NDA 21-758/S-003 Approved 1/10/07

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ELOXATIN safely and effectively. See full prescribing information for ELOXATIN.

ELOXATIN® (oxaliplatin) powder, for solution for intravenous use
Initial U.S. Approval: 2002

WARNING: ANAPHYLACTIC REACTIONS
See full prescribing information for complete boxed warning.
Anaphylactic reactions to ELOXATIN have been reported, and may occur within minutes of ELOXATIN administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms. (5.1)

----------INDICATIONS AND USAGE----------
ELOXATIN is a platinum-based drug used in combination with infusional 5-fluorouracil (5-FU)/leucovorin (LV), which is indicated for:
- adjuvant treatment of stage III colon cancer in patients who have undergone complete resection of the primary tumor. The indication is based on an improvement in disease-free survival, with no demonstrated benefit in overall survival after a median follow up of 4 years. (1)
- treatment of advanced colorectal cancer. (1)

----------DOSAGE AND ADMINISTRATION----------
- Administer ELOXATIN in combination with 5-FU/LV every 2 weeks. (2.1):
  - Day 1: ELOXATIN 85 mg/m^2 intravenous (IV) infusion in 250-500 mL 5% Dextrose Injection, USP (D5W) and LV 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/m2 IV infusion in 500 mL D5W (recommended) as a 22-hour continuous infusion.
  - Day 2: LV 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.
- Reduce the dose of ELOXATIN to 75 mg/m² (adjuvant setting) or 65 mg/m² (advanced colorectal cancer) (2.2):
  - if there are persistent grade 2 neurosensory events that do not resolve.
  - after recovery from grade 3/4 gastrointestinal toxicities (despite prophylactic treatment) or grade 4 neutropenia or grade 3/4 thrombocytopenia. Delay next dose until neutrophils ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L.
- Discontinue ELOXATIN if there are persistent Grade 3 neurosensory events. (2.2)
- Never reconstitute or prepare final dilution with a sodium chloride solution or other chloride-containing solutions. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
Single-use vials of 50 mg or 100 mg oxaliplatin as a sterile, preservative-free lyophilized powder for reconstitution. (3)

----------CONTRAINDICATIONS----------
- Known allergy to ELOXATIN or other platinum compounds. (4, 5.1)

----------WARNINGS AND PRECAUTIONS----------
- Allergic Reactions: Monitor for development of rash, urticaria, erythema, pruritis, bronchospasm, and hypotension. (5.1)
- Neuropathy: Reduce the dose or discontinue ELOXATIN if necessary. (5.2)
- Pulmonary Toxicity: May need to discontinue ELOXATIN until interstitial lung disease or pulmonary fibrosis are excluded. (5.3)
- Hepatotoxicity: Monitor liver function tests. (5.4)
- Pregnancy. Fetal harm can occur when administered to a pregnant woman. Women should be apprised of the potential harm to the fetus. (5.5, 8.1)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥ 40%) were peripheral sensory neuropathy, neutropenia, thrombocytopenia, anemia, nausea, increase in transaminases and alkaline phosphatase, diarrhea, emesis , fatigue and stomatitis. Other adverse reactions, including serious adverse reactions, have been reported. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis U.S. LLC at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: January 2007

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Dosage
2.2 Dose Modification Recommendations
2.3 Preparation of Infusion Solution
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Allergic Reactions
5.2 Neuropathy
5.3 Pulmonary Toxicity
5.4 Hepatotoxicity
5.5 Pregnancy
5.6 Recommended Laboratory Tests
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Patients with Renal Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Combination Adjuvant Therapy with ELOXATIN and Infusional 5-FU/LV in Patients with Stage II or III Colon Cancer
14.2 Combination Therapy with ELOXATIN and 5-FU/LV in Patients Previously Untreated for Advanced Colorectal Cancer
14.3 Combination Therapy with ELOXATIN and 5-FU/LV in Previously Treated Patients with Advanced Colorectal Cancer
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How supplied
16.2 Storage
16.3 Handling and Disposal
17 PATIENT COUNSELING INFORMATION
17.1 Information for Patients
17.2 FDA-Approved Patient Labeling

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ANAPHYLACTIC REACTIONS

Anaphylactic reactions to ELOXATIN have been reported, and may occur within minutes of ELOXATIN administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms of anaphylaxis *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

ELOXATIN, used in combination with infusional 5-FU/LV, is indicated for:

- adjuvant treatment of stage III colon cancer in patients who have undergone complete resection of the primary tumor. The indication is based on an improvement in disease-free survival, with no demonstrated benefit in overall survival after a median follow up of 4 years.
- treatment of advanced colorectal cancer.

2 DOSAGE and ADMINISTRATION

ELOXATIN (oxaliplatin 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.

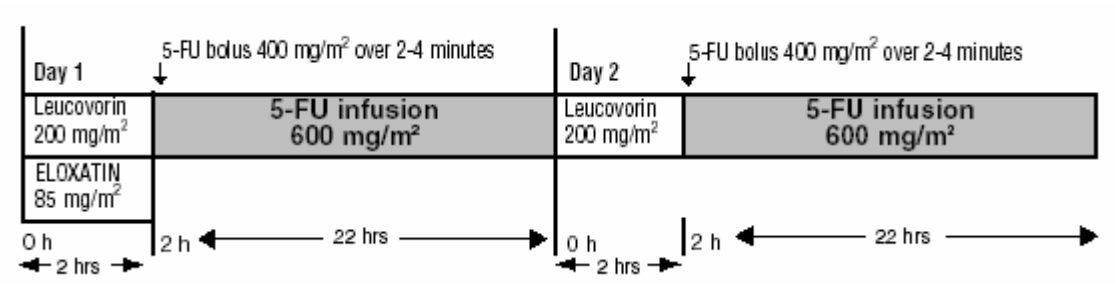
2.1 Dosage

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

Day 1: ELOXATIN 85 mg/m^2 IV infusion in 250-500 mL 5% Dextrose injection, USP (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/m2 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 1



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.

2.2 Dose Modification Recommendations

Prior to subsequent therapy cycles, patients should be evaluated for clinical toxicities and recommended laboratory tests *[see Warnings and Precautions (5.6)]*. Prolongation of infusion time for ELOXATIN from 2 hours to 6 hours may mitigate acute toxicities. The infusion times for 5-FU and leucovorin do not need to be changed.

Adjuvant Therapy in Patients with Stage III Colon Cancer

Neuropathy and other toxicities were graded using the NCI CTC scale version 1 *[see Warnings and Precautions (5.2)]*.

For patients who experience persistent Grade 2 neurosensory events that do not resolve, a dose reduction of ELOXATIN to 75 mg/m^2 should be considered. For patients with persistent Grade 3 neurosensory events, discontinuing therapy should be considered. The infusional 5-FU/LV regimen need not be altered.

A dose reduction of ELOXATIN to 75 mg/m^2 and infusional 5-FU to 300 mg/m^2 bolus and 500 mg/m^2 22 hour infusion is recommended for patients after recovery from grade 3/4 gastrointestinal (despite prophylactic treatment) or grade 4 neutropenia or 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.

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

Neuropathy was graded using a study-specific neurotoxicity scale *[see Warnings and Precautions (5.2)]*. Other toxicities were graded by the NCI CTC, Version 2.0.

For patients who experience persistent Grade 2 neurosensory events that do not resolve, a dose reduction of 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 x 10^9/L and platelets $\geq$75 x 10^9/L.

2.3 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.

3 DOSAGE FORMS AND STRENGHS

ELOXATIN is supplied in single-use vials containing 50 mg or 100 mg of oxaliplatin as a sterile, preservative-free lyophilized powder for reconstitution.

4 CONTRAINDICATIONS

ELOXATIN should not be administered to patients with a history of known allergy to ELOXATIN or other platinum compounds *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Allergic Reactions

See boxed warning

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

5.2 Neuropathy

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. In adjuvant patients the median cycle of onset for grade 3 peripheral sensory neuropathy was 9 in the previously treated patients the median number of cycles administered on the ELOXATIN with 5 FU/LV combination arm was 6.

An acute syndrome of pharyngolaryngeal dysesthesia seen in 1-2% (grade 3/4) of patients previously untreated for advanced colorectal cancer, and the previously treated patients, is characterized by subjective sensations of dysphagia or dyspnea, without any laryngospasm or bronchospasm (no stridor or wheezing). Ice (mucositis prophylaxis) should be avoided during the infusion of ELOXATIN because cold temperature can exacerbate acute neurological symptoms.

A persistent (>14 days), primarily peripheral, sensory neuropathy that is usually characterized by paresthesias, dysesthesias, hypoesthesias, but may also include deficits in

proprioception that can interfere with daily activities (e.g., writing, buttoning, swallowing, and difficulty walking from impaired proprioception). These forms of neuropathy occurred in 48% of the study patients receiving 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.

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

Table 1 - NCI CTC Grading for Neuropathy in Adjuvant Patients

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

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

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

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

Grade	Definition
Grade 1	Resolved and did not interfere with functioning
Grade 2	Interfered with function but not daily activities
Grade 3	Pain or functional impairment that interfered with daily activities
Grade 4	Persistent impairment that is disabling or life-threatening

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

5.3 Pulmonary Toxicity

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

5.4 Hepatotoxicity

Hepatotoxicity as evidenced in the adjuvant study, by increase in transaminases (57% vs. 34%) and alkaline phosphatase (42% vs. 20%) was observed more commonly in the ELOXATIN combination arm than in the control arm. The incidence of increased bilirubin was similar on both arms. Changes noted on liver biopsies include: peliosis, nodular regenerative hyperplasia or sinusoidal alterations, perisinusoidal fibrosis, and veno-occlusive lesions. Hepatic vascular disorders should be considered, and if appropriate, should be investigated in case of abnormal liver function test results or portal hypertension, which cannot be explained by liver metastases *[see Clinical Trials Experience (6.1)*.

5.5 Pregnancy

Pregnancy Category D

ELOXATIN may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of ELOXATIN in pregnant women. 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. *[See Use in Specific Patient Populations (8.1)]*

5.6 Recommended Laboratory Tests

Standard monitoring of the white blood cell count with differential, hemoglobin, platelet count, and blood chemistries (including ALT, AST, bilirubin and creatinine) is recommended before each ELOXATIN cycle *[see Dosage and Administration (2)]*.

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.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Serious adverse reactions including anaphylaxis and allergic reactions, neuropathy, pulmonary toxicities and hepatotoxicities can occur *[See Warnings and Precautions (5.1)]*

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

More than 1100 patients with stage II or III colon cancer and more than 4,000 patients with advanced colorectal cancer have been treated in clinical studies with ELOXATIN. The most common adverse reactions in patients with stage II or III colon cancer receiving adjuvant therapy were peripheral sensory neuropathy, neutropenia, thrombocytopenia, anemia, nausea, increase in transaminases and alkaline phosphatase, diarrhea, emesis, fatigue and stomatitis. The most common adverse reactions in previously untreated and treated patients were peripheral sensory neuropathies, fatigue, neutropenia, nausea, emesis, and diarrhea *[see Warnings and Precautions (5)]*.

Combination Adjuvant Therapy with ELOXATIN and Infusional 5-FU/LV in Patients with Colon Cancer

One thousand one hundred and eight patients with stage II or III colon cancer, who had undergone complete resection of the primary tumor, have been treated in a clinical study with ELOXATIN in combination with infusional 5-FU/LV *[see Clinical Studies (14)]*. The incidence of grade 3 or 4 adverse events was 70% on the ELOXATIN combination arm, and 31% on the infusional 5-FU/LV arm. The adverse reactions in this trial are shown in the tables below. Discontinuation of treatment due to adverse events occurred in 15% of the patients receiving ELOXATIN and infusional 5-FU/LV. Both 5-FU/LV and ELOXATIN are associated with gastrointestinal or hematologic adverse events. When ELOXATIN is administered in combination with infusional 5-FU/LV, the incidence of these events is increased.

The incidence of death within 28 days of last treatment, regardless of causality, was 0.5% (n=6) in both the ELOXATIN combination and infusional 5-FU/LV arms, respectively. Deaths within 60 days from initiation of therapy were 0.3% (n=3) in both the ELOXATIN combination and infusional 5-FU/LV arms, respectively. On the ELOXATIN combination arm, 3 deaths were due to sepsis/neutropenic sepsis, 2 from intracerebral bleeding and one from eosinophilic pneumonia. On the 5-FU/LV arm, one death was due to suicide, 2 from Steven-Johnson Syndrome (1 patient also had sepsis), 1 unknown cause, 1 anoxic cerebral infarction and 1 probable abdominal aorta rupture.

The following table provides adverse events reported in the adjuvant therapy colon cancer clinical trial *[see Clinical Studies (14)]* by body system and decreasing order of frequency in the ELOXATIN and infusional 5-FU/LV arm for events with overall incidences ≥ 5% and for NCI grade 3/4 events with incidences ≥ 1%.

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

	ELOXATIN + 5-FU/LV N=1108		**5-FU/LV N=1111**	
Adverse Event (WHO/Pref)	**All Grades (%)**	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**
Any Event	100	70	99	31
Allergy/Immunology				
Allergic Reaction	10	3	2	<1
Constitutional Symptoms/Pain				
Fatigue	44	4	38	1
Abdominal Pain	18	1	17	2
Dermatology/Skin				
Skin Disorder	32	2	36	2
Injection Site Reaction[1]	11	3	10	3
Gastrointestinal				
Nausea	74	5	61	2
Diarrhea	56	11	48	7
Vomiting	47	6	24	1
Stomatitis	42	3	40	2
Anorexia	13	1	8	<1
Fever/Infection				
Fever	27	1	12	1
Infection	25	4	25	3
Neurology				
Overall Peripheral Sensory Neuropathy	92	12	16	<1

[1] Includes thrombosis related to the catheter

The following table provides adverse events reported in the adjuvant therapy colon cancer clinical trial *[see Clinical Studies (14)]* by body system and decreasing order of frequency in the ELOXATIN and infusional 5-FU/LV arm for events with overall incidences ≥ 5% but with incidences <1% NCI grade 3/4 events.

Table 4 - Adverse Experiences Reported in Patients with Colon Cancer receiving Adjuvant Treatment (≥ 5% of all patients, but with <1% NCI Grade 3/4 events)

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

Although specific events can vary, the overall frequency of adverse events was similar in men and women and in patients <65 and ≥65 years. However, the following grade 3/4 events were more common in females: diarrhea, fatigue, granulocytopenia, nausea and vomiting. In patients ≥65 years old, the incidence of grade 3/4 diarrhea and granulocytopenia was higher than in younger patients. Insufficient subgroup sizes prevented analysis of safety by race. The following additional adverse events, 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): pain, leukopenia, weight decrease, coughing.

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 (14)]*. 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 (14)]* 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%.

Table 5 – Adverse Experiences 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

	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 (%)**
Diarrhea-colostomy	13	2	16	7	16	3
Gastrointestinal NOS*	5	2	4	2	3	2
Hematology/Infection						
Infection normal ANC**	10	4	5	1	7	2
Infection low ANC**	8	8	12	11	9	8
Lymphopenia	6	2	4	1	5	2
Febrile neutropenia	4	4	15	14	12	11
Hepatic/Metabolic/Laboratory/Renal						
Hyperglycemia	14	2	11	3	12	3
Hypokalemia	11	3	7	4	6	2
Dehydration	9	5	16	11	14	7
Hypoalbuminemia	8	0	5	2	9	1
Hyponatremia	8	2	7	4	4	1
Urinary frequency	5	1	2	1	3	1
Neurology						
Overall Neuropathy	82	19	18	2	69	7
Paresthesias	77	18	16	2	62	6
Pharyngo-laryngeal dysesthesias	38	2	1	0	28	1
Neuro-sensory	12	1	2	0	9	1
Neuro NOS*	1	0	1	0	1	0
Pulmonary						
Cough	35	1	25	2	17	1
Dyspnea	18	7	14	3	11	2
Hiccups	5	1	2	0	3	2

* Not otherwise specified
** Absolute neutrophil count

The following table provides adverse events reported in the previously untreated for advanced colorectal cancer study *[see Clinical Studies (14)]* 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 6 - Adverse Experiences 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 (%)
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 normal ANC*	16	9	9
Hepatic/Metabolic/Laboratory/Renal			
Hypocalcemia	7	5	4
Elevated Creatinine	4	4	5
Neurology			
Insomnia	13	9	11
Depression	9	5	7
Dizziness	8	6	10
Anxiety	5	2	6

* Absolute neutrophil count

Adverse 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 (14)]*. 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 percent 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 (14)]* 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 7 – Adverse Experiences 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

	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 (%)**
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 (14)]* 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 8 - Adverse Experiences 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 (%)
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, pruritus, hemoptysis, purpura, vaginal hemorrhage, melena, somnolence, pneumonia, proctitis, involuntary muscle contractions, intestinal obstruction, gingivitis, tenesmus, hot flashes, enlarged abdomen, urinary incontinence.

Hematologic Changes

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

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

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

Table 10 – Adverse Hematologic 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 11 – Adverse Hematologic Experiences in 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 and Bleeding

Thrombocytopenia was frequently reported with the combination of ELOXATIN and infusional 5-FU/LV. The incidence of all hemorrhagic events in the adjuvant and previously treated patients was higher on the ELOXATIN combination arm compared to the infusional 5-FU/LV arm. These events included gastrointestinal bleeding, hematuria, and epistaxis. In the adjuvant trial, two patients died from intracerebral hemorrhages.

The incidence of Grade 3/4 thrombocytopenia was 2% in adjuvant patients with colon cancer. In patients treated for advanced colorectal cancer the incidence of Grade 3/4 thrombocytopenia was 3-5%, and the incidence of these events was greater for the combination of ELOXATIN and 5-FU/LV over the irinotecan plus 5-FU/LV or 5-FU/LV control groups. Grade 3/4 gastrointestinal bleeding was reported in 0.2% of adjuvant patients receiving ELOXATIN and 5-FU/LV. 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.

Neutropenia

Neutropenia was frequently observed with the combination of ELOXATIN and 5-FU/LV, with Grade 3 and 4 events reported in 29% and 12% of adjuvant patients with colon cancer, respectively. In the adjuvant trial, 3 patients died from sepsis/neutropenic sepsis. Grade 3 and 4 events were reported in 35% and 18% of the patients previously untreated for advanced colorectal cancer, respectively. Grade 3 and 4 events were reported in 27% and 17% of previously treated patients, respectively. In adjuvant patients the incidence of either febrile neutropenia (0.7%) or documented infection with concomitant grade 3/4 neutropenia (1.1%) was 1.8% in the ELOXATIN and 5-FU/LV arm. The incidence of febrile neutropenia in the patients previously untreated for advanced colorectal cancer was 15% (3% of cycles) in the irinotecan plus 5-FU/LV arm and 4% (less than 1% of cycles) in the 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 receiving the combination of ELOXATIN plus infusional 5-FU/LV for adjuvant treatment for colon cancer the incidence of Grade 3/4 nausea and vomiting was greater than those receiving infusional 5-FU/LV alone (see table). 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 Grade 3/4 skin disorders was 2% in both the ELOXATIN plus infusional 5-FU/LV and the infusional 5-FU/LV alone arms in the adjuvant colon cancer patients. The incidence of hand-foot syndrome in patients previously untreated for advanced colorectal cancer was 2% in the irinotecan plus 5-FU/LV arm and 7% in the 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.

Intravenous Site Reactions

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

Anticoagulation and Hemorrhage

There have been reports while on study and from post-marketing surveillance of prolonged prothrombin time and INR occasionally associated with hemorrhage in patients who received 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. Serum creatinine measurements were not reported in the adjuvant trial.

Hepatic

Hepatotoxicity (defined as elevation of liver enzymes) appears to be related to ELOXATIN combination therapy *[see Warnings and Precautions (5.4)]*. 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 adjuvant patients and patients previously untreated for advanced colorectal cancer, laboratory values and NCI CTC grade for previously treated patients.

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

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

Table 13 – Adverse Hepatic – Clinical Chemistry 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 14 – 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 in adjuvant patients with colon cancer was 6% (1.8% grade 3/4) in the infusional 5-FU/LV arm and 6% (1.2% grade 3/4) in the ELOXATIN and infusional 5-FU/LV combined arm, respectively. The incidence was 6 and 9% of the patients previously untreated for advanced colorectal cancer and previously treated patients in the ELOXATIN and 5-FU/LV combination arm, respectively.

6.2 Postmarketing Experience

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

Body as a whole:
angioedema, anaphylactic shock

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

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

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, immuno-allergic hemolytic anemia

Renal disorders:
Acute tubulo-interstitial nephropathy leading to acute renal failure.

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

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

7 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. Because 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 (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.5)]*

8.3 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.

8.4 Pediatric Use

The effectiveness of oxaliplatin in children has not been established. Oxaliplatin has been tested in 2 Phase I and 2 Phase II trials in 159 patients ages 7 months to 22 years with solid tumors (see below) and no significant activity observed.

In a Phase I/II study, oxaliplatin was administered as a 2-hour IV infusion on days 1, 8 and 15 every 4 weeks (1 cycle), for a maximum of 6 cycles, to 43 patients with refractory or relapsed malignant solid tumors, mainly neuroblastoma and osteosarcoma. Twenty eight pediatric patients in the Phase I study received oxaliplatin at 6 dose levels starting at 40 mg/m² with escalation to 110 mg/m². The dose limiting toxicity (DLT) was sensory neuropathy at the 110 mg/m² dose. Fifteen patients received oxaliplatin at a dose of 90 mg/m² IV in the Phase II portion of the study. At this dose, paresthesia (60%, G3/4: 7%), fever (40%, G3/4: 7%) and thrombocytopenia (40%, G3/4: 27%) were the main adverse events. No responses were observed.

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

In one Phase II study, 43 pediatric patients with recurrent or refractory embryonal CNS tumors received oxaliplatin 130 mg/m^2 every 3 weeks for a maximum of 12 months in absence of progressive disease or unacceptable toxicity. In patients < 10 kg the oxaliplatin dose used was 4.3 mg/kg. The most common adverse events reported were leukopenia (67%, G3/4: 12%), anemia (65%, G3/4: 5%), thrombocytopenia (65%, G3/4: 26%), vomiting (65%, G3/4: 7%), neutropenia (58%, G3/4: 16%) and sensory neuropathy (40%, G3/4: 5%). One partial response was observed.

In a second Phase II study, 47 pediatric patients with recurrent solid tumors, including Ewing sarcoma or peripheral PNET, osteosarcoma, rhabdomyosarcoma and neuroblastoma, received oxaliplatin 130 mg/m^2 every 3 weeks for a maximum of 12 months or 17 cycles. In patients $\leq$ 12 months old the oxaliplatin dose used was 4.3 mg/kg. The most common adverse events reported were sensory neuropathy (53%, G3/4: 15%), thrombocytopenia (40%, G3/4: 26%), anemia (40%, G3/4: 15%), vomiting (32%, G3/4: 0%), nausea (30%, G3/4: 2%) and AST increased (26%, G3/4: 4%). No responses were observed.

The pharmacokinetic parameters of ultrafiltrable platinum have been evaluated in 105 pediatric patients during the first cycle. The mean clearance in pediatric patients estimated by the population pharmacokinetic analysis was 4.7 L/h/m^2. The inter-patient variability of platinum clearance in pediatric cancer patients was 41%. Mean platinum pharmacokinetic parameters in ultrafiltrate were C_{max} of 0.75 $\pm$ 0.24 mcg/mL, AUC_{0-48} of 7.52 $\pm$ 5.07 mcg·h/mL and AUC_{inf} of 8.83 $\pm$ 1.57 mcg·h/mL at 85 mg/m² of oxaliplatin and C_{max} of 1.10 $\pm$ 0.43 mcg/mL, AUC_{0-48} of 9.74 $\pm$ 2.52 mcg·h/mL and AUC_{inf} of 17.3 $\pm$ 5.34 mcg·h/mL at 130 mg/m² of oxaliplatin.

8.5 Geriatric Use

No significant effect of age on the clearance of ultrafilterable platinum has been observed. In the adjuvant therapy colon cancer randomized clinical trial, *[see Clinical Studies (14)]* 723 patients treated with ELOXATIN and infusional 5-FU/LV were <65 years and 400 patients were ≥65 years. The effect of ELOXATIN on disease free survival benefit in patients >65 years of age was not conclusive.

In the previously untreated for advanced colorectal cancer randomized clinical trial *[see Clinical Studies (14)]* 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 (14)]* 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 all studies. The incidence of diarrhea, dehydration, hypokalemia, leukopenia, fatigue and syncope were higher in patients ≥65 years old. No adjustment to starting dose was required in patients ≥65 years old.

8.6 Patients with Renal Impairment

The safety and effectiveness of the combination of ELOXATIN and 5-FU/LV in patients with renal impairment have 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 Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*.

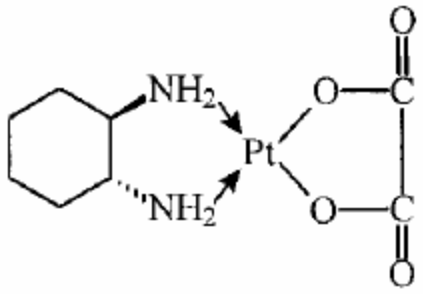
10 OVERDOSAGE

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.

11 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Oxaliplatin undergoes nonenzymatic conversion in physiologic solutions to active derivatives via displacement of the labile oxalate ligand. Several transient reactive species are formed, including monoaquo and diaquo DACH platinum, which covalently bind with macromolecules. Both inter- and intrastrand Pt-DNA crosslinks are formed. Crosslinks are formed between the *N7* positions of two adjacent guanines (GG), adjacent adenine-guanines (AG), and guanines separated by an intervening nucleotide (GNG). These crosslinks inhibit DNA replication and transcription. Cytotoxicity is cell-cycle nonspecific.

12.2 Pharmacodynamics

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)].

12.3 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 mcg/mL and volume of distribution of 440 L. Interpatient and intrapatient variability in ultrafilterable platinum exposure ($AUC_{0\text{-}48hr}$) 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.

Pharmacokinetics in Special Populations

Pediatric

[See Use In Specific Patient Populations (8.4)].

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 Adverse Reactions (6), Drug Interactions (7) and Use In Specific Patient Populations (8.6)]*.

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.

13 NONCLINICAL TOXICOLOGY

13.1 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.

14 CLINICAL STUDIES

14.1 Combination Adjuvant Therapy with ELOXATIN and Infusional 5-FU/LV in Patients with Colon Cancer

An international, multicenter, randomized study compared the efficacy and evaluated the safety of ELOXATIN in combination with an infusional schedule of 5-FU/LV to infusional 5-FU/LV alone, in patients with stage II (Dukes' B2) or III (Dukes' C) colon cancer who had undergone complete resection of the primary tumor. The primary objective of the study was to compare the 3-year disease-free survival (DFS) in patients receiving ELOXATIN and infusional 5-FU/LV to those receiving 5-FU/LV alone. Patients were to be treated for a total of 6 months (i.e., 12 cycles). A total of 2246 patients were randomized; 1123 patients per study arm. Patients in the study had to be between 18 and 75 years of age, have histologically proven stage II (T_3-T_4 N0 M0; Dukes' B2) or III (any T N_{1-2} M0; Dukes' C) colon carcinoma (with the inferior pole of the tumor above the peritoneal reflection, i.e., ≥15 cm from the anal margin) and undergone (within 7 weeks prior to randomization) complete resection of the primary tumor without gross or microscopic evidence of residual disease. Patients had to have had no prior chemotherapy, immunotherapy or radiotherapy, and have an ECOG performance status of 0,1, or 2 (KPS ≥ 60%), absolute neutrophil count (ANC) > $1.5x10^9$/L, platelets ≥$100x10^9$/L, serum creatinine ≤ 1.25 x ULN total bilirubin < 2 x ULN, AST/ALT < 2 x ULN and carcino-embyrogenic antigen (CEA) < 10 ng/mL. Patients with preexisting peripheral neuropathy (NCI grade ≥ 1) were ineligible for this trial.

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

Table 15 - Dosing Regimens in Adjuvant Therapy Study

Treatment Arm	Dose	Regimen
ELOXATIN + 5-FU/LV (FOLFOX4) (N =1123)	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 12 cycles
5-FU/LV (N=1123)	Day 1: LV: 200 mg/m^2 (2-hour infusion), followed by 5-FU: 400 mg/m^2 (bolus), 600 mg/m^2 (22-hour infusion) Day 2: LV: 200 mg/m^2 (2-hour infusion), followed by 5-FU: 400 mg/m^2 (bolus), 600 mg/m^2 (22-hour infusion)	q2w 12 cycles

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

Table 16 - Patient Characteristics in Adjuvant Therapy Study

	ELOXATIN + infusional 5-FU/LV N=1123	Infusional 5-FU/LV N=1123
Sex: Male (%)	56.1	52.4
Female (%)	43.9	47.6
Median age (years)	61.0	60.0
<65 years of age (%)	64.4	66.2
≥65 years of age (%)	35.6	33.8
Karnofsky Performance Status (KPS) (%)		
100	29.7	30.5
90	52.2	53.9
80	4.4	3.3
70	13.2	11.9
≤60	0.6	0.4
Primary site (%)		
Colon including cecum	54.6	54.4
Sigmoid	31.9	33.8
Recto sigmoid	12.9	10.9

Other including rectum	0.6	0.9
Bowel obstruction (%)		
Yes	17.9	19.3
Perforation (%)		
Yes	6.9	6.9
Stage at Randomization (%)		
II (T=3,4 N=0, M=0)	40.1	39.9
III (T=any, N=1,2, M=0)	59.6	59.3
IV (T=any, N=any, M=1)	0.4	0.8
Staging – T (%)		
T1	0.5	0.7
T2	4.5	4.8
T3	76.0	75.9
T4	19.0	18.5
Staging – N (%)		
N0	40.2	39.9
N1	39.4	39.4
N2	20.4	20.7
Staging – M (%)		
M1	0.4	0.8

Table 17 - Dosing in Adjuvant Therapy Study

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

The following table and figures summarize the disease-free survival (DFS) results in the overall randomized population and in patients with stage II and III disease based on an ITT analysis.

Table 18 - Summary of DFS analysis
[ITT analysis (minimum follow-up of 41 months)]

Parameter	ELOXATIN + Infusional 5-FU/LV	Infusional 5-FU/LV
Overall		
N	1123	1123
Median follow-up (months)*	47.7	47.4

Number of events – relapse or death (%)	267 (23.8)	332 (29.6)
4-year Disease-free survival % [95% CI]	75.9 [73.4, 78.5]	69.1 [66.3, 71.9]
Hazard ratio [95% CI]	0.76 [0.65, 0.90]	
Stratified Logrank test	p=0.0008	
Stage III		
N	672	675
Number of events –relapse or death (%)	200 (29.8)	252 (37.3)
4-year Disease-free survival % [95% CI]	69.7 [66.2, 73.3]	61.0 [57.1, 64.8]
Hazard ratio [95% CI]	0.75 [0.62, 0.90]	
Logrank test	p=0.002	
Stage II		
N	451	448
Number of events – relapse or death (%)	67 (14.9)	80 (17.9)
4-year Disease-free survival % [95% CI]	85.1 [81.7, 88.6]	81.3 [77.6, 85.1]
Hazard ratio [95% CI]	0.80 [0.58, 1.11]	
Logrank test	p=0.179	

*For patients alive or lost to follow-up

In the overall study population DFS was statistically significantly improved in the ELOXATIN combination arm compared to infusional 5-FU/LV alone. A statistically significant improvement in DFS was noted in Stage III patients, but not in Stage II patients.

Figure 2 shows the Kaplan-Meier DFS curves for the comparison of ELOXATIN and infusional 5-FU/LV combination and infusional 5-FU/LV alone for the overall population (ITT analysis). Figure 3 shows the Kaplan-Meier DFS curves for the comparison of ELOXATIN and infusional 5-FU/LV combination and infusional 5-FU/LV alone for the Stage III Subgroup.

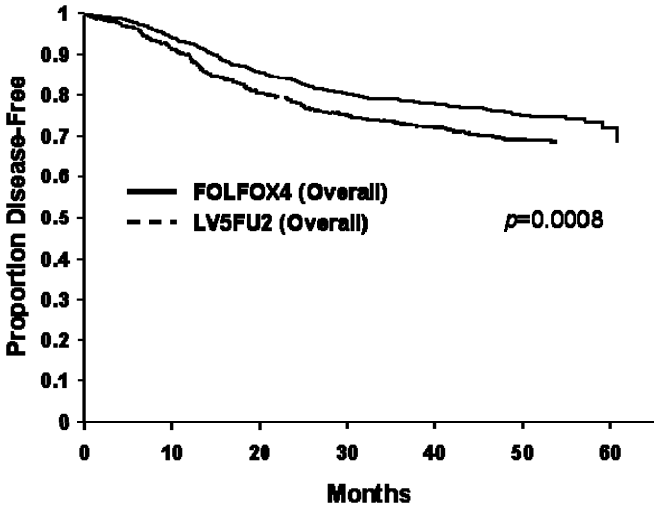


Figure 2 - Kaplan-Meier DFS curves by treatment arm for Overall Population

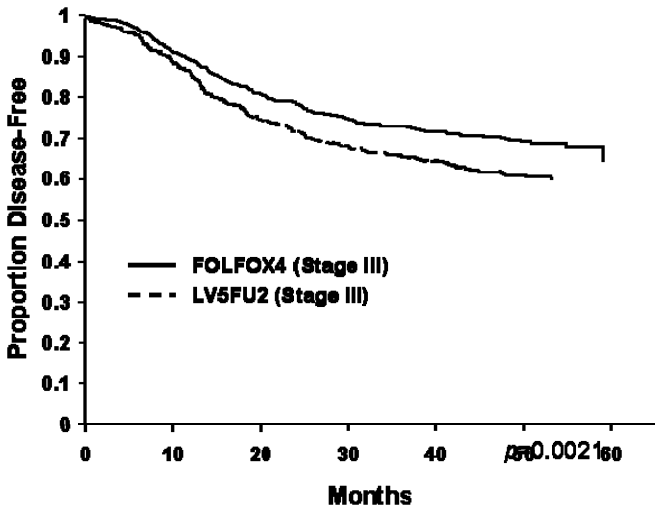


Figure 3 - Kaplan-Meier DFS curves by treatment arm for Stage III Subgroup

Survival data were not mature at the time of the analysis with a median follow-up of 47 months. No statistically significant difference in overall survival [Hazard Ratio 0.89 (95% CI 0.72, 1.09) p=0.236] was shown between the two treatment arms in the entire population or in the Stage II [Hazard Ratio 0.98 (95% CI 0.63, 1.53) p=0.94] or Stage III [Hazard Ratio 0.86 (95%CI 0.68, 1.08) p=0.196] subgroups.

A descriptive subgroup analysis demonstrated that the improvement in DFS for the ELOXATIN combination arm compared to the infusional 5-FU/LV alone arm appeared to be maintained across genders. The effect of ELOXATIN on disease free survival benefit in patients ≥65 years of age was not conclusive. Insufficient subgroup sizes prevented analysis by race.

14.2 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 ≥ 1.5 x 10^9/L, platelets ≥ 100 x 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 19 – 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) 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 of the patient population entered into this study.

Table 20 – Patient Demographics 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 21 – 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	0.65 (0.53-0.80)*		

interval)			
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 4 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.

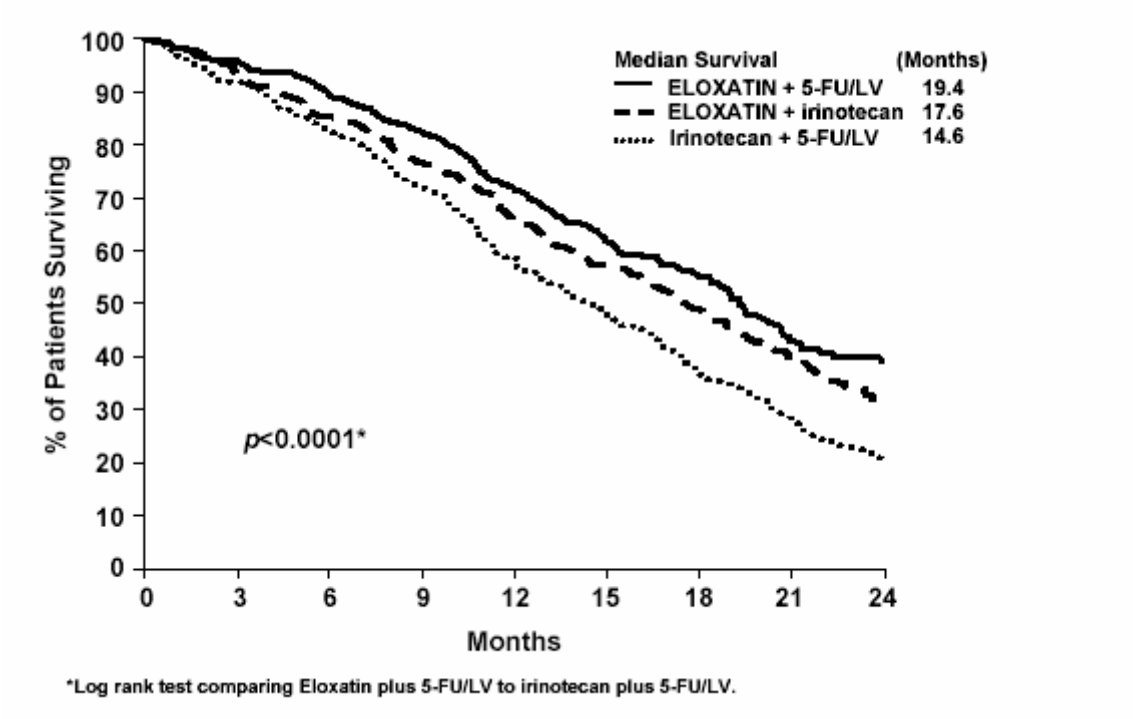


Figure 4 – Kaplan-Meier Overall Survival by treatment arm

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.

14.3 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 22 – 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 23 – 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 24 - 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 25 - 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.

15 REFERENCES

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.

2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. ttp://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html

3. NIH [2002]. 1999 recommendations for the safe handling of cytotoxic drugs. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, NIH Publication No. 92-2621.

4. American Society of Health-System Pharmacists. (2006) ASHP Guidelines on Handling Hazardous Drugs.

5. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 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.

16.2 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].

16.3 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 *[see References (15)]*. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

17 PATIENT COUNSELING INFORMATION

17.1 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.

17.2 FDA-Approved Patient Labeling

PATIENT INFORMATION

ELOXATIN®
(OXALIplatin for injection)
and
ELOXATIN®
(OXALIplatin injection)
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 with other anti-cancer medicines called 5-fluorouracil (5-FU) and leucovorin (LV):

- to treat adults with stage III colon cancer after surgery to remove the tumor
- to treat adults with advanced colon or rectal cancer (colo-rectal cancer).

ELOXATIN with infusional 5-FU and LV was shown to lower the chance of colon cancer returning when given to patients with stage III colon cancer after surgery to remove the tumor. It is not known if ELOXATIN increases survival in patients with stage III colon cancer. ELOXATIN with infusional 5-FU and LV was also shown to increase survival, shrink tumors and delay growth of tumors in some patients with advanced colorectal cancer.

The use of ELOXATIN in children has not been studied.

Who should not use ELOXATIN?

Do not use ELOXATIN 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.
- 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. You will receive ELOXATIN on the first day only. There are usually 14 days between each chemotherapy treatment course.

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 ELOXATIN?

- 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 can I 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 can I 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.
- Do not 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.

Paraplatin® and Platinol® are registered trademarks of Bristol-Myers Squibb Company.

Manufactured for:
sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

© 2007 sanofi-aventis U.S. LLC