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ELOXATIN™
(oxaliplatin for injection)

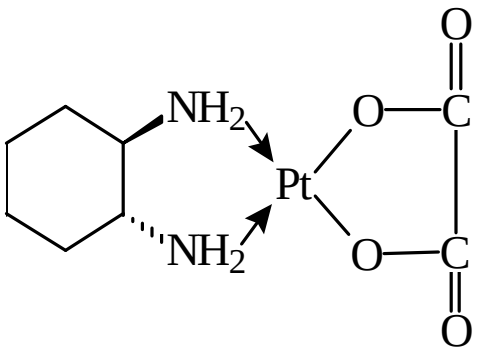
WARNING

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 infusional 5-FU has been observed in patients treated every 2 weeks, but increases of 5-FU plasma concentrations by approximately 20% have been observed with doses of 130 mg/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 Infusional 5-FU/LV in Previously Treated Patients with Advanced Colorectal Cancer

A multicenter, randomized, three arm controlled study was conducted in the US and Canada comparing the efficacy and safety of 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 1 – 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)** **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) 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 2 – 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 infusional 5-FU/LV combination and 3 each for infusional 5-FU/LV alone and ELOXATIN alone.

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

Table 3 - 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 4 - 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 infusional 5-FU/LV alone.

Of the 13 patients who had tumor response to the combination of ELOXATIN and infusional 5-FU/LV, 5 were female and 8 were male, and included patients <65 years old and ≥65 years old. The small number of non-Caucasian participants made efficacy analyses in these populations uninterpretable.

INDICATIONS AND USAGE

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

The approval of ELOXATIN is based on response rate and an interim analysis showing improved time to radiographic progression. No results are available at this time that demonstrate a clinical benefit, such as improvement of disease-related symptoms or increased survival (see CLINICAL STUDIES).

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). 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 infusional 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% of patients is characterized by subjective sensations of dysphagia or dyspnea, without any laryngospasm or bronchospasm (no stridor or wheezing).

- **A persistent (>14 days), primarily peripheral, sensory neuropathy that is usually characterized by paresthesias, dysethesias, hypoesthesias, but may also include deficits in proprioception that can interfere with daily activities (e.g., writing, buttoning, swallowing, and difficulty walking from impaired proprioception).** These forms of neuropathy occurred in 48% of the study patients receiving ELOXATIN with infusional 5-FU/LV. Persistent neuropathy can occur without any prior acute neuropathy event. The majority of the patients (80%) who developed grade 3 persistent neuropathy progressed from prior Grade 1 or 2 events. These symptoms may improve in some patients upon discontinuation of ELOXATIN.

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 (0.7% of study patients), which may be fatal. In case of unexplained respiratory symptoms such as non-productive cough, dyspnea, crackles, or radiological pulmonary infiltrates, 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 infusional 5-FU/LV in patients with renal impairment has not been evaluated. The combination of ELOXATIN and infusional 5-FU/LV should be used with caution in patients with preexisting renal impairment since the primary route of platinum elimination is renal. Clearance of 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 randomized clinical trial (see CLINICAL STUDIES) of ELOXATIN, 95 patients treated with ELOXATIN and infusional 5-FU/LV were <65 years and 55 patients were ≥ 65 years. The rates of overall adverse events, including grade 3 and 4 events, were similar across and within arms in the different age groups. The incidence of diarrhea, dehydration, hypokalemia, and fatigue were higher in patients ≥65 years old.

Drug Interactions - No specific cytochrome P-450-based drug interaction studies have been conducted. No pharmacokinetic interaction between 85 mg/m^2 ELOXATIN and infusional 5-FU has been observed in patients treated every 2 weeks. Increases of 5-FU plasma concentrations by approximately 20% have been observed with doses of 130 mg/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 1500 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, neutropenia, nausea, emesis, and diarrhea (See PRECAUTIONS). 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 infusional 5-FU/LV-combination arm and 18% in the infusional 5-FU/LV arm had to discontinue treatment because of adverse effects related to gastrointestinal or hematologic adverse events, or neuropathies. Both 5-FU and ELOXATIN are associated with gastrointestinal and hematologic adverse events. When ELOXATIN is administered in combination with infusional 5-FU, the incidence of these events is increased.

The incidence of death within 30 days of treatment, regardless of causality, was 5% with the ELOXATIN and infusional 5-FU/LV combination, 8% with ELOXATIN alone, and 7% with infusional 5-FU/LV. Of the 7 deaths that occurred on the ELOXATIN and infusional 5-FU/LV combination arm within 30 days of stopping treatment, 3 may have been treatment-related, associated with gastrointestinal bleeding or dehydration.

The following table provides adverse events reported in the study (see CLINICAL STUDIES) in decreasing order of frequency in the ELOXATIN and infusional 5-FU/LV combination arm for events with overall incidences ≥5% and for grade 3/4 events with incidences ≥ 1%. This table does not include hematologic and blood chemistry abnormalities; these are shown separately below.

Table 5 – Adverse Experience Reported In 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/Preferred)	**All Grades (%)**	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**
Any Event	98	41	100	46	99	73
Fatigue	52	6	61	9	68	7
Diarrhea	44	3	46	4	67	11
Nausea	59	4	64	4	65	11
Neuropathy	17	0	76	7	73	7
Acute	10	0	65	5	56	2
Persistent	9	0	43	3	48	6
Vomiting	27	4	37	4	40	9
Stomatitis	32	3	14	0	37	3
Abdominal Pain	31	5	31	7	33	4
Fever	23	1	25	1	29	1
Anorexia	20	1	20	2	29	3
Dyspnea	11	2	13	7	20	4
Back Pain	16	4	11	0	19	3
Coughing	9	0	11	0	19	1
Edema	13	1	10	1	15	1
Pain	9	3	14	3	15	2
Injection Site Reaction	5	1	9	0	10	3
Thromboembolism	4	2	2	1	9	8
Hypokalemia	3	1	3	2	9	4
Dehydration	6	4	5	3	8	3
Chest Pain	4	1	5	1	8	1
Febrile Neutropenia	1	1	0	0	6	6
Gastroesophageal Reflux	3	0	1	0	5	2

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

Table 6 - Adverse Experience Reported In Colorectal Cancer Clinical Trial

(≥5% of all patients but with <1% NCI Grade 3/4 events)

Adverse Event (WHO/Preferred)	5-FU/LV (N = 142) All Grades (%)	ELOXATIN (N = 153) All Grades (%)	ELOXATIN + 5-FU/LV (N = 150) All Grades (%)
Constipation	23	31	32
Headache	8	13	17
Rhinitis	4	6	15
Dyspepsia	10	7	14
Taste Perversion	1	5	13
Dizziness	8	7	13
Hand-Foot Syndrome	13	1	11
Flushing	2	3	10
Peripheral Edema	11	5	10
Allergic Reaction	1	3	10
Arthralgia	10	7	10
Upper Resp Tract Infection	4	7	10
Pharyngitis	10	2	9
Rash	5	5	9
Insomnia	4	11	9
Epistaxis	1	2	9
Mucositis	10	2	7
Alopecia	3	3	7
Abnormal Lacrimation	6	1	7
Rigors	6	9	7
Hematuria	4	0	6
Dysuria	1	1	6
Hiccup	0	2	5
Flatulence	6	3	5

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 infusional 5-FU/LV combination arm (listed in decreasing order of frequency): anxiety, myalgia, erythematous rash, increased sweating, conjunctivitis, weight decrease, dry mouth, rectal hemorrhage, depression, ataxia, ascites, hemorrhoids, muscle weakness, nervousness, tachycardia, abnormal micturition frequency, dry skin, pruritis, hemoptysis, purpura, vaginal hemorrhage, melena, somnolence, pneumonia, proctitis, involuntary muscle contractions, intestinal obstruction, gingivitis, tenesmus, hot flashes, enlarged abdomen, urinary incontinence.

Hematologic

The following table lists the hematologic changes occurring in ≥5% of patients, based on laboratory values and NCI grade.

Table 7 – Adverse Hematologic Experiences
(³ 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 infusional 5-FU/LV. The incidence of Grade 3/4 thrombocytopenia was 4%. Grade 3/4 hemorrhagic events were reported at low frequency and the incidence of these events was similar for the combination of ELOXATIN and infusional 5-FU/LV and the infusional 5-FU/LV control group. The incidence of all hemorrhagic events, however, was 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 infusional 5-FU/LV, with Grade 3 and 4 events reported in 27% and 17% of previously treated patients, respectively. The incidence of febrile neutropenia was 1% in the infusional 5-FU/LV arm and 6% (less than 1% of cycles) in the ELOXATIN and infusional 5-FU/LV combination arm.

Gastrointestinal

In patients receiving the combination of ELOXATIN and infusional 5-FU/LV, the incidence of Grade 3 and 4 nausea, vomiting, diarrhea, and mucositis/stomatitis increased compared to infusional 5-FU/LV controls (See table).

The incidence of gastrointestinal adverse events 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 infusional 5-FU/LV, and should be managed with appropriate supportive care. Since cold temperature can exacerbate acute neurological symptoms, ice (mucositis prophylaxis) should be avoided during the infusion of ELOXATIN.

Dermatologic

ELOXATIN did not increase the incidence of alopecia compared to infusional 5-FU/LV alone. No complete alopecia was reported. The incidence of hand-foot syndrome was 13% in the infusional 5-FU/LV arm and 11% in the ELOXATIN and infusional 5-FU/LV combination arm.

Care of Intravenous Site:

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

Neurologic

ELOXATIN is consistently associated with two types of peripheral neuropathy (see PRECAUTIONS, Neuropathy). Seventy-four percent of patients experienced neuropathy. The incidence of overall and Grade 3/4 persistent peripheral neuropathy was 48% and 6%, respectively, in the study. These events can occur without any prior acute event. The majority of the patients (80%) that developed grade 3 persistent neuropathy progressed from prior Grade 1 or 2 events. The median number of cycles administered on the ELOXATIN with infusional 5-FU/LV combination arm was 6 cycles. In clinical trials that have studied similar administration schedules of this combination regimen, (median cycles ranged 10-12), a higher incidence (17%) of Grade 3/4 persistent neurotoxicity was observed.

Allergic reactions

Hypersensitivity to ELOXATIN has been observed (<1% Grade 3/4) in clinical studies. These allergic reactions, which can be fatal, were similar in nature and severity to those reported with other platinum-containing compounds- i.e., rash, urticaria, erythema, pruritis, and, rarely, bronchospasm and hypotension. These reactions are usually managed with standard epinephrine, corticosteroid, and antihistamine therapy, (see WARNINGS for anaphylactic/anaphylactoid reactions.)

Renal

About 10% of patients in all groups had some degree of elevation of serum creatinine. The incidence of Grade 3/4 elevations in serum creatinine in the ELOXATIN and infusional 5-FU/LV combination arm was 1%.

Hepatic

The following table lists the clinical chemistry changes associated with hepatic toxicity occurring in ≥ 5% of patients, based on laboratory values and NCI CTC grade.

Table 8 – Adverse Hepatic – Clinical Chemistry Experience (³ 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 4% in the infusional 5-FU/LV arm, and 9% in the ELOXATIN and infusional 5-FU/LV combination arm.

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

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

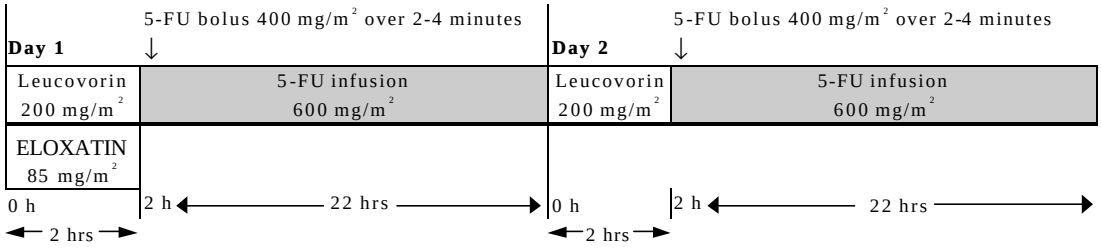
OVERDOSAGE

There have been four 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. 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.



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 infusional 5-FU and leucovorin do not need to be changed.

For patients who experience persistent Grade 2 neurosensory events that do not resolve, a dose reduction of ELOXATIN to 65 mg/m^2 should be considered. For patients with persistent Grade 3 neurosensory events, discontinuing therapy should be considered. The infusional 5-FU/LV regimen need not be altered.

A dose reduction of ELOXATIN to 65 mg/m^2 and infusional 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 3/4 hematologic toxicity (neutrophils $<1.5 \times 10^9$/L, platelets $<100 \times 10^9$/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.

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8. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines). *Am J Hosp Pharm* 1996;53:1669-1685.

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PATIENT INFORMATION

ELOXATIN ä
(oxaliplatin for injection)

Read this information carefully as you start using ELOXATIN. It will help you learn more about ELOXATIN. This information does not take the place of talking to your doctor about your medical condition or your treatment. Ask your doctor about any questions you have.

What is ELOXATIN?

ELOXATIN (eh-LOX-ah-tin) is an anticancer (chemotherapy) medicine that is used to treat adults with advanced colon or rectal (colo-rectal) cancer. ELOXATIN is used:

- With other anti-cancer medicines called 5-fluorouracil (5-FU) and leucovorin (LV).
- When treatment with 5-FU/LV and irinotecan has not worked or stops working (cancer has progressed within 6 months of stopping treatment). Irinotecan is also called Camptosar®.

ELOXATIN with infusional 5-FU and LV was shown to shrink tumors and delay progression of tumors in some patients with advanced colorectal cancer. Data are not yet available to show if ELOXATIN prolongs survival or decreases symptoms caused by cancer.

The use of ELOXATIN in children has not been studied.

Who should not use ELOXATIN?

Do not use ELOXATIN if:

- If you are allergic to platinum. The active ingredient in ELOXATIN is oxaliplatin, which is a platinum-containing drug. Cisplatin (Platinol®) and carboplatin (Paraplatin®) are other chemotherapy medicines that also contain platinum.
- If you are pregnant. ELOXATIN may harm your unborn child. You should avoid becoming pregnant while taking ELOXATIN. Talk with your doctor about how to avoid pregnancy.

Tell your doctor if:

- You are breast feeding. We do not know if ELOXATIN can pass through your milk and if it can harm your baby. You will need to decide whether to stop breast feeding or not to take ELOXATIN.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines and herbal supplements. ELOXATIN may affect how they work in your body.

How is ELOXATIN given to me?

ELOXATIN is given to you through your veins (blood vessels).

Your doctor will prescribe ELOXATIN in an amount that is appropriate for you. Your doctor will treat you with several medicines for your cancer. It is very important that you do exactly what your doctor and nurse have taught you to do. Some medicines may be given to you before ELOXATIN to help prevent nausea and vomiting.

ELOXATIN is given with 2 other chemotherapy drugs, leucovorin and 5-FU. Each treatment course is given to you over 2 days. There are usually 14 days between starting chemotherapy treatment courses. You will receive ELOXATIN on the first day only.

Treatment Day 1:

ELOXATIN and leucovorin are put into a vein through a thin plastic tube (intravenous infusion or I.V.) and given for 2 hours. You will be watched by a healthcare provider during this time.

Right after the ELOXATIN and leucovorin are finished, 2 doses of 5-FU will be given. The first dose is given right away into your I.V. tube. The second dose will be given into your I.V. tube over the next 22 hours, using a pump device.

Treatment Day 2:

You will not get ELOXATIN on Day 2. Leucovorin and 5-FU will be given the same way as on Day 1.

During your treatment with ELOXATIN:

- It is important for you to keep all appointments. Call your doctor if you must miss an appointment. There may be special instructions for you.
- Your doctor may change how often you get ELOXATIN, how much you get, or how long the infusion will take.
- You and your doctor will discuss how many times you will get ELOXATIN.

The 5-FU will be given through your I.V. with a pump. If you have any problems with the pump or the tube, call your doctor, your nurse, or the person who is responsible for your pump. You should never allow anyone other than a healthcare provider to touch your infusion pump or tubing.

What activities should I avoid while under treatment with ELOTAXIN?

- Avoid cold temperatures and cold objects. Cover your skin if you must go outside in cold temperatures.
- Do not drink cold drinks or use ice cubes in drinks.
- Do not put ice or ice packs on your body.

See the end of this leaflet, ("How I can help reduce the side effects caused by cold temperatures?")

You need to discuss your level of activity during treatment with your doctor and your nurse. You should follow their advice.

What are the possible side effects of ELOXATIN?

ELOXATIN can cause allergic reactions.

Get emergency help right away if:

- You suddenly have trouble breathing.
- Your throat feels like it is closing up.

Call your doctor right away if you have any of the following:

- Other signs of allergic reaction
  - Rash
  - Hives
  - Swelling of your lips or tongue
  - Sudden cough

Call your doctor if you get any of the following:

- Fever or signs of infection (redness and swelling at the intravenous site, pain on swallowing, cough that brings up mucous, sore throat, shivering, pain on urination)
- Vomiting that is persistent
- Diarrhea (frequent, loose, watery bowel movements)
- Signs of dehydration (too much water loss)
  - tiredness

- thirst
- dry mouth
- lightheadedness (dizziness)
- decreased urination

Tell your doctor if you get a dry cough and have trouble breathing (shortness of breath) before your next treatment. These may be signs of a serious lung disease.

ELOXATIN can affect how your nerves work and make you feel (peripheral neuropathy). Tell your doctor right away, if you get any signs of nerve problems listed below:

- very sensitive to cold temperatures and cold objects
- trouble breathing, swallowing, or saying words, jaw tightness, odd feelings in your tongue, or chest pressure
- pain, tingling, burning, (pins and needles, numb feeling) in your hands, feet, or around your mouth or throat, which may cause problems walking or performing activities of daily living

The first signs of nerve problems may occur with the initial treatment. The nerve problems can also start up to 2 days afterwards. If you develop nerve problems, the amount of ELOXATIN in your next treatment may be changed.

For information on ways to lessen or help with the nerve problems see the end of this leaflet, "How I can help reduce the side effects caused by cold temperatures?" Other common side effects from ELOXATIN include nausea, vomiting, diarrhea, constipation, mouth sores, stomach pain, fever, loss of appetite, and tiredness.

These are not all the possible side effects of ELOXATIN. For more information, ask your doctor or pharmacist.

How can I reduce the side effects caused by cold temperatures?

- Cover yourself with a blanket while you are getting your ELOXATIN infusion.
- Do not breathe deeply when exposed to cold air.
- Wear warm clothing in cold weather at all times. Cover your mouth and nose with a scarf or a pull-down cap (ski cap) to warm the air that goes to your lungs.
- Don’t take things from the freezer or refrigerator without wearing gloves.
- Drink fluids warm or at room temperature.
- Always drink through a straw.
- **Do not** use ice chips if you have nausea or mouth sores. Ask your nurse about what you can use.

- Be aware that most metals are cold to touch especially in the winter. These include your car door and mailbox. Wear gloves to touch cold objects.
- Do not run the air conditioning at high levels in the house or in the car in hot weather.
- If your body gets cold, warm-up the affected part. If your hands get cold, wash them with warm water.
- Always let your nurse and doctor know **before** your next treatment how well you did since your last visit.

This list is not complete and your healthcare provider may have other useful tips for helping you with these side effects.

General Information about the safe and effective use of ELOXATIN.

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets.

This leaflet summarizes the most important information about ELOXATIN. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about ELOXATIN that is written for health professionals.

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Colors: CMYK
Pms 289 CV
x = .01
Date: 6/12/02

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SINGLE USE VIAL
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100 mg
(oxaliplatin for injection)
Eloxatin™

E-184
NDC 0024-0597-04 **100 mg**

Eloxatin™
(oxaliplatin for injection)
100 mg

FOR INTRAVENOUS USE ONLY
SINGLE USE VIAL

Sterile Lyophilized Powder - Preservative Free

Must be reconstituted and diluted before use

DO NOT RECONSTITUTE WITH SODIUM CHLORIDE/ CHLORIDE-CONTAINING SOLUTIONS

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Each vial contains: oxaliplatin, 100 mg, lactose monohydrate, NF, 900 mg.

Dosage and Administration: See package insert.

Prior to Reconstitution: Store at 25° C (77° F); excursions permitted to 15°- 30°C (59° - 86° F) [see USP Controlled Room Temperature]

Reconstitute with 20 mL of Water for Injection, USP or 5% Dextrose Injection, USP.

Discard Unused Portion

(see package insert for storage of reconstituted and diluted solutions)

E-184
NDC 0024-0597-04 **100 mg**

Eloxatin™
(oxaliplatin for injection)
100 mg

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Sterile Lyophilized Powder - Preservative Free

Must be reconstituted and diluted before use

DO NOT RECONSTITUTE WITH SODIUM CHLORIDE/ CHLORIDE-CONTAINING SOLUTIONS

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Size:1.75" x 1.5" x 2.75"
Scale: 100%
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Pms 289 CV
x = .01
Date: 6/12/02

EXP
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SINGLE USE VIAL
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Eloxatin™

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Sterile Lyophilized Powder-Preservative Free
Must be reconstituted and diluted before use
DO NOT RECONSTITUTE WITH SODIUM CHLORIDE/ CHLORIDE-CONTAINING SOLUTIONS
sanofi~synthelabo

Each vial contains: oxaliplatin, 50 mg, lactose monohydrate, NF, 450 mg.

Dosage and Administration: See package insert.

Prior to Reconstitution: Store at 25° C (77° F); excursions permitted to 15°- 30°C (59° - 86° F) [see USP Controlled Room Temperature]

Reconstitute with 10 mL of Water for Injection, USP or 5% Dextrose Injection, USP.

Discard Unused Portion

(see package insert for storage of reconstituted and diluted solutions)

E-182
NDC 0024-0596-02 50 mg
Eloxatin™
(oxaliplatin for injection)
50 mg
FOR INTRAVENOUS USE ONLY
SINGLE USE VIAL
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Must be reconstituted and diluted before use
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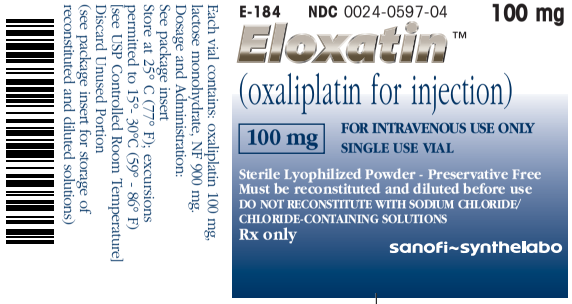

Each vial contains: oxaliplatin 100 mg, lactose monohydrate, NF 900 mg.

Dosage and Administration:
See package insert

Store at 25° C (77° F); excursions permitted to 15°- 30°C (59° - 86° F) [see USP Controlled Room Temperature]

Discard Unused Portion
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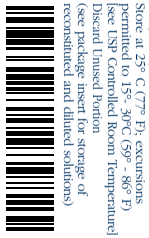

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Each vial contains: oxaliplatin 50 mg, lactose monohydrate, NF 450 mg.
Dosage and Administration:
See package insert.
Store at 25° C (77° F); excursions permitted to 15° -30°C (59° - 86° F) [see USP Controlled Room Temperature]
Discard Unused Portion
(see package insert for storage of reconstituted and diluted solutions)

E-182 **NDC** 0024-0596-02 **50 mg**

Eloxatin™

(oxaliplatin for injection)

50 mg **FOR INTRAVENOUS USE ONLY**
SINGLE USE VIAL

Sterile Lyophilized Powder - Preservative Free
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