

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only OR for Specialist Use only

Oxaliplatin injection 50mg/25 ml

Oxaliplatin injection 100mg/50 ml

X-plat – 50

X-plat – 100

Composition

X-plat – 50
Each ml contains:
Oxaliplatin Ph.Eur.2 mg.
Water for Injection IP.....q.s

X-plat – 100
Each ml contains:
Oxaliplatin Ph.Eur.2 mg.
Water for Injection IP.....q.s

Dosage Form

Pharmacology

Pharmacodynamics

Mechanism of Action

Oxaliplatin undergoes nonenzymatic conversion in physiological solutions to active derivatives via displacement of the labile oxalate ligand. Several transient reactive species are formed, including monoquo and diaquo DA-CH 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 (AG), adjacent adenine-guanines (AG), and guanines separated by an intervening nucleotide (2-GC). These crosslinks inhibit DNA replication and transcription. Cytotoxicity is cell-cycle non-specific.

Oxaliplatin shows *in vitro* activity of oxaliplatin against colon carcinomas. In combination with 5-fluorouracil, 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 $\geq 60\%$), absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$, platelets $\geq 100 \times 10^9/L$, serum creatinine $\leq 1.25 \times$ ULN total bilirubin $< 2 \times$ ULN, AST/ALT $< 2 \times$ ULN and carcino-embryonic antigen (CEA) < 40 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 1 - Dosing Regimens in Adjuvant Therapy Study

Treatment Arm	Dose	Regimen
Oxaliplatin + 5-FU/LV (FOLFFOX4) (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/m ² (bolus), 600 mg/m ² (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 2 - 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	28.7	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	18.0	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 3 - 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 and figures summarize 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 4 - Summary of DFS analysis - ITT analysis

Parameter	Oxaliplatin + Infusional 5-FU/LV N=267	Infusional 5-FU/LV N=264
Overall	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)	672	675
Number of events – relapse or death (%)	228 (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)	451	448
N	78 (17.3)	89 (19.9)
Number of events – relapse or death (%)		
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.

Figure 1 shows the DFS Kaplan-Meier curves for the comparison of oxaliplatin and infusional 5-fluorouracil/leucovorin combination and infusional 5-fluorouracil/leucovorin alone for the overall population (ITT analysis). Figure 2 shows the DFS Kaplan-Meier curves for the comparison of oxaliplatin and infusional 5-fluorouracil/leucovorin combination and infusional 5-fluorouracil/leucovorin alone in Stage III patients.

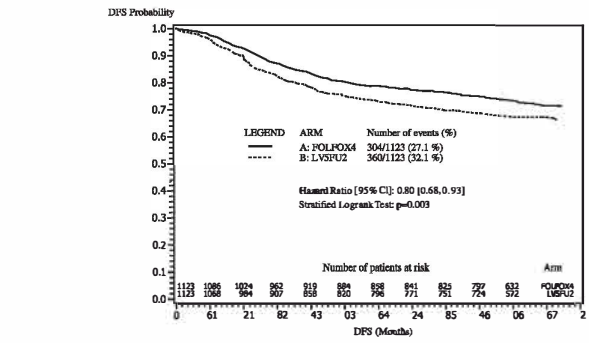


Figure 1 - DFS Kaplan-Meier curves by treatment arm (cutoff: 1 June 2006) – ITT population

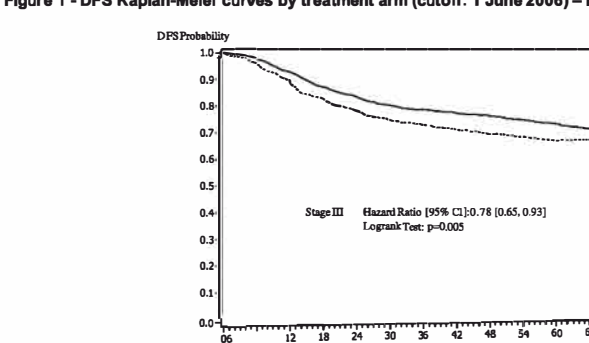


Figure 2 - DFS Kaplan-Meier curves by treatment arm in Stage III patients (cutoff: 1 June 2006) – ITT

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 5 - Summary of OS analysis - ITT analysis

Parameter	Oxaliplatin + Infusional 5-FU/LV N=1123	Infusional 5-FU/LV N=1123
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 (%)	192 (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]	

* A hazard ratio of less than 1.00 favors Oxaliplatin + Infusional 5-fluorouracil/leucovorin Data cut off for overall survival 18 January 2007

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 enrollment, 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, local recurrence, 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 $\geq 1.5 \times 10^9/L$, platelets $\geq 100 \times 10^9/L$, hemoglobin ≥ 90 g/mL, creatinine $\leq 1.5 \times$ ULN, total bilirubin ≤ 1.5 mg/dL, AST $\leq 5 \times$ ULN, and alkaline phosphatase $\leq 5 \times$ 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 6 - Dosing Regimens in Patients Previously Untreated for Advanced Colorectal Cancer Clinical Trial

Treatment Arm	Dose	Regimen
Oxaliplatin + 5-FU/LV (FOLFFOX4) (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, followed by 5-FU 500 mg/m ² intravenous bolus weekly x 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 7 – 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	94.4	95.5	94.7
1	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

	6.4	3.8	5.3
Lung only			
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 8 – Summary of Efficacy

	Oxaliplatin + 5-FU/LV N=287	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*		
TTT (ITT, investigator assessment)			
Percentage of progressors	8.7	81.8	89.4
Median TTP (months)	82.8	6.9	6.5
Hazard Ratio and (95% confidence interval)	0.74 (0.61-0.89)		
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

** Based on all patients with measurable disease at baseline

The numbers in the response rate and TTP analysis are based on unblinded investigator assessment.

*** A hazard ratio of less than 1.00 favors Oxaliplatin + Infusional 5-fluorouracil/leucovorin

Figure 3 illustrates the Kaplan-Meier survival curves for the comparison of oxaliplatin and 5-fluorouracil/leucovorin combination and oxaliplatin plus irinotecan to irinotecan plus 5-fluorouracil/leucovorin.

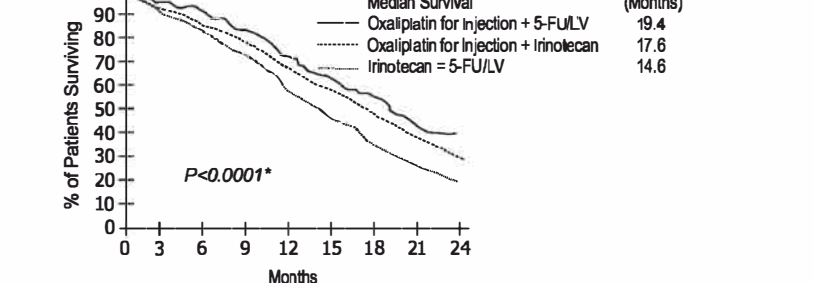


Figure 3 – Kaplan-Meier Overall Survival by treatment arm

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 or 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 $\geq 50\%$. Patients had to have SGOT (AST) and SGPT (ALT) $\leq 2 \times$ 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 $\leq 5 \times$ ULN was permitted. Patients had to have alkaline phosphatase $\leq 2 \times$ the institution's ULN, unless liver metastases were present and documented at baseline by CT or MRI scan, in which case $\leq 5 \times$ 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 9 – 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 ≥ 20 mm using conventional CT or MRI scans, or ≥ 10 mm 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 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 10 – Patient Demographics in Refractory and Relapsed Colorectal Cancer Clinical Trial

	5-FU/LV (N = 151)	Oxaliplatin (N =
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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 4.5% (any grade) and 1.1% (grade 3) with no grade 3 or 4 events in the infusional 5-fluorouracil/leucovorin arm compared to 4.5% (any grade) and no grade 3 or 4 events in the infusional 5-fluorouracil/leucovorin alone arm in advanced colon cancer patients. In this 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-fluorouracil/leucovorin arm compared to 32% (any grade) and 5% (grade 3 and 4) in the irinotecan plus 5-fluorouracil/leucovorin 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 than in the control arm. The incidence of increased aspartate aminotransferase was similar on both arms. Changes noted on liver biopsies include: peliosis, nodular regenerative hyperplasia or sinusoidal alterations, periportal 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. (See Undesirable Effects)

Cardiovascular Toxicity

QT prolongation and ventricular arrhythmias including fatal Torsade de Pointes have been reported in postmarketing experiences 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 (See Undesirable Effects).

Use in Pregnancy

Oxaliplatin may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of Oxaliplatin in pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Oxaliplatin. (See **Warnings and Precautions** and **Reproductive Toxicology**)

Recommended Laboratory Tests

Standard monitoring of the white blood cell count with differential, hemoglobin, platelet count, and blood chemistry (including ALT, AST, bilirubin and creatinine) is recommended before each oxaliplatin cycle. (See **Dosage and Method of Administration**)

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.

Drug Interactions

No specific cytochrome P-450-based drug interaction studies have been conducted. No pharmacokinetic interaction between 85 mg/m² oxaliplatin and 5-fluorouracil has been observed in patients treated every 2 weeks. Increases of 5-fluorouracil plasma concentrations by approximately 20% have been observed with doses of 130 mg/m² oxaliplatin dosed every 3 weeks. Because platinum-containing species are eliminated primarily through the kidney, clearance of these species may be decreased by coadministration of potentially nephrotoxic compounds; although, this has not been specifically studied (See **Warnings and Precautions**).

Fertility, Pregnancy and Lactation

Pregnancy Category D
Based on animal reproduction 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 embryonic development at maternal doses that were below 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 risks to the fetus. The potential of oxaliplatin to cause fetal harm 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 87% post-implantation loss in animals that received approximately one-tenth the recommended human dose based on the body surface area.

Lactation

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 discontinue the drug, taking into account the importance of the drug to the mother.

Undesirable Effects

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Anaphylaxis and Allergic reactions. (See **Warnings and Precautions**)
- Neurotoxicity (See **Warnings and Precautions**)
- Severe Neutropenia (See **Warnings and Precautions**)
- Pulmonary Toxicity (See **Warnings and Precautions**)
- Hepatotoxicity (See **Warnings and Precautions**)
- Cardiovascular Toxicity (See **Warnings and Precautions**)
- Rhabdomyolysis (See **Warnings and Precautions**)

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 4,000 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 with oxaliplatin in combination with infusional 5-fluorouracil/leucovorin, 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 (See **Warnings and Precautions**).

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-fluorouracil/leucovorin. (See **Pharmacodynamics**). The incidence of grade 3 or 4 adverse reactions was 70% on the oxaliplatin combination arm, and 31% on the infusional 5-fluorouracil/leucovorin arm. The adverse reactions observed 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-fluorouracil/leucovorin. Both 5-fluorouracil/leucovorin and oxaliplatin are associated with gastrointestinal or hematologic adverse reactions. When oxaliplatin is administered in combination with infusional 5-fluorouracil/leucovorin, the incidence of these events is increased.

The incidence of death within 28 days of last treatment, regardless of causality, was 0.6% (n=6) in both the oxaliplatin combination and infusional 5-fluorouracil/leucovorin arms, respectively. Deaths within 60 days from initiation of therapy were 0.3% (n=3) in both the oxaliplatin combination and infusional 5-fluorouracil/leucovorin arms, respectively. On the oxaliplatin combination arm, 3 deaths were due to sepsis/neutropenic sepsis, 2 from intracranial bleeding and one from eosinophilic pneumonia. On the 5-fluorouracil/leucovorin arm, one death was due to sepsis, 2 from Steven-Johnson Syndrome (1 patient also had hepatic). Unknown cause, 1 acute cerebral infarction and 1 probable abdominal aortic rupture.

The following table provides adverse reactions reported in the adjuvant therapy colon cancer clinical trial. (See **Pharmacodynamics**) by body system and decreasing order of frequency in the oxaliplatin and infusional 5-fluorouracil/leucovorin arm for events with overall incidences ≥5% and for NCI grade 3/4 events with incidences ≥1%.

Adverse reaction (WHO/Prof)	Oxaliplatin + 5-FULV N=1108		5-FULV N=1111	
	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	81	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

¹Includes thrombosis related to the catheter.
The following table provides adverse reactions reported in the adjuvant therapy colon cancer clinical trial (See **Pharmacodynamics**) by body system and decreasing order of frequency in the oxaliplatin and infusional 5-fluorouracil/leucovorin arm for events with overall incidences ≥5% but with incidences <1% NCI grade 3/4 events.

Adverse reaction (WHO/Prof)	Oxaliplatin + 5-FULV N=1108		5-FULV N=1111	
	All Grades (%)	All Grades (%)	All Grades (%)	All Grades (%)
Rhinitis	6		8	
Epistaxis	16		12	

Weight Increase	10		10	
Conjunctivitis	9		15	
Headache	7		4	7
Rhinitis	11		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
Swearing	5		6	12
Sensory Disturbance	8		1	
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-fluorouracil/leucovorin 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-fluorouracil/leucovorin combination arm of the randomized trial in patients previously untreated for advanced colorectal cancer (See **Pharmacodynamics**). The adverse reaction 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. High 5-fluorouracil and oxaliplatin are associated with gastrointestinal and hematologic adverse reactions. When oxaliplatin is administered in combination with 5-fluorouracil, 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-fluorouracil/leucovorin combination, 5% with irinotecan plus 5-fluorouracil/leucovorin, and 3% with oxaliplatin plus irinotecan. Deaths within 60 days from initiation of therapy were 2.3% with the oxaliplatin and 5-fluorouracil/leucovorin combination, 5.1% with irinotecan plus 5-fluorouracil/leucovorin, and 3.1% with oxaliplatin plus irinotecan. The following table provides adverse reactions reported in the previously untreated for advanced colorectal cancer study (See **Pharmacodynamics**) by body system and decreasing order of frequency in the oxaliplatin and 5-fluorouracil/leucovorin combination arm for events with overall incidences ≥5% and for grade 3/4 events with incidences ≥1%.

Table 17 – 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)

Adverse reaction (WHO/Prof)	Oxaliplatin + 5-FULV N=259		Irinotecan + 5-FULV N=256		Oxaliplatin + Irinotecan N=258	
	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
Visual 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	46	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 ¹	5	2	4	2	3	2
Hematology/Infection						
Infection normal ANC**	10	4	5	1	7	2
Infection low ANC**	8	8	12	11	9	8
Lymphopenia	6	2	4	1	5	2
Felible neutropenia	4	4	15	14	12	11
Hepatic/Metabolic/Laboratory/Renal						
Hyperglycemia	14	2	11	3	12	3
Hypokalemia	11	3	7	4	8	2
Dehydration	9	5	16	11	14	7
Hypophosphatemia	8	0	5	2	9	1
Hypothermia	8	2	7	4	4	1
Urinary frequency	5	1	2	1	3	1

¹Not otherwise specified
²Abolished 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-fluorouracil/leucovorin combination arm (listed in decreasing order of frequency): metabolic, pneumonia, catheter infection, vertigo, prothrombin time, pulmonary, rectal bleeding, dysuria, nail changes, chest pain, renal 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-fluorouracil/leucovorin) were studied in a randomized trial in patients with refractory and relapsed colorectal cancer (See **Pharmacodynamics**). The adverse reaction 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-fluorouracil/leucovorin combination arm and 18% in the 5-fluorouracil/leucovorin arm of the previously treated study had to discontinue treatment because of adverse effects related to gastrointestinal or hematologic adverse reactions, or neuropathies. Both 5-fluorouracil and oxaliplatin are associated with gastrointestinal and hematologic adverse reactions. When oxaliplatin is administered in combination with 5-fluorouracil/leucovorin, 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-fluorouracil/leucovorin combination, 8% with oxaliplatin alone, and 7% with 5-fluorouracil/leucovorin. Of the 7 deaths that occurred on the oxaliplatin and 5-fluorouracil/leucovorin 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 (See **Pharmacodynamics**) by body system and in decreasing order of frequency in the oxaliplatin and 5-fluorouracil/leucovorin 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, which are shown separately below.

Adverse reaction (WHO/Prof)	5-FULV (N = 142)		Oxaliplatin (N = 153)		Oxaliplatin + 5-FULV (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
Cardiovascular						
Arteriosclerosis	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
Felible Neutropenia	1	1	0	0	6	6
Hepatic/Metabolic/Laboratory/Renal						
Hypokalemia	3	1	3	2	9	4
Dehydration	6	1	5	3	8	3
Neurology						
Neuro-sensory	12	1	2	0	9	1
Neuro NOS ¹	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

¹Not otherwise specified
²Abolished neutrophil count
The following table provides adverse reactions reported in the previously untreated for advanced colorectal cancer study (See **Pharmacodynamics**) by body system and decreasing order of frequency in the oxaliplatin and 5-fluorouracil/leucovorin combination arm for events with overall incidences ≥5% but with incidences <1% NCI Grade 3/4 events.

Adverse reaction (WHO/Prof)	Oxaliplatin + 5-FULV N=259		Irinotecan + 5-FULV N=256		Oxaliplatin + Irinotecan N=258	
	All Grades (%)	All Grades (%)	All Grades (%)	All Grades (%)		
Rhinitis	4		6	15		
Allergic Reaction	1		3	10		
Rash	5		5	9		

Allergy/Immunology				
Rhinitis	11		4	7
Headache	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
Swearing	5		6	12
Arthralgia	5		5	8
Dermatology/Skin				
Alopecia	38		44	67
Flushing	7		2	5
Pruritis	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 ¹	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

¹Abolished 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-fluorouracil/leucovorin combination arm (listed in decreasing order of frequency): metabolic, pneumonia, catheter infection, vertigo, prothrombin time, pulmonary, rectal bleeding, dysuria, nail changes, chest pain, renal pain, syncope, hypertension, hypoxia, unknown infection, bone pain, pigmentation changes,