m^2 of oxaliplatin and in fusional 5-fluorouracil has been observed in patients treated every 2 weeks, but increases of 5-fluorouracil 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.

4.6 Fertility, Pregnancy and Lactation

Pregnancy

Pregnancy Category D

Based on direct interaction with DNA, oxaliplatin may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of oxaliplatin in pregnant women. Reproductive toxicity studies in rats demonstrated adverse effects on fertility and embryo-fetal development at maternal doses that were the recommended human dose based on body surface area. 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 and use effective contraception while receiving treatment with oxaliplatin. Pregnant rats were administered oxaliplatin at less than one-tenth the recommended human dose based on body surface area during gestation days 1-5 (pre-implantation), 6-10, or 11-16 (during organogenesis). Oxaliplatin caused developmental mortality (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. Administration of oxaliplatin to male and female rats prior to mating resulted in 97 % post-implantation loss in animals that received approximately one-seventh the recommended human dose based on the body surface area.

Breast-feeding

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 the importance of the drug to the mother.

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 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 patient's 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 following serious adverse reactions are discussed in greater detail in other sections of the label:

- Anaphylaxis and Allergic reactions
- Neuropathy
- Severe Neutropenia
- Pulmonary Toxicities
- Hepatotoxicity
- Cardiovascular Toxicities
- Rhabdomyolysis

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

More than 1100 patients with stage II or III colon cancer and more than 4000 patients with advanced colorectal cancer have been treated in clinical studies with oxaliplatin. The most common adverse reactions in patients with stage II or III colon cancer receiving adjuvant therapy were peripheral sensory neuropathy, neutropenia, thrombocytopenia, anemia, nausea, increase in transaminases and alkaline phosphatase, diarrhea, emesis, fatigue, and stomatitis. The most common adverse reactions in previously untreated and treated patients were peripheral sensory neuropathies, fatigue, neutropenia, nausea, emesis, and diarrhea.

Combination Adjuvant Therapy with Oxaliplatin and Infusional 5-fluorouracil/leucovorin in Patients with Colon Cancer

One thousand one hundred and eight patients with stage II or III colon cancer, who had undergone complete resection of the primary tumor, have been treated in a clinical study with oxaliplatin in combination with infusional 5-FU/LV. The incidence of grade 3 or 4 adverse reactions was 70% on the oxaliplatin combination arm, and 31% on the infusional 5-FU/LV arm. The adverse reactions in this trial are shown in the tables below. Discontinuation of treatment due to adverse reactions occurred in 15% of the patients receiving oxaliplatin and infusional 5-FU/LV. Both 5-FU/LV and oxaliplatin are associated with gastrointestinal or hematologic adverse events. When oxaliplatin is administered in combination with infusional 5-FU/LV, the incidence of these events is increased.

The incidence of death within 28 days of last treatment, regardless of causality, was 0.5% (n=6) in both the oxaliplatin combination and infusional 5-FU/LV arms, respectively. Deaths within 60 days from initiation of therapy were 0.3% (n=3) in both the oxaliplatin combination and infusional 5-FU/LV arms, respectively. On the oxaliplatin combination arm, 3 deaths were due to sepsis/neutropenic sepsis, 2 from intracerebral bleeding, and one from eosinophilic pneumonia. On the 5-FU/LV arm, one death was due to suicide, 2 from Steven-Johnson

Syndrome (1 patient also had sepsis), 1 unknown cause, 1 anoxic cerebral infarction, and 1 probable abdominal aorta rupture.
The following table provides adverse reactions reported in the adjuvant therapy colon cancer clinical trial by body system and decreasing order of frequency in the oxaliplatin and infusional 5-FU/LV arm for events with overall incidences >5% and for NCI grade 3/4 events with incidences >1%.

Table 3 – Adverse Reactions Reported in Patients with Colon Cancer receiving Adjuvant Treatment (≥5 % of all patients and with ≥1 % NCI grade 3/4 events)

	Oxaliplatin + 5-FU/LV N=1108		**5-FU/LV N=1111**	
Adverse Reaction (WHO/Pref)	**All Grades (%)**	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**
Any Event	100	70	99	31
Allergy/Immunology				
Allergic Reaction	10	3	2	<1
Constitutional Symptoms/Pain				
Fatigue	44	4	38	1
Abdominal Pain	18	1	17	2
Dermatology/Skin				
Skin Disorder	32	2	36	2
Injection Site Reaction[1]	11	3	10	3
Gastrointestinal				
Nausea	74	5	61	2
Diarrhea	56	11	48	7
Vomiting	47	6	24	1
Stomatitis	42	3	40	2
Anorexia	13	1	8	<1
Fever/Infection				
Fever	27	1	12	1
Infection	25	4	25	3
Neurology				

Overall Peripheral Sensory Neuropathy	92	12	16	<1

[1]Includes thrombosis related to the catheter

The following table provides adverse reactions reported in the adjuvant therapy colon cancer clinical trial by body system and decreasing order of frequency in the oxaliplatin and infusional 5-FU/LV arm for events with overall incidences ≥5 % but with incidences <1 % NCI grade 3/4 events.

Table 4 – Adverse Reactions Reported in Patients with Colon Cancer Receiving Adjuvant Treatment (≥5 % of all patients, but with <1 % NCI grade 3/4 events)

Adverse reaction (WHO/Pref)	**Oxaliplatin + 5-FU/LV N=1108**	**5-FU/LV N=1111**
	All Grades (%)	**All Grades (%)**
Allergy/Immunology		
Rhinitis	6	8
Constitutional Symptoms/Pain/Ocular/Visual		
Epistaxis	16	12
Weight Increase	10	10
Conjunctivitis	9	15
Headache	7	5
Dyspnea	5	3
Pain	5	5
Lacrimation Abnormal	4	12
Dermatology/Skin		
Alopecia	30	28
Gastrointestinal		
Constipation	22	19
Taste Perversion	12	8
Dyspepsia	8	5
Metabolic		
Phosphate Alkaline Increased	42	20
Neurology		
Sensory Disturbance	8	1

Although specific events can vary, the overall frequency of adverse reactions was similar in men and women and in patients <65 and >65 years. However, the following grade 3/4 events were more common in females: diarrhea, fatigue, granulocytopenia, nausea, and vomiting. In patients >65 years old, the incidence of grade 3/4 diarrhea and granulocytopenia was higher than in younger patients. Insufficient subgroup sizes prevented analysis of safety by race. The following additional adverse reactions 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): pain, leukopenia, weight decrease, coughing.
The number of patients who developed secondary malignancies was similar; 62 in the oxaliplatin combination arm and 68 in the infusional 5-fluorouracil/leucovorin arm. An exploratory analysis showed that the number of deaths due to secondary malignancies was 1.96 % in the oxaliplatin combination arm and 0.98 % in infusional 5-fluorouracil/leucovorin arm. In addition, the number of cardiovascular deaths was 1.4% in the oxaliplatin combination arm as compared to 0.7 % in the infusional 5-fluorouracil/leucovorin arm. Clinical significance of these findings is unknown.
Patients Previously Untreated for Advanced Colorectal Cancer
Two hundred and fifty-nine patients were treated in the oxaliplatin and 5-FU/LV combination arm of the randomized trial in patients previously untreated for advanced colorectal cancer. The adverse reactions 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.

Both 5-FU and oxaliplatin are associated with gastrointestinal and hematologic adverse reactions. When oxaliplatin is administered in combination with 5-FU, the incidence of these events is increased.
The incidence of death within 30 days of treatment in the previously untreated for advanced colorectal cancer study, regardless of causality, was 3% with the oxaliplatin and 5-FU/LV combination, 5% with irinotecan plus 5-FU/LV, and 3% with oxaliplatin plus irinotecan. Deaths within 60 days from initiation of therapy were 2.3% with the oxaliplatin and 5-FU/LV combination, 5.1% with irinotecan plus 5-FU/LV, and 3.1% with oxaliplatin plus irinotecan.

The following table provides adverse reactions reported in the previously untreated for advanced colorectal cancer study by body system and decreasing order of frequency in the oxaliplatin and 5-FU/LV combination arm for events with overall incidences >5% and for grade 3/4 events with incidences > 1%.
Table 5 – Adverse Reactions Reported in Patients Previously Untreated for Advanced Colorectal Cancer Clinical Trial (≥5 % of all patients and with ≥1 % NCI grade 3/4 events)

	Oxaliplatin + 5-FU/LV N=259		Irinotecan + 5-FU/LV N=256		Oxaliplatin + irinotecan N=258	
Adverse reaction (WHO/Pref)	**All Grades (%)**	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**
Any Event	99	82	98	70	99	76
Allergy/Immunology						
Hypersensitivity	12	2	5	0	6	1
Cardiovascular						
Thrombosis	6	5	6	6	3	3
Hypotension	5	3	6	3	4	3
Constitutional Symptoms/Pain/Ocular/Visual						
Fatigue	70	7	58	11	66	16
Abdominal Pain	29	8	31	7	39	10
Myalgia	14	2	6	0	9	2
Pain	7	1	5	1	6	1
Vision Abnormal	5	0	2	1	6	1
Neuralgia	5	0	0	0	2	1
Dermatology/Skin						
Skin Reaction - hand/foot	7	1	2	1	1	0
Injection site reaction	6	0	1	0	4	1
Gastrointestinal						
Nausea	71	6	67	15	83	19
Diarrhea	56	12	65	29	76	25
Vomiting	41	4	43	13	64	23
Stomatitis	38	0	25	1	19	1
Anorexia	35	2	25	4	27	5
Constipation	32	4	27	2	21	2
Diarrhea - colostomy	13	2	16	7	16	3
Gastrointestinal NOS*	5	2	4	2	3	2

Hematology/Infection						
Infection no ANC**	10	4	5	1	7	2
Infection low ANC**	8	8	12	11	9	8
Lymphopenia	6	2	4	1	5	2
Febrile Neutropenia	4	4	15	14	12	11
Hepatic/Metabolic/Laboratory/Renal						
Hyperglycemia	14	2	11	3	12	3
Hypokalemia	11	3	7	4	6	2
Dehydration	9	5	16	11	14	7
Hypoalbuminemia	8	0	5	2	9	1
Hyponatremia	8	2	7	4	4	1
Urinary Frequency	5	1	2	1	3	1
Neurology						
Overall Neuropathy	82	19	18	2	69	7
Paresthesias	77	18	16	2	62	6
Pharyngo-laryngeal Dysesthesias	38	2	1	0	28	1
Neuro-sensory	12	1	2	0	9	1
Neuro NOS*	1	0	1	0	1	0
Pulmonary						
Cough	35	1	25	2	17	1
Dyspnea	18	7	14	3	11	2
Hiccups	5	1	2	0	3	2

* Not otherwise specified
** Absolute neutrophil count

The following table provides adverse reactions reported in the previously untreated for advanced colorectal cancer study by body system and decreasing order of frequency in the oxaliplatin and 5-FU/LV combination arm for events with overall incidences >5 % but with incidences < 1 % NCI grade 3/4 events.

Table 6 – Adverse Reactions Reported in Patients Previously Untreated for Advanced Colorectal Cancer Clinical Trial (≥ 5 % of all patients but with < 1% NCI grade 3/4 events)

Adverse reaction (WHO/Pref)	Oxaliplatin + 5-FU/LV N=259	Irinotecan + 5-FU/LV N=256	Oxaliplatin + irinotecan N=258
	All Grades (%)	All Grades (%)	All Grades (%)
Allergy/Immunology			
Rash	11	4	7
Rhinitis Allergic	10	6	6
Cardiovascular			
Edema	15	13	10
Constitutional Symptoms/Pain/Ocular/Visual			
Headache	13	6	9
Weight Loss	11	9	11
Epistaxis	10	2	2
Tearing	9	1	2
Rigors	8	2	7
Dysphasia	5	3	3
Sweating	5	6	12
Arthralgia	5	5	8
Dermatology/Skin			
Alopecia	38	44	67
Flushing	7	2	5
Pruritus	6	4	2
Dry Skin	6	2	5
Gastrointestinal			
Taste Perversion	14	6	8
Dyspepsia	12	7	5
Flatulence	9	6	5
Mouth Dryness	5	2	3
Hematology/Infection			
Fever normal ANC*	16	9	9
Hepatic/Metabolic/Laboratory/Renal			

Hypocalcemia	7	5	4
Elevated Creatinine	4	4	5
Neurology			
Insomnia	13	9	11
Depression	9	5	7
Dizziness	8	6	10
Anxiety	5	2	6

*Absolute neutrophil count

Adverse reactions were similar in men and women and in patients <65 and >65 years, but older patients may have been more susceptible to diarrhea, dehydration, hypokalemia, leukopenia, fatigue, and syncope.

The following additional adverse reactions, at least possibly related to treatment and potentially important, were reported in >2 % and <5 % of the patients in the oxaliplatin and 5-FU/LV combination arm (listed in decreasing order of frequency): metabolic, pneumonitis, catheter infection, vertigo, prothrombin time, pulmonary, rectal bleeding, dysuria, nail changes, chest pain, rectal pain, syncope, hypertension, hypoxia, unknown infection, bone pain, pigmentation changes, and urticaria.

Previously Treated Patients with Advanced Colorectal Cancer

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 reactions 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 percent of patients in the oxaliplatin and 5-FU/LV combination arm and 18% in the 5-FU/LV arm of the previously treated study 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 reactions. When oxaliplatin is administered in combination with 5-FU, the incidence of these events is increased.

The incidence of death within 30 days of treatment in the previously treated study, regardless of causality, was 5% with the oxaliplatin and 5-FU/LV combination, 8% with oxaliplatin alone, and 7% with 5-FU/LV. Of the 7 deaths that occurred on the oxaliplatin and 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 reactions reported in the previously treated study by body system and in decreasing order of frequency in the oxaliplatin and 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.

Table 7 – Adverse Reactions Reported in Previously Treated Colorectal Cancer Clinical Trial (≥5 % of all patients and with ≥1 % NCI grade 3/4 events)

	5-FU/LV (N=142)		**Oxaliplatin (N=153)**		**Oxaliplatin + 5-FU/LV (N=150)**	
Adverse reaction (WHO/Pref)	**All Grades (%)**	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**
Any Event	98	41	100	46	99	73
Cardiovascular						
Dyspnea	11	2	13	7	20	4
Coughing	9	0	11	0	19	1
Edema	13	1	10	1	15	1
Thromboembolism	4	2	2	1	9	8
Chest Pain	4	1	5	1	8	1
Constitutional Symptoms/Pain						
Fatigue	52	6	61	9	68	7
Back Pain	16	4	11	0	19	3
Pain	9	3	14	3	15	2
Dermatology/Skin						
Injection Site Reaction	5	1	9	0	10	3
Gastrointestinal						
Diarrhea	44	3	46	4	67	11
Nausea	59	4	64	4	65	11
Vomiting	27	4	37	4	40	9
Stomatitis	32	3	14	0	37	3
Abdominal Pain	31	5	31	7	33	4
Anorexia	20	1	20	2	29	3
Gastroesophageal Reflux	3	0	1	0	5	2
Hematology/Infection						
Fever	23	1	25	1	29	1

Febrile Neutropenia	1	1	0	0	6	6
Hepatic/Metabolic/Laboratory/Renal						
Hypokalemia	3	1	3	2	9	4
Dehydration	6	4	5	3	8	3
Neurology						
Neuropathy	17	0	76	7	74	7
Acute	10	0	65	5	56	2
Persistent	9	0	43	3	48	6

The following table provides adverse reactions reported in the previously treated study by body system and in decreasing order of frequency in the oxaliplatin and 5-FU/LV combination arm for reactions with overall incidences >5 % but with incidences <1 % NCI grade 3/4 events.

Table 8 – Adverse Reactions Reported in Previously Treated Colorectal Cancer Clinical Trial (≥5 % of all patients but with < 1 % NCI grade 3/4 events)

Adverse reaction (WHO/Pref)	**5-FU/LV (N=142)**	**Oxaliplatin (N=153)**	**Oxaliplatin + 5-FU/LV (N=150)**
	All Grades (%)	**All Grades (%)**	**All Grades (%)**
Allergy/Immunology			
Rhinitis	4	6	15
Allergic Reaction	1	3	10
Rash	5	5	9
Cardiovascular			
Peripheral Edema	11	5	10
Constitutional Symptoms/Pain/Ocular/Visual			
Headache	8	13	17
Arthralgia	10	7	10
Epistaxis	1	2	9
Abnormal Lacrimation	6	1	7
Rigors	6	9	7
Dermatology/Skin			
Hand-Foot Syndrome	13	1	11
Flushing	2	3	10
Alopecia	3	3	7

Gastrointestinal			
Constipation	23	31	32
Dyspepsia	10	7	14
Taste Perversion	1	5	13
Mucositis	10	2	7
Flatulence	6	3	5
Hepatic/Metabolic/Laboratory/Renal			
Hematuria	4	0	6
Dysuria	1	1	6
Neurology			
Dizziness	8	7	13
Insomnia	4	11	9
Pulmonary			
Upper Resp Tract Infection	4	7	10
Pharyngitis	10	2	9
Hiccup	0	2	5

Adverse reactions 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 reactions, at least possibly related to treatment and potentially important, were reported in >2 % and <5 % of the patients in the oxaliplatin and 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, pruritus, hemoptysis, purpura, vaginal hemorrhage, melena, somnolence, pneumonia, proctitis, involuntary muscle contractions, intestinal obstruction, gingivitis, tenesmus, hot flashes, enlarged abdomen, urinary incontinence.

Hematologic changes

The following tables list the hematologic changes occurring in >5 % of patients, based on laboratory values and NCI grade, with the exception of those reactions occurring in adjuvant patients and anemia in the patients previously untreated for advanced colorectal cancer, which are based on AE reporting and NCI grade alone.

Table 9– Adverse Hematologic Reactions in Patients with Colon Cancer Receiving Adjuvant Therapy (≥5 % of patients)

Hematology Parameter	Oxaliplatin + 5-FU/LV (N=1108)		5-FU/LV (N=1111)	
	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Anemia	76	1	67	<1
Neutropenia	79	41	40	5
Thrombocytopenia	77	2	19	<1

Table 10 – Adverse Hematologic Reactions in Patients Previously Untreated for Advanced Colorectal Cancer (≥5 % of patients)

Hematology Parameter	Oxaliplatin + 5-FU/LV N=259		Irinotecan + 5-FU/LV N=256		Oxaliplatin + irinotecan N=258	
	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Anemia	27	3	28	4	25	3
Leukopenia	85	20	84	23	76	24
Neutropenia	81	53	77	44	71	36
Thrombocytopenia	71	5	26	2	44	4

Table 11 – Adverse Hematologic Reactions in Previously Treated Patients (≥5 % of patients)

Hematology Parameter	5-FU/LV (N=142)		Oxaliplatin (N=153)		Oxaliplatin + 5-FU/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
Thrombocytopenia	20	0	30	3	64	4

Thrombocytopenia and Bleeding

Thrombocytopenia was frequently reported with the combination of oxaliplatin and infusional 5-FU/LV. The incidence of all hemorrhagic

reactions in the adjuvant and previously treated patients was higher on the oxaliplatin combination arm compared to the infusional 5-FU/LV arm. These reactions included gastrointestinal bleeding, hematuria, and epistaxis. In the adjuvant trial, two patients died from intracerebral hemorrhages.

The incidence of grade 3/4 thrombocytopenia was 2 % in adjuvant patients with colon cancer. In patients treated for advanced colorectal cancer the incidence of grade 3/4 thrombocytopenia was 3-5 %, and the incidence of these reactions was greater for the combination of oxaliplatin and 5-FU/LV over the irinotecan plus 5-FU/LV or 5-FU/LV control groups. Grade 3/4 gastrointestinal bleeding was reported in 0.2 % of adjuvant patients receiving oxaliplatin and 5-FU/LV. In the previously untreated patients, the incidence of epistaxis was 10% in the oxaliplatin and 5-FU/LV arm, and 2 % and 1 %, respectively, in the irinotecan plus 5-FU/LV or irinotecan plus oxaliplatin arms.

Neutropenia

Neutropenia was frequently observed with the combination of oxaliplatin and 5-FU/LV, with grade 3 and 4 events reported in 29 % and 12 % of adjuvant patients with colon cancer, respectively. In the adjuvant trial, 3 patients died from sepsis/neutropenic sepsis. Grade 3 and 4 events were reported in 35 % and 18 % of the patients previously untreated for advanced colorectal cancer, respectively. Grade 3 and 4 events were reported in 27 % and 17 % of previously treated patients, respectively. In adjuvant patients the incidence of either febrile neutropenia (0.7 %) or documented infection with concomitant grade 3/4 neutropenia (1.1 %) was 1.8 % in the oxaliplatin and 5-FU/LV arm. The incidence of febrile neutropenia in the patients previously untreated for advanced colorectal cancer was 15 % (3 % of cycles) in the irinotecan plus 5-FU/LV arm and 4 % (less than 1 % of cycles) in the oxaliplatin and 5-FU/LV combination arm. Additionally, in this same population, infection with grade 3 or 4 neutropenia was 12 % in the irinotecan plus 5-FU/LV and 8 % in the oxaliplatin and 5-FU/LV combination. The incidence of febrile neutropenia in the previously treated patients was 1 % in the 5-FU/LV arm and 6 % (less than 1 % of cycles) in the oxaliplatin and 5-FU/LV combination arm.

Gastrointestinal

In patients receiving the combination of oxaliplatin plus infusional 5-FU/LV for adjuvant treatment for colon cancer the incidence of grade 3/4 nausea and vomiting was greater than in those receiving infusional 5-FU/LV alone. In patients previously untreated for advanced colorectal cancer receiving the combination of oxaliplatin and 5-FU/LV, the incidence of grade 3 and 4 vomiting and diarrhea was less compared to irinotecan plus 5-FU/LV controls. In previously treated patients receiving the combination of oxaliplatin and 5-FU/LV, the incidence of grade 3 and 4 nausea, vomiting, diarrhea, and mucositis/stomatitis increased compared to 5-FU/LV controls.

The incidence of gastrointestinal adverse reactions in the previously untreated and previously treated patients appears to be similar across cycles. Premedication with antiemetics, including 5-HT3 blockers, is recommended. Diarrhea and mucositis may be exacerbated by the addition of oxaliplatin to 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.

Dermatologic

Oxaliplatin did not increase the incidence of alopecia compared to 5-FU/LV alone. No complete alopecia was reported. The incidence of grade 3/4 skin disorders was 2 % in both the oxaliplatin plus infusional 5-FU/LV and the infusional 5-FU/LV alone arms in the adjuvant colon cancer patients. The incidence of hand-foot syndrome in patients previously untreated for advanced colorectal cancer was 2 % in the irinotecan plus 5-FU/LV arm and 7 % in the oxaliplatin and 5-FU/LV combination arm. The incidence of hand-foot syndrome in previously treated patients was 13 % in the 5-FU/LV arm and 11 % in the oxaliplatin and 5-FU/LV combination arm.

Intravenous Site Reactions

Extravasation, in some cases including necrosis, has been reported. Injection site reaction, including redness, swelling, and pain, has been reported.

Anticoagulation and Hemorrhage

There have been reports while on study and from post-marketing surveillance of prolonged prothrombin time and INR occasionally associated with hemorrhage in patients who received oxaliplatin plus 5-fluorouracil/leucovorin while on anticoagulants. Patients receiving oxaliplatin plus 5-fluorouracil/leucovorin and requiring oral anticoagulants may require closer monitoring.

Renal

About 5-10 % 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 5-FU/LV combination arm was 1 % in the previously treated patients. Serum creatinine measurements were not reported in the adjuvant trial.

Hepatic

Hepatotoxicity (defined as elevation of liver enzymes) appears to be related to oxaliplatin combination therapy. The following tables list the clinical chemistry changes associated with hepatic toxicity occurring in >5 % of patients, based on adverse reactions reported and NCI CTC grade for patients previously untreated for advanced colorectal cancer, laboratory values, and NCI CTC grade for previously treated patients.

Table 12 – Adverse Hepatic Reactions in Patients with Stage II or III Colon Cancer Receiving Adjuvant Therapy (≥5 % of patients)

Hepatic Parameter	Oxaliplatin + 5-FU/LV (N=1108)		5-FU/LV (N=1111)	
	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Increase in Transaminases	57	2	34	1
ALP Increased	42	<1	20	<1
Bilirubinaemia	20	4	20	5

Table 13 – Adverse Hepatic Clinical Chemistry Abnormalities in Patients Previously Untreated for Advanced Colorectal Cancer (≥5 % of patients)

Clinical Chemistry	Oxaliplatin + 5-FU/LV N=259		Irinotecan + 5-FU/LV N=256		Oxaliplatin + irinotecan N=258	
	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
ALT (SGPT-ALAT)	6	1	2	0	5	2
AST (SGOT-ASAT)	17	1	2	1	11	1
Alkaline Phosphatase	16	0	8	0	14	2
Total Bilirubin	6	1	3	1	3	2

Table 14 – Adverse Hepatic - Clinical Chemistry Abnormalities in Previously Treated Patients (≥5 % of patients)

Clinical Chemistry	5-FU/LV (N=142)		Oxaliplatin (N=153)		Oxaliplatin + 5-FU/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 reactions in adjuvant patients with colon cancer was 6 % (1.8
% grade 3/4) in the infusional 5-FU/LV arm and 6 % (1.2 % grade 3/4) in the oxaliplatin and infusional 5-FU/LV combined arm, respectively. The incidence was 6 and 9 % of the patients previously untreated for advanced colorectal cancer and previously treated patients in the oxaliplatin and 5-FU/LV combination arm, respectively.

Others

The following adverse reactions have been identified during post-approval use of oxaliplatin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a whole:

Angioedema, anaphylactic shock

Cardiovascular disorders:

QT prolongation leading to ventricular arrhythmias including fatal Torsade de Pointes

Central and peripheral nervous system disorders:

Loss of deep tendon reflexes, dysarthria, Lhermitte's sign, cranial nerve palsies, fasciculations, convulsion, Reversible Posterior Leukoencephalopathy Syndrome (RPLS, also known as PRES).

Hearing and vestibular system disorders:

Deafness

Infections:

Septic shock, including fatal outcomes

Infusion reactions/hypersensitivity:

Laryngospasm

Liver and Gastrointestinal system disorders:

Severe diarrhea/vomiting resulting in hypokalemia, colitis (including Clostridium difficile diarrhea), metabolic acidosis; ileus; intestinal obstruction, pancreatitis; veno-occlusive disease of liver also known as sinusoidal obstruction syndrome, and perisinusoidal fibrosis which rarely may progress.

Musculoskeletal and connective tissue disorders:

Rhabdomyolysis, including fatal outcomes.

Platelet, bleeding, and clotting disorders:

Immuno-allergic thrombocytopenia prolongation of prothrombin time and of INR in patients receiving anticoagulants

Red Blood Cell disorders:

Hemolytic uremic syndrome, immuno-allergic hemolytic anemia

Renal disorders:

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

Respiratory system disorders:
Pulmonary fibrosis, and other interstitial lung diseases (sometimes fatal)
Vision disorders:
Decrease of visual acuity, visual field disturbance, optic neuritis and transient vision loss (reversible following therapy discontinuation)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Pharmacy and Poisons Board-Pharmacovigilance Electronic Reporting System (PvERS); https://pv.pharmacyboardkenya.org .

4.9 Overdose

There is no known antidote for oxaliplatin overdose. In addition to thrombocytopenia, the anticipated complications of an Oxaliplatin overdose include hypersensitivity reaction, myelosuppression, nausea, vomiting, diarrhea and neurotoxicity. Several cases of overdoses have been reported with Oxaliplatin. Adverse reactions observed were Grade 4 thrombocytopenia (<25,000/mm3) without any bleeding, anemia, sensory neuropathy such as paresthesia, dysesthesia, laryngospasm and facial muscle spasms, gastrointestinal disorders such as nausea, vomiting, stomatitis, flatulence, abdomen enlarged and Grade 4 intestinal obstruction, Grade 4 dehydration, dyspnea, wheezing, chest pain, respiratory failure, severe bradycardia and death.
Patients suspected of receiving an overdose should be monitored, and supportive treatment should be administered. The maximum dose of oxaliplatin that has been administered in a single infusion is 825 mg.

5 Pharmacological Properties

5.1 Pharmacodynamic Properties

Mechanism of action
Oxaliplatin undergoes nonenzymatic 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 macromolecules. Both inter- and intrastrand Pt-DNA crosslinks are formed. Crosslinks are formed between the N7 positions of two adjacent guanines (GG), adjacent adenine-guanines (AG), and guanines separated by an intervening nucleotide (GNG). These crosslinks inhibit DNA replication and transcription. Cytotoxicity is cell-cycle nonspecific.
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)].

Clinical studies

Combination Adjuvant Therapy with Oxaliplatin and Infusional 5-fluorouracil/leucovorin in Patients with Colon Cancer

An international, multicenter, randomized study compared the efficacy and evaluated the safety of oxaliplatin in combination with an infusional schedule of 5-fluorouracil/leucovorin to infusional 5-fluorouracil/leucovorin alone, in patients with stage II (Dukes' B2) or III (Dukes' C) colon cancer who had undergone complete resection of the primary tumor. The primary objective of the study was to compare the 3-year disease-free survival (DFS) in patients receiving oxaliplatin and infusional 5-fluorouracil/leucovorin to those receiving 5-fluorouracil/leucovorin alone. Patients were to be treated for a total of 6 months (i.e., 12 cycles). A total of 2246 patients were randomized; 1123 patients per study arm. Patients in the study had to be between 18 and 75 years of age, have histologically proven stage II (T3–T4 N0 M0; Dukes' B2) or III (any T N1-2 M0; Dukes' C) colon carcinoma (with the inferior pole of the tumor above the peritoneal reflection, i.e., ≥15 cm from the anal margin) and undergone (within 7 weeks prior to randomization) complete resection of the primary tumor without gross or microscopic evidence of residual disease. Patients had to have had no prior chemotherapy, immunotherapy or radiotherapy, and have an ECOG performance status of 0,1, or 2 (KPS ≥ 60%), absolute neutrophil count (ANC) > 1.5x109 /L, platelets ≥100×109 /L, serum creatinine ≤ 1.25 × ULN total bilirubin < 2 × ULN, AST/ALT < 2 × ULN and carcino-embyrogenic antigen (CEA) < 10 ng/mL. Patients with preexisting peripheral neuropathy (NCI grade ≥ 1) were ineligible for this trial.

The following table shows the dosing regimens for the two arms of the study.

Table 15 - Dosing Regimens in Adjuvant Therapy Study

Treatment Arm	Dose	Regimen
Oxaliplatin + 5-FU/LV(FOLFOX4) (N =1123)	Day 1: Oxaliplatin: 85 mg/m^2 (2-hour infusion) + LV: 200 mg/m^2 (2-hour infusion), followed by 5-FU: 400 mg/m^2 (bolus), 600 mg/m^2 (22-hour infusion) Day 2: LV: 200 mg/m^2 (2-hour infusion), followed by 5-FU: 400 mg/m^2 (bolus), 600 mg/m^2 (22-hour infusion)	every 2 weeks 12 cycles
5-FU/LV (N=1123)	Day 1: LV: 200 mg/m^2 (2-hour infusion), followed by 5-FU: 400 mg/m^2 (bolus), 600 mg/m^2 (22-hour infusion) Day 2: LV: 200 mg/m^2 (2-hour infusion), followed by 5-FU: 400 mg/m2 (bolus), 600 mg/m2 (22-hour infusion)	every 2 weeks 12 cycles

The following tables show the baseline characteristics and dosing of the patient population entered into this study. The baseline characteristics were well balanced between arms.

Table 16 - Patient Characteristics in Adjuvant Therapy Study

	Oxaliplatin + infusional 5-FU/LV N=1123	**Infusional 5-FU/LV N=1123**
Sex: Male (%)	56.1	52.4
Female (%)	43.9	47.6
Median age (years)	61.0	60.0
<65 years of age (%)	64.4	66.2
≥65 years of age (%)	35.6	33.8
Karnofsky Performance Status (KPS) (%)		
100	29.7	30.5
90	52.2	53.9
80	4.4	3.3
70	13.2	11.9
≤60	0.6	0.4
Primary site (%)		
Colon including cecum	54.6	54.4
Sigmoid	31.9	33.8
Recto sigmoid	12.9	10.9
Other including rectum	0.6	0.9
Bowel obstruction (%)		
Yes	17.9	19.3
Perforation (%)		
Yes	6.9	6.9
Stage at Randomization (%)		
II (T=3,4 N=0, M=0)	40.1	39.9
III (T=any, N=1,2, M=0)	59.6	59.3
IV (T=any, N=any, M=1)	0.4	0.8
Staging – T (%)		
T1	0.5	0.7
T2	4.5	4.8
T3	76.0	75.9
T4	19.0	18.5
Staging – N (%)		
N0	40.2	39.9
N1	39.4	39.4
N2	20.4	20.7
Staging – M (%)		
M1	0.4	0.8

Table 17 - Dosing in Adjuvant Therapy Study

	Oxaliplatin + infusional 5-FU/LV N=1108	**Infusional 5-FU/LV N=1111**
Median Relative Dose Intensity (%)		
5-FU	84.4	97.7
Oxaliplatin	80.5	N/A
Median Number of Cycles	12	12
Median Number of cycles with oxaliplatin	11	N/A

The following table summarizes the disease-free survival (DFS) results in the overall randomized population and in patients with stage II and III disease based on an ITT analysis. The median duration of follow-up was approximately 77 months.

Table 18 - Summary of DFS analysis – ITT analysis*

	Oxaliplatin + Infusional 5-FU/LV	**Infusional 5-FU/LV**
Parameter		
Overall		
N	1123	1123
Number of events – relapse or death (%)	304 (27.1)	360 (32.1)
Disease-free survival % [95% CI] †	73.3 [70.7, 76.0]	67.4 [64.6, 70.2]
Hazard ratio [95% CI] ‡	0.80 [0.68, 0.93]	
Stratified Logrank test	p=0.003	
Stage III (Dukes' C)		
N	672	675
Number of events –relapse or death (%)	226 (33.6)	271 (40.1)
Disease-free survival % [95% CI] †	66.4 [62.7, 70.0]	58.9 [55.2, 62.7]
Hazard ratio [95% CI] ‡	0.78 [0.65, 0.93]	
Logrank test	p=0.005	
Stage II (Dukes' B2)		
N	451	448
Number of events – relapse or death (%)	78 (17.3)	89 (19.9)
Disease-free survival % [95% CI] †	83.7 [80.2, 87.1]	79.9 [76.2, 83.7]
Hazard ratio [95% CI] ‡	0.84 [0.62, 1.14]	
Logrank test	p=0.258	

* Data cut off for disease free survival 1 June 2006

† Disease-free survival at 5 years

‡ A hazard ratio of less than 1.00 favors oxaliplatin + Infusional 5-fluorouracil/leucovorin

In the overall and stage III colon cancer populations DFS was statistically significantly improved in the oxaliplatin combination arm compared to infusional 5-fluorouracil/leucovorin alone. However, a statistically significant improvement in DFS was not noted in Stage II patients.

The following table summarizes the overall survival (OS) results in the overall randomized population and in patients with stage II and III disease, based on the ITT analysis.

Table 19 - Summary of OS analysis - ITT analysis*

Parameter	**Oxaliplatin + Infusional 5-FU/LV**	**Infusional 5-FU/LV**
Overall		
N	1123	1123
Number of death events (%)	245 (21.8)	283 (25.2)
Hazard ratio † [95% CI]	0.84 [0.71 , 1.00]	
Stage III (Dukes' C)		
N	672	675
Number of death events (%)	182 (27.1)	220 (32.6)
Hazard ratio † [95% CI]	0.80 [0.65 , 0.97]	
Stage II (Dukes' B2)		
N	451	448
Number of death events (%)	63 (14.0)	63 (14.1)
Hazard ratio † [95% CI]	1.00 [0.70 , 1.41]	

* Data cut off for overall survival 16 January 2007

† A hazard ratio of less than 1.00 favors oxaliplatin + Infusional 5-fluorouracil/leucovorin

Combination Therapy with oxaliplatin and 5-fluorouracil/leucovorin in Patients Previously Untreated for Advanced Colorectal Cancer

A North American, multicenter, open-label, randomized controlled study was sponsored by the National Cancer Institute (NCI) as an intergroup study led by the North Central Cancer Treatment Group (NCCTG). The study had 7 arms at different times during its conduct, four of which were closed due to either changes in the standard of care, toxicity, or simplification. During the study, the control arm was changed to irinotecan plus 5-fluorouracil/leucovorin. The results reported below compared the efficacy and safety of two experimental regimens, oxaliplatin in combination with infusional 5-fluorouracil/leucovorin and a combination of oxaliplatin plus irinotecan, to an approved control regimen of irinotecan plus 5-fluorouracil/leucovorin in 795 concurrently randomized patients previously untreated for locally advanced or metastatic colorectal cancer. After completion of enrolment, the dose of irinotecan plus 5-fluorouracil/leucovorin was decreased due to toxicity. Patients had to be at least 18 years of age, have known locally advanced, locally recurrent, or metastatic colorectal adenocarcinoma not curable by surgery or amenable to radiation therapy with curative intent, histologically proven colorectal adenocarcinoma, measurable or evaluable

disease, with an ECOG performance status 0,1, or 2. Patients had to have granulocyte count ≥1.5×109/L, platelets ≥ 100 × 109/L, hemoglobin ≥9.0 gm/dL, creatinine ≤ 1.5 × ULN, total bilirubin ≤ 1.5 mg/dL, AST ≤ 5 × ULN, and alkaline phosphatase ≤ 5 × ULN. Patients may have received adjuvant therapy for resected Stage II or III disease without recurrence within 12 months. The patients were stratified for ECOG performance status (0, 1 vs. 2), prior adjuvant chemotherapy (yes vs. no), prior immunotherapy (yes vs. no), and age (<65 vs. ≥65 years). Although no post study treatment was specified in the protocol, 65 to 72% of patients received additional post study chemotherapy after study treatment discontinuation on all arms.
Fifty-eight percent of patients on the oxaliplatin plus 5-fluorouracil/leucovorin arm received an irinotecan-containing regimen and 23% of patients on the irinotecan plus 5-fluorouracil/leucovorin arm received oxaliplatin-containing regimens. Oxaliplatin was not commercially available during the trial.

The following table presents the dosing regimens of the three arms of the study.

Table 20 – Dosing Regimens in Patients Previously Untreated for Advanced Colorectal Cancer Clinical Trial

Treatment Arm	Dose	Regimen
Oxaliplatin +5-FU/LV (FOLFOX4) (N=267)	Day 1: Oxaliplatin: 85 mg/m^2 (2-hour infusion) + LV 200 mg/m^2 (2-hour infusion), followed by 5-FU: 400 mg/m^2 (bolus), 600 mg/m^2 (22-hour infusion) Day 2: LV 200 mg/m^2 (2-hour infusion), followed by 5-FU: 400 mg/m^2 (bolus), 600 mg/m^2 (22-hour infusion)	every 2 weeks
Irinotecan + 5-FU/LV (IFL) (N=264)	Day 1: Irinotecan 125 mg/m^2 as a 90–min infusion + LV 20 mg/m^2 as a 15-min infusion or intravenous push, followed by 5-FU 500 mg/m^2 intravenous bolus weekly × 4	every 6 weeks
Oxaliplatin + Irinotecan (IROX) (N=264)	Day 1: Oxaliplatin: 85 mg/m^2 intravenous (2-hour infusion) + irinotecan 200 mg/m^2 intravenous over 30 minutes	every 3 weeks

The following table presents the demographics of the patient population entered into this study.

Table 21 – Patient Demographics in Patients Previously Untreated for Advanced Colorectal Cancer Clinical Trial

	Oxaliplatin + 5-FU/LV N=267	Irinotecan + 5-FU/LV N=264	Oxaliplatin + irinotecan N=264
Sex: Male (%)	58.8	65.2	61.0
Female (%)	41.2	34.8	39.0
Median age (years)	61.0	61.0	61.0
<65 years of age (%)	61	62	63

≥65 years of age (%)	39	38	37
ECOG (%)			
0.1	94.4	95.5	94.7
2	5.6	4.5	5.3
Involved organs (%)			
Colon only	0.7	0.8	0.4
Liver only	39.3	44.3	39.0
Liver + other	41.2	38.6	40.9
Lung only	6.4	3.8	5.3
Other (including lymph nodes)	11.6	11.0	12.9
Not reported	0.7	1.5	1.5
Prior radiation (%)	3.0	1.5	3.0
Prior surgery (%)	74.5	79.2	81.8
Prior adjuvant (%)	15.7	14.8	15.2

The length of a treatment cycle was 2 weeks for the oxaliplatin and 5-fluorouracil/leucovorin regimen; 6 weeks for the irinotecan plus 5-fluorouracil/leucovorin regimen; and 3 weeks for the oxaliplatin plus irinotecan regimen. The median number of cycles administered per patient was 10 (23.9 weeks) for the oxaliplatin and 5-fluorouracil/leucovorin regimen, 4 (23.6 weeks) for the irinotecan plus 5-fluorouracil/leucovorin regimen, and 7 (21.0 weeks) for the oxaliplatin plus irinotecan regimen. Patients treated with the oxaliplatin and 5-fluorouracil/leucovorin combination had a significantly longer time to tumor progression based on investigator assessment, longer overall survival, and a significantly higher confirmed response rate based on investigator assessment compared to patients given irinotecan plus 5-fluorouracil/leucovorin. The following table summarizes the efficacy results.

Table 22 – Summary of Efficacy*

	Oxaliplatin + 5-FU/LV N=267	**irinotecan + 5-FU/LV N=264**	**oxaliplatin + irinotecan N=264**
Survival (ITT)			
Number of deaths N (%)	155 (58.1)	192 (72.7)	175 (66.3)
Median survival (months)	19.4	14:6	17:6
Hazard Ratio and (95% confidence interval)	0.65 (0.53–0.80)†		
P-value	<0.0001†	-	-
TTP (ITT, investigator assessment)			
Percentage of progressors	82.8	81.8	89.4
Median TTP (months)	8.7	6.9	6.5

Hazard Ratio and (95% confidence interval)‡	0 .74 (0.6 1–0.8 9)†		
P-value	† 0.0014	-	-
Response Rate (investigator assessment)§			
Patients with measurable disease	210	212	215
Complete response N (%)	13 (6.2)	5 (2.4)	7 (3.3)
Partial response N (%)	82 (39.0)	64 (30.2)	67 (31.2)
Complete and partial response N (%)	95 (45.2)	69 (32.5)	74 (34.4)
95% confidence interval	(38.5 – 52.0)	(26.2 – 38.9)	(28.1 – 40.8)
P-value	† 0.0080	-	-

† Compared to irinotecan plus 5-fluorouracil/leucovorin (IFL) arm
‡ A hazard ratio of less than 1.00 favors oxaliplatin + Infusional 5-fluorouracil/leucovorin
§ Based on all patients with measurable disease at baseline

A descriptive subgroup analysis demonstrated that the improvement in survival for oxaliplatin plus 5-fluorouracil/leucovorin compared to irinotecan plus 5-fluorouracil/leucovorin appeared to be maintained across age groups, prior adjuvant therapy, and number of organs involved. An estimated survival advantage in oxaliplatin plus 5-fluorouracil/leucovorin versus irinotecan plus 5-fluorouracil/leucovorin was seen in both genders; however it was greater among women than men. Insufficient subgroup sizes prevented analysis by race.

Combination Therapy with oxaliplatin and 5-fluorouracil/leucovorin in Previously Treated Patients with Advanced Colorectal Cancer

A multicenter, open-label, 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-fluorouracil/leucovorin to the same dose and schedule of 5-fluorouracil/leucovorin alone and to single agent oxaliplatin in patients with advanced colorectal cancer who had relapsed/progressed during or within 6 months of first-line therapy with bolus 5-fluorouracil/leucovorin 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 in the completed study. Accrual to this study is

complete, with 821 patients enrolled. Patients in the study had to be at least 18 years of age, have unresectable, measurable, histologically proven colorectal adenocarcinoma, with a Karnofsky performance status >50%. Patients had to have SGOT(AST) and SGPT(ALT) ≤2× 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 ≤5× ULN was permitted. Patients had to have alkaline phosphatase ≤2× the institution's ULN, unless liver metastases were present and documented at baseline by CT or MRI scan, in which cases ≤5× 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.

Table 23 – 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/m^2 (2-hour infusion) + LV 200 mg/m^2 (2-hour infusion), followed by 5-FU: 400 mg/m^2 (bolus), 600 mg/m^2 (22-hour infusion) Day 2: LV 200 mg/m^2 (2 hour infusion), followed by 5-FU: 400 mg/m^2 (bolus), 600 mg/m^2 (22-hour infusion)	every 2 weeks
5-FU/LV (N=151)	Day 1: LV 200 mg/m^2 (2-hour infusion), followed by 5-FU: 400 mg/m^2 (bolus), 600 mg/m^2 (22-hour infusion) Day 2: LV 200 mg/m^2 (2-hour infusion), followed by 5-FU: 400 mg/m^2 (bolus), 600 mg/m^2 (22-hour infusion)	every 2 weeks
Oxaliplatin (N=156)	Day 1: Oxaliplatin 85 mg/m^2 (2-hour infusion)	every 2 weeks

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.

Table 24 – Patient Demographics in Refractory and Relapsed Colorectal Cancer Clinical Trial

	5-FU/LV (N = 151)	Oxaliplatin (N = 156)	Oxaliplatin + 5-FU/LV (N = 152)
Sex: Male (%)	54.3	60.9	57.2
Female (%)	45.7	39.1	42.8
Median age (years)	60.0	61.0	59.0
Range	21-80	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 – 100	94.7	92.3	95.4
50 – 60	2.6	4.5	2.0
Not reported	2.6	3.2	2.6
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 5-fluorouracil/leucovorin combination and 3 each for 5-fluorouracil/leucovorin alone and oxaliplatin alone.
Patients treated with the combination of oxaliplatin and 5-fluorouracil/leucovorin had an increased response rate compared to patients given 5-fluorouracil/leucovorin or oxaliplatin alone. The efficacy results are summarized in the tables below.

Table 25 - Response Rates (ITT Analysis)

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

Table 26 - Summary of Radiographic Time to Progression*

Arm	5-FU/LV (N=151)	Oxaliplatin (N=156)	Oxaliplatin + 5-FU/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 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 5-fluorouracil/leucovorin alone.
Of the 13 patients who had tumor response to the combination of oxaliplatin and 5-fluorouracil/leucovorin, 5 were female and 8 were male, and responders included patients <65 years old and ≥ 65 years old. The small number of non-Caucasian participants made efficacy analyses in these populations uninterpretable.

5.2 Pharmacokinetic Properties

The reactive oxaliplatin derivatives are present as a fraction of the unbound platinum in plasma ultrafiltrate. The decline of ultrafilterable platinum levels following oxaliplatin administration is triphasic, characterized by two relatively short distribution phases (t1/2α; 0.43 hours and t1/2β; 16.8 hours) and a long terminal elimination phase (t1/2γ; 391 hours). Pharmacokinetic parameters obtained after a single 2-hour IV infusion of oxaliplatin at a dose of 85 mg/m2 expressed as ultrafilterable platinum were Cmax of 0.814 µg/ml and volume of distribution of 440 L.
Interpatient and intrapatient variability in ultrafilterable platinum exposure (AUC0-48 hr) assessed over 3 cycles was moderate to low (23 % and 6 %, respectively). A pharmacodynamic relationship between platinum ultrafiltrate 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

gammaglobulins. 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 ultrafiltrate 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 ultrafiltrate samples from patients, including several cytotoxic species (monochloro DACH platinum, dichloro DACH platinum, and monoaquo and diaquo DACH platinum) and a number of noncytotoxic, 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 ultrafilterable platinum. The renal clearance of ultrafilterable platinum is significantly correlated with GFR.

Pharmacokinetics in Special Populations

Renal Impairment

A study conducted in 38 patients with advanced GI cancer and varying degrees of renal impairment with patients in the normal (creatinine clearance (CrCL) > 80 ml/min, N=11), mild (CrCL=50-80 ml/min, N=13), and moderate (CrCL=30-49 ml/min, N=10) groups treated with 85 mg/m2 oxaliplatin and those in the severe (CrCL < 30 ml/min, N=4) group treated with 65 mg/m2 oxaliplatin. The mean AUC of unbound platinum was 40 %, 95 %, and 342 % higher in the mild, moderate, and severe groups, respectively, than in the normal group. Mean Cmax of unbound platinum appeared to be similar among the normal, mild and moderate renal function groups, but was 38 % higher in the severe group than in the normal group. Caution should be exercised in renally impaired patients. The starting dose of oxaliplatin should be reduced in patients with severe renal impairment.

5.3 Preclinical Safety Data

Carcinogenicity and Mutagenicity

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).

Impairment of Fertility

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.

6 Pharmaceutical Particulars

6.1 List of excipients

Water for Injection USP

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 for handling and disposal section, oxaliplatin can be coadministered 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 others drugs. Alkaline drugs or solutions will adversely affect the stability of oxaliplatin.

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. Do not use injection equipment containing aluminium.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at a temperature below 25°C. Protect from light. Do not freeze.

6.5 Nature and contents of container

OXITAN 50 mg: 10mL USP Type I, tubular clear glass vial with 10 mL fill

OXITAN 100 mg: 20mL USP Type I, tubular clear glass vial with 20 mL fill

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.

<u>Instructions for Handling</u>

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 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 infusion solution should come into contact with skin, wash immediately and thoroughly with water.
If oxaliplatin concentrate or infusion solution should come into contact with mucous membranes, wash immediately and thoroughly with water.
Special precautions for administration
Do not use injection equipment containing aluminium. Do not administer undiluted.
Only Dextrose 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 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 others 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 85 mg/m² IV infusion in 250 to 500 ml of 5% Dextrose solution is given at the same time as folinic acid IV infusion in 5 % Dextrose e 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 % Dextrose 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.

Concentrate for solution for infusion

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

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

Dilution before infusion

Withdraw the required amount of concentrate from the vial(s) and then dilute with 250 ml to 500 ml of a 5% Dextrose solution to give an oxaliplatin concentration between not less than 0.2 mg/ml and 0.7 mg/ml. The concentration range for which the physico-chemical stability of oxaliplatin has been demonstrated is 0.2 mg/ml to 0.7 mg/ml.

Administer by IV infusion

After dilution in 5 % Dextrose, chemical and physical in-use stability has been demonstrated for 48 hours at +2°C to +8°C and for 24 hours at +25°C. From a microbiological point of view, this infusion preparation should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C unless dilution has taken place in controlled and validated aseptic conditions.

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

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

Never use sodium chloride or chloride containing solutions for 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 % Dextrose 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

Any unused medicinal product or waste material should be disposed of according to standard procedures applicable to cytotoxic agents in accordance with local requirements.

7. Marketing Authorization Holder

Fresenius Kabi South Africa (Pty) Limited,
6 Gibaud Road, Korsten 6020,
Gqeberha South Africa

8. Marketing Authorization Number (S)

H2022/CTD8522/16925

9. Date Of First Authorization /Renewal of the Authorization

2023 March 28

10. Date Of Revision of the Text

2023 March 28