**ELOXATIN™**
**(oxaliplatin for injection)**

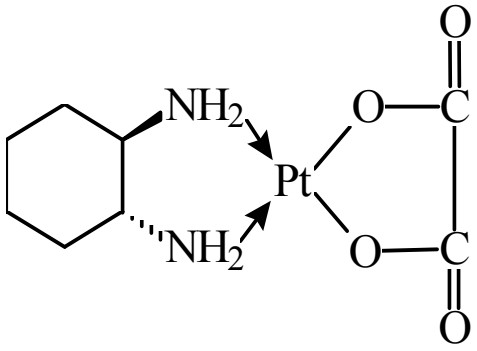
**WARNING**

ELOXATIN (oxaliplatin for injection) should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

Anaphylactic-like reactions to ELOXATIN have been reported, and may occur within minutes of ELOXATIN administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms. (See WARNINGS and ADVERSE REACTIONS).

## DESCRIPTION

ELOXATIN™ (oxaliplatin for injection) is an antineoplastic agent with the molecular formula $C_8H_{14}N_2O_4Pt$ and the chemical name of *cis*-[(1*R*,2*R*)-1,2-cyclohexanediamine-*N,N'*] [oxalato(2-)-*O,O'*] platinum. Oxaliplatin is an organoplatinum complex in which the platinum atom is complexed with 1,2- diaminocyclohexane (DACH) and with an oxalate ligand as a leaving group.




The molecular weight is 397.3. Oxaliplatin is slightly soluble in water at 6 mg/mL, very slightly soluble in methanol, and practically insoluble in ethanol and acetone.

ELOXATIN is supplied in vials containing 50 mg or 100 mg of oxaliplatin as a sterile, preservative-free lyophilized powder for reconstitution. Lactose monohydrate is present as an inactive ingredient at 450 mg and 900 mg in the 50 mg and 100 mg dosage strengths, respectively.

## CLINICAL PHARMACOLOGY

### Mechanism of Action

Oxaliplatin undergoes 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 intra-strand Pt-DNA cross-links 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.

### Pharmacology

*In vivo* studies have shown antitumor activity of oxaliplatin against colon carcinoma. In combination with 5-fluorouracil (5-FU), oxaliplatin exhibits *in vitro* and *in vivo* antiproliferative activity greater than either compound alone in several tumor models [HT29 (colon), GR (mammary), and L1210 (leukemia)].

### Human Pharmacokinetics

The reactive oxaliplatin derivatives are present as a fraction of the unbound platinum in plasma ultrafiltrate. The decline of ultrafilterable platinum levels following oxaliplatin administration is triphasic, characterized by two relatively short distribution phases ($t_{1/2\alpha}$; 0.43 hours and $t_{1/2\beta}$; 16.8 hours) and a long terminal elimination phase ($t_{1/2\gamma}$; 391 hours). Pharmacokinetic parameters obtained after a single 2-hour IV infusion of ELOXATIN at a dose of 85 mg/m$^2$ expressed as ultrafilterable platinum were $C_{max}$ of 0.814 μg/mL and volume of distribution of 440 L.

Interpatient and intrapatient variability in ultrafilterable platinum exposure ($AUC_{0-48}$) 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 ELOXATIN, approximately 15% of the administered platinum is present in the systemic circulation. The remaining 85% is rapidly distributed into tissues or eliminated in the urine. In patients, plasma protein binding of platinum is irreversible and is greater than 90%. The main binding proteins are albumin and gamma-globulins. Platinum also binds irreversibly and accumulates (approximately 2-fold) in erythrocytes, where it appears to have no relevant activity. No platinum accumulation was observed in plasma ultrafiltrate following 85 mg/m$^2$ 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 ELOXATIN, 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. (See ADVERSE REACTIONS)

## Pharmacokinetics in Special Populations

## Renal Impairment

The $AUC_{0\text{-}48hr}$ of platinum in the plasma ultrafiltrate increases as renal function decreases. The $AUC_{0\text{-}48hr}$ of platinum in patients with mild (creatinine clearance, $CL_{cr}$ 50 to 80 mL/min), moderate ($CL_{cr}$ 30 to <50 mL/min) and severe renal ($CL_{cr}$ <30 mL/min) impairment is increased by about 60, 140 and 190%, respectively, compared to patients with normal renal function ($CL_{cr}$ >80 mL/min)]. (See PRECAUTIONS and ADVERSE REACTIONS)

## Drug - Drug Interactions

No pharmacokinetic interaction between 85 mg/m$^2$ of ELOXATIN and 5-FU has been observed in patients treated every 2 weeks, but increases of 5-FU plasma concentrations by approximately 20% have been observed with doses of 130 mg/m$^2$ of ELOXATIN administered every 3 weeks. *In vitro*, platinum was not displaced from plasma proteins by the following medications: erythromycin, salicylate, sodium valproate, granisetron, and paclitaxel. *In vitro,* oxaliplatin is not metabolized by, nor does it inhibit, human cytochrome P450 isoenzymes. No P450-mediated drug-drug interactions are therefore anticipated in patients.

Since platinum containing species are eliminated primarily through the kidney, clearance of these products may be decreased by co-administration of potentially nephrotoxic compounds, although this has not been specifically studied.

## CLINICAL STUDIES

### Combination Therapy with ELOXATIN and 5-FU/LV 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-FU/LV. The results reported below compared the efficacy and safety of two experimental regimens, ELOXATIN in combination with infusional 5-FU/LV and a combination of ELOXATIN plus irinotecan, to an approved control regimen of irinotecan plus 5-FU/LV in 795 concurrently randomized patients previously untreated for locally advanced or metastatic colorectal cancer. After completion of enrollment, the dose of irinotecan plus 5-FU/LV 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 $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, hemoglobin ≥9.0 gm/dL, creatinine ≤ 1.5 x ULN, total bilirubin ≤ 1.5 mg/dL, AST ≤ 5 x ULN, and alkaline phosphatase ≤ 5 x 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 ELOXATIN plus 5-FU/LV arm received an irinotecan-containing regimen and 23% of patients on the irinotecan plus 5-FU/LV 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 1 – Dosing Regimens in Patients Previously Untreated for Advanced Colorectal Cancer Clinical Trial**

| Treatment Arm | Dose | Regimen |
|---|---|---|
| **ELOXATIN + 5-FU/LV FOLFOX4 (N =267)** | **Day 1: ELOXATIN: 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)**<br><br>**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)** | **q2w** |
| 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 IV push, followed by 5-FU 500 mg/m$^2$ IV bolus weekly x 4 | q6w |
| ELOXATIN + Irinotecan IROX (N=264) | Day 1: ELOXATIN: 85 mg/m$^2$ IV (2-hour infusion) + irinotecan 200 mg/m$^2$ IV over 30 minutes. | q3w |

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

**Table 2 – Patient Demographics and Dosing in Patients Previously Untreated for Advanced Colorectal Cancer Clinical Trial**

| | ELOXATIN + 5-FU/LV N=267 | irinotecan + 5-FU/LV N=264 | ELOXATIN + 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 ELOXATIN and 5-FU/LV regimen; 6 weeks for the irinotecan plus 5-FU/LV regimen; and 3 weeks for the ELOXATIN plus irinotecan regimen. The median number of cycles administered per patient was 10 (23.9 weeks) for the ELOXATIN and 5-FU/LV regimen, 4 (23.6 weeks) for the irinotecan plus 5-FU/LV regimen, and 7 (21.0 weeks) for the ELOXATIN plus irinotecan regimen.

Patients treated with the ELOXATIN and 5-FU/LV 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-FU/LV. The following table summarizes the efficacy results.

**Table 3 – Summary of Efficacy**

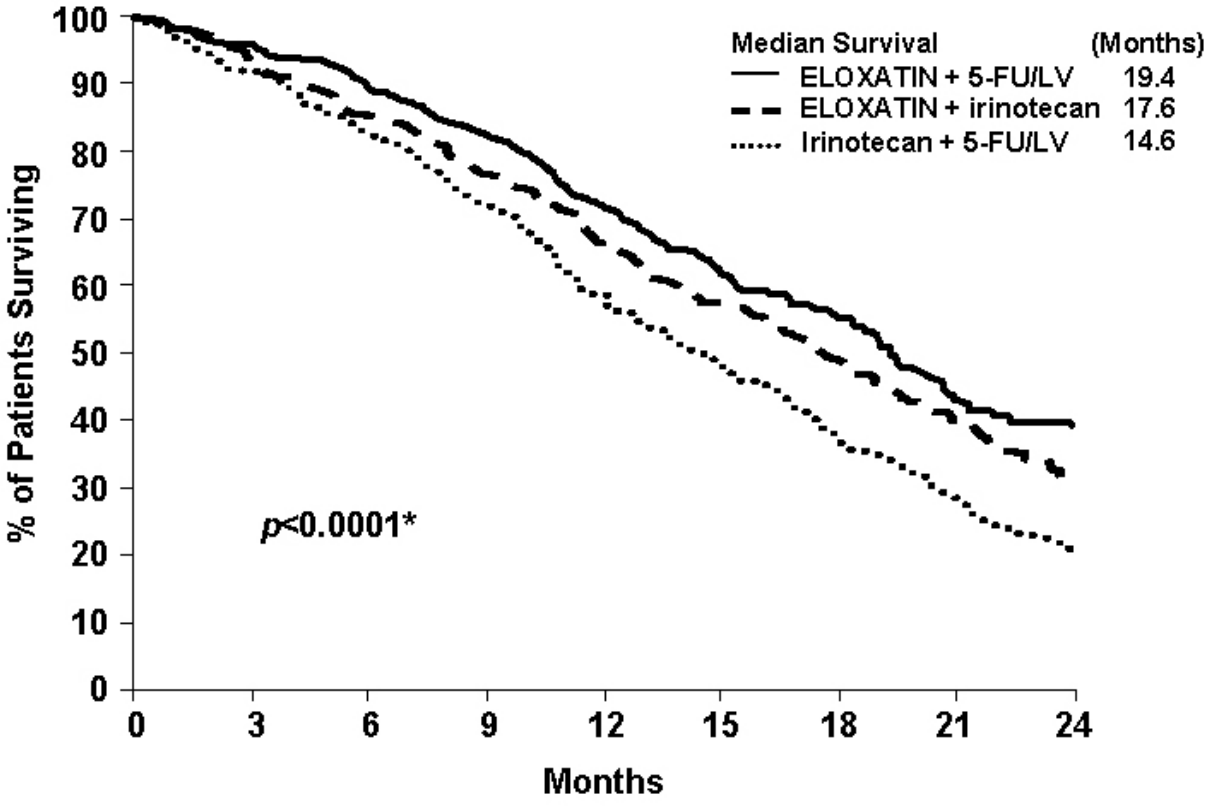
| | **ELOXATIN + 5-FU/LV N=267** | **irinotecan + 5-FU/LV N=264** | **ELOXATIN + irinotecan N=264** |
|---|---|---|---|
| **Survival (ITT)** | | | |
| Number of deaths N (%) | 155 (58.1) | 192 (72.7) | 175 (66.3) |
| Median survival (months) | 19.4 | 14.6 | 17.6 |
| Hazard Ratio and (95% confidence interval) | 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 (0.61-0.89)* | | |
| 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-FU/LV (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.

Figure 1 illustrates the Kaplan-Meier survival curves for the comparison of ELOXATIN and 5-FU/LV combination and ELOXATIN plus irinotecan to irinotecan plus 5-FU/LV.




*Log rank test comparing Eloxatin plus 5-FU/LV to irinotecan plus 5-FU/LV.

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

## Combination Therapy with ELOXATIN and 5-FU/LV 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 ELOXATIN in combination with an infusional schedule of 5-FU/LV to the same dose and schedule of 5-FU/LV alone and to single agent oxaliplatin in patients with advanced colorectal cancer who had relapsed/progressed during or within 6 months of first line therapy with bolus 5-FU/LV and irinotecan. The study was intended to be analyzed for response rate after 450 patients were enrolled. Survival will be subsequently assessed in all patients enrolled 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) ≤ 2x the institution's upper limit of normal (ULN), unless liver metastases were present and documented at baseline by CT or MRI scan, in which case ≤ 5x ULN was permitted. Patients had to have alkaline phosphatase ≤ 2x the institution's ULN, unless liver metastases were present and documented at baseline by CT or MRI scan, in which cases ≤ 5x ULN was permitted. Prior radiotherapy was permitted if it had been completed at least 3 weeks before randomization.

The dosing regimens of the three arms of the study are presented in the table below.

**Table 4 – Dosing Regimens in Refractory and Relapsed Colorectal Cancer Clinical Trial**

| Treatment Arm | Dose | Regimen |
|---|---|---|
| **ELOXATIN + 5-FU/LV (N =152)** | **Day 1: ELOXATIN: 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)**<br><br>**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)** | **q2w** |
| 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)<br><br>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) | q2w |
| ELOXATIN (N=156) | Day 1: ELOXATIN 85 mg/m$^2$ (2-hour infusion) | q2w |

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

The demographics of the patient population entered into this study are shown in the table below.

**Table 5 – Patient Demographics in Refractory and Relapsed Colorectal Cancer Clinical Trial**

| | **5-FU/LV (N = 151)** | **ELOXATIN (N = 156)** | **ELOXATIN + 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 ELOXATIN and 5-FU/LV combination and 3 each for 5-FU/LV alone and ELOXATIN alone.

Patients treated with the combination of ELOXATIN and 5-FU/LV had an increased response rate compared to patients given 5-FU/LV or oxaliplatin alone. The efficacy results are summarized in the tables below.

**Table 6 - Response Rates (ITT Analysis)**

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

**Table 7 - Summary of Radiographic Time to Progression***

| Arm | 5-FU/LV (N=151) | ELOXATIN (N=156) | ELOXATIN + 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-FU/LV alone.

Of the 13 patients who had tumor response to the combination of ELOXATIN and 5-FU/LV, 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.

## INDICATIONS AND USAGE

ELOXATIN, used in combination with infusional 5-FU/LV, is indicated for the treatment of advanced carcinoma of the colon or rectum.

## CONTRAINDICATIONS

ELOXATIN should not be administered to patients with a history of known allergy to ELOXATIN or other platinum compounds.

## WARNINGS

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

### Pregnancy Category D

ELOXATIN may cause fetal harm when administered to a pregnant woman. Pregnant rats were administered 1 mg/kg/day oxaliplatin (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. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with ELOXATIN.

## PRECAUTIONS

### General

ELOXATIN should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

## Neuropathy

Neuropathy was graded using a study-specific neurotoxicity scale, which was different than the National Cancer Institute Common Toxicity Criteria, Version 2.0 (NCI CTC) (See below).

In the previously treated study, neuropathy information was collected to establish that ELOXATIN 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 ELOXATIN with 5-FU/LV. In any individual cycle acute neurotoxicity was observed in approximately 30% of patients. Ice (mucositis prophylaxis) should be avoided during the infusion of ELOXATIN because cold temperature can exacerbate acute neurological symptoms. (See DOSAGE AND ADMINISTRATION: Dose Modifications).

  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).

- **A persistent (>14 days), primarily peripheral, sensory neuropathy that is usually characterized by paresthesias, dysethesias, hypoesthesias, but may also include deficits in proprioception that can interfere with daily activities (e.g. writing, buttoning, swallowing, and difficulty walking from impaired proprioception).** These forms of neuropathy occurred in 48% of the study patients receiving ELOXATIN 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 ELOXATIN.

**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.**

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

## Pulmonary Toxicity

ELOXATIN has been associated with pulmonary fibrosis (<1% of study patients), which may be fatal. The combined incidence of cough, dyspnea and hypoxia was 43% (any grade) and 7% (grade 3 and 4) in the ELOXATIN 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, ELOXATIN should be discontinued until further pulmonary investigation excludes interstitial lung disease or pulmonary fibrosis.

## Information for Patients

Patients and patients' caregivers should be informed of the expected side effects of ELOXATIN, particularly its neurologic effects, both the acute, reversible effects, and the persistent neurosensory toxicity. Patients should be informed that the acute neurosensory toxicity may be precipitated or exacerbated by exposure to cold or cold objects. Patients should be instructed to avoid cold drinks, use of ice, and should cover exposed skin prior to exposure to cold temperature or cold objects.

Patients must be adequately informed of the risk of low blood cell counts and instructed to contact their physician immediately should fever, particularly if associated with persistent diarrhea, or evidence of infection develop.

Patients should be instructed to contact their physician if persistent vomiting, diarrhea, signs of dehydration, cough or breathing difficulties occur, or signs of allergic reaction appear.

## Laboratory Tests

Standard monitoring of the white blood cell count with differential, hemoglobin, platelet count, and blood chemistries (including ALT, AST, bilirubin and creatinine) is recommended before each ELOXATIN cycle (See DOSAGE AND ADMINISTRATION).

## Laboratory Test Interactions

None known.

## Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of oxaliplatin. Oxaliplatin was not mutagenic to bacteria (Ames test) but was mutagenic to mammalian cells *in vitro* (L5178Y mouse lymphoma assay). Oxaliplatin was clastogenic both *in vitro* (chromosome aberration in human lymphocytes) and *in vivo* (mouse bone marrow micronucleus assay).

In a fertility study, male rats were given oxaliplatin at 0, 0.5, 1, or 2 mg/kg/day for five days every 21 days for a total of three cycles prior to mating with females that received two cycles of oxaliplatin on the same schedule. A dose of 2 mg/kg/day (less than one-seventh the recommended human dose on a body surface area basis) did not affect pregnancy rate, but caused developmental mortality (increased early resorptions, decreased live fetuses, decreased live births) and delayed growth (decreased fetal weight). Testicular damage, characterized by degeneration, hypoplasia, and atrophy, was observed in dogs administered oxaliplatin at 0.75 mg/kg/day x 5 days every 28 days for three cycles. A no effect level was not identified. This daily dose is approximately one-sixth of the recommended human dose on a body surface area basis.

## Pregnancy Category D - See WARNINGS

**Nursing Mothers -** It is not known whether ELOXATIN 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 ELOXATIN, 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.

**Pediatric Use -** The safety and effectiveness of ELOXATIN in pediatric patients have not been established.

**Patients with Renal Impairment** The safety and effectiveness of the combination of ELOXATIN and 5-FU/LV in patients with renal impairment has not been evaluated. The combination of ELOXATIN and 5-FU/LV should be used with caution in patients with preexisting renal impairment since the primary route of platinum elimination is renal. Clearance of ultrafilterable platinum is decreased in patients with mild, moderate, and severe renal impairment. A pharmacodynamic relationship between platinum ultrafiltrate levels and clinical safety and effectiveness has not been established. (See CLINICAL PHARMACOLOGY and ADVERSE REACTIONS)

**Geriatric Use** - No significant effect of age on the clearance of ultrafilterable platinum has been observed. In the previously untreated for advanced colorectal cancer randomized clinical trial (see CLINICAL STUDIES) of ELOXATIN, 160 patients treated with ELOXATIN and 5-FU/LV 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 randomized clinical trial (see CLINICAL STUDIES) of ELOXATIN, 95 patients treated with ELOXATIN and 5-FU/LV were < 65 years and 55 patients were ≥ 65 years. The rates of overall adverse events, including grade 3 and 4 events, were similar across and within arms in the different age groups in both 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.

**Drug Interactions** - No specific cytochrome P-450-based drug interaction studies have been conducted. No pharmacokinetic interaction between 85 mg/m$^2$ ELOXATIN and 5-FU/LV has been observed in patients treated every 2 weeks. Increases of 5-FU plasma concentrations by approximately 20% have been observed with doses of 130 mg/m$^2$ ELOXATIN dosed every 3 weeks. Since platinum containing species are eliminated primarily through the kidney, clearance of these products may be decreased by coadministration of potentially nephrotoxic compounds; although, this has not been specifically studied. (see CLINICAL PHARMACOLOGY)

## ADVERSE REACTIONS

More than 4,000 patients with advanced colorectal cancer have been treated in clinical studies with ELOXATIN either as a single agent or in combination with other medications. The most common adverse reactions were peripheral sensory neuropathies, fatigue, neutropenia, nausea, emesis, and diarrhea (See PRECAUTIONS).

### Patients Previously Untreated for Advanced Colorectal Cancer

Two-hundred and fifty nine patients were treated in the ELOXATIN and 5-FU/LV combination arm of the randomized trial in patients previously untreated for advanced colorectal cancer (See CLINICAL STUDIES). The adverse event profile in this study was similar to that seen in other studies and the adverse reactions in this trial are shown in the tables below.

Both 5-FU and ELOXATIN are associated with gastrointestinal and hematologic adverse events. When ELOXATIN 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 ELOXATIN and 5-FU/LV combination, 5% with irinotecan plus 5-FU/LV, and 3% with ELOXATIN plus irinotecan. Deaths within 60 days from initiation of therapy were 2.3% with the ELOXATIN and 5-FU/LV combination, 5.1% with irinotecan plus 5-FU/LV, and 3.1% with ELOXATIN plus irinotecan.

The following table provides adverse events reported in the previously untreated for advanced colorectal cancer study (see CLINICAL STUDIES) by body system and decreasing order of frequency in the ELOXATIN 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 8 – Adverse Experience Reported in Patients Previously Untreated for Advanced Colorectal Cancer Clinical Trial (≥5% of all patients and with ≥1% NCI Grade 3/4 events)**

| | ELOXATIN + 5-FU/LV N=259 | | irinotecan + 5-FU/LV N=256 | | ELOXATIN + irinotecan N=258 | |
|---|---|---|---|---|---|---|
| **Adverse Event (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 –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 |

The following table provides adverse events reported in the previously untreated for advanced colorectal cancer study (see CLINICAL STUDIES) by body system and decreasing order of

frequency in the ELOXATIN and 5-FU/LV combination arm for events with overall incidences ≥5% but with incidences < 1% NCI Grade 3/4 events.

**Table 9 - Adverse Experience Reported in Patients Previously Untreated for Advanced Colorectal Cancer Clinical Trial**

| (≥5% of all patients but with < 1% NCI Grade 3/4 events) Adverse Event (WHO/Pref) | ELOXATIN + 5-FU/LV N=259 All Grades (%) | irinotecan + 5-FU/LV N=256 All Grades (%) | ELOXATIN + irinotecan N=258 All Grades (%) |
|---|---|---|---|
| | 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 |
| 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 no 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 |

Adverse events 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 events, at least possibly related to treatment and potentially important, were reported in ≥2% and <5% of the patients in the ELOXATIN 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 ELOXATIN and 5-FU/LV) were studied in a randomized trial in patients with refractory and relapsed colorectal cancer (See CLINICAL STUDIES). The adverse event profile in this study was similar to that seen in other studies and the adverse reactions in this trial are shown in the tables below.

Thirteen per cent of patients in the ELOXATIN 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 ELOXATIN are associated with gastrointestinal and hematologic adverse events. When ELOXATIN 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 ELOXATIN and 5-FU/LV combination, 8% with ELOXATIN alone, and 7% with 5-FU/LV. Of the 7 deaths that occurred on the ELOXATIN 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 events reported in the previously treated study (see CLINICAL STUDIES) by body system and in decreasing order of frequency in the ELOXATIN 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 10 – Adverse Experience 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) | | ELOXATIN (N = 153) | | ELOXATIN + 5-FU/LV (N = 150) | |
|---|---|---|---|---|---|---|
| **Adverse Event (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 events reported in the previously treated study (see CLINICAL STUDIES) by body system and in decreasing order of frequency in the ELOXATIN and 5-FU/LV combination arm for events with overall incidences ≥5% but with incidences < 1% NCI Grade 3/4 events.

**Table 11 - Adverse Experience Reported In Previously Treated Colorectal Cancer Clinical Trial**
**(≥5% of all patients but with < 1% NCI Grade 3/4 events)**

| Adverse Event (WHO/Pref) | 5-FU/LV (N = 142) All Grades (%) | ELOXATIN (N = 153) All Grades (%) | ELOXATIN + 5-FU/LV (N = 150) All Grades (%) |
|---|---|---|---|
| | 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 events were similar in men and women and in patients <65 and ≥65 years, but older patients may have been more susceptible to dehydration, diarrhea, hypokalemia and fatigue. The following additional adverse events, at least possibly related to treatment and potentially important, were reported in ≥2% and <5% of the patients in the ELOXATIN 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, pruritis, hemoptysis, purpura, vaginal hemorrhage, melena, somnolence, pneumonia, proctitis, involuntary muscle contractions, intestinal obstruction, gingivitis, tenesmus, hot flashes, enlarged abdomen, urinary incontinence.

## Hematologic

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

**Table 12 – Adverse Hematologic Experiences in Patients Previously Untreated for Advanced Colorectal Cancer (≥5% of patients)**

| Hematology Parameter | ELOXATIN + 5-FU/LV N=259 | | irinotecan+ 5-FU/LV N=256 | | ELOXATIN + 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 13 – Adverse Hematologic Experiences Previously Treated Patients (≥5% of patients)**

| Hematology Parameter | 5-FU/LV (N=142) | | ELOXATIN (N=153) | | ELOXATIN + 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

Thrombocytopenia was frequently reported with the combination of ELOXATIN and 5-FU/LV. The incidence of Grade 3/4 thrombocytopenia in the patients previously untreated for advanced colorectal cancer and the previously treated patients was 3-5%. Grade 3/4 hemorrhagic events in both patient populations were reported at low frequency and the incidence of these events were greater for the combination of ELOXATIN and 5-FU/LV over the irinotecan plus 5-FU/LV or 5-FU/LV control groups. In the previously untreated patients, the incidence of epistaxis was 10% in the ELOXATIN and 5-FU/LV arm, and 2% and 1% respectively in the irinotecan plus 5-FU/LV or irinotecan plus ELOXATIN arms. The requirement for platelet transfusion was not increased in the ELOXATIN and 5-FU/LV arm. The incidence of all hemorrhagic events in the previously treated patients was also higher on the ELOXATIN combination arm compared to the 5-FU/LV arm. These events included gastrointestinal bleeding, hematuria and epistaxis.

### Neutropenia

Neutropenia was frequently observed with the combination of ELOXATIN and 5-FU/LV, with Grade 3 and 4 events 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. 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 ELOXATIN 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 ELOXATIN 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 ELOXATIN and 5-FU/LV combination arm.

### **Gastrointestinal**

In patients previously untreated for advanced colorectal cancer receiving the combination of ELOXATIN and 5-FU/LV, the incidence of Grade 3 and 4 vomiting and diarrhea was less compared to irinotecan plus 5-FU/LV controls (See table). In previously treated patients receiving the combination of ELOXATIN and 5-FU/LV, the incidence of Grade 3 and 4 nausea, vomiting, diarrhea, and mucositis/stomatitis increased compared to 5-FU/LV controls (See table).

The incidence of gastrointestinal adverse events in the previously untreated and previously treated patients appears to be similar across cycles. Premedication with antiemetics, including 5-$HT_3$ blockers, is recommended. Diarrhea and mucositis may be exacerbated by the addition of ELOXATIN 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 ELOXATIN.

### Dermatologic

ELOXATIN did not increase the incidence of alopecia compared to 5-FU/LV alone. No complete alopecia was reported. 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 ELOXATIN 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 ELOXATIN and 5-FU/LV combination arm.

Care of Intravenous Site:

Extravasation may result in local pain and inflammation that may be severe and lead to complications, including necrosis. Injection site reaction, including redness, swelling, and pain have been reported.

### Neurologic

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. ELOXATIN is consistently associated with two types of peripheral neuropathy (see PRECAUTIONS, Neuropathy). In the previously treated patients, the incidence of overall and Grade 3/4 persistent peripheral neuropathy was 48% and 6%, respectively. The majority of the patients (80%) that developed grade 3 persistent neuropathy progressed from prior Grade 1 or 2 events. The median number of cycles administered on the ELOXATIN with 5-FU/LV combination arm in the previously treated patients was 6.

### Pulmonary

ELOXATIN has been associated with pulmonary fibrosis (see PRECAUTIONS, Pulmonary Toxicity).

### Allergic reactions

Hypersensitivity to ELOXATIN has been observed (<2% Grade 3/4) in clinical studies. These allergic reactions which can be fatal, can occur at any cycle, and were similar in nature and severity to those reported with other platinum-containing compounds such as, rash, urticaria, erythema, pruritis, and, rarely, bronchospasm and hypotension. The symptoms associated with hypersensitivity reactions reported in the previously untreated patients were urticaria, pruritis, 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 may require discontinuation of therapy. (see WARNINGS for anaphylactic/anaphylactoid reactions.)

### 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 ELOXATIN plus 5-FU/LV while on anticoagulants. Patients receiving ELOXATIN plus 5-FU/LV 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 ELOXATIN and 5-FU/LV combination arm was 1% in the previously treated patients

### Hepatic

The following tables list the clinical chemistry changes associated with hepatic toxicity occurring in ≥ 5% of patients, based on adverse events reported and NCI CTC grade for patients previously untreated for advanced colorectal cancer, laboratory values and NCI CTC grade for previously treated patients.

**Table 14 – Adverse Hepatic – Clinical Chemistry Experience in Patients Previously Untreated for Advanced Colorectal Cancer (≥5% of patients)**

| Clinical Chemistry | ELOXATIN + 5-FU/LV N=259 | | irinotecan + 5-FU/LV N=256 | | ELOXATIN + 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 15 – Adverse Hepatic – Clinical Chemistry Experience in Previously Treated Patients (≥5% of patients)**

| Clinical Chemistry | 5-FU/LV (N=142) | | ELOXATIN (N=153) | | ELOXATIN + 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 events was 6 and 9% of the patients previously untreated for advanced colorectal cancer and previously treated patients in the ELOXATIN and 5-FU/LV combination arm, respectively.

### Postmarketing Experience

The following events have been reported from worldwide postmarketing experience.

*Body as a whole:*
-angioedema, anaphylactic shock

*Central and peripheral nervous system disorders:*
-loss of deep tendon reflexes, dysarthria, Lhermittes' sign, cranial nerve palsies, fasciculations

*Gastrointestinal system disorders:*
-severe diarrhea/vomiting resulting in hypokalemia, metabolic acidosis; ileus; intestinal obstruction, pancreatitis

*Hearing and vestibular system disorders:*
-deafness

*Platelet, bleeding, and clotting disorders:*
-immuno-allergic thrombocytopenia
-prolongation of prothrombin time and of INR in patients receiving anticoagulants

*Red Blood Cell disorders*
-hemolytic uremic syndrome

*Respiratory system disorders:*
-pulmonary fibrosis, and other interstitial lung diseases

*Vision disorders:*
-decrease of visual acuity, visual field disturbance, optic neuritis

## OVERDOSAGE

There have been five ELOXATIN overdoses reported. One patient received two 130 mg/m$^2$ doses of ELOXATIN (cumulative dose of 260 mg/m$^2$) within a 24 hour period. The patient experienced Grade 4 thrombocytopenia (<25,000/mm$^3$) without any bleeding, which resolved. Two other patients were mistakenly administered ELOXATIN instead of carboplatin. One patient received a total ELOXATIN dose of 500 mg and the other received 650 mg. The first patient experienced dyspnea, wheezing, paresthesia, profuse vomiting and chest pain on the day of administration. She developed respiratory failure and severe bradycardia, and subsequently did not respond to resuscitation efforts. The other patient also experienced dyspnea, wheezing, paresthesia, and vomiting. Her symptoms resolved with supportive care. Another patient who was mistakenly administered a 700 mg dose experienced rapid onset of dysesthesia. Inpatient supportive care was given, including hydration, electrolyte support, and platelet transfusion. Recovery occurred 15 days after the overdose. The last patient received an overdose of oxaliplatin at 360 mg instead of 120 mg over a 1-hour infusion by mistake. At the end of the infusion, the patient experienced 2 episodes of vomiting, laryngospasm, and paresthesia. The patient fully recovered from the laryngospasm within half an hour. At the time of reporting, 1 hour after onset of the event, the patient was recovering from paresthesia. There is no known antidote for ELOXATIN overdose. In addition to thrombocytopenia, the anticipated complications of an ELOXATIN overdose include myelosuppression, nausea and vomiting, diarrhea, and neurotoxicity. Patients suspected of receiving an overdose should be monitored, and supportive treatment should be administered.

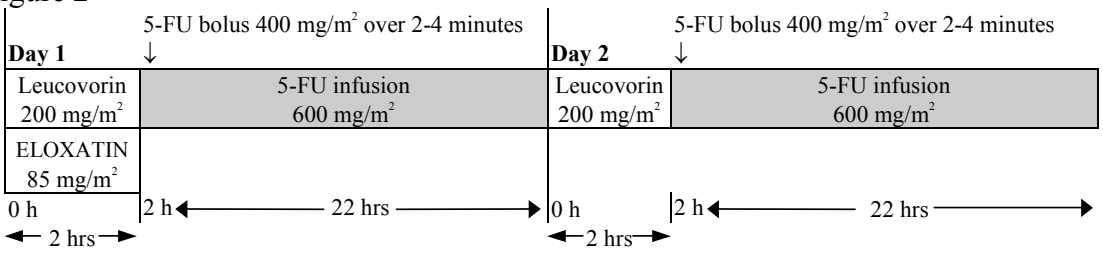
## DOSAGE AND ADMINISTRATION

The recommended dose schedule given every two weeks is as follows:

Day 1: ELOXATIN 85 mg/m$^2$ IV infusion in 250-500 mL D5W and leucovorin 200 mg/m$^2$ IV infusion in D5W both given over 120 minutes at the same time in separate bags using a Y-line, followed by 5-FU 400 mg/m$^2$ IV bolus given over 2-4 minutes, followed by 5-FU 600 mg/m$^2$ IV infusion in 500 mL D5W (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 D5W (recommended) as a 22-hour continuous infusion.

Figure 2




Repeat cycle every 2 weeks.

The administration of ELOXATIN does not require prehydration.

Premedication with antiemetics, including 5-HT$_3$ 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 (see Laboratory Tests). Neuropathy was graded using a study-specific neurotoxicity scale (see PRECAUTIONS, Neuropathy). Other toxicities were graded by the NCI CTC, Version 2.0.

Prolongation of infusion time for ELOXATIN from 2 hours to 6 hours decreases the $C_{max}$ by an estimated 32% and may mitigate acute toxicities. The infusion time for 5-FU and leucovorin do not need to be changed.

For patients who experience persistent Grade 2 neurosensory events that do not resolve, a dose reduction of ELOXATIN 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 ELOXATIN to 65 mg/m$^2$ 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 $\geq 1.5 \times 10^9$/L, and platelets $\geq 75 \times 10^9$/L.

### Preparation of Infusion Solution

**RECONSTITUTION OR FINAL DILUTION MUST NEVER BE PERFORMED WITH A SODIUM CHLORIDE SOLUTION OR OTHER CHLORIDE-CONTAINING SOLUTIONS.**

The lyophilized powder is reconstituted by adding 10 mL (for the 50 mg vial) or 20 mL (for the 100 mg vial) of Water for Injection, USP or 5% Dextrose Injection, USP. **Do not administer the reconstituted solution without further dilution**. The reconstituted solution must be further diluted in an infusion solution of 250-500 mL of 5% Dextrose Injection, USP.

After reconstitution in the original vial, the solution may be stored up to 24 hours under refrigeration [2-8°C (36-46°F)]. After final dilution with 250-500 mL of 5% Dextrose Injection, USP, the shelf life is **6 hours at room temperature [20-25°C (68-77°F)] or up to 24 hours under refrigeration [2-8°C (36-46°F)]**. ELOXATIN is not light sensitive.

ELOXATIN is incompatible in solution with alkaline medications or media (such as basic solutions of 5-FU) and must not be mixed with these or administered simultaneously through the same infusion line. **The infusion line should be flushed with D5W prior to administration of any concomitant medication.**

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and discarded if present.

Needles or intravenous administration sets containing aluminum parts that may come in contact with ELOXATIN should not be used for the preparation or mixing of the drug. Aluminum has been reported to cause degradation of platinum compounds.

## HOW SUPPLIED

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

NDC 0024-0596-02: 50 mg single-use vial with green flip-off seal individually packaged in a carton.

NDC 0024-0597-04: 100 mg single-use vial with dark blue flip-off seal individually packaged in a carton.

### Storage

Store under normal lighting conditions at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP controlled room temperature].

### Handling and Disposal

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions prepared from ELOXATIN. The use of gloves is recommended. If a solution of ELOXATIN contacts the skin, wash the skin immediately and thoroughly with soap and water. If ELOXATIN contacts the mucous membranes, flush thoroughly with water.

Procedures for the handling and disposal of anticancer drugs should be considered. Several guidelines on the subject have been published [1-8]. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

## REFERENCES


1. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and Recommendations for Practice. Pittsburgh, Pa: Oncology Nursing Society; 1999:32-41.
2. Recommendations for the safe handling of parenteral antineoplastic drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.
3. AMA Council Report. Guidelines for handling parenteral antineoplastics. *JAMA* 1985;253(11):1590-1592.
4. National Study Commission on Cytoxic Exposure. Recommendations for handling cytoxic agents. Available from Louis P. Jeffrey, Sc.D., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.
5. Clinical Oncological Society of Australia. Guidelines and recommendations for safe handling of antineoplastic agents. *Med J Australia* 1983;1:426-428.
6. Jones RB, et al. Safe handling of chemotherapeutic agents: a report from the Mount Sinai Medical Center. *Ca - A Cancer Journal for Clinicians.* Sept./Oct. 1983:258-263.
7. American Society of Hospital Pharmacists. ASHP Technical Assistance Bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm* 1990;47:1033-1049.
8. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines). *Am J Hosp Pharm* 1996;53:1669-1685.



Distributed by Sanofi-Synthelabo Inc.
New York, NY 10016

Manufactured for Sanofi-Synthelabo Inc. by Ben Venue Laboratories
Bedford, Ohio 44146-0568
Made in USA

Printed in USA
Date of Revision